Original Article

Role of D-dimer and CA-125 in the Detection of Ovarian Malignancy

Roshini Shekhar[1], Ganga S Pilli[2], Ramadevi V Wani[3], Mrityunjay C Metgud[4]

Aims and Objectives : The aim of our study was to analyze the role of D-dimer and CA-125 in the pre-operative diagnosis of ovarian malignancy and understand its significance.

Materials and Methods : The present prospective study was carried out on patients with ovarian tumors for a period of one year at the department of pathology. A total of 40 cases were studied. Demographic data, a thorough history and clinical findings were recorded in a pre-designed format. D-dimer and CA-125 levels were estimated in the blood samples. Histopathological study was carried out on the operated ovarian neoplasms in all the patients. D-dimer value <0.3 mg/L and CA 125 value ≤35 U/ml were considered normal. Statistical analysis was done using the Chi-square test and student's t-test. A probability value 'p' of ≤0.05 was considered statistically significant.

Results : Out of 40 patients, 24 patients had benign tumours and 16 had malignant tumours. As regards the prediction of malignancy D-dimer showed a sensitivity of 81.25% and specificity of 62.5% and CA-125 showed a sensitivity of 50% and specificity of 87.5%.The association between D-dimer and CA-125 showed a 'p' value of 0.036 thus suggesting that D-dimer is useful in diagnosing ovarian cancer. Compared to CA125, D-dimer was found to be a more sensitive predictor of ovarian malignancy.

Conclusion : Sensitivity for detecting ovarian malignancy was better with D-dimer than with CA-125. D-dimer levels also co-related with the advancing stage of ovarian malignancy. Hence, this marker may be used as a diagnostic as well as a prognostic marker in ovarian malignancy.

[*J Indian Med Assoc* 2023; **121(10):** 28-31]

Key words **: Ovarian Tumours, Ovarian Malignancy, Ovarian Carcinoma, D-dimer, CA-125.**

Ovarian malignancy is the eighth most common cancer among women worldwide[1] and third most common among Indian women[2] accounting for 6.7% of all cancers. The majority of ovarian cancers (90%) are derived from epithelial cells and cancers from germ cells and sex cord-stromal cells comprise the reminder[3]. If diagnosed and treated in stage I the survival is more than 90%. But most patients are only diagnosed in the advanced stage which is associated with poor survival (5-year survival of 27% for stage III and 17% for stage IV)[4]. Thus, to improve survival, it is important that ovarian canceris detected in the early stage. It is difficult to diagnose ovarian cancer in its early stages, as it may be asymptomatic or present with vague complaints like pain abdomen, bloating, loss of appetite etc, which can be confused with other common benign conditions. Hence, several biomarkers are used in an attempt to distinguish between benign and malignant epithelial ovarian tumours and to detect ovarian malignancy in the early stage.

Editor's Comment :

- Our study showed sensitivity for detecting ovarian malignancy to be better with D-dimer than with CA-125. However, larger studies are required for confirmation.
- D-dimer levels can be used as a prognostic marker as the levels co-related with the advancing stage of ovarian cancer.

Aims and Objectives

CA-125 is extensively used as a tumour marker for the detection of epithelial ovarian cancer. However, it is also elevated in certain physiologic conditions like menstruation and pregnancy and certain benign conditions like fibroids, endometriosis, pelvic inflammatory diseases, etc leading to false positive results[5]. It is raised in just 50% of Stage-1 epithelial ovarian cancer and 75-90% of patients with advanced disease[6]. Therefore, it is not a suitable biomarker for the early detection of ovarian epithelial cancer. The search for reliable tumour markers continues. Of late the role of hemostatic markers is being studied. Tumour cells secrete procoagulant/ fibrinolytic substances in addition to other factors resulting in a state of

[1]MD, Consultant Pathologist, Department of Pathology, Manipal Hospital, Bangalore, Karnataka 560017

[2]MD, Professor and Head, Department of Pathology, KLE JGMM Medical College, Hubballi, Karnataka 580028 and Corresponding Author

[3]MRCOG, Consultant, Department of Obstetrics & Gynaecology, KLE's Dr Prabhakar Kore Hospital & Medical Research Centre, Karnataka 590010

[4]MD, Professor, Department of Obstetrics & Gynaecology, KLE's Dr Prabhakar Kore Hospital & Medical Research Centre, Karnataka 590010

Received on : 27/12/2022
Accepted on : 25/06/2023

hypercoagulation and fibrinolysis in patients with cancer, especially in the advanced stage. D-dimer, a signal of activated coagulation and an end product of fibrinogen is elevated in many cancers[7]. Few studies have found that the D-dimer level is increased significantly in patients with ovarian cancer[8,9]. To explore further we took up this study. The aim of our study was to evaluate the role of D-dimer and CA-125 in the pre-operative diagnosis of ovarian cancer and understand its clinical significance.

