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Clinical Significance of Thrombocytosis and CA125 as Predictor of Malignancy in Gynecological Pelvic Mass

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Abstract

We attempted to determine the increasing of platelet counts (> 450.000 /microliter) and Cancer Antigen 125 (CA125) serum level (> 35 U/mL) as useful tools for predicting and confirming malignancy in gynaecological pelvic mass. A prospective unmatched hospital based case-control study carried out about One hundred & ten women were enrolled in our study, divided into two group 60 women were control group (free of gynaecological pelvic mass) which were considered as "eligible entrants" into the study. Other group include 50 women above 15 years old with gynaecological pelvic mass were all candidate for laparotomy and using different diagnostic methods like clinical examination, imaging techniques (U/S, CT scan and MRI) and laboratory test (platelet count, CA125 and Histopathology). The data of those were subjected to statistical analysis (sensitivity, specificity, accuracy, NPV and PPV) which calculated to considered if it is statistically significant or not. Serum CA125 and blood platelets count were tested for validity when used as a test to predict a diagnosis of malignancy in gynaecological pelvic mass differentiating it from benign gynaecological pelvic mass. Both tests showed a very high validity in diagnosis (ROC area >0.95), with serum CA125 showing a marginally higher validity (ROC area larger by 0.017 only). Both ROC areas were significantly higher than the 0.5 area associated with an equivocal test. Platelets counts had a perfect cut-off value of ≥385.000 All study subjects with a blood platelets count equal or greater than 385.000 were malignant, while everybody below this cut-off value was healthy. For serum CA125 testing negative at the highest sensitivity (100% sensitive) cut-off value of (≤27.1) would excluded a possible diagnosis of malignancy in favor of being healthy with 100% confidence. The optimum cut-off value is ≥41.7, which is also the 100% specific and thus 100% diagnostic cut-off value. Both blood platelet count (≥ 385 X 10^3microlitter) & serum level of CA125 (≥ 41.7 U/mL) are useful predictor tools to confirm malignancy in gynecological pelvic mass.

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Malignancy,
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Introduction

The female pelvis is an anatomic region which is quite complex. A gynaecologicalpelvic mass can arise from various organs including the fallopian tubes, ovaries, uterus, bladder, bowel and retroperitoneal structures. To establish a diagnosis requires a thorough history, examination and appropriate investigations. There is an extensive differential diagnosis and the treatment options are numerous. Pelvic masses may originate from gynecological organs (cervix, uterus, uterine adnexa) or from other pelvic organs (intestine, bladder, ureters,

skeletal muscle, and bone). So a medical professional should differentiate between them[1].

The age of the woman dictates the type of evaluation as different kinds of pelvic masses present during the reproductive years versus during menopause [2,3].

Laboratory evaluation of gynecological pelvic mass

These includeβ-hCGlevel test [5], complete blood count test [4], gonorrhea/Chlamydia Test[6]. Based on the history and physical examination, other tests that should be considered include Rh blood typing (if pregnant), urine culture, complete blood count, erythrocyte sedimentation rate, and a fecal occult blood test. Erythrocyte sedimentation rate is a nonspecific marker of inflammation that can be associated with ectopic pregnancy [7].

Tumor Markers

Tumor markers are substances that can be found in the body when cancer is present. Ideally, a tumor marker would always be found in the blood in higher level than normal, but only when a certain type of cancer is present. Some tumor markers are found in blood, but others are found in urine or other body fluids. Still others are found in tumors and other tissues. They may be produced by the cancerous cells themselves, or by the body in response to cancer or other conditions. Most tumor markers are proteins, but some newer markers are genes or other substances. There are many different tumor markers. Some are linked only to one type of cancer, while others can be detected in many cancers. Tumor marker can be tested either by laboratory examination of blood or urine sample taken from patient or Sometimes a piece of the tumor itself is tested for tumor markers[8].

Literature data showed that combined multiple tumor markers can improve the overall diagnostic accuracy[9,10,11]. The sensitivity of a serum markers combination was significantly greater than the sensitivity of the CA 125 assay alone in patients with all stages of primary ovarian epithelial tumors of different histological types. When used as single markers, however, only the CA125-II assay could distinguish invasive Stage I tumors from apparently healthy women [12]. A combination of serum and molecular markers such as serum CA125, CA19 and mRNA for Survivin gene could allow a better triage between endometriosis and malignant adnexal masses [13]. HE4 in combination with CA125 appears to be the most effective tool for the early diagnosis of ovarian carcinoma [12]. Different risk models and screening algorithms that combine and evaluate tumor markers together, aimed at improving the specificity and sensitivity of diagnostic tests, allowing for an effective triage of women to appropriate institutions for their care, have been made so far. The most commonly used is Risk of Ovarian Malignancy Algorithm [ROMA] that utilizes the dual marker combination of HE4 and CA125 to stratify both postmenopausal and premenopausal women into high- and low-risk groups [13,14]. This model achieves the highest sensitivity and specificity. Furthermore, some researchers advise that in patients with an undiagnosed tumor in the pelvis, the CA125/CEA ratio may be used to preoperatively identify a substantial fraction of patients with ovarian and non-ovarian malignancies [15], and confirm again that combination of serum tumor markers could improve ovarian cancer diagnosis [16,17].CA125 is an antigenic determinant found in benign and malignant conditions

Causes of Elevated CA125 Levels:

Benign conditions

Cirrhosis with or without ascites, Disease involvement of a serosal surface, Endometriosis, Pelvic inflammatory disease, Pleural or peritoneal fluid or disease, Uterine leiomyoma

Malignant conditions

Breast, Lung, Endometrial, Pancreatic cancers, and Ovarian malignancies.

