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Study of the Role of Migration Inducting Gene 7 as a Molecular Marker for Early Detection of Endometrial Carcinoma Micrometastasis

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ABSTRACT

Background and objectives: Endometrial carcinoma is diagnosed early by abnormal uterine bleeding especially in postmenopausal women. MIG-7, a protein rich in cysteine, was initially discovered in endometrial cancer cells following treatment with hepatocyte growth factor (HGF).

Subjects and methods: This case-control study was done at Mansoura University, Egypt, on a total of 75 patients, with 25 age-matched healthy female volunteers as control group and 50 patients classified according to standard criteria based on data of International Federation of Gynecology and Obstetrics (FIGO) into two groups (non-metastatic endometrial carcinoma and metastatic endometrial carcinoma). Total RNA extracted from peripheral blood, cDNA synthesized from RNA and Real-time PCR done for quantification of MIG7.

Results: Comparison between the control group, there are significant changes in the expression of the MIG7 gene between patients with non-metastatic endometrial cancer and patients with metastatic endometrial carcinoma ((0.69±0.21), (1.38±0.39) and (1.97±0.45)) respectively, P-values (all< 0.001). AUC values for MIG7 equal 0.945 while MIG7 show sensitivity percentage of 88% and 88% specificity percent.In the univariable analysis MIG7 gives an odds ratio (ORs) 1.077 at p-values of 0.002 while in the multivariable analysis demonstrate elevated ORs, p-values (0.024).

In conclusion, the current study documented the critical role of MIG7 in understanding the molecular distinctions between non-metastatic and metastatic endometrial carcinoma.

Keywords:

endometrial carcinoma, gene expression, MIG7.

1. INTRODUCTION

Endometrial carcinoma is the predominant gynecologic cancer in industrialized nations and the second most prevalent in developing nations, following cervical carcinoma. It has a favorable prognosis because of diagnosing it early by abnormal uterine bleeding especially in postmenopausal women. However, in premenopausal women, uterine bleeding may not relate to menstrual cycle or long heavy bleeding during menstrual cycle may occur [1]. Endometrial Carcinoma initially metastasizes to the myometrium and serosa before spreading to additional reproductive and pelvic systems. The lymphatic system often first involves the pelvic and para-aortic nodes. Distant metastases occur by the blood often to lungs, liver, brain and bone [2]. Metastasis is a complex series of steps. The process begins with the infiltration of nearby host tissue by cells derived from the main tumor. Cells subsequently infiltrate into either blood or lymphatic channels, allowing them to spread to far organs. They attach themselves to the capillary beds of the target organ. Subsequently, they infiltrate the organ's parenchyma, where they undergo rapid multiplication and initiate the formation of new blood vessels within the organ. Throughout these stages, the tumor cells must evade the host's immune response and programmed cell death (apoptosis) in order to endure [3]. The cells that have shed into the blood stream from the primary tumor knew as circulating tumor cells (CTCs) and carried out by the blood all over the body to distant organs causing metastasis. CTCs thus represent seeds for the subsequent growth of another tumor (metastases) in distant organs. Micrometastases are often undetectable by classical imaging [4]. Therefore, detection of specific molecular markers on CTCs from peripheral blood can predict the survival of patient Increase the level of expression of some of these markers in endometrial cancer [5]. Migration-Inducing Gene 7 (MIG-7) is a protein that has a high amount of cysteine. It was initially discovered in endometrial cancer cells after being exposed to hepatocyte growth factor (HGF). Subsequent research revealed that MIG-7 exhibited increased expression on the cell membrane and inside the cytoplasm of many cancer types, while maintaining low or undetectable levels in non-cancerous tissues[6]. Therefore, MIG-7 shows potential as a valuable indicator for the identification and diagnosis of cancer. So, the aim of the present work was to Study the role of MIG7 as molecular marker for early detection of endometrial carcinoma micrometastases, and use blood sample instead of using invasive biopsies or expensive imaging techniques for detection of endometrial carcinoma micrometastases.

2. STUDY AREA

Arab Republic of Egypt.