Materials and Methods

The present study was carried out on patients with ovarian tumours for a period of one year in the Department of pathology of a reputed Medical College with its attached Tertiary Care Hospital. All pre-operative patients presenting with an ovarian mass detected by clinical examination and /or Ultrasonography were included in the study. The patients with pre-existing liver disease, inherited bleeding disorders, on anticoagulant therapy or oral contraceptives were excluded from the study.

A total of 40 cases were studied. Ethical clearance for the study was obtained from Institutional Ethics Committee on Human subjects Research. Written informed consent was obtained from the patients. Demographic data such as age, marital status, a thorough history of presenting complaints and significant past history were recorded in a predesigned and pre-tested proforma.

Blood samples for D-dimer and CA-125 were tested and a histopathological study of the ovarian tumour was done for all the patients. Plasma D-dimer estimation was done using Nyco Card assay. In the presence of D-dimer levels above 0.1 mg/L in the sample, the membrane appears reddish with a colour intensity proportional to the D-dimer concentration. The colour intensity was evaluated using Nyco Card reader. Blood samples for quantitative estimation of serum CA-125 were done using radioimmunoassay. Values <35U/ml were considered normal. Ovarian specimens in 10% formalin were grossly examined and findings were noted. The laterality, size, consistency, cystic and solid areas, necrosis, haemorrhage and papillae were evaluated and noted. Histopathology findings from the cyst wall, solid areas, papillae and any other suspicious appearing areas were studied.

Statistical analysis for correlation for categorical data was done by Chi-square test and correlation of continuous data was done by student's 't' test. A probability value 'p' of ≤ 0.05 was considered statistically significant.

Observations

The present one-year hospital-based prospective study was carried out on 40 patients with ovarian neoplasms detected pre-operatively by clinical examination/ultrasonography and confirmed by histopathology.

The age of patients (Table1) in our study ranged from 13-74 years. The mean age of presentation for malignant cases was 43.1±16.25 years and the most prevalent age group for ovarian carcinoma was >50 years accounting for 7 cases (17.5%). This was followed in descending order by 31-50 years with 6 cases (15%) and 0-15 years age group with 2 cases (10%) respectively and 16-30 year age group with 1 case (2.5%). The most common age group for benign tumours was 16-30 years (25%). The youngest patient with a malignant tumour was aged 13 years (mixed germ cell tumour) while the oldest was 74 years (mucinous cystadenocarcinoma).

D-dimer (Table 2) was raised in 22 patients (55%) and was normal in 18 (45%) patients. D-dimer was raised in 13 out of 16 patients with malignant tumours ie, 81.25% and was raised in 37.5% of patients with benign tumours. As regards the prediction of malignancy, the sensitivity was 81.25% and specificity was 62.5%. The positive predictive value was 59.09% whilst the negative predictive value was 83.33%.

CA-125 (Table 3) was raised in 11 patients (27.5%) and was normal in 29 (72.5%) patients. CA-125 was raised in 8 out of 16 patients with malignant tumours, ie, 50% and was raised in 12.5% of patients with benign tumours. Sensitivity was 50% and specificity was

Table 1 — *Age distribution of the study patients*

Age group (Years)	Distribution (n=40)			
	Benign	Malignant	Total	Percent
0-15	0	2	2	5
16-30	10	1	11	27.5
31-50	7	6	13	32.5
> 50	7	7	14	35
Total	24	16	40	100

Table 2 — *D-dimer levels in the study patients*

D-dimer levels	Distribution (n=40)			
	Malignant	Benign	Total	Percent
Raised (>0.3)	13	9	22	55
Normal (0.1-0.3)	3	15	18	45
Total	16	24	40	100

Table 3 — *CA-125 levels in the study patients*

CA-125 Level	Distribution (n=40)			
	Malignant	Benign	Total	Percent
Raised	8	3	11	27.5
Normal	8	21	29	72.5
Total	16	24	40	100

87.5%. The positive predictive value was 72.73% while the negative predictive value was 72.41%.

Therefore, an association exists between D-dimer levels and CA-125 levels (Table 4).

Out of 40 patients, 16 had malignant tumours and 24 had benign tumours. The most common benign tumour was serous cystadenoma, 11 patients (27.5%). Surface epithelial tumours were the most common group comprising 31 patients (77.5%). The most common malignant tumour was papillary serous cyst adenocarcinoma accounting for 6 patients (15%). 4 patients (10%) had germ cell tumours while 3 patients (7.5%) had stromal tumours and 2 patients (5%) had metastatic tumours (Table 5).

Discussion

Worldwide, in the year 2020, nearly 3,14,000 women were diagnosed with ovarian cancer and over 2,07,000 died from this disease[1]. In India, the age-adjusted incidence varies from 0.9- 8.4 per 100,000 women in various population-based registries[10]. Ovarian cancer has the worst prognosis among all the gynaecological malignancies. There is a continued search for tumour markers to detect ovarian cancer in the early stage, as it has a very good prognosis if detected in the early stages.

