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(RESEARCH ARTICLE)

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Modeling adjusted for age and menopause statuses dependent on PET/CT scan for ovarian cancer diagnosis and staging

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Abstract

Aims: The main objective of this observational study is to develop a linear regression model that incorporates age, menopausal status, and family history to predict the risk and severity of ovarian cancer.

Methods: In early 2023, the King Hussein Medical Centre's gynaecological clinic began using PET/CT scanning and histopathological analysis to identify ovarian cancer cases. The data was then used to strategize interventions for each patient. The study aimed to assess the probability of ovarian cancer in female patients by analysing their age, menopausal onset, and family history. Patients were classified as pre-menopausal or post-menopausal, and PET/CT scan results were converted into FIGO classifications. Histopathological findings were analysed using ROC and binary logistic regression analyses. The study also used multiple linear regression to determine correlations and variations in the estimated Federation of Obstetrics and Gynaecology (FIGO) grade for females with suspected ovarian cancer. The research developed a pragmatic model to forecast ovarian cancer likelihood and severity levels.

Results: The study examined 105 patients with suspected ovarian cancer at King Hussein Medical Centre between 2021 and mid-2023. Only 97 patients (92.38%) had matched FIGO-derived PET/CT scans with biopsy-based histopathological positivity. The optimal FIGO grade was 3.5, with a sensitivity of 77.2%, a specificity of 76.92%, a positive predictive value of 95.95%, a negative predictive value of 32.26%, an accuracy index of 77.14%, and a Youden index of 54.10%.

Conclusion: A regression-based model was developed to triage the risk of ovarian cancer. This model enables us to early prioritise suspected females who should undergo PET/CT at the clinic level, with a high positive predictive value of over 90%.

Keywords: Ovarian cancer; PET/CT scan; Malignancy staging; Multiple Regression; Diagnostic and staging modeling

1. Introduction

Approximately 22,000 new cases of ovarian cancer are reported each year. Approximately 80% of women with ovarian cancer experience a recurrence within five years of receiving treatment. Debulking surgery, chemotherapy, and managing postoperative residual disease are typical first-line treatments for advanced serous ovarian cancer (ESOC). Patients who are at risk of inadequate tumour removal must be identified prior to surgery. PET/CT is effective in

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determining cancer stages and detecting metastases beyond the abdomen and lymph nodes. The PET/CT prediction model for partial resection in ovarian cancer patients lacks sufficient research [1-2].

Ovarian cancer is staged surgically according to the FIGO classification. Preoperative staging CT or MRI aids in detecting metastatic disease and identifying individuals who are not suitable candidates for debulking surgery. Enhanced CT technology has advanced the detection of metastatic disease, and combining FDG-PET/CT with CT yields superior results compared to using CT alone. The American Joint Committee on Cancer (AJCC) uses the TNM staging system, while the International Federation of Gynaecology and Obstetrics (FIGO) method stages ovarian cancer. Greater numbers indicate increased burden and metastases. The latest AJCC stage grouping differentiates primary peritoneal cancer, fallopian tube cancer, and ovarian cancer based on different criteria. [3-4]

Transvaginal ultrasound (TVU) tests for ovarian cancer show moderate sensitivity and a low positive predictive value (PPV). Advancements in technology, such as multidetector CT, have enhanced the detection and analysis of adnexal masses in CT imaging. MRI is effective in diagnosing hemorrhagic cysts, endometriomas, and benign cystic teratomas. The sophisticated PET imaging technique identifies glycolytic activity in cancerous cells for the purposes of staging, diagnosing, and restaging. Recent studies indicate that FDG-PET/CT is more sensitive and specific than CT alone in detecting adnexal masses. [5-6] Ovarian cancer has been linked to the use of talcum powder in the vagina, uterus, and fallopian tubes. Research has yielded varying results, with some indicating a slight rise in risk and others showing no change. To reduce the risk of ovarian cancer, the American Cancer Society advises consuming fruits, vegetables, whole grains, and avoiding red and processed meats, sugary drinks, and highly processed meals.[7] This observational study aims to create a linear regression model that includes age, menopausal status, and family history to forecast the likelihood and intensity of ovarian cancer.