3. SUBJECTS AND METHODS

Patients and controls

This study included 50 cases of female patients and 25 control subjects matched in age. The mean age of non-metastatic and metastatic groups was:(49.0-73.0) and (48.0-83.0) years, respectively. Patients were classified according to standard criteria based on data of international federation of Gynecology and Obstetrics (FIGO) staging systems into two groups: The first group: 25 cases of non-metastatic endometrial carcinoma (stage I-II). The second group: 25 cases of metastatic endometrial carcinoma (stage III-IV). all collected randomly from the oncology Center, Mansoura University Hospital, in the period from December 2019 to February 2022.

Sampling and management of specimens

A 5 mL sample of peripheral venous blood was taken from individuals using EDTA tubes, properly labeled, transferred on ice to Medical Biochemistry Department and stored at -20 ºC until processing.

Another blood sample collected in anti-coagulant free tubes and left at room temperature for 20 minutes and then centrifuged to separate serum and stored at -20 ºC until processing.

Laboratory analysis

Circulating Tumor Cells separated by density- gradient centrifugation throw Ficoll (Biocoll Separating Solution) were used (English and Andersen, 1974). The item was acquired from Biochrom-Gmb, with the catalog number L 6113, and originated from Germany. Extraction of total RNA were from peripheral blood, RNA concentration and purity were assayed, cDNA was synthesized from RNA, primer design was done and primer conditioning was done using PCR, Real-time PCR for quantification of MIG7.

Statistical analysis:

The data were summarized, tabulated, and analyzed using SPSS software version 21. IBM Corp. was released in 2017.The software used is IBM SPSS Statistics for Windows, specifically Version 25.0. It is developed by IBM Corp. and is based in Armonk, NY. The suitable statistical tests employed for data analysis. A P value below 0.05 is deemed statistically significant.

4. RESULTS

Table 1 presents a comprehensive comparison of demographic and anthropometric data among three different groups: Control group, non-metastatic endometrial carcinoma group and metastatic endometrial carcinoma.

The study reveals that there is no statistically significant variation in age among the three groups, as evidenced by the p-value being greater than 0.05. This suggests that the age distribution is similar across these groups. However, there is a highly significant difference in weight among the groups ($p < 0.001$), with metastatic endometrial carcinoma group having the highest mean weight, followed by non-metastatic endometrial carcinoma group and Control group. Post hoc tests reveal that the differences in weight are significant between all pairs of groups except for the comparison between non-metastatic endometrial carcinoma group and metastatic endometrial carcinoma group, where the p-value >0.05. There was no statistically significant difference in the number of pregnancies among the three groups, as indicated by a p-value greater than 0.05. Similarly, when examining the ratio of individuals who have given birth (parous) and those who have not (nulliparous), there are no statistically significant variations observed among the different categories.

Table 1. Comparative analysis of demographic and anthropometric data among three investigated groups.

	Group I n = 25	Group IIA n = 25	Group IIB n = 25
Age (years)			
Mean ± SD.	61.48 ± 7.98	61.92 ± 6.83	64.80 ± 7.67
Median (Min. – Max.)	62.0(48.0 – 75.0)	62.0(49.0 – 73.0)	65.0(48.0 – 83.0)
Weight (kg)			
Mean ± SD.	75.76 ± 9.20	93.24 ± 7.92	97.56 ± 6.12
Median (Min. – Max.)	75.0 (57.0 – 91.0)	95.0 (75.0 – 110.0)	99.0 (88.0 – 110.0)

Number of pregnancy			
Mean ± SE.	2.52 ± 0.28	2.76 ± 0.37	3.36 ± 0.34
Median (Min. – Max.)	3.0 (0.0 – 5.0)	3.0 (0.0 – 6.0)	4.0 (0.0 – 6.0)
Parous	23 (92.0%)	21 (84.0%)	23 (92.0%)
Nulliparous	2 (8.0%)	4 (16.0%)	2 (8.0%)

Group I: Control, Group IIA: Non-metastatic endometrial carcinoma, Group IIB: Metastatic endometrial carcinoma

Table 2. Comparison of three studied groups regarding menopause status.

