RESEARCH ARTICLE

The Optimal Cut-Off Point of the ADNEX Model for the Prediction of the Ovarian Cancer Risk

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Abstract

Objective: This study aimed to assess the effectiveness and determine the optimal cut-off point of the ADNEX model in women presenting with a pelvic or adnexal tumor. Method: All women presented with adnexal mass and were scheduled for operation at Hue University of Medicine and Pharmacy Hospital and Hue Central Hospital, Vietnam during June 2019 – May 2021 were included and categorized according to their histopathologic reports into ovarian cancer groups and benign ovarian tumor groups. Multivariable logistic regression was used to explore for potential predictors. The ADNEX model with and without CA125 was used to assess the risk of ovarian cancer preoperative. The goldden standard to evaluate the accuracy of ultrasonography using the ADNEX model was the pathological report. In addition, the accuracy as well as optimum cut-off point of the ADNEX model was estimated with and without CA125. Results: A total of 461 participants were included in analysis and predictive model development, 65 patients in ovarian cancer group and 361 in benign tumor group. The ADNEX model combined with CA125 proved to be a useful predictor with an area under ROC of 0.961 (0.940 – 0.977) with Youden's index of 0.8395, p < 0.001. The ADNEX model without CA125 also had high predictive value between benign and malignant tumors, with an area under ROC of 0.956 (0.933 – 0.973) with Youden's index of 0.8551, p < 0.001. Cut-off of the ADNEX with CA125 was 13.5 and without CA125 was 13.1 for sensitivities were 90.8 (81.0 – 96.5) and 93.9 (85.0 – 97.5), specificities 93.2 (90.2 – 95.5) and 91.67 (88.5 – 94.2). The difference in the predictive value of malignancy-risk between the ADNEX model with CA125, without CA125 was not statistically significant, p=0.4883. Conclusion: The ADNEX model, with or without the combining marker CA 125, provides a valuable predictive value for ovarian tumor malignancy preoperative.

Keywords: IOTA-ADNEX models- ovarian cancer- ovarian tumor

Introduction

Ovarian cancer is one of the most prevalent cancers in women, with a substantial gynecological malignancy death rate (Sung et al., 2021). Ovarian cancer is most commonly diagnosed clinically at a late stage, with stage III-IV accounting for roughly 70% of overall prevalence, resulting in a higher mortality rate (Torre et al., 2018). Early diagnosis of ovarian cancer has a significant impact on a patient's survival and quality of life. The outcome of surgery depends on the preoperative diagnosis of a benign or malignant ovarian tumor (Heintz et al., 2006).A consensus has been reached regarding laparoscopic surgery as surgery for benign ovarian tumors, and it is being performed widely (Aoki, 2014). The diagnosis of ovarian cancer is necessary to develop an effective treatment plan that includes chemotherapy or surgery to remove the tumor, uterus, adnexa, and omentum.

IOTA (international research group on ovarian tumors) was founded in 1999 to standardize ovarian tumor definitions, terms, and ultrasound characteristics. The IOTA team built the ADNEX model, the first multi-layered predictive staging for ovarian cancer, with high accuracy (Aoki, 2014; Van Calster et al., 2015). Only qualified sonographers and ultrasound systems are necessary to verify the ADNEX model's prediction value for malignancy in a preoperative ovarian tumor. Cancer antigen 125 (CA125) and HE4 are two biomarkers recommended for clinical application in the differential diagnosis of benign from malignant ovarian tumors. Differentiating between benign and malignant tumors is a critical step in the clinical evaluation process. The accurate preoperative diagnosis remains a significant challenge (Froyman et al., 2017; Meys et al., 2017).

There are many methods to assess the possibilityof ovarian cancer before surgery. There have not been many studies evaluating the value of the ADNEX model

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clinically applied to predict the malignancy of ovarian tumors. Early diagnosis and proper treatment improve patient survival and quality of life. The IOTA ADNEX model is still rarely used in Thua Thien Hue province to predict malignancy in ovarian tumors before surgery. As a result, we performed research on the subject with the following objective: assess the effectiveness and determine the optimal cut-off point of the ADNEX model in women presenting with a pelvic or adnexal tumor.