2. Methods

Early in 2023, the King Hussein Medical Centre gynaecological clinic began using PET/CT scanning and histology of biopsied tissue to confirm probable ovarian cancer and accurately assess FIGO stage. The optimal intervention for each patient was planned using this information. Female patients had PET/CT scans after clinical, biochemical, and radiological exams. Integrated PET and CT imaging was possible with 3D lutetium oxyorthosilicate crystals. Before receiving the FDG injection, patients must fast for four hours and have normal blood glucose. After blood sugar stabilises, patients receive 10–20 mCi (370–740 MBq) of FDG, depending on weight. CT scans are corrected for attenuation one hour after the tracer is given to diagnose belly, chest, and neck issues. Early luteal phase FDG uptake was higher in premenopausal ovaries.

The patient's age, menopausal onset (<50, 50-60, or >60), and family history of ovarian cancer were determined in the clinic before PET/CT. This analysis scanned data in early 2023. Menstrual cycle frequency and time since last period determined pre- or post-menopausal status in the study. FIGO classification (1-10) was used to classify PET/CT scan results. FIGO-grade PET/CT scan findings were based on biopsies histopathologist results. FIGO grade >0 matched biopsy-based histo-positivity, while 0 or NA (none PET/CT findings) matched histo-negativity. We did not investigate mismatching (e.g., FIGO grade>0 corresponding histo-positivity). They ensured the findings' accuracy and trustworthiness, the inquiry's authenticity, and the prevention of outcome manipulation.

The Multivariable Linear Regression Test was utilised to assess the extent to which the combined independent variables (age, menopausal onset, and family history) explain the variations in the dependent variable, the estimated Federation of Obstetrics & Gynaecology (FIGO) grade, for females with suspected ovarian cancer, as well as to evaluate the prediction accuracy. We obtained the coefficients necessary for predicting the expected FIGO grade at the clinic level prior to the PET/CT scans from this test, which also revealed our final multiple linear regression model. Menopausal onset can be categorised into three values: 1 for females under 50 years, 0 for those between 50 and 55 years, and -1 for those aged 55 years and above. The family history variable can take on three values: 1 for no family history of ovarian cancer, 0 for a second positive case of ovarian cancer, and -1 for a first positive case of ovarian cancer.

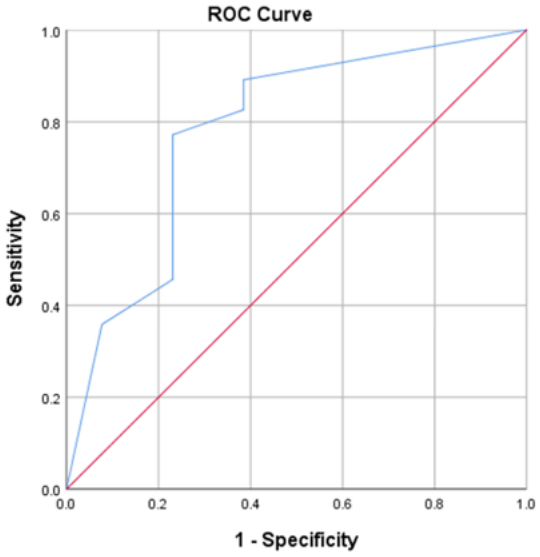
3. Results

First, only 97 (92.38%) of 105 patients who visited the King Hussein Medical Centre's gynaecological clinic between 2021 and mid-2023 with biochemically, clinically, and radiologically suspected ovarian cancer had matched FIGO grading-derived translated PET/CT scans with biopsy-based histopathological positivity. The results showed that 94.8% (92 out of 97 tested females) had confirmatory histo-positivity matched for FIGO-related PET/CT findings from

grade 1 to grade 9. The results showed that 5.2% (5 females) had confirmatory histo-negativity matched for those who did not have any significant FIGO-derived PET/CT scan findings.

The receiver operating characteristic demonstrated sensitivity vs. false positives, with 23.71% (23 females) in Group I and 76.29% (74 females) in Group II. The area under the ROC curve and sensitivity indices were calculated. The results of the PET/CT scan showed a good agreement between the SEM image and the histological findings (0.781±.076, p-value = 0.001, 95% CI: 0.633–0.930). From 105 histological findings, 92 were positive and 13 were negative.