	Group I n = 25		**Group IIA n = 25**		**Group IIB n = 25**	
	No.	**%**	**No.**	**%**	**No.**	**%**
Menopause status						
Pre-Menopause	4	16.0	2	8.0	0	0.0
Menopause	21	84.0	23	92.0	25	100

Group I: Control, Group IIA: Non-metastatic endometrial carcinoma, Group IIB: Metastatic endometrial carcinoma

Table 2 presents a detailed comparison of menopause status among three distinct groups: Control group, non-metastatic endometrial carcinoma group and Metastatic endometrial carcinoma group. The analysis reveals that there is no difference in menopause status distribution among the three groups, Metastatic endometrial carcinoma group having a higher percentage of individuals in the "Menopause" category compared to Control group and non-metastatic endometrial carcinoma group. However, this difference is not statistically significant (p1 >0.05). Further post hoc tests conducted to explore pairwise comparisons. The tests indicate that there is no statistically significant disparity between the Control group and the non-metastatic endometrial cancer group, Control group and Metastatic endometrial carcinoma group, or between non-metastatic endometrial carcinoma group and Metastatic endometrial carcinoma group.

Table 3. Comparison of endometrial carcinoma groups with and without metastasis regarding stage and primary tumor size.

	Group IIA n = 25		**Group IIB n = 25**	
	No.	**%**	**No.**	**%**
Stage				
I	14	56.0	0	0.0
II	11	44.0	0	0.0
III	0	0.0	13	52.0
IV	0	0.0	12	48.0
Primary tumor size (cm)				
<5 cm	16	64.0	12	48.0
>5 cm	9	36.0	13	52.0

Group IIA: Non-metastatic endometrial carcinoma, Group IIB: Metastatic endometrial carcinoma

Table 3 presents a comparison between two groups of endometrial carcinoma patients, non-metastatic group and metastatic group, in terms of their cancer stage and primary tumor size. Group of non-metastatic endometrial carcinoma includes 25 patients, primarily in Stage I and II, with 56% at Stage I and 44% at Stage II. None of the Group IIA patients is in Stage III or IV. Group of Metastatic endometrial carcinoma (consisting of 25 patients) falls into Stage III (52%) and Stage IV (48%), with no patients in Stage I or II. When comparing primary tumor size, there is no statistically significant distinction between the two groups, as 64% of Group IIA and 52% of Group IIB have tumors smaller than 5 cm.The statistical test ($p>0.05$) indicates that there is no statistically significant difference in tumor size between the groups.

Table 4. Distribution of metastatic endometrial carcinoma group regarding to metastatic sites.

	No.	**%**
Metastatic site		
Bone	4	16.0
Lung	7	28.0
Pelvic	7	28.0
Peritoneum	7	28.0

Table 4 presents data on the distribution of metastatic sites in the endometrial carcinoma group. It shows that metastasis in this group is quite diverse, with the highest frequency of cases occurring in the lung, pelvic region, and peritoneum, each accounting for 28% of the cases. Meanwhile, bone metastasis is less common, comprising only 16% of the cases. These findings highlight the propensity of endometrial carcinoma to spread to various anatomical sites, with a preference for intrapelvic and intraperitoneal locations.

Table 5. Comparison of three studied groups regarding the MIG7 gene expression.

	Group I n = 25	**Group IIA n = 25**	**Group IIB n = 25**
MIG7 gene expression level			
Mean ± SD.	0.69 ± 0.21	1.38 ± 0.39	1.97 ± 0.45
Median (Min. – Max.)	0.7 (0.3 – 1.0)	1.5 (0.7 – 1.9)	1.9 (0.8 – 2.7)

Group I: Control, Group IIA: Non-metastatic endometrial carcinoma, Group IIB: Metastatic endometrial carcinoma

The table 5 provides a comprehensive comparison of three distinct groups: Group I, representing the control group; Group IIA, comprising patients with non-metastatic endometrial carcinoma; and Group IIB, consisting of individuals with metastatic endometrial carcinoma. The focus of this comparison lies in evaluating key parameter MIG7 gene expression. The findings reveal highly significant differences among all three groups for each of the parameters examined. The p-values (all <0.001) suggest that these differences are indicative of real disparities in gene expression. Interestingly, the post hoc tests, we notice that Group IIB consistently exhibits the highest mean values for MIG7 gene expression (1.97).This pattern suggests a potential association between elevated MIG7 levels and the metastatic progression of endometrial carcinoma. Group IIA, representing non-metastatic endometrial carcinoma, also demonstrates significantly higher expression levels compared to the control group (Group I). These findings indicate that MIG7 gene expression may serve as valuable biomarker for distinguishing between non-metastatic and metastatic forms of endometrial carcinoma.

