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Original Research Article

The diagnostic significance of hyperfibrinogenemia and thrombocytosis in patients with ovarian tumors/adnexal masses

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ABSTRACT

Background: We aim to study the correlation of thrombocytosis and hyperfibrinogenemia with ovarian tumors and its role in the diagnosis of ovarian malignancy. And to evaluate the platelet and fibrinogen levels in early and advanced stage ovarian disease.
Methods: This is a single centre prospective study. We evaluated plasma fibrinogen levels and plasma platelet levels in 250 patients in women presenting in our OPD with adnexal masses/ovarian tumors. Thrombocytosis was defined as a platelet count greater than >410,000/uL. Hyperfibrinogenemia was defined as a fibrinogen level higher than 360 mg/dL. The association between plasma fibrinogen, platelet levels and clinico-pathological, histopathological parameters were investigated in regards to: 1. Malignant or benign ovarian tumor. 2. Early or advanced disease in malignant ovarian tumors. A multivariate logistic regression model was performed to identify an independent association.
Results: Thrombocytosis and hyperfibrinogenemia are seen to be associated with malignant ovarian tumors. In a multivariate model, plasma fibrinogen and plasma platelet levels were identified to be independently associated with the malignant ovarian tumours. Within the EOC cohort, patients with advanced stage disease had higher plasma fibrinogen levels than patients with early stage.
Conclusions: In this study, we demonstrated that both thrombocytosis and hyperfibrinogenemia were positively associated with malignant ovarian tumors. They were also associated with advanced disease stage, elevated CA125 level and other markers. These finding are in accordance with the previous published data from patients with ovarian cancer, indicating that the platelet and fibrinogen levels increase in parallel with tumor progression and metastasis. Thus confirming the role of elevated platelet and fibrinogen levels in diagnosis and prognosis of ovarian Malignancy.

Keywords: Adnexal masses, Hyperfibrinogenemia, Ovarian malignancy, Ovarian tumors, Thrombocytosis

INTRODUCTION

Ovarian cancer makes up 25-30% of all cases of cancers of the female genital tract with highest mortality rate in gynaecological cancers.[1] Early detection and prompt treatment at higher centres by gynaecological oncologists is known to improve survival outcome.[2,3] Even though adnexal masses are quite common in women of all ages, approximately 75% of tumours are benign.[4,5] It's challenging to identify those with a high risk of having ovarian cancer, especially in young women who wish for to preserve fertility.[6] Thus the importance to differentiate with accuracy between benign and malignant adnexal masses to avoid unnecessary surgical procedures and to deliver optimal care to females with an ovarian cancer.

In the present clinical scenario, transabdominal/ transvaginal sonography and serum measurements of CA-

125 and other markers are used for risk assessment at a primary level. In contrast to the technique of sonography and other imaging methods, which are examiner and experience based procedures, tumor markers have the advantage of being easily reproducible, objective parameters for the differential diagnosis of ovarian tumors.[4, 9,10] Therefore, a number of tumor markers have been tested for their potential to aid in diagnosis and help in the clinical management of women with ovarian tumors. Tumor markers like CA125, vascular endothelial growth factor (VEGF), human epididymal protein (HE)-4 etc have been studied.[11-14] Many other factors involved in inflammation and coagulation such as platelets, C-reactive protein (CRP), D-dimer, FDP, thrombopoietin, serum tissue factor have been shown to be helpful as additional parameters for the differential diagnosis of ovarian tumors[15-17] Malignancies are known to induce thrombocytosis and hyperfibrinogenemia. Around 35-40% of patients with ovarian cancer have hyperfibrinogenemia. Advanced tumor stage was associated with raised fibrinogen levels indicating that the plasma fibrinogen level seems to rise with tumor growth and progression. In ovarian carcinoma, elevated fibrinogen, von Willebrand factor and D-dimer together with reduced antithrombin III levels were found to be associated with advanced stage of disease and poor survival outcome. Studies have shown that raised fibrinogen levels and thrombocytosis are associated with advanced disease stage, high grade histological type at diagnosis and poor prognosis in various malignancies such as carcinoma ovary, cervical cancer, endometrial cancer, breast cancer and lung cancer. Many solid tumours have been detected with concomitant thrombocytosis and hyperfibrinogenemia.[18]

Fibrinogen is one of the most prominent proteins involved in various inflammations and coagulation pathway and its measurement is now routinely available in most clinical laboratories.[19] Platelet count is an easily available investigation in almost all clinical laboratories.

Thus the aim of the present study is to examine the potential of plasma fibrinogen levels and raised platelet counts as additional markers in the differential diagnosis of patients with ovarian tumors.