CA 125 level should not be used as a screening tool or when a mass is not identified[18], and should not be routinely used during the diagnostic workup of an adnexal mass in a premenopausal patient[19]. On the other hand, CA 125 level should be drawn in a postmenopausal patient with an adnexal mass to guide treatment options. A value greater than 35 U per mL should prompt further evaluation[20]. CA 125 levels are elevated in 80% of epithelial ovarian cancers. Only 50% of stage I cancers have elevated CA 125 levels[21]. CA 125 levels are ordered preoperatively. If ovarian cancer is diagnosed, CA 125 level is used to monitor the patient's response postoperatively. If a granulosa cell tumor is suspected, inhibin A and B levels are followed post-operatively. If germ cell tumors are suspected, serum α-fetoprotein and quantitative β-hCG levels should be obtained. Hereditary ovarian cancer accounts

for only a small percentage of overall cancer cases. Patients should have genetic counseling before undergoing *BRCA* mutation testing[22].It has been proved that serum CA125 are helpful in the diagnostic evaluation of pelvic masses, particularly in adnexal masses.An increase (ranging from 80 to 90%) of CA125 serum levels are associated with ovarian epithelial malignant non-mucinous tumors.

Besides, CA125 is related to the volume of the tumor mass. CA125 represents the gold standard tumoral markers for ovarian cancer in two different clinical conditions: as a diagnostic tool for evaluating the risk of malignancy of an adnexal mass and as a monitoring tool in the evaluation of the disease state, in patients already treated for adnexal cancer [23,24].

CA125 serum levels equal or below (35 U/ml) are normal. CA125 serum levels greater than (50-65 U/ml) (in the 80-90% of postmenopausal patients) is associated with a malignancy. Classifying patients with increased CA125 and a pelvic mass by age, permits a rise in positive predictive value of the association of (80%) in patients older than (50) years and only (50%) in younger ones. On the other hand this marker increases (in 60-70% of the cases) also in advanced endometrial adenocarcinoma and/or in recurrence. Other non gynaecological malignant solid tumors can increase CA125 serum levels (60% in pancreatic cancer, 20-25% in breast, lung and colon tumors). Other non tumoral conditions can be associated with increased levels of CA125 such as endometriosis, peritonitis, tubo-ovarian abscess, diverticulitis, adenomyosis, uterine fibroids and ascites.

Best specificity and sensitivity results have been reached by integrating different diagnostic techniques like markers and ultrasonography and clinical history to create risk index [25].The United State Preventive Services Task Force recommends against routine screening for ovarian cancer, including use of transvaginal ultrasonography, cancer antigen (CA) 125 level, and screening pelvic examination[18].

Radiological Evaluation

Despite advances in technology, gray-scale transvaginal ultrasonography remains the standard for the evaluation of adnexal masses [26,27]. Ultrasonography should assess the size of the mass, its characteristics (cystic, solid, or both), complexity (internal septae, excrescences and papillae), and the presence or absence of abdominal or pelvic fluid (ascites or blood). Ultrasonography characteristics of simple cysts include: anechoic mass; smooth, thin walls; no mural nodules or septations; and association with acoustic enhancement. The combination of ultrasonography and doppler flow studies are superior to either alone [28,29,30].

In one study, three-dimensional ultrasonography (3D) was superior to two-dimensional ultrasonography (2D) for the prediction of malignant cases[31].

Dimensional Ultrasonography and computed tomography have similar sensitivity and specificity for evaluation of adnexal masses, but ultrasonography is generally more cost-effective [26]. In the future, magnetic resonance imaging and positron emission tomography may have a role in the evaluation of adnexal masses[32,33].

Thrombocytosis & gynecological pelvic mass

Thrombocytosis is the presence of high platelet counts in the blood, and can be either primary (also termed essential and caused by a myeloproliferative disease) or reactive (also termed secondary). Although often symptomless (particularly when it is a secondary reaction), it can predispose to thrombosis in some patients [34].In a healthy individual, a normal platelet count ranges from (150–450 x 10^9/L). These limits, however, are determined by the 2.5th lower and upper percentile and a deviation does not necessary imply any form of disease. Nevertheless, counts over (750,000) per microliter (and especially over a million) are considered serious enough to warrant investigation and intervention. Tumor cells interact with all major components of the hemostatic system, including platelets. Platelets and platelet activation have been linked to key steps in cancer progression. The contribution of platelets to malignancy progression has been suggested to be organized process that underlies the pathobiology of cancer growth, maintenance & propagation & identify potential targets & directions for platelet-directed anticancer therapy in the future. High levels of thrombopoietin have been found in patients with reactive thrombocytosis and with solid tumors. Patients with reactive thrombocytosis and with solid tumors had higher levels of thrombopoietin than patients with non-neoplastic conditions associated with reactive thrombocytosis or essential thrombocytosis [34]. Tumorrelated humeral factors with thrombopoietin-like activity [36] and overcompensated megakaryocytopoiesis due to tumor-induced disseminated intravascular coagulopathy[37] have been proposed in the etiology of reactivethrombocytosis in

patients with malignant disease.Interleukin-6 (IL-6), granulocyte-macrophage colony stimulating factor (GmCSF), erythropoietin and tumor necrosis factor have been postulated to play a role in the development of thrombopoiesis and thrombocytosis. IL-6 is a potent stimulator of megakaryocytopoiesis and responsible for maturation of megakaryocytes [(38)].