In conclusion, Table 5 underscores the critical role of MIG7 in understanding the molecular distinctions between non-metastatic and metastatic endometrial carcinoma. The results suggest the potential use of this biomarker to assist in diagnosing, predicting the course of the disease, and making treatment decisions for patients with endometrial cancer, particularly in differentiating between various phases of the illness.

Table 6. Assessing the effectiveness of MIG7 in differentiating between individuals without any health problems and those who have been diagnosed with endometrial cancer.

	MIG7 gene expression level
AUC	0.945
95% CI	0.898 – 0.991
P	<0.001*
Cut off	>0.85
Sensitivity (%)	84

Specificity (%)	96
PPV (%)	97.7
NPV (%)	75.0
Accuracy (%)	88.0

AUC, area under ROC curve; CI, confidence interval;

PPV, positive predictive value; NPV, negative predictive value.

Significant ≤0.05 *:

Table 6 provides crucial insights into the validity of using MIG7 as diagnostic marker to discriminate between healthy subjects and patients with endometrial carcinoma. The data indicates remarkably high AUC values for all three parameters, with AUC values of 0.945 for MIG7 gene expression. These AUC values suggest that marker are excellent at distinguishing between healthy individuals and those with endometrial carcinoma. Additionally, high sensitivity and specificity percentages reinforce their effectiveness as diagnostic tools, the positive predictive values (PPV) and negative predictive values (NPV) further highlight the accuracy of these markers in predicting disease presence or absence. This underscores the high diagnostic potential of MIG7 in identifying endometrial carcinoma, making them valuable candidates for clinical use in early detection and patient management.

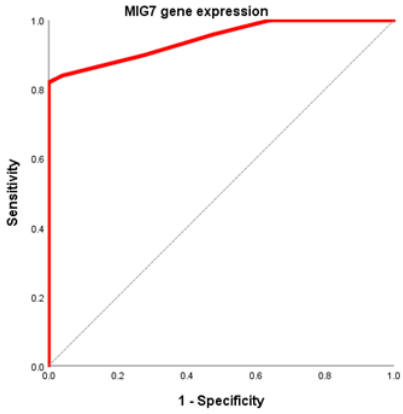

Figure (1). ROC Curve of MIG7 for discrimination between healthy subjects and patients with endometrial carcinoma.

Table (7). Validity of MIG7 for discrimination between non-metastatic and metastatic endometrial carcinoma

	MIG7 gene expression level
AUC	0.880
95% CI	0.775 – 0.985
P	<0.001*
Cut off	>1.75

Sensitivity (%)	88
Specificity (%)	88
PPV (%)	88
NPV (%)	88
Accuracy (%)	88

AUC, area under ROC curve; CI, confidence interval;

PPV, positive predictive value; NPV, negative predictive value.

Significant ≤0.05*:

Table 7 provides valuable insights into the validity of using MIG7 as discriminative marker for distinguishing between non-metastatic and metastatic endometrial carcinoma cases. The data reveals that while marker exhibit some ability to differentiate between these two groups, their performance varies. The AUC values are moderate, with MIG7 gene expression at 0.880. MIG7 gene expression show sensitivity percentages of 88%.Specificity is also closely high by MIG7 gene expression (88%).Table 7 highlights the potential of MIG7 gene expression as a particularly promising marker for differentiating between non-metastatic and metastatic endometrial carcinoma cases.

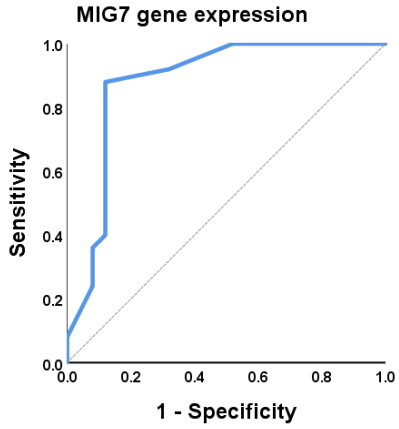

Figure (2). ROC Curve of MIG7 between non-metastatic and metastatic endometrial carcinoma.