METHODS

This is a single centre prospective study conducted at Gujarat cancer and Research institute. 211 patients with adnexal masses/ovarian tumors from September 2020 to September 2021 were studied. Plasma fibrinogen and platelet levels along with other markers and imaging, clinico-pathological, histopathological reports, were evaluated. Thrombocytosis is defined as a platelet count >410,000/uL. Hyperfibrinogenemia is defined as a fibrinogen level higher than 360 mg/dL.

The relation of fibrinogen and platelet levels in malignant and benign ovarian tumor, also relation in early and advanced stage disease in malignant ovarian tumors were studied. After establishing the above association, sensitivity, specificity, negative predictive value and positive predictive value of plasma fibrinogen and platelets in ovarian masses was assessed.

A multivariate logistic regression model was performed to identify an independent association.

Inclusion criteria

All patients 18 yrs and above with adnexal masses were included.

Exclusion criteria

Exclusion criteria were patients with history of other malignancies, myeloproliferative disease, inflammatory disease, splenectomy, known congenital thrombophilia, ongoing anticoagulant treatment, pregnancy, stroke or neurosurgery within last 6 months were excluded to remove any cofounding variables.

The stage of malignancy was confirmed histopathologically in all patients and FIGO stage allotted.

Levels of plasma fibrinogen were measured using ALL 300(top), platelet by using automated CBC machine and cancer antigen 125 (CA-125) levels were measured using the ROCHE, COBAS PRO, ECLIA-electric chemiillumination kit. Other blood tests, plasma prothrombin time, activated partial thromboplastin time, Human epididymis 4(HE4) etc was determined by standard methodology.

Statistical analysis

Differences of fibrinogen and platelet level among groups were analysed by one-way analysis of variance. Differences in fibrinogen level and platelet count between the two groups (benign vs malignant) were evaluated by the Student's t-test. Differences in fibrinogen level and platelet count between the two groups (early vs advanced stage) were evaluated by the Student's t-test. The correlation between the levels of plasma fibrinogen, platelet count and stage of disease was evaluated. The correlation between the levels of plasma fibrinogen and plasma CA-125 was evaluated with Pearson's correlation test. A P-value <0.05 was considered to be statistically significant.

Statistical analysis

Statistical analysis was performed using SPSS 16.0 software. Unpaired t-test was used to analyze continuous data. Categorical data was compared using Chi-square test. P<0.05 was taken as statistically significant. Relative risk was calculated for abnormal UA PI, UA RI, UA S/D, MCA PI and cerebral-umbilical PI ratio. Multivariate regression was used to analyze effect of multiple variables.

RESULTS

Total 211 patients with adnexal masses were included. The overall incidence of ovarian tumors in our hospital was 24.17%. Disease prevalence in pre-menopausal was 17.13% and 47.6% in postmenopausal patients. 160 (75.83%) patients were diagnosed as malignant ovarian tumors and 51 (24.17%) were benign.

Epithelial ovarian malignancy was found in 146 patients (91.25%), serous in 138 (94.52%) patients, mucinous in 6 (3.75%), borderline ovarian tumors in 6 (3.75%), small cell carcinoma in 2 (1.25%), and 1 (0.62%) patient each with endometriod carcinofibroma, Brenner tumour and sertoli leydig cell tumor and teratoma with squamous transformation 5 (3.12%).

Metastatic tumors were found in 9 (17.65%). Benign tumours were as follows: benign haemorrhagic/complex cyst cyst: 18 (35.30%), teratoma: 10 (19.61%), kochs (tuberculosis) 9 (17.65%), serous/benign cystadenoma: 4 (7.84%), cystadenofibroma/fibroma: 2 (3.91%), and endometriosis: 2 (3.91%).

The mean age 44.1 and 50.4 years in benign and malignant cases respectively. Of the 211 patients studied, 142 were postmenopausal (67.3%) and 69 (32.7%) were premenopausal (Table 1).

Table 1: Pre-operative characteristics 211 pts with adnexal masses.

	HPR					
	Benign			Malignant		
	No	Mean	SD	No	Mean	SD
Age	51	44.1	13.6	160	50.4	12.9
CA_125	51	145.33	292.07	160	975.83	1740.89
HE4	51	104.82	158.03	160	863.50	1292.72
ROMA	51	23.5	28.2	160	72.3	31.6
Platelets	51	348.5	98.7	160	468.4	180.0
Fibrinogen	51	301.6	80.6	160	421.4	126.5

Table 2: Levels of fibrinogen, platelets in benign and malignant ovarian masses.