Various epithelial ovarian cancer cell lines have been found to produce IL-6. Elevated levels of IL-6 have been found in ascitic fluid and serum of patients with ovarian cancer. High levels of IL-6 in ascitic fluid were significantly correlated with the circulating platelet count, suggesting a role for IL-6 in the development of tumor-associated thrombocytosis. Similarly, high levels of IL-6 in fluids from malignant ovarian cysts have been significantly correlated with increased platelet counts and low hemoglobin levels [(39)].Also, administration of recombinant human IL-6 increases the platelet count and decreases hemoglobin levels. Some cervical cancer cell lines have been found to secrete IL-6 and utilize it as an autocrine or paracrine growth factor, or both. High levels of IL-6 have been found in sera andcervico-vaginal secretions of patients with advanced cervical cancer[(40)].

Platelets and metastasis

There is evidence suggesting that platelets play a role in the development of tumor metastasis. Tumor cell-platelet interactions may influence the process of metastasis at different levels [(41)].Tumor cell-platelet aggregates have been shown to form during initial arrest of tumor cells in the capillary vascular bed and to play an important role in hematogenous tumor spread. Also, tumor cells can directly activate platelets. Platelets may protect tumor cells by coating the tumor cells and blocking their antigenic determinants from the host's humoral and cellular defense mechanisms. Anti-platelet agents and anticoagulants have potent inhibitory effects on tumor cell-platelet interactions and can prevent metastases in experimental settings in various malignancies [(42)].

Thrombospondin-1 is an adhesive glycoprotein, richly secreted by platelets and an extracellular matrix component of many cell types including tumor cells and vascular endothelial cells. Thrombospondin-1 supports the adhesion of tumor cells to endothelium and may promote metastasis by increasing the secretion of plasminogen activator inhibitor-1 and urokinase-type plasminogen activator levels. This facilitates urokinase-type plasminogen activator-mediated cell invasion and metastatic spread of cancer cells[(43)].

Patients & Methods

This is a prospective hospital based case-control study conducted at obstetrics& gynecology department at Baghdad teaching hospital over a period of one year from June 2013 to June 2014. Fifty women older than 15 years with proved diagnosed gynecological pelvic mass were enrolled in this study in addition to 60 apparently healthy women as controls

Woman with one or more of the following were excluded from the study; myeloproliferative disease, recent or chronic infection, autoimmune disease or SLE, currently on medications, chemotherapy or radiotherapy which can affect platelets count, Postpartum or postoperative patients, recent trauma and splenectomy.

A full history and complete physical andthorough systemic and gynecological examination were performed in all patients and controls.

Blood tests: 10ml of venous blood was aspirated, 5ml was put in non EDTA tube and sent for routine blood tests. Thrombocytosis was identified when the platelets count exceeds $450x10^9$ /L. The other 5ml was put in EDTA tube & shake gently to prevent clotting of sample and sent to the lab to assess CA 125.

Laparotomy was done for each the fifty pelvic mass patientsby specialist expert gynecologist

For each patient the abnormal tissue had been sent for histopathological examination.

Signed consents were obtained from all participants. The data were analyzed using the statistical package for social sciences (version 16) and appropriate statistical tests and procedures were applied accordingly, level of significance was set at 0.05.

Results and Discussion

As it shown in (Table 1) Malignant pathologies were proved in 19 patients (38%), their mean age (44.9±12.4) years for the malignant groups, for the remaining 31 women with benign masses the mean age was (42.4 ± 12.5) years while for the healthy controls, mean age was (29.5±8.5) years, with statistically significant difference, ($P<0.001$).The mean of hemoglobin concentration in3groups were (10.6±1.5), (10.7±2.5) and (11.6±1.1) for benign, malignant and healthy controls group respectively. Both the benign & healthy control group

show platelets count range were between (132-560) and (108-366) with mean (311.5±104.1) & (232.9±70) respectively while malignant group the platelets range between (405-762) and the mean of it was (543.8±100.7).

A very obvious variation in range & the mean value of serum CA125 between 3 groups. The range of healthy control group was (8.3-38.3) and the mean was (17.8±11.3) while range of benign group was (12-65) and the mean was (28.8±10.9), in contrast the malignant group rang was (34-185) & mean was (85.5±47.9).

Table 2 show the malignant-benign group difference in site of pelvis mass but the ovarian site of pelvic mass is the domain for both malignant (57.9%) and benign (51.6%) group. In the benign group we had fibroid as main histopathological type which its cases reach to (45.2%) from total cases of benign pelvic mass as shown in (Table 3) while mucinous adenocarcinoma cases were main histopathological type in malignant study group which reach to (26.3%) from total group cases as shown in (Table 4).

Serum CA125 and blood platelets count were tested for validity when used as a test to predict a diagnosis of malignancy in gynaecological pelvic mass differentiating it from benign gynaecological pelvic mass. Both tests showed a very high validity in diagnosis (ROC area >0.95), with serum CA125 showing a marginally higher validity (ROC area larger by 0.017 only). Both ROC areas were significantly higher than the 0.5 area associated with an equivocal test, (Table 5 and Figure 2).