Table 8. Correlation between MIG7 gene expressions with different parameters among all studied subjects.

	MIG7 gene expression level	
	R	*P*
Age	0.150	0.199
Weight	0.603	<0.001*
No. of pregnancy	0.123	0.294

R, correlation coefficient.

Table 8 provides insights into the correlation between MIG7 gene expression and various parameters among all the studied subjects. There is a strong and positive association between the expression of the MIG7 gene and weight (r=0.603, p<0.001*), suggesting that individuals with higher body weights tend to have elevated MIG7 gene expression. Age, number of pregnancies does not exhibit a significant correlation with MIG7 gene expression (p>0.05).

Table (9). Conducting a logistic regression analysis to estimate the likelihood of developing endometrial cancer.

	Univariable			Multivariable		
	P	**OR**	**95% C.I**	**P**	**OR**	**95% C.I**
Age	0.309	1.034	0.969 – 1.104			
Weight	<0.001*	1.325	1.163 – 1.510	0.092	1.012	0.946-1.018
Nulliparous	0.599	1.568	0.293 – 8.396			
Menopause status	0.093	4.571	0.776 – 26.92			
MIG7 expression	0.002*	1.077	1.028 – 1.128	0.024*	1.088	1.012-1.252

OR, odds ratio; CI, confidence interval.

Significant ≤0.05*:

Table 9 provides valuable insights into the logistic regression analysis aimed at predicting susceptibility to endometrial carcinoma. In the univariable analysis, several variables examined for their individual associations with endometrial carcinoma risk. Among these variables, weight stands out with a significant p-value (<0.001) and an odds ratio (OR) of 1.325, indicating that higher body weight is strongly associated with an increased risk of endometrial carcinoma. MIG7 gene expressions also show significant associations with p-values of 0.002, and ORs of 1.077 suggesting that elevated expression levels of this gene are associated with an increased risk of endometrial carcinoma. In the multivariable analysis, which considers multiple variables simultaneously, weight lost the significance (p=0.092). Notably, MIG7 gene expression maintain their significance (p=0.024) and demonstrate elevated ORs. These findings highlight the potential utility of MIG7 gene expression as independent predictor of endometrial carcinoma susceptibility. The results emphasize the importance of this molecular marker in assessing individual risk and may have implication for preventive strategies and early intervention in endometrial carcinoma.

Table (10). Logistic Regression analysis for prediction of metastatic endometrial carcinoma.

	Univariable			Multivariable		
	P	**OR**	**95% C.I**	**P**	**OR**	**95% C.I**
Age	0.168	1.058	0.976 – 1.147			
Weight	0.044*	1.094	1.002 – 1.195	0.476	1.102	0.844 – 1.438
Nulliparous	0.393	0.457	0.076 – 2.755			
Menopause stage	0.999	-	-			
Primary tumour size	0.257	1.926	0.621 – 5.977			
MIG7 expression	0.001*	1.037	1.015 – 1.059	0.021*	1.384	1.179-2.431

OR, odds ratio; CI, confidence interval.

Significant ≤0.05

Table 10 provides valuable insights into logistic regression analysis aimed at predicting the risk of developing metastatic endometrial carcinoma. In the univariable analysis, several variables examined for their individual associations with metastatic endometrial carcinoma risk. Among these variables, weight emerges as significant with a p-value of 0.044 and an odds ratio (OR) of 1.094, suggesting that higher body weight is associated with an increased risk of metastatic endometrial carcinoma. MIG7 gene expression show significant associations with p-values of 0.001* and ORs of 1.037, indicating that elevated expression level of this gene are linked to a higher risk of metastasis. In the multivariable analysis, which considers multiple variables simultaneously, weight loses its significance ($p>0.05$), suggesting that its association with metastatic endometrial carcinoma risk may be influenced by other factors in the model. However, MIG7 gene expression maintain their significance ($p=0.021$) and demonstrate increased ORs, emphasizing their potential as independent predictors of metastatic endometrial carcinoma risk. These findings underscore the importance of MIG7 gene expressions in assessing the risk of metastasis in endometrial carcinoma patients, potentially aiding in personalized treatment decisions and prognosis.