Total -211	Fibrinogen in mg/dl		Platelet in $10^3/mm^3$	
	<360 (%)	>360 (%)	<400 (%)	>400 (%)
Benign- 52	40 (77)	12 (23)	39 (75)	13 (25)
Malignant -159	48 (30.18)	111 (69.8)	53 (33.34)	106 (66.66)
Premenopausal	40 (58)	29 (42)	33 (47.83)	36 (52.17)
Post-menopausal	48 (33.8)	94 (66.5)	59 (41.55)	83 (52.17)

Fibrinogen was elevated in 94 (66.5%) postmenopausal patients and 29 (42%) in premenopausal patients. Platelets were elevated in 83 (52.17%) postmenopausal patients and 36 (52.17%) in premenopausal patients (Table 2).

Using the fibrinogen levels along with serum platelets, Ca 125, HE4 and ROMA- a prediction was made as to whether the ovarian mass will be malignant or benign depending on our investigation values. The prediction was then confirmed with final histopathology acquired either from biopsy or from final histopathology after primary surgery.

In our study, predictive assessment 60 out of 211 (28.44%) were benign and 151 (71.56%) were predicted malignant. On final histopathology, 38 0f 60 predicted benign cases (63.33%) were confirmed benign, whereas 22 (36.67%) turned out to be malignant. Similarly 138 of 151 predicted malignant cases (91.4%) were confirmed to be malignant, and 13 (8.61%) turned out to be benign (Table 3).

Table 3: Relation between study results and final histopathology.

Study result HPR cross tabulation				
	HPR			Total
	Benign (%)		Malignant (%)	
Result	Benign	38 (63.33)	22 (36.67)	60
	Malignant	13 (8.61)	138 (91.4)	151
Total	51		160	211

The levels of plasma fibrinogen in patients with advanced stages ovarian carcinoma were significantly higher than for benign patients (P<0.05). The levels of plasma fibrinogen in patients with stage III and stage IV ovarian carcinoma were significantly higher than those in patients with stage I and II ovarian carcinoma (P<0.05), but there was no statistically significant difference in the fibrinogen level between patients with stage III and stage IV.

The levels of platelets was significantly higher in patients with advanced stage ovarian tumors as compared to benign cases (p 0.005). The higher platelet count was associated with increased association with thrombogenic episodes, presenting as deep venous thrombosis in patients with stage III C and above (Table 4).

Table 4: Levels of fibrinogen, platelets in early and advanced ovarian malignancy.

Total -211 (%)	Fibrinogen in mg/dl (%)		Platelet in $10^3/mm^3$ (%)	
Malignant- 160	<360	>360	<400	>400
Early -47 (22.27)	41 (87.23)	06 (12.77)	30 (63.83)	17 (36.17)
Advanced -11 3(53.55)	01 (0.9)	112 (99.1)	16 (14.16)	97 (85.84)

Table 5: Statistics.

	Hyperfibrinogenemia (%)		Thrombocytosis (%)	
Statistic	**Value**	**95% CI**	**Value**	**95% CI**
Sensitivity	74.51	60.37 to 85.67	76.47	62.51 to 87.21
Specificity	86.25	79.93 to 91.18	61.25	53.24 to 68.84
Disease prevalence	24.17	18.56 to 30.52	24.17	18.56 to 30.52
Positive predictive value	63.33	53.16 to 72.44	38.61	32.94 to 44.61
Negative predictive value	91.39	86.86 to 94.46	89.09	83.06 to 93.15

On statistical analysis, sensitivity was 74.51%, specificity 86.25%, positive predictive value (PPV) 63.33%, negative predictive value (NPV) 91.39%, and accuracy was 83.41% for the plasma fibrinogen level as tumor marker for assessment of ovarian tumor. Similarly for platelet values, sensitivity was 76.47%, specificity 61.25%, positive predictive value (PPV) 38.61%, negative predictive value (NPV) 89.09%, accuracy 64.93% (Table 5).

A linear correlation was found between the levels of plasma fibrinogen and plasma CA125 in patients with stage II and above ovarian carcinoma. A Pearson chi square test was utilised (P 0.002). No such relationship was found in patients with early stage of ovarian carcinoma (Table 6).

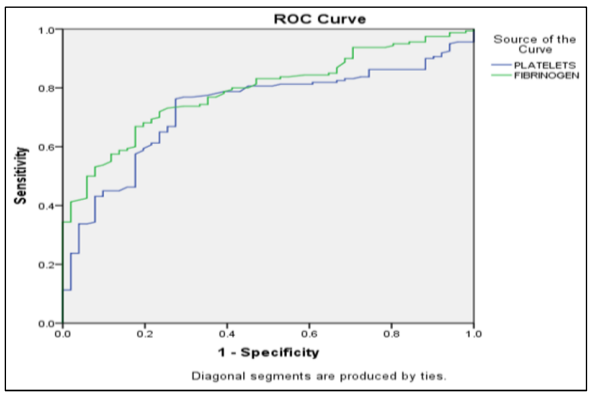

Figure 1: Area under the curve.