As shown in (Table 6), the optimum (typical) cut-off value associated with highest accuracy (94%) for blood platelets count is ≥ 400.000 (which is also the most sensitive cut-off value). For serum CA125 the optimal cut-off value is ≥ 41 (accuracy=94%). Testing positive for blood platelets count at the optimum cut-off value (having a platelets count of 400.000 and higher) is 100% sensitive and 90.3% specific. Testing positive at this cut-off value would establish the diagnosis of malignancy in an US observed gynaecological pelvic mass with 91.2% confidence in a clinical context where the odds for having malignancy versus benign condition are equal (50% chance). The PPV (confidence in positive test result) is further increased to an almost perfect test (98.9%) when the diagnosis of malignancy is highly probable (90% pretest probability) based on clinical impression and US findings only. Testing positive for serum CA125 at the optimum cut-off value (having a serum value of 41 and higher) is 94.7% sensitive and 93.5% specific. Testing positive at this cut-off value would establish the diagnosis of malignancy in an US observed gynaecological pelvic mass with 93.6% confidence in a clinical context where the odds for having malignancy versus benign condition are equal (50% chance). The PPV (confidence in positive test result) is further increased to an almost perfect test (99.2%) when the diagnosis of malignancy is highly probable (90% pretest probability) based on clinical impression and US findings only.

Both tests (serum CA125 and blood platelets count) has a cut-off value associated with a perfect sensitivity (the33.5 and 400 respectively). The tests would be more useful if it's negative at this highly sensitive cut-off value. Testing negative (having a serum CA125 concentration of <33.5 or platelets count <400.000) would exclude the possible diagnosis of malignancy with 100% confidence in any clinical context.

On the other hand testing positive at the highest specificity cut-off value of 100% for both tests would establish the diagnosis of malignancy with 100% confidence under any pretest probability. The cut-off value that is 100% diagnostic of malignant gynaecological pelvic mass is ≥ 560 for platelets count and ≥ 65.5 for serum CA125.

Since the accuracy of both tests at the optimum cut-off value was 94% in classifying female patients with gynaecological pelvic mass into benign and malignant conditions, one would try serial combination of both tests to increase the specificity and the PPV in diagnosing malignant lymph node, since the sensitivity was already high. A serial combination test is considered positive only if both criteria were positive, while a negative test result is considered when any or both criteria were negative. The specificity of this serial combination was only marginally increased to 96.8%. The overall accuracy of this combination was increased to 96%. The PPV of serial tests combination is slightly increased over that of each test alone to 96.7% under the equal odds pretest probability and 99.6% under the high suspicion pretest probability of 90%. The predictive value of negative serial tests combination is 99.4% under the low pretest probability of 10%, which is slightly lower than that for blood platelets count of 100%, (Table 7). Serum CA125 and blood platelets count were tested for validity when used as a test to predict a diagnosis of malignant gynaecological pelvic mass differentiating it from healthy control female.

Table.1 The difference in mean of selected parameters between the 3 study groups

Variable	Healthy Controls (N=60)	Benign pelvic mass (N = 31)	Malignant pelvic mass (N = 19)	P (ANOVA)
Age (years)				
Mean	29.5 ± 8.5	42.4 ± 12.5	44.9 ± 12.4	<0.001
Range	(17 to 52)	(20 to 76)	(24 to 65)	
P (LSD) for difference in mean between:				
Benign pelvic mass x Healthy controls<0.001				
Malignant pelvic mass x Healthy controls<0.001				
Malignant pelvic mass x Benign pelvic mass=0.41[NS]				
Blood Hb (gm/dl)				
Mean	11.6 ± 1.1	10.6 ± 1.5	10.7 ± 2.5	0.004
Range	(9.1 to 14)	(7 to 13.6)	(7 to 15.6)	
P (LSD) for difference in mean between:				
Benign pelvic mass x Healthy controls=0.002				
Malignant pelvic mass x Healthy controls=0.029				
Malignant pelvic mass x Benign pelvic mass=0.72[NS]				
Blood platelets count				
Mean	232.9 ± 70	311.5 ± 104.1	543.8 ± 100.7	<0.001
Range	(108 to 366)	(132 to 560)	(405 to 762)	
P (LSD) for difference in mean between:				
Benign pelvic mass x Healthy controls<0.001				
Malignant pelvic mass x Healthy controls<0.001				
Malignant pelvic mass x Benign pelvic mass<0.001				
Serum Ca125				
Mean	17.8 ± 11.3	28.8 ± 10.9	85.5 ± 47.9	<0.001
Range	(8.3 to 38.3)	(12 to 65)	(34 to 185)	
P (LSD) for difference in mean between:				
Benign pelvic mass x Healthy controls=0.29[NS]				
Malignant pelvic mass x Healthy controls<0.001				

Table.2 The malignant – benign group difference in site of pelvic mass

	Benign pelvic mass		Malignant pelvic mass	
	N	%	N	%
Site of pelvic mass				
Uterus	15	48.4	6	31.6
Ovary	16	51.6	11	57.9
Cervix	0	0.0	2	10.5
Total	31	100.0	19	100.0

Table.3 Frequency distribution of cases with benign pelvic mass by histopathology

Pathologic type of pelvic mass	N	%
Corpus Leutium Cyst	**4**	**12.9**
Cyst Adenoma	**1**	**3.2**
Dermoid Cyst	**6**	**19.4**
Endomterioma	**1**	**3.2**
Endomteriosis	**1**	**3.2**
Fiberiod	**14**	**45.2**
Hemoragic Cyst	**1**	**3.2**
Invasive Mole	**1**	**3.2**
Serous Cyst Adenoma	**2**	**6.5**
Total	**31**	**100.0**