5. DISCUSSION

Uterine cancer has a different incidence distribution in different regions of the world. It is the second most common gynecologic malignancy in developing countries after cervical cancer [7, 8]. The variation in uterine cancer incidence rates across the world can be explained by differences in exposure to risk factors and different levels of health care in the different regions [9]. Based on Globocan, corpus uteri cancer is ranked as the tenth most common cancer among women in Egypt. According to the Middle East Cancer Consortium (MECC) Report of 2006, the incidence rate of uterine cancer in Egypt (3.5/100,000) is the lowest compared to other countries in the Middle East such as Israeli Jews (13.8/100,000), Cypriots (11.8/100,000), Israeli Arabs (8.7/100,000), and Jordanians (5.8/100,000) [10].In order to comprehend, handle, and maybe prevent these diseases, it is crucial to distinguish between type 1 endometriosis and type 2 serous endometrial carcinomas, as well as other highly aggressive non-endometriosis carcinoma histotypes. The development of most endometrial endometriosis carcinomas starts with continuous growth of the endometrium, which is driven by either natural or artificial estrogen without any counteracting effect from progesterone or progestin. This growth progresses from simple to more complex forms of endometrial hyperplasia (EH) [11].

While there are numerous reports regarding momentum metastasis, there is a lack of research specifically examining micro metastases, especially isolated microscopic metastases in endometrial mental cancer (EC). Serum biomarker used for screening, diagnosis, prognosis, or treatment monitoring of endometrial cancer micro metastasis, playing a fundamental role in primary and secondary prevention [12].

Migration-Inducing Gene 7 (MIG-7) is a protein that has a high amount of cysteine. It was initially discovered in endometrial cancer cells after being exposed to hepatocyte growth factor (HGF). Subsequent research demonstrated that MIG-7 exhibited increased expression on the cell membrane and in the cytoplasm of many cancer types, while maintaining low or undetectable levels in non-cancerous tissues. Therefore, MIG-7 has the potential to serve as a highly promising indicator for the identification and diagnosis of cancer. These findings are reinforced by immune histochemical (IHC) investigations that demonstrate the presence of MIG-7 in circulating tumor cells, indicating its potential as an early indicator for metastatic carcinomas [13].

Therefore, the aim of the present work was to study of the role of MIG7 as a molecular marker for early detection of endometrial carcinoma micro metastases, and use blood sample instead of using invasive biopsies or expensive imaging techniques for detection of endometrial carcinoma micro metastases. This case control study contained 50 patients and 25 age-matched healthy female volunteers as control group. Endometrial carcinoma patients recruited from Obstetrics and gynecology department at Mansoura