Materials and Methods

The methodology was a descriptive cross-sectional study of 461 women with ovarian tumors who had oophorectomy at the Hue University of Medicine and Pharmacy Hospital and Hue Central Hospital, Vietnam, from 06/2019 and 05/2021.

Inclusion criteria: Patients ≥ 14 years old, diagnosed with an ovarian tumor and indicated for surgery or tumor biopsy or cytology of abdominal fluid. There were postoperative pathological results. Women who had an ovarian mass, including a para-ovarian mass, and had an ultrasound examination preoperative. Patients agree to participate in the research.

Exclusion Criteria: Postoperative diagnosis pseudocysts, hydrosalpinx, para-ovarian cysts, uterine fibroids, history of ovarian or any associated cancer. Patients with mental illnesses.

The ADNEX - IOTA model was used to select all patients for ovarian tumor surgery using ultrasound at the hospital. Patients were chosen for the study based on the inclusion and exclusion criteria. Explain the research and ask the patient to agree to participate. Then conduct an interview using the study form to determine and categorize the following study variables: age, occupation, geography, ethnicity, marital status, number of births, number of miscarriages, menstrual status, history of gynecological surgery, and time of ovarian tumor detection. The study included postoperative patients with ovarian tumor pathological results, which were compared to ultrasound results.

Step 1: Ask the patient according to the research sheet to identify and classify the following research variables: age, occupation, geography, ethnicity, marital status, number of births, number of miscarriages, menstrual period, history of gynecological surgery, and time of detection of ovarian tumor.

Step 2: The patient's general condition and medical history are assessed, and the clinical examination is performed.

Uterine and adnexa ultrasound: The patient underwent an ultrasound of the uterus, adnexa, and characteristics of ovarian tumors according to the IOTA - ADNEX model. Record the following characteristics: tumor location, the maximum diameter of the lesion (mm), the proportion of solid tissue (that is, the maximum diameterof the largest solid component divided by the maximum diameter of the lesion), presence of more than 10 cyst locules (yes/no),number of papillary projections (0, 1, 2, 3, >3), presence of acoustic shadows (yes/no), and presence of ascites (yes/no).

Before the ultrasound, instruct the patient to hold urine for 30 to 60 minutes so that the bladder is full but not too distended. The patient lies supine on a flatbed, legs extended, hands resting on the chest, exposing the ultrasound area from the lower ribs to the pubic bone. Abdominal ultrasound using a 3,5 MHz transducer, the pelvis, and genitals were examined using standard views. If abdominal ultrasound is difficult to visualize the uterus and adnexa or if the patient has no urine, a transvaginal ultrasound with a transducer frequency of 7,5 MHz can be used.

Based on ADNEX model to calculate the malignancy risk of ovarian tumor before surgery

Algorithm to calculate the risk of malignancy according to ADNEX.

Step 3: Surgery, staging ovarian cancer after surgery

Step 4: Postoperative histopathological diagnosis

Postoperative specimens were sent for histopathological examination at the Department of Pathology. Description of surgical specimens with ovarian tumor if any such as the uterus, omentum, lymph nodes, appendix... The histopathological results of ovarian tumors were classified according to the World Health Organization in 2014.

Step 5: Analyze and calculate the diagnostic value of ADNEX model compared with histopathological results. From the calculated data, compare with the histopathology results to calculate the sensitivity and specificity of the ADNEX model in predicting the risk of malignancy of ovarian tumors, finding the optimal cut-off point

Statistical analysis

Data analyses were performed using the statistical software SPSS 20.0. Evaluate intergroup differences $p<0.05$. Categorical variables were expressed as numbers percentages. Continuous variables are reported as median curve (ROC) analysis was performed with MedCalc. Categorical variables were reported as percentages, and continuous variables were reported as medians. Curve ROC analysis was performed with MedCalc

Results

Ovarian tumors were found in 51.8% of people aged 20 to 39. Ovarian cancer was found in 78.4%, aged 40 and ovẻ, and 64.6% aged 50 and up. The cancer group's median age was 54 (48–62), which was higher than the benign tumor group's median age of 35 (26–44), $p<0.001$ The percentage of unilateral and bilateral sites in the cancer group was 86.2% and 13.8%, respectively, while 85.1% and 14.9% were in the benign group. There were