Table.4 Frequency distribution of cases with malignant pelvic mass by histopathology

Pathologic type of pelvic mass	N	%
mucinous adenocarcinoma	**5**	**26.3**
endometrial adenocacinoma	**4**	**21.1**
serous adenocarcinoma	**4**	**21.1**
leiomyosarcoma	**2**	**10.5**
seq.cell carcinoma	**2**	**10.5**
granulosa cell tumor	**1**	**5.3**
immature teratoma	**1**	**5.3**
Total	**19**	**100.0**

Table.5 Area under ROC curve (AUC) for platelets count and serum C125

	AUC	P
Serum CA125	0.972	<0.001
Blood platelets count	0.955	<0.001

Table.6 Optimum cutoff points for platelets count and serum C125

Positive if ≥ cut-of value	Sensitivity	Specificity	Accuracy	PPV at pretest probability = 50%	PPV at pretest probability = 90%	NPV at pretest probability = 10%
Blood platelets count ≥ 400 (Highest sensitivity and optimum cut-off)	100.0	90.3	94.0	91.2	98.9	100.0
Serum CA125						

Table.7 Validity parameters for a serial combination of positive CA125 and platelets count (at their optimum cut-off values) tests to predict malignant gynaecological pelvic mass differentiating them from benign gynaecological pelvic mass

	Final diagnosis		
	Benign pelvic mass	Malignant pelvic mass	Total
Serial combination of platelets count and CA125			
Negative (any or both tests negative)	30	1	31
Positive (both tests positive)	1	18	19
Total	31	19	50

NPV at 10% pretest probability = 99.4%
PPV at 90% pretest probability =99.6%
PPV at 50% pretest probability =96.7%
Sensitivity = 94.7%
Specificity = 96.8%
Accuracy = 96%

Table.8 Area under ROC curve (AUC) for selected quantitative parameters when used as tests to predict malignant gynaecological pelvic mass differentiating them from healthy control females

	AUC	P
Blood platelets count	1.000	<0.001
Serum CA125	0.99	<0.001

Table.9 Validity parameters for selected quantitative variables when used as tests to predict malignant gynecological pelvic mass differentiating them from healthy control females

Positive if ≥ cut-of value	Sensitivity	Specificity	Accuracy	PPV at pretest probability = 50%	PPV at pretest probability = 90%	NPV at pretest probability = 10%
Blood platelets count ≥ 385	100.0	100.0	100.0	100.0	100.0	100.0
Serum CA125						
≥ 27.1 (Highest sensitivity)	100.0	80.0	93.1	83.3	97.8	100.0
≥ 36.0	94.7	80.0	89.7	82.6	97.7	99.3
≥ 38.1	94.7	90.0	93.1	90.5	98.8	99.4
≥ 41.7 (Highest specificity and optimum cut-off)	94.7	100.0	96.6	100.0	100.0	99.4

Fig.1 The difference in mean serum CA125 concentration between the 3 study groups

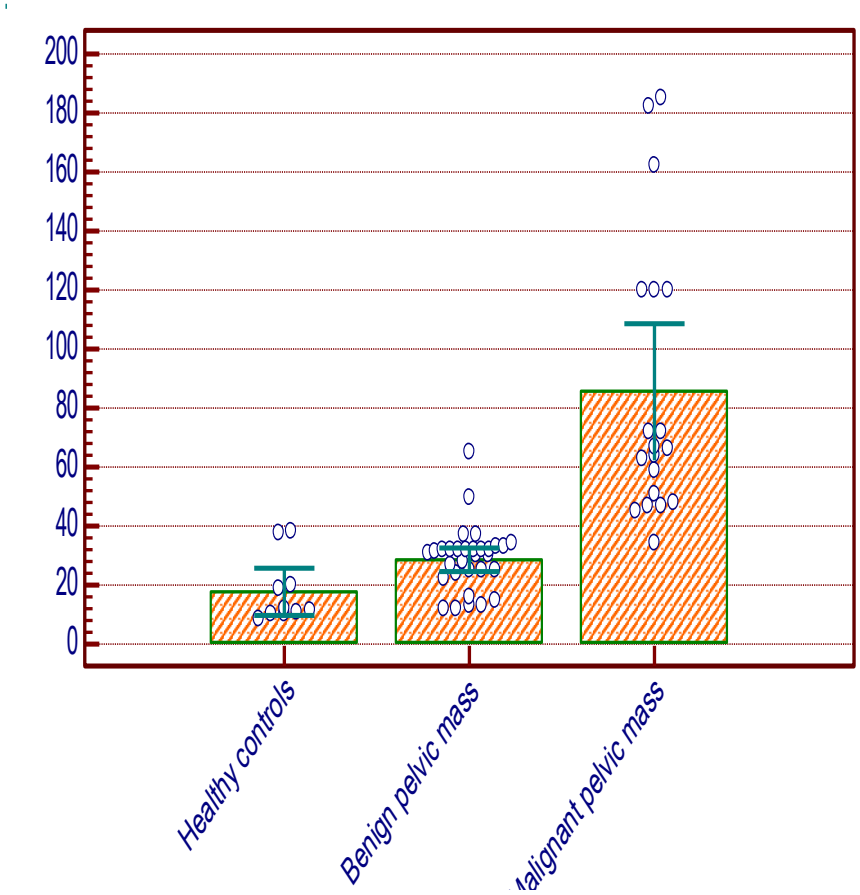


Fig.2 ROC curve for the validity of platelets count and serum C125 in prediction of malignancy from healthy status