Table 6: Correlation of level of plasma fibrinogen and plasma CA 125.

Chi-Square tests			
	Value	**df**	**Asymp. Sig. (2 sided)**
Pearson Chi-square	31368.667[a]	30646	0.002
Likelihood ratio	2068.480	30646	1.000
Linear-by-linea association	5.311	1	0.021

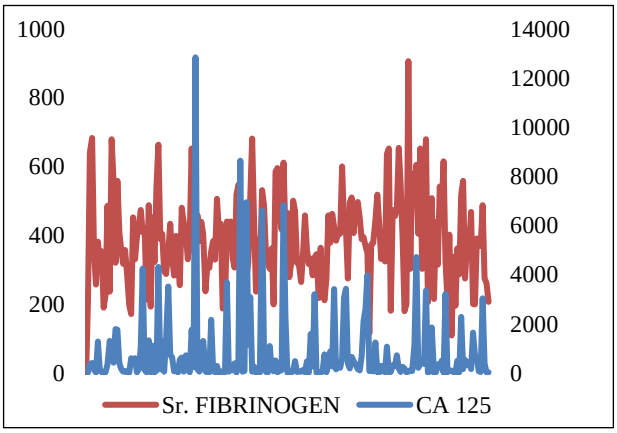

Figure 2: Positive correlation between CA125 and fibrinogen.

On assessment of relationship of fibrinogen with final HPR using binary logistic regression, in benign cases the marginal percentage was 24.2%, whereas in malignant cases it was 75.8%.

There were no differences in the plasma fibrinogen levels of patients with different BMI, age and pathological type.

DISCUSSION

Adnexal masses are commonly found in women of all ages and whether or not to surgically explore them is a critical decision to make. Ovarian cancer makes up 25-30% of all cases of cancers in the females after breast cancer with highest mortality rate in oncological gynaecology. Surgical intervention carries the risk of removing one or both the ovaries which may be detrimental in women in the reproductive age group. Accurate prediction of the risk of having a malignancy or not could help avoiding wrongful treatment, as well as it could facilitate timely referral to higher centres for expert care.

Various scoring systems have been investigated to pre-operatively estimate the risk for malignancy in patients with adnexal masses, two of which have been approved by the FDA. The ROMA incorporates measurements of CA-125 and HE4 along with the menopausal status of the patient. ROMA demonstrated a highly favourable sensitivity and specificity of 93.8% and 74.9%, respectively in diagnosis of ovarian carcinoma.[24] Several other studies have been performed reporting partly divergent results. The second test approved by the FDA, OVA1 ovarian triage test, combines a panel of five biomarkers for ovarian cancer (CA125, transthyretin, apolipoprotein A1, ß2-microglobulin, and transferrin). The OVA1 test has a sensitivity and specificity of 93% and 43%, respectively, with a PPV of 42% and a NPV of 93%.[20]

The IOTA study group utilised standardised ultrasound examination protocols and definitions for developing and validating diagnostic models for adnexal masses.[9,10] A meta-analysis, comparing various ultrasound-based prediction models for OC, suggested the IOTA group's models Logistic Regression (LR) 2 and Simple Rules (SR) to have the strongest test performance.[21] transvaginal ultrasound is the key tool in daily practice for evaluating adnexal masses, it is subjective and its performance is dependent upon the experience and skills of the examiner. Due to lack of training occasionally, and shortage of time, risk assessment based only on a subjective evaluation of ultrasound and, eventually, on pre-operative CA-125 measurement.

Seebacher et al evaluated and developed a tool development for prediction of ovarian cancer in patients with adnexal masses using plasma fibrinogen, where a nomogram was generated to predict the probability of ovarian cancer (Figure 1).[22] A nomogram is a prediction tool that incorporates various risk factors with the attempt to quantify the individualized probability of an outcome using a continuous risk scale. The graphic depiction of the probability of a particular outcome on a continuous scale, which is usually 0-100%, thereby provides a user-friendly interface, which does not require computer software for interpretation. In both uni and multivariate logistic regression analyses, plasma fibrinogen >342 mg/dl, CA125 >35 kU/L, postmenopausal status (or age >50 years), and the presence of M-criteria on ultrasound were independently associated with a higher risk for the presence of OC. These four variables formed the basis for the nomogram (Figure 1). Internal validation with split-sample analysis was performed. Decision curve analysis (DCA) was then used to evaluate the clinical net benefit of the prediction model. The overall predictive accuracy of the model, as measured by AUC, was 0.91 (95% CI 0.87–0.94).[22]