University hospital. The present study divided their participants into three Groups: control group, non-metastatic endometrial carcinoma and metastatic endometrial carcinoma and revealed that the mean age of them are ((61.48 ± 7.98) years, (61.92 ± 6.83) years and (64.80 ± 7.67) years) respectively with no statistically significant difference between them. Alemdaroglu et al conducted a study on 397 patients who were diagnosed with EC. Among these patients, 301 (75.8%) were younger than 70 years old, while 96 (24.2%) were older than 70 years old. The overall group had a median age of 63, with a minimum age of 33 and a maximum age of 89. In the age group under 70, the median age was 60, with a minimum age of 33 and a maximum age of 69. In the age group over 70, the median age was 74, with a minimum age of 70 and a maximum age of 89. These findings align with our results [14]. The present study found a significant difference in weight between three groups, Metastatic endometrial carcinoma group has (97.56 ± 6.12) kg and non-metastatic endometrial carcinoma group has (93.24 ± 7.92) kg compared to control group (75.76 ± 9.20) kg. The primary risk factors for developing endometrial cancer include elevated levels of estrogens, with obesity being linked to an excess of estrogen [15]. Therefore, obesity is known to heighten the risk of developing endometrial cancer. Gao et al discovered that the median BMI of women diagnosed with stage 1 endometrial cancer was notably greater than that of women diagnosed with stage II or III. Additionally, they observed no disparity in BMI between stage II and stage III cancer. This implies that the inverse association between BMI and endometrial cancer is limited to early-stage cases, suggesting that patients with higher BMI may experience more favorable clinical outcomes [16]. The present study revealed no significant difference between three groups regarding number of pregnancies and proportion of parous and nulliparous individuals. Conversely, certain characteristics related to pregnancy are linked to a decreased risk of endometrial cancer. Trabert et al. discovered that a higher number of pregnancies (four or more compared to just one) and a shorter period since the last birth (less than 10 years compared to 30 years or more) were linked to a decreased risk of endometrial cancer. These relationships were constant across most subtypes of the disease. Therefore, it is important to acknowledge the contribution of both hormonal exposures and cell clearance, as well as immunologic/inflammatory factors, to the development of endometrial cancer [17]. The current study revealed slight difference in menopause stage distribution between the three groups, with a higher percentage of individuals in cases of non-metastatic endometrial carcinoma and metastatic endometrial carcinoma being in the menopause stage compared to control (92.0% and 100% VS 84.0%). Which was not statistically significant. In agreement with previous meta-analysis that examined eighteen articles including 957242 subjects with 4781 cases. The pooled RR (95%CI) of endometrial cancer for the highest versus the lowest age at menopause was 1.89. For dose-response analysis, a nonlinear relationship was found between age at menopause and endometrial cancer, and the positive association became statistically significant when age at menopause was greater than 46.5 years old [18]. The present study divides cases with EC into 2 groups, Group IIA (non- metastatic EC) and Group IIB (metastatic EC). There was a highly significant difference in weight among three groups. The group of patients with metastatic endometrial carcinoma has the highest average weight, followed by the group with non-metastatic endometrial carcinoma and the control group, in terms of age. Prior meta-analysis studies have shown a distinct heightened risk of death from any cause in endometrial cancer patients who are obese. The probability of mortality from any cause dramatically rose as BMI climbed, and women with the highest risk of death were those classified as having class III obesity, also known as morbid obesity or super morbid obesity, which is defined as having a BMI of 40 or 50 or above, respectively [19]. Additional study have confirmed a correlation between obesity and a higher likelihood of mortality in women diagnosed with endometrial cancer [20].The present study revealed no statistically significant differences between groups of the study regarding number of pregnancies, proportion of parous and nulliparous individuals, there are no statistically significant differences among the groups and menopause status distribution. The present study showed that non-metastatic endometrial group includes 25 patients, primarily in Stage I and II, with 56% at Stage I and 44% at Stage II. None of the non-metastatic