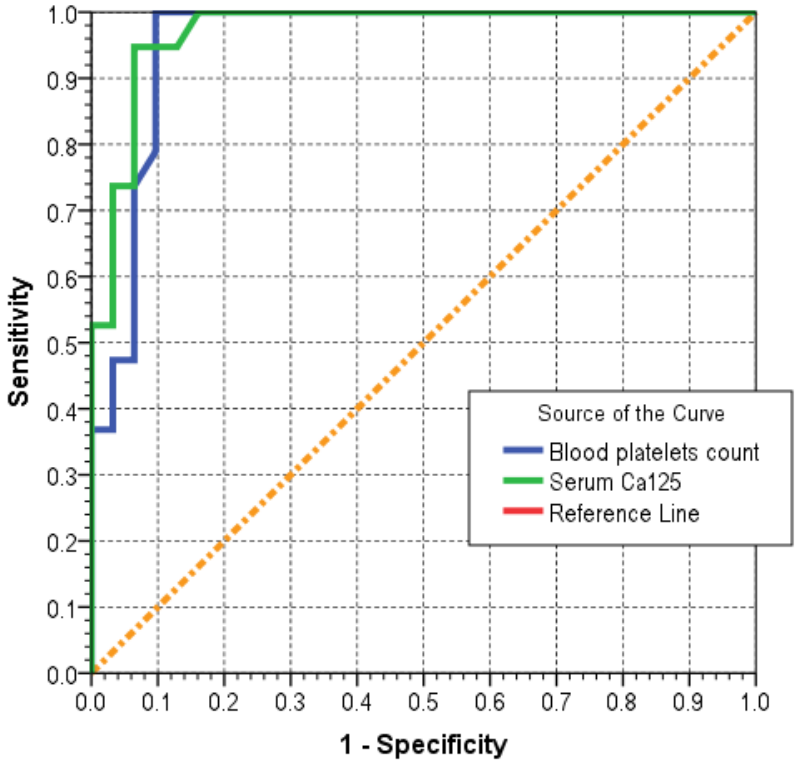
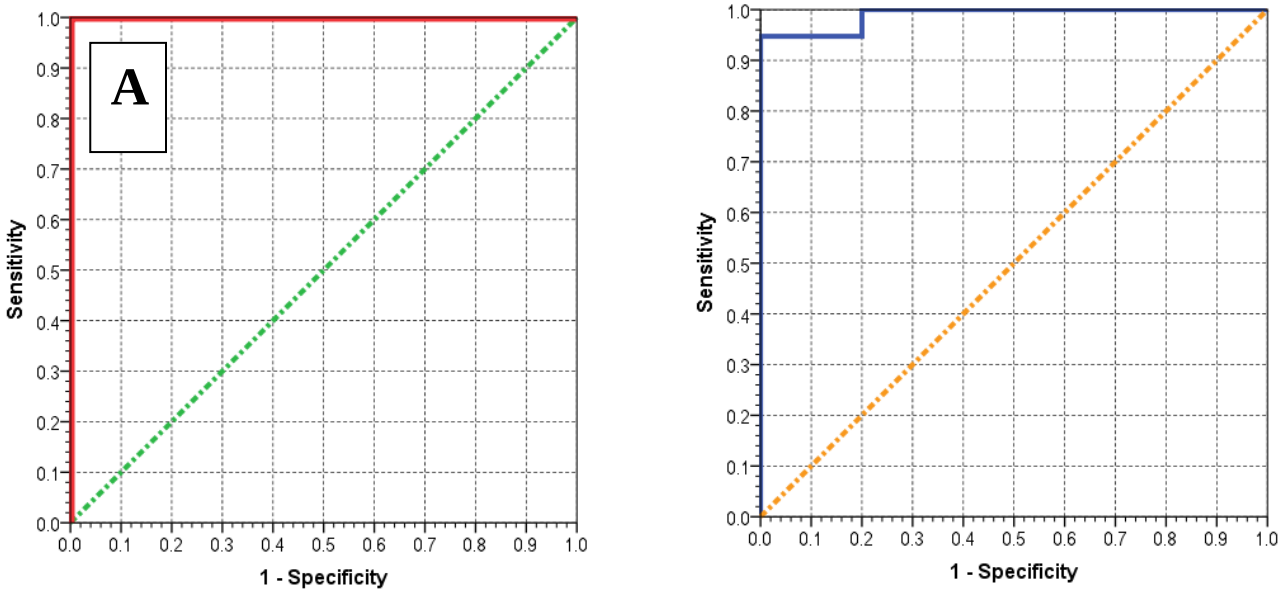


Fig.3 ROC curve showing the trade-off between sensitivity (rate of true positive) and 1-specificity (rate of false positive) for serum CA125 (A) and blood platelets count (B) when used as test to predict malignant gynaecological pelvic mass differentiating them from healthy control females



Both tests showed a very high validity in diagnosis (ROC area >0.99), with blood platelets count being a perfect test (100% accurate), which is marginally better than serum CA125 (ROC area larger by 0.01 only).

Both ROC areas were significantly higher than the 0.5 area associated with an equivocal test, (Table 8 and figure 6).