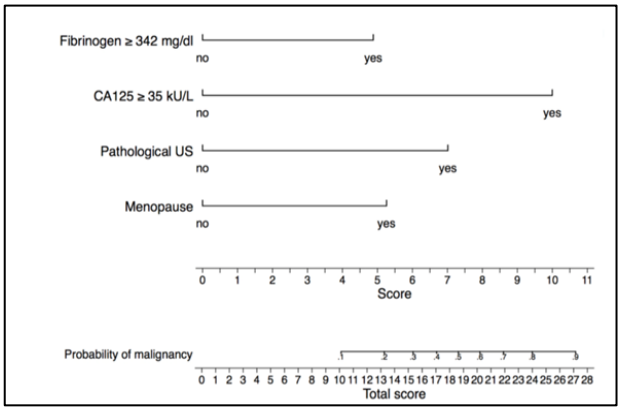

Figure 1: Nomogram to predict ovarian cancer in patients with adnexal masses.

(To use the nomogram, locate the patient's variable on the corresponding axis; draw a line to the "score" axis, sum the scores, and draw a line from the "total score" axis to the "probability of malignancy" axis).

Hefler-Frischmuth et al studied plasma fibrinogen levels in patients with benign and malignant ovarian tumors, also investigated the predictive role of plasma fibrinogen to distinguish between benign and malignant ovarian tumours a logistic regression model, was derived where patients' age, serum CA-125 (< vs >35 kU/L) and plasma fibrinogen were included.[23] Plasma fibrinogen levels were found to be an independent predictor for the presence of a malignant ovarian tumor and might serve as additional differential diagnosis parameter especially in the subgroup of patients <50 years.

Feng et al studied the role of thrombocytosis and hyperfibrinogenemia as predictive factors of clinical outcomes in high-grade serous ovarian cancer patients.[25] Qui et al studied the preoperative plasma fibrinogen, platelet count and prognosis in epithelial ovarian cancer and found a positive corealtion between the factors and diagnosis and prognosis of ovarian tumors.[21]

Compared to the results of the ROMA and OVA1 test, the accuracy of this model was relatively similar though clinical trials is lacking validity. An advantage of this model is the measurement of serum fibrinogen, which is readily available and cheap to perform, while the FDA approved tests are costlier.[22]

Approximately 20 to 30 % of ovarian cancer patients have preoperative thrombocytosis, and approximately 40% of patients have preoperative hyperfibrinogenemia. Cancer is a prothrombotic state, the bidirectional link between cancer and thrombosis observed in various epidemiological studies is well recognized. Recently, blood coagulation proteins have been proposed to play a role in cancer progression. Abnormalities of platelets or blood coagulation factors, such as factor III, factor VIIa factor IIa (thrombin)-factor II receptors and factor XIIIa-factor Ia (fibrin), have been described in various malignancies.

Our study evaluated and confirmed the value of pre-operative plasma fibrinogen and platelet level as a strong predictor for ovarian malignancies in a big cohort of patients with adnexal masses. Pre-operative fibrinogen and platelet were associated with ovarian carcinoma in uni and multivariate analyses that adjusted for the effects of menopausal status, serum HE4 and elevated plasma CA-125(used to calculate ROMA).

Thrombocytosis was more frequently found in stage III and IV cancers. Patients with thrombocytosis were found to have shorter survival periods and shorter time free from disease. Thus the grounds for measuring platelet count before the primary surgical intervention, and suggesting that the platelet count should be included in the panel of diagnostic factors for patients with ovarian tumours.

In previous studies, it was shown that the coagulation system may be affected by many factors, such as age, obesity, ABO blood group and the pathological type of malignant disease.[23,24] In our study, no association between fibrinogen and pathological type, age, BMI or blood group was found.

CONCLUSION

Preoperative thrombocytosis and hyperfibrinogenemia reflected tumor burden and thus useful in diagnosis and influencing treatment outcomes. Strengths of our study include the single institution uniform approach to management, relatively large sample size, an easily procurable investigation and a simplified approach to diagnosis. These finding shall be helpful in primary care, for GPs and practitioners at peripheries, who attend patients with adnexal masses at primary level who receive blood test results unexpectedly showing high platelet counts. Addition of a simple other blood test like fibrinogen and CA125 can be utilised for prediction of malignancy. Further research is needed to identify the cancers that are most strongly associated with thrombocytosis and hyperfibrinogenemia.

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