83.1 % of cancer patients with solid parts, the presence of papillations was 64.6%, no presence of acoustic shadows, and ascites were 98.5% and 40%. Ovarian tumors accounted for 86.2% of the solid parts in the cancer group, with a ratio <50% (71.9%). There are more solid parts in the cancer group than in the benign tumor group. ($p < 0.05$) The ADNEX model with CA125 had 92.3% sensitivity and 90.9% specificity at the 10% cut-off point, respectively; at the 30% cut-off point, sensitivity was

Table 1. Age Characteristics of Participants

Age	Ovarian cancer		Benign tumor		Total	
	n	%	n	%	n	%
< 20	1	1.5	27	6.8	28	6.1
20 – 39	13	20.0	226	57.1	239	51.8
40 – 49	9	13.8	76	19.2	85	18.4
≥ 50	42	64.6	67	16.9	109	23.6
Total	65	100.0	396	100.0	461	100.0
Median	54		35		36	
(Q1 – Q3)	(48 – 62)		(26 – 44)		(27 – 49)	

Table 2. Characteristics of Ultrasound

Characteristics		Cancer group		Benign group		p
		n	%	n	%	
Position	Unilateral	56	86.2	337	85.1	> 0.05
	Bilateral	9	13.8	59	14.9	
Solid	Yes	54	83.1	42	10.6	< 0.05
	None	11	16.9	354	89.4	
Lobe	> 10 lobe	8	12.3	5	1.3	< 0.05
	≤ 10 lobe	57	87.7	391	98.7	
Papillations	None	23	35.4	373	94.2	< 0.05
	1	20	30.8	20	5.1	
	2	11	16.9	3	0.8	
	3	5	7.7	0	0.0	
	>3	6	9.2	0	0.0	
Acoustic shadows	Yes	1	1.5	89	22.5	< 0.05
	None	64	98.5	307	77.5	
Ascites	Yes	26	40.0	5	1.3	< 0.05
	None	39	60.0	391	98.7	

84.6%, and specificity was 97.7%. The area under ROC of ADNEX model with CA125 had a good predictive value of 0.961 (0.940 – 0.977) in predicting malignant tumors. Youden's index J= 0.8395, p < 0.001.

The ADNEX model without CA125 had 93.9% sensitivity and 90.2% specificity in predicting malignancy at the 10% cut-off and 83.1% and 96.5% sensitivity and specificity at the 30.6% cut-off, respectively. In predicting malignant tumors, the area under the ROC of the ADNEX model without CA125 was 0.956 (0.933 – 0.973). Youden's index J= 0.8551, p < 0.001. The ADNEX model had a cut-off of 13.5 with CA125 and 13.1 without CA125 for sensitivities of 90.8 (81.0 – 96.5)

and 93.9 (85.0 – 97.5), respectively, and specificities of 93.2 (90.2 – 95.5) and 91.67 (88.5 – 94.2). The predictive value of the malignancy-risk difference between the ADNEX model with CA125 and without CA125 was not statistically significant, with Z = 0.693 and p = 0.4883. The ADNEX model's area under ROC with and without CA 125 was 0.961 (0.939 – 0.977) and 0.956 (0.933 – 0.973), respectively.

Discussion

A multimodal approach that includes anthropometric, clinical, and subclinical characteristics is an effective

Table 3. Characteristics of Solid Parts

Solid parts (%)	Cancer group		Benign group		Total	
	n	%	n	%	n	%
< 50	33	61.1	36	85.7	69	71.9
50 – 79.9	14	25.9	4	9.5	18	18.8
≥ 80	7	13.0	2	4.8	9	9.4
Total	54	100.0	42	100.0	96	100.0
Median	42.4		27.5		37	

| (Q1 – Q3) | (31.2 – 61.9) | (17.0 – 41.6) | (22.8 – 51.5) |

Table 4. The Predictive Value of Malignancy-Risk of the Adnex Model in Combination with CA125. the Cut-off of the Adnex Model with CA125