As shown in (Table 9), blood platelets had a perfect cut-off value of ≥385. All study subjects with a blood platelets count equal or greater than 385 are malignant, while everybody below this cut-off value is healthy.

For serum CA125 testing negative at the highest sensitivity (100% sensitive) cut-off value of ≤ 27.1 would excluded a possible diagnosis of malignancy in favor of being healthy with 100% confidence. The optimum cut-off value is ≥41.7, which is also the 100% specific and thus 100% diagnostic cut-off value.

Recent studies have addressed the prevalence and prognostic impact of thrombocytosis in various gynaecological and non-gynaecological malignancies [44,45]. CA125 has also been tested for the ability to distinguish malignant from benign pelvic masses. The ability to predict whether a tumor is malignant or benign before surgery is important[46].

The most prevalent type of pelvic tumors (benign or malignant) in this study was the ovarian tumor (benign 51.6%, malignant 57.9%). In Iraq, cancer of the ovary is relatively a common form of malignancy representing (3.2%) of all female cancer and second to the cervical carcinoma in the female genital tract [47-49]. Majmudar T, *et al.,* in UK (2008) [50] concluded in their study that benign ovarian tumors are the main presentation of pelvic tumors. The incidence of cancer is increasing in developing countries [51,52]. There are marked differences in distribution of different cancers in different regions of the world [68,69]. Ovarian cancer is the most frequent cause of death from gynaecological cancers and the fourth most frequent cause of death from cancer in women in Europe, United States[53] and Eastern India [54].

The predominant pathological type of pelvic benign tumor in this study was fibroid (45.2%). This finding is consistent with Sschwärzler P, *et al.,* study in UK (1998) [55]. Ashraf A, *et al.,* in Pakistan (2012) [56] and Makwana H, *et al.,* in India (2013)[57]. They concluded in their studies that the serous cystadenoma was the prevalent pathological type of pelvic tumors.

The predominant pathological type of pelvic malignant tumor in this study was mucinous cyst adenocarcinoma. This finding is inconsistent with Ashraf A, *et al.,* study in Pakistan (2012) [56] and Makwana H, *et al.,* study in India (2013) [57] in which the serous cyst adenocarcinoma was the prevalent pathological type. Diverse histopathology is common in ovarian lesions. Relative frequency of different ovarian tumors is different for western world & Asian countries. For example surface epithelial tumors account for 50-55% of all ovarian tumors & their malignant counterpart for approximately 90% of all ovarian cancers in western world whereas this figure is 46-50% and 70-75% respectively in Japan. Similarly mucinous tumors account for 12 to 15% of all ovarian tumors in western world. This figure is 20-23% for Japan. Germ cell tumor accounts for 30% of primary ovarian tumors & malignant germ cell tumor accounts for 3% of all ovarian cancers in western world [58]. Determination of these patterns is important for diagnosis, management and prognosis.

In the present study ANOVA analysis revealed mean age of the studied patients was significantly higher among patients with malignant pelvic mass ($p<0.001$). This finding is consistent with results of Kline RC, *et al.,* study in USA (2010) [59] and Berker B, *et al.,* study in UK (2010) [60]. The incidence of ovarian cancer is low in young women and epithelial ovarian cancers are not known to occur before menarche, and most of them (though rare) are germ cell tumor, juvenile granulosa cell tumor and serous borderline tumors. Age specific incidence is 40/100,000 by the age of 50 and rises to 50 per 100,000 women by the age of 65 years [61].

ANOVA analysis of this study revealed a significant lower hemoglobin level among patients with malignant pelvic type as compared to healthy women ($P<0.05$). This finding is similar to results of Gücer F, *et al.,* study in Turkey (2004)[57] and Rani AK, *et al.,* study in India (2012) [62]. Interaction between tumor cell populations and the immune system can lead to the release of cytokines, especially interferon-γ, interleukin1 and tumor-necrosis factor-α. This release disrupts endogenous erythropoietin synthesis in the kidney and suppresses differentiation of erythroid precursor cells in the bone marrow. As a result, patients with tumor anemia can have relatively low levels of erythropoietin for the grade of anemia observed [63]. The present study revealed by ANOVA analysis a significant increase in platelets count among patients with malignant pelvic tumor ($p<0.001$). This finding is consistent with results of previous Iraqi literature by Al-Nakaash N, *et al.,* study

(2008) [64]which reported that high preoperative platelet count in women presenting with pelvic mass may predict a final diagnosis of cancer. The body produces about 2 x 10 [11]platelets per day. Platelet production is preceded by megakaryocytopoiesis and is regulated by a number of circulating humoral factors, including thrombopoietin. Primitive proliferating progenitor cells are committed to immature megakaryocytes and are finally differentiated to post-mitotic megakaryocytes, losing their proliferative capacity in the process. High levels of thrombopoietin have been found in patients with reactive thrombocytosis and with solid tumors [38]. Patients with reactive thrombocytosis and with solid tumors had higher levels of thrombopoietin than patients with non-neoplastic conditions associated with reactive thrombocytosis or essential thrombocytosis [39]. Tumorrelated humoral factors with thrombopoietin-like activity [65,66] and overcompensated megakaryocytopoiesis due to tumor-induced disseminated intravascular coagulopathy [65-67] have been proposed in the etiology of reactive thrombocytosis in patients with malignant disease. Interleukin-6 (IL-6), granulocyte-macrophage colony stimulating factor (GmCSF), erythropoietin and tumor necrosis factor have been postulated to play a role in the development of thrombopoiesis and thrombocytosis [86-91].