The best FIGO threshold for our female with probable ovarian cancer is 3.5. The appropriate FIGO grade-derived translated PET/CT scan threshold was 3.5. We rounded the FIGO grade to the nearest upper valid value, despite its ordered categorical nature. The study discovered that a FIGO grade-4 translated PET/CT scan was the best cutoff level for biopsy-based histopathological positivity. It had a sensitivity of 77.2%, a specificity of 76.92%, a positive predictive value of 95.95%, a negative predictive value of 32.26%, an accuracy index of 77.14%, and a Youden index of 54.10% (Figure 1).



Case Processing Summary	
Histo_G01	Valid N (listwise)
Positive	92
Negative	13

Area Under the ROC Curve (AUROC)			
Test Result Variable(s): FIGO			
		Asymptotic 95% Confidence Interval	
Area±SEM	Asymptotic Sig	Lower Bound	Upper Bound
0.781±.076	0.001	0.633	0.930

FIGO Threshold	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Accuracy Inex	Youden Index
3.5	77.2%	76.92%	95.95%	32.26%	77.14%	54.10%

Figure 1 Receiver operating characteristic was conducted to illustrate sensitivity vs false positive values. Accordingly, both the area under ROC curve and the sensitivity indices were yielded. The AUROC±SEM for the PET/CT scanning derived translated FIGO grade against the confirmatory histopathological findings was 0.781±.076, p-value=0.001, 95% CI; 0.633-0.930. From 105 histopathological findings, 92 were positive and 13 were negative. The optimal FIGO threshold for our attended tested female with suspected ovarian cancer is 3.5

We used a multiple linear regression to figure out what FIGO-grade women with clinically, biochemically, and radiologically suspected ovarian cancer would get before they got a PET/CT scan. We did this by looking at their age, when they started menopause, and their family history. These 3 tested independent variables statistically significantly predicted FIGO grade ($F(3, 99) = 31.741$, $p < .0005$, $R = 0.70$, $R2 = 0.490$, and adjusted $R2 = 0.475$). The final form of our proposed multiple linear regression model can be formulated as follows: [3.624+0.049 Age-1.834 Menopausal Onset-2.492 Family History] (Table 1). The study uses SPSS 25 and a 5% significance level.

Table 1 Multiple linear regression analysis for constructing a prediction model for FIGO grade in highly suspected ovarian cancer female before PET/CT scanning

Tested variables	Mean±SD	Coefficient's summary		95% CI	p-Value
		B±SEM	Beta		
Constant		3.624±0.948		(95% CI; 1.743-5.505)	0.000
Age (Yrs)	50.39±15.242	0.049±0.018	0.198	(95% CI; 0.014-0.085)	0.007
Menopausal Onset	-0.04±0.641	-1.834±0.508	-0.309	(95% CI; -2.842--0.826)	0.000
Family history	-0.03±0.649	-2.492±0.501	-0.425	(95% CI; -3.485--1.499)	0.000
The Multivariable Linear Regression Test was conducted to explore the degree of correlations, how much of the total variations in the investigated dependent variable of estimated Federation of Obstetrics & Gynecology (FIGO) grade for the attended female with suspected ovarian cancer, can be explained by the three explored independent variables (age, menopausal onset, and family history of ovarian cancer), and the quality of the prediction of the dependent variable. Also, this test was conducted to abstract the necessary coefficients to collectively predict the estimated FIGO grade at clinic level before Positron Emission Tomography/Computed Tomography (PET/CT) scanning and to present the final form of our proposed multiple linear regression model which can be formulated as follows [3.624+0.049×Age-1.834×Menopausal Onset*-2.492×Family history**].					
Menopausal onset* has 3 possible values→1 for female<50 years, 0 for female 50—55 years, and -1 for female ≥55 years. Family history** has also 3 possible values→1 for female with No family history for ovarian cancer, 0 for female who has a positive ovarian cancer in her 2nd relationship, and -1 for female who has a positive ovarian cancer in her 1st relationship.					