Cut-off	Se (%) (95% CI)	Sp (%) (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)
3%	98.5 (91.7 – 100)	35.6 (30.9 – 40.5)	20.1 (18.8 – 21.4)	99.3 (95.5 – 99.9)
5%	95.4 (87.1 – 99.0)	72.7 (68.1 – 77.1)	36.5 (32.6 – 40.5)	99 (96.9 – 99.7)
10%	92.3 (83.0 – 97.5)	90.9 (87.6 – 93.6)	62.5 (54.8 – 69.6)	98.6 (96.9 – 99.4)
15%	89.2 (79.1 – 95.6)	93.4 (90.5 – 95.7)	69 (60.4 – 76.6)	98.1 (96.3 – 99.1)
20%	89.2 (79.1 – 95.6)	94.2 (91.4 – 96.3)	71.6 (62.7 – 79.1)	98.2 (96.4 – 99.1)
30%	84.6 (73.5 – 92.4)	97.7 (95.7 – 99.0)	85.9 (76.1 – 92.2)	97.5 (95.6 – 98.6)
50.60%	69.2 (56.6 – 80.1)	99 (97.4 – 99.7)	91.8 (80.7 – 96.8)	95.1 (93.2 – 96.6)

Table 5. The Evaluation of Adnex Model without ca125 to Predict Risk of Malignancy in Ovarian Mass

Cut-off	Se (%) (95% CI)	Sp (%) (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)
3%	96.9 (89.3 – 99.6)	33.3 (28.7 – 38.2)	19.3 (18.0 – 20.6)	98.5 (94.4 – 99.6)
5%	96.9 (89.3 – 99.6)	72.7 (68.1 – 77.1)	36.8 (33.1 – 40.8)	99.3 (97.4 – 99.8)
10%	93.9 (85.0 – 98.3)	90.2 (86.8 – 92.9)	61 (53.6 – 68.0)	98.9 (97.2 – 99.6)
15.30%	90.8 (81.0 – 96.5)	92.7 (89.7- 95.0)	67 (58.7 – 74.4)	98.4 (96.6 – 99.2)
21%	87.7 (77.2 – 94.5)	94.2 (91.4 – 96.3)	71.3 (62.3 – 78.8)	97.9 (96.1 – 98.9)
30.60%	83.1 (71.7 – 91.2)	96.5 (94.1 – 98.1)	79.4 (69.5 – 86.7)	97.2 (95.3 – 98.3)
50%	69.2 (56.6 – 80.1)	98.2 (96.4 – 99.3)	86.5 (75.2 – 93.2)	95.1 (93.1 – 96.6)

Table 6. The Optimal Cut-off Point of Adnex Model

	ADNEX with CA125	ADNEX without CA125
Optimal cut-off point (%)	13.5	13.1
AUC	0.961 (0.939 – 0.977)	0.956 (0.933 – 0.973)
Se (%)	90.8 (81.0 – 96.5)	93.9 (85.0 – 97.5)
Sp (%)	93.2 (90.2 – 95.5)	91.67 (88.5 – 94.2)
PPV (%)	68.6 (60.1 – 76.0)	64.9 (57.0 – 72.0)
NPV (%)	98.4 (96.6 – 99.2)	98.9 (97.2 – 99.6)

method to predict ovarian cancer in women who had a mass in the pelvic or adnexal. Age of patient, the ability of gyn-oncol center, features of ultrasound, and serum were critical predictive criteria for discriminating between ovarian cancer and non-cancer masses in the research and were thus included in IOTA – ADNEX grading system. Menopausal status has affected cancer development and is associated with ovarian incidence. Our data was showed that ovarian cancer mainly affects older women, with the risk increasing after 40. The average age in our studyis similar to that of some domestic and foreign authors. According to Bindman R. S., 76.7% of ovarian cancer occurs in women ≥ 50 years old. We discovered that ovarian cancer mostly affects older women, with the risk increasing after 40, with the average age being between 50 and 59. The cancer group's median age was 54 (48–62), which was higher than the benign tumor group's median age of 35 (26–44), p<0.001. The average age in our study is similar to that of some domestic and foreign authors. 76.7% of ovarian cancer occurs in women ≥ 50 years old (Smith-Bindman et al., 2019).