IL-6 is a potent stimulator of megakaryocytopoiesis and responsible for maturation of megakaryocytes [42,68]. Various epithelial ovarian cancer cell lines have been found to produce IL-6 [69-71]. Elevated levels of IL-6 have been found in ascitic fluid and serum of patients with ovarian cancer [43,72]. High levels of IL-6 in ascitic fluid were significantly correlated with the circulating platelet count, suggesting a role for IL-6 in the development of tumor-associated thrombocytosis [72]. Similarly, high levels of IL-6 in fluids from malignant ovarian cysts have been significantly correlated with increased platelet counts and low hemoglobin levels [41]. Also, administration of recombinant human IL-6 increases the platelet count and decreases hemoglobin levels [73-75]. Some cervical cancer cell lines have been found to secrete IL-6 and utilize it as an autocrine [76-78] or paracrine [79] growth factor, or both [80]. High levels of IL-6 have been found in sera [81,82] and cervico-vaginal secretions [83] of patients with advanced cervical cancer. However, studies of IL-6 levels in patients with endometrial cancer are conflicting. Chopra *et al.*, [84] found normal IL-6 levels in 59 women with stage I-IV disease whereas Scambia *et al.*, [85] found elevated levels in 37% of their patients.

Chopra *et al.*, found elevated levels of GmCSF in patients with advanced stage endometrial carcinoma, but GmCSF levels were not compared with the platelet count [85]. Although erythropoietin has been postulated to play a role in the development of thrombocytosis in animal studies, recombinant erythropoietin has not been found to have a significant effect on the platelet count in humans [86,87]. ANOVA analysis in the present study revealed significant increase in serum CA125 among patients with pelvic malignant tumor ($p<0.001$). This finding is similar to results of Asher V, *et al.*, study in UK (2010) [88], Kulkarni M, *et al.*, study in USA (2013) [89] and Rani AK, *et al.*, study in India (2012) [62].CA125 is a high molecular weight glycoprotein and is the most useful tumor marker for epithelial ovarian carcinoma [90].

Many benign conditions like pelvic inflammatory disease, endometriosis, uterine fibroids etc. may also give rise to moderate elevation of serum CA125 [112]. The most common benign gynecological conditions associated with high serum CA125 are ovarian endometrioma and deeply infiltrating endometriosis [90].

Pelvic mass can range from adenomyosis, fibroid uterus, ovarian or fallopian tube cysts, ovarian or uterine malignancy or an inflammatory mass. The management is also very varied and crucial; torsion of an ovarian cyst requires immediate surgery whereas an ovarian malignancy requires planned surgery and chemotherapy [91]. Bridging the gap between the least invasive aid, i.e. pelvic examination and the invasive laparotomy, is the biomarker CA125 which is widely distributed on the surface of both healthy and malignant cells of mesothelial origin, including pleural, pericardial, peritoneal and endometrial cells, as well as in normal genital tract and amniotic membrane. Interestingly the molecule is not present on the surface of normal ovarian cells, but is present in 80% of malignant ovarian tissues of non-mucinous origin [92]. The value of CA125 varies between laboratories depending on the type of assay used but levels less than 35u/ml are considered to be normal [93].

The study of parity history of participated women by ANOVA analysis revealed significant increase of parity number among patients with malignant pelvic tumor ($p=0.03$). This finding is consistent with results of Valentine L, *et al.*, study in Sweden (2006) [115]. Many literatures have found that a higher number of ovulatory cycles are associated with an increasing risk for ovarian cancer [94].

ROC curve analysis in the present study revealed that serum CA125 and thrombocytosis were significant predictors of malignant pelvic tumors among patients with pelvic mass ($p<0.001$). This finding is consistent with results of Moore RG, *et al.*, study in USA (2007) [95].

ROC curve analysis in the present study revealed that serum CA125 and thrombocytosis were significant predictors of pelvic tumors (malignant and benign) among healthy women ($p<0.001$). This finding is consistent with results of Yavuzkan A, *et al.*, study in Turkey (2013) [96]. In the same direction, this study revealed that the sensitivity of using both serum CA125 and platelets count as predictor of pelvic tumors was 100% among healthy females with appropriate predictive value. In the past 20 years, various investigators have proposed risk of malignancy indexes (RMIs) to successfully differentiate benign from malignant masses on an objective basis [119]. Four different indexes utilizing CA125 levels, menopausal status and findings of malignancy on performed USG as the basic variables have yielded a sensitivity ranging from 71-86.8%, and a specificity ranging from 91-96% [97].

Any studies evaluating RMI scales in Asian and Pacific countries have reported different cut-off values compared to those originally reported by the investigators who proposed these indexes at the first place [98-102]. On the other hand, according to the report by van denAkker *et al.*,from Holland, a cut-off value of 200 for RMI-3 and 450 for RMI-4 showed the best performance and yielded success rates similar to that reported by the original investigators.However this subject need further assessment and further debate[99-102]

Both CA125 and thrombocytosis are significant predictors of pelvic tumors, and have the ability to distinguish benign from malignant pelvic tumors.Women with malignant pelvic tumors were older age with higher parity and had higher levels of serum CA125, higher platelets count and lower hemoglobin levels Therefore we suggested to use CA125 and platelets count in addition to physical examination and ultrasonography as a predictor of malignancy in patient with pelvic mass. Further studies with larger sample size, longer duration including other centers are highly suggested.

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