4. Discussion

The PET/CT has a sensitivity of 91% and a specificity of 88%. Surgery and chemotherapy enhance the outlook, particularly in cases where there is no remaining cancer. Patients need to be meticulously chosen to achieve the best therapy results. SUVmax is a strong indicator of aggressive behaviour in patients with recurrent epithelial ovarian cancer, with a cutoff value of 13 suggesting a negative prognosis. Prognosis was not influenced by triglycerides and metabolic tumour volume. [8]

An analysis of 1,283 Chinese women with primary malignant or borderline ovarian cancer revealed that the median age at diagnosis was 53 years for malignant cases and 35 years for borderline cases. Approximately 58% of epithelial ovarian cancers were diagnosed after menopause, while about 80% of borderline ovarian cancers were diagnosed before menopause.[9]

In this study, we investigated the clinical impact of patients' ageing on the ovarian cancer risk and severity on our constructed multiple linear regression modelling in a continuous fashion, in which the ovarian cancer risk and severity, as estimated FIGO grade, were significantly increased by approximately 0.049±0.018 (95% CI: 0.014-0.085) for each 1-year incremental rate. Indeed, the tested patients' mean age in this study was 50.39±15.242 years.[10]

Recent studies indicate that the combination of positron emission tomography (PET) and computed tomography (CT) is effective in identifying distant metastases and unclear abnormalities. PET/CT aids in distinguishing between stages III, C–IV, and I–IIIB cancer. FDG-PET-CT is more effective than CT in detecting malignant lymph nodes, peritoneal metastases, and recurrent diseases. The maximum standardised uptake value (SUVmax) of the tumour was used to quantify the uptake of fluorodeoxyglucose (FDG).[11]

The ROC curve identified the optimal SUVmax threshold. The standard was histopathology. The study analysed SUVmax and the International Federation of Gynaecology and Obstetrics stage in borderline and malignant tumours through one-factor analysis of variance and an unpaired t test with Bonferroni correction. The maximum standardised uptake value (SUVmax) for benign, borderline, and malignant lesions were 2.00±1.02, 2.72±1.04, and 7.55±4.29, respectively. FDG-PET/CT scans accurately identified malignant or borderline tumours with sensitivities of 82.4%, 76.9%, and 81.1%, as well as specificities and accuracies of the same percentages. The SUVmax results were significantly distinct

from the IFGO stages. The study concluded that FDG-PET/CT scanning effectively differentiates between malignant and benign tumours, but performs inadequately when it comes to borderline and benign tumours. [12-13]

However, our study stated that about 35.1% (34 females) had already advanced metastatic ovarian cancer (FIGO grade IV) at the time of PET/CT scanning. Additionally, stages III of A, B, and C were followed with incidence rates of [9 (9.3%), 6 (6.2%), and 11 (11.3%), respectively]. The unfavourable PET/CT scanning results of the Jordanian female patients prompted us to develop an obligatory ovarian cancer risk triaging model. This model will allow us to prioritise early detection and further confirmatory procedures for the patients in question.

The research was effective as it utilised three predetermined independent variables to assess ovarian cancer risk. We developed a practical model to forecast the likelihood and seriousness of ovarian cancer. This model can be used in clinical settings prior to lengthy procedures such as PET/CT scans and histological confirmation. Due to the scarcity of PET/CT scanning at our facility for Jordanians, female patients at higher risk will be given priority.

5. Conclusion

FDG PET/CT is essential for preoperative evaluation of primary ovarian cancer patients and postoperative recurrence assessment. More study with a larger, prospective sample of patients, including those with recurrent epithelial ovarian cancer who are sensitive or insensitive to chemotherapy, is needed to confirm the findings. In this study, a regression-based model was developed to triage the risk of ovarian cancer. This model enables us to early prioritise suspected females who should undergo PET/CT at the clinic level, with a high positive predictive value of over 90%.

Compliance with ethical standards

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Disclosure of conflict of interest

There is no conflict of interest in this manuscript.

Statement of ethical approval

There is no animal/human subject involvement in this manuscript.

Statement of informed consent

Owing to the retrospective design of this study, the informed consent form was waived.

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