The present study identified menopausal status as a significant predictive factor for OC, with 64% of postmenopausal women with pelvic or adnexal masses

diagnosed with OC. The rate of ovarian cancer in postmenopausal women from several studies was 59,7% and 41,1% (Yanaranop et al., 2016; Tran et al., 2021). We also indicated that age ≥ 50 was a risk of ovarian cancer (OR = 0.9). Thus, ovarian cancer is mainly seen in older women, especially after 50. Women with ovarian masses were often not diagnosed early in Vietnam and many other low- and middle-income countries due to a lack of a systematic screening program using tumor markers or ultrasound. Postmenopausal women's often centrally overweight status could lead to late detection of abdominal masses in those women. These factors may explain why postmenopausal women have a greater incidence of ovarian cancer than other women. As a result, the menopausal state is a fundamental clinical indicator for determining ovarian cancer risk.

We also discovered that the average age of participants in our study, which included benign tumors and ovarian cancer, was comparable to domestic and foreign studies. Furthermore, the age of the cancer group was consistently higher than that of the benign tumor group.(p < 0.05). Over 55, the risk of ovarian cancer was 2.3 times greater (OR = 2.3). Ultrasound was the first device to identify and define ovarian cancers to determine whether they are benign or malignant, benefiting doctors in screening and management. The ADNEX model was created using 9 variables, 6 of which are ultrasound-related. Furthermore, the current study looked at the location of the ovarian tumor on ultrasonography.

According to IOTA, the Papillary projeckon is characterized as a solid tissue with a height of less than 3 mm. Our research found that the proportion of papillary in the ovarian cancer group was much more significant than in the benign group. According to Sayasneh et al.'s study,the proportion of benign tumors with papillary was 13%,

while the rate of malignant tumors with papillary was 38% in borderline and 30% in stage I cancers (Sayasneh et al., 2016). IOTA's report showed that 14% were benign tumors and 30.2% were malignant tumors that had papillary on ultrasound. According to studies, papillary projeckon is one of the prevalent signs of malignant ovarian tumor on ultrasonography. One factor that increases the risk of ovarian tumor malignancy is the presence of solid papillary projeckon (Van Calster etal., 2015).

Revealed that ovarian tumors were prevalent, accounting for 86.2% of cancer cases and 85.1% of benign tumors. The results also showed the proportion of specific characteristics found in ovarian tumors, such as solid components (83.1%), papillations (64.6%), no acoustic shadows (98.5%), and ascites (40%), the solid parts with ratio < 50% (71.9%). The cancer group has a higher percentage of solid components than the benign tumor one (p< 0.05). Ultrasound result depends on subjective assessment of the reader. Wouter Froyman predicts that the positive predictive value of screening could enhance if the IOTA's method for detecting abnormal screening results were applied. The ADNEX model has not been widely used in research centers to predict ovarian cancer before surgery (Froyman et al., 2017). According to some authors 50% of ovarian tumors are toxic on both sides, while the rate of bilateral tumors in the healthy group is 18.4% (Tran et al., 2021).

The cancer group has a higher percentage of solid components than the benign tumor one (p< 0.05). Ultrasound result depends on the subjective assessment of the reader. Wouter Froyman predicts that the positive predictive value of screening could enhance if the IOTA's method for detecting abnormal screening results were applied (Timmerman et al., 2016). The ADNEX model has not been widely used in research centers to predict ovarian cancer before surgery . According to some authors, 50% of ovarian tumors on both sides, while the rate of bilateral tumors in the benigh group is 18.4% (Tran et al., 2021) . Our findings were similar to those of others, with rates of solid components of 11% and 87% in benignand malignant tumors, respectively, but lower than thoseof Sayasneh et al. This difference could be related to thefact that the author Sayasneh's study was conducted in 3 European oncology cancer with a greater sample size than ours (Sayasneh et al., 2016).

The present study showed that the malignancy prediction value of the ADNEX model with CA125 at the 10% cut-off point has a sensitivity and specificity of 92.3% and 90.9%, respectively, and the 30% cut-off point has a sensitivity of 84.6% and a specificity of 97.7%. The ADNEX model with CA125 has a good predictive value between benign and malignant tumors with an areaunder ROC of 0.961 (0.940 – 0.977). Youden's index J=0.8395, p < 0.001. The malignancy prediction value of the ADNEX model without CA125 at the 10% cut-off point has a sensitivity and specificity of 93.9% and 90.2%, respectively. The cut-off point of 30.6% has a sensitivity of 83.1% and a specificity of 96.5%. The ADNEX model without CA125 also has a good predictive value between benign and malignant tumors with an area under ROC

of 0.956 (0.933 – 0.973). Youden's index J= 0.8551, p< 0.001. Van Calster's research shows that without the value of CA125, there was little impact on differentiating between benign and malignant tumors; the results recorded the area under the curve as using CA125 is 0.943 and 0.932 when not using CA125 in the model as a predictor. The difference in the area under ROC in the model with and without CA125 was low. This difference was not significant in our study, and it was similar to the studies of Van Calster and A Sayasneh (Van Calster et al., 2015; Sayasneh et al., 2016).