endometrial carcinoma Group patients is in Stage III or IV. On the other hand, metastatic endometrial carcinoma group also consisting of 25 patients falls into Stage III (52%) and Stage IV (48%), with no patients in Stage II or I. Lee et al. discovered that the majority (about 75%) of patients with endometrial cancer are identified with early-stage illness (Stage I and II), while the remaining 25% are diagnosed with advanced-stage disease (Stage III and IV) [21]. Regarding metastasis in the current study, metastasis in this group is quite diverse, with the highest frequency of cases occurring in the lung, pelvic region, and peritoneum, each accounting for 28% of the cases. Meanwhile, bone metastasis is less common, comprising only 16% of the cases. These findings highlight the propensity of endometrial carcinoma to spread to various anatomical sites, with a preference for intrapelvic and intraperitoneal locations. Sohaib et al. conducted a review of 86 patients who had recurrent endometrial carcinoma after their initial surgery. The study revealed that the disease recurred in different ways: locally in 30 patients (35%) with a median time to relapse of 11.5 months, distally in 32 patients (37%) with a median time to relapse of 20.5 months, and both locally and distally in 24 patients (28%) with a median time to relapse of 8.5 months. The sites where the cancer recurred were as follows: lymph nodes in 41 (48%) patients, vagina in 36 (42%) patients, peritoneum in 23 (27%) patients, lung in 21 (24%) patients, hydronephrosis in 20 (23%) patients, bladder in 7 (8%) patients, liver in 6 (7%) patients, bone in 6 (7%) patients, abdominal wall in 6 (7%) patients, spleen in 4 (5%) patients, rectum in 3 (3%) patients, pancreas in 1 (1%) patient, muscle in 1 (1%) patient, and brain in 1 (1%) patien [22]. Regarding MIG7 gene expression in the present study, Group II exhibited a significantly higher mean value (1.68 ± 0.51) compared to Group I (0.69 ± 0.21). MIG-7 expression is little or cannot be detected in normal non-cancerous tissues, but is markedly elevated in various types of cancer tissues, including breast, lung, colon, and endometrial cancer [23]. The majority of studies investigating the role of MIG-7 in tumor formation have primarily concentrated on tumor invasion and metastasis. Recent investigations have indicated a link between increased expression of MIG-7 and the spread of lung cancer to other parts of the body. This correlation may be due to the activation of the COX-2-PDE2 pathway and the stimulation of E-cadherin suppressors, which promote a process called epithelial-mesenchymal transition [24]. To best of our knowledge, the current study was the first to investigate MIG-7 level in EC cases and their metastasis. Huang et al had revealed that patients with epithelial ovarian cancer (EOC) had increased level of MIG-7 than control group [13]. Thus, the current study suggested a potential association between elevated MIG7 and the metastatic progression of endometrial carcinoma. Group IIA, representing non-metastatic endometrial carcinoma, also demonstrates significantly higher expression levels compared to the control group (Group I). These findings indicate that MIG7 gene expression may serve as valuable biomarker for distinguishing between non-metastatic and metastatic forms of endometrial carcinoma. Conversely, in EOC tissues, the expression of MIG-7 was found to have a positive correlation with tumor stage and a negative correlation with histological differentiation. In addition, patients with EOC who had elevated levels of MIG-7 expression in their ovaries exhibited a notable increase in the volume of ascites and a higher occurrence of lymph node metastases compared to those with low levels of MIG-7 expression in their ovaries. No statistically significant correlation was seen between the expression of MIG-7 and other clinic-pathological markers, including serum CA-125 level and histological type. Thus, increased ovarian MIG-7 expression is strongly linked to the advancement, loss of differentiation, and spread of EOC [13]. The present study revealed a remarkably high area under the ROC curve (AUC) values for parameter, with AUC values of 0.945 for MIG7 gene expression. These AUC values suggest that marker is excellent at distinguishing between healthy individuals and those with endometrial carcinoma. With high diagnostic potential of MIG7 in identifying endometrial carcinoma, making it valuable candidates for clinical use in early detection and patient management. The current study revealed that the AUC values are moderate for MIG7 gene expression at 0.880, MIG7 gene expression showing sensitivity percentages of 88% while Specificity for MIG7 gene expression is (88%). The current investigation identified a substantial and favorable association between the expression of the MIG7 gene and weight. There is no significant link

between age, number of pregnancies, and MIG7 gene expression. In the univariable analysis conducted in this study, there is a robust correlation between higher body weight and an elevated risk of endometrial cancer. The expression of the MIG7 gene also has a strong correlation, indicating that higher levels of gene expression are linked to a greater likelihood of developing endometrial cancer. Jenabi and Poorolajal conducted a meta-analysis that comprised a total of 40 investigations. These studies consisted of 20 prospective cohort studies and 20 case-control studies, comprising a combined total of 32,281,242 participants. The findings from both cohort and case-control studies demonstrated a substantial correlation. In comparison to individuals with normal weight, the estimated relative risk (RR) of developing endometrial cancer was 1.34 for overweight individuals and 1.43 for obese individuals in the cohort study. In the case-control study, the estimated RR was 2.54 for overweight individuals and 3.3 for obese individuals. These results strongly indicate that there is a significant association between body mass index (BMI) and an elevated risk of endometrial cancer. Additional research is necessary to understand the underlying mechanisms of endometrial cancer resulting from overweight and obesity [25]. In the multivariable analysis, MIG7 gene expression, maintain their significance, findings highlight the potential utility of MIG7 gene expression as independent predictor of endometrial carcinoma susceptibility. The present study had many limitations, the small sample size and thus this was the first study investigating the MIG7 level in EC cases.

6. CONCLUSION

In conclusion, the current study documented the critical role of MIG7 in understanding the molecular distinctions between non-metastatic and metastatic endometrial carcinoma. The results suggest that this biomarker could be utilized to assist in the diagnosis, prognosis, and treatment planning for individuals with endometrial cancer, particularly in discriminating between various phases of the illness.

7. REFERENCES

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