The optimal cut-off of the ADNEX model with CA125 was 13.5 and without CA125 was 13.1 for sensitivities were 90.8 (81.0 – 96.5) and 93.9 (85.0 – 97.5), specificities were 93.2 (90.2 – 95.5) and 91.67 (88.5 – 94.2). Regarding the predictive value of malignancy-risk between the ADNEX model with CA125 and without CA125, the difference was not statistically significant with Z = 0.693 and p = 0.4883. However, the model's sensitivity with CA 125 was higher than the model without CA 125, similar to other studies. Although the IOTA recommended a cut-off of 10%, which was evaluated in many centers, our research indicated that the optimal cut-off was 13.5 with CA125 and 13.1 without CA125 (Van Calster et al., 2015). We indicated the area under ROC of the ADNEX model with and without CA 125 were 0.961 (0.939 – 0.977) and 0.956 (0.933 – 0.973), which shows that both models have high values. Serum CA125 testing wasnot always available to patients. In fact, in the study of the IOTA group, 31% of cases did not perform this test. Therefore, in the absence or lack of data for CA125, the ADNEX model without serum CA125 can be applied and used to predict preoperative malignancy ovarian tumors. These were similar to Le Ngoc Diep's study but had lower sensitivity and higher specificity than Sayasneh's (97.3 % and 67.7%) and Meys's (98% and 62%)9. This could be attributed to differences in sample size, period and place, cancer rates, cancer stage distribution, and the experience and qualifications of the sonographers in the research (Sayasneh et al., 2016; Meys et al., 2017; Le and To, 2019). When we compare the values of the ADNEX model with CA125 and without CA125, the difference was not statistically significant (p>0.05). However, our study found that the ADNEX model with CA125 missed fewer malignancy cases than the ADNEX model without CA125. However, both models could predict the malignancy of ovarian tumors before surgery, and the difference is not statistically significant. So as recommended by the IOTA, the model without CA125 should be used in hospitals where this test has not been performed. In our research, all patients were tested for serum CA125. This study will be the basis for the proposal to decide the cut-off in practice and meet the requirements of preoperative cancer diagnosis in obstetrics and gynecology and oncology facilities at two hospitals in Hue, Vietnam.

The ADNEX model was valuable in predicting ovarian cancer before surgery aid the prognosis of the surgery. This appropriate treatment will reduce the mortality caused by ovarian cancer and improve the quality of life for the patient.

In conclusion, the value of the ADNEX model with

CA125 at the 10% cut-off point has a sensitivity and CA125 at the 10% cut-off point has a sensitivity and specificity of 92.3% and 90.9%, respectively. The 30% cut-off point has a sensitivity of 84.6% and a specificity of 97.7%. The ADNEX model with CA125 has a good predictive value between benign and malignant tumors with an area under ROC of 0.961 (0.940 – 0.977). Youden's index J= 0.8395, p < 0.001. The malignancy prediction value of the ADNEX model without CA125 at the 10% cut-off point has a sensitivity and specificity of 93.9% and 90.2%, respectively. The cut-off point of 30.6% has a sensitivity of 83.1% and a specificity of 96.5%. The ADNEX model without CA125 also has a good predictive value between benign and malignant tumors with an area under ROCof 0.956 (0.933 – 0.973). Youden's index J= 0.8551, p < 0.001. Cut-off of the ADNEX model with CA125 was 13.5 and without CA125 was 13.1 for sensitivities were 90.8 (81.0 – 96.5) and 93.9 (85.0 – 97.5), specificities were 93.2 (90.2 – 95.5) and 91.67 (88.5 – 94.2). Regarding the predictive value of malignancy-risk between the ADNEX model with CA125 and without CA125, the difference was not statistically significant with Z = 0.693 and p = 0.4883.

Author Contribution Statement

Acknowledgements

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