Table 4 — *D-dimer and CA-125 association*

		CA-125 Levels		
		Raised	Normal	Total
D-dimer Levels	Raised	9	13	22
	Normal	2	16	18
	Total	11	29	40

Kappa = 0.282 and p value= 0.036

Table 5 — *Distribution of the histological types of primary ovarian tumour*

Type	Number	Percentage
Benign (24)		
Serous cystadenoma	11	27.5
Mucinous cystadenoma	6	15
Mature teratoma	2	5
Granulosa cell tumour	2	5
Adenofibroma	1	2.5
Brenner's tumour	1	2.5
Mixed sero-mucinous adenoma	1	2.5
Malignant (16)		
Papillary serous cyst adenocarcinoma	6	15
Mucinous cystadenocarcinoma	2	5
Clear cell carcinoma	1	2.5
Endometrioid carcinoma	1	2.5
Transitional cell carcinoma	1	2.5
Malignant mixed Mullerian tumour	1	2.5
Dysgerminoma+yolk sac tumour	2	5
Metastatic adenocarcinoma	2	5

Ultrasonography and estimation of CA- 125 are the standard procedures to evaluate ovarian tumours for malignancy. However, CA-125 shows positive results in various benign gynaecological conditions and other cancers. It has low sensitivity and low specificity when used as a marker for the diagnosis of ovarian carcinoma. Al Musalhi K, *et al* in their study showed that CA-125 was raised in 69% of patients with malignant ovarian tumours[11]. Our study too showed a poor sensitivity of 50% in the detection of ovarian carcinoma.

A study by Worasthsin P and Narkwichian A[8] showed that the measurement of D-dimer and CA-125 were beneficial in differentiating benign from malignant ovarian tumours. In their study, D-dimer was better than CA-125, in differentiating benign from malignant ovarian tumours. Recently the meta-analysis by Wu J, *et al*[12] concluded that the plasma D-dimer level was higher in ovarian cancer patients compared to benign controls. Our study showed similar results to these studies. D- dimer was raised in 81.25% (13 out of 16 patients) of patients with malignant tumours, compared to the raised levels in only 37.5% of patients with benign tumours. In 3 patients with false positive D-dimer results, though there was no ovarian malignancy and they had a benign ovarian tumour, the raised D-dimer level directed to diagnose coexisting other malignancies (2 soft tissue sarcomas and 1 case of Fallopian tube adenocarcinoma).

In the present study, the association (kappa value) between D-dimer and CA-125 was 0.282 and the p-value was 0.036. Compared to CA-125, D-dimer is therefore a more sensitive predictor of ovarian malignancy. Similar findings were noted by Sakurai, *et al*. They also showed that D-dimer values are more sensitive in predicting advanced stages and prognosis than CA-125[13]. Several other studies[8, 14] also showed that the D-dimer levels positively correlated with FIGO classification. D-dimer is even more increased in patients with advanced ovarian cancer and metastatic malignant disease[11]. We had four patients with Stage IV ovarian carcinoma. These patients showed the highest D-Dimer levels with a mean value of 0.525 U/ml. Thus, our study results were concordant with these results.

Conclusion

Sensitivity for detecting ovarian malignancy is better with D-dimer than with CA-125. D-dimer levels also co-related with the advancing stage of ovarian cancer. Hence, this marker may be used as a diagnostic as well as a prognostic marker in ovarian malignancy.

References

1 Hyuna Sung, Jacques Ferlay, Rebecca L. Siegel, Mathieu Laversanne, Isabelle Soerjomataram, Ahmedin Jemal, Freddie Bray Global Cancer Statistics 2020; GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries CA CANCER J CLIN 2021; **71:** 209-49.

2 https://gco.iarc.fr>data>356-india-fact-sheets

3 Torre LA, Trabert B, DeSantis CE — Ovarian cancer statistics. CA: A Cancer Journal for Clinicians 2018; **68:** 284-96.

4 Cancer Research UK — Ovarian cancer survival statistics. https://www.cancerresearchuk.orghealth-professional/cancer-statistics/statistics-by-cancer-type/ovarian -cancer/survival# heading-Three (2018)

5 Miralles C, Orea M, Espana P — Cancer antigen 125 associated with multiple benign and malignant pathologies. *Ann Surg Oncol* 2003; **10:** 150-4.

6 Moss EL, Hollingworth J, Reynolds TM — The role of CA 125 in clinical practice. *J Clin Pathol* 2005; **58(3):** 308-12.

7 Siddiqui N A, Malik M, Wijeratne Fernando R — D-Dimer: a Potential Solutions to Problems of Cancer Screening, Surveillance, and Prognosis Assessment. *Cureus* 2021; **13(5):** e15064.

8 Worasethsin P, Narkwichean A — D-dimer as a tumour marker in the pre-operative assessment of adnexal masses. *J Med Assoc Thai* 2013; **96(11):** 1395-400.

9 Wu X, Xue X, Tang J, Cheng X, Tian W, Jiang R, *et al* — Evaluation of risk factors for venous thromboembolism in Chinese women with epithelial ovarian cancer. *Int J Gynecol Cancer* 2013; **23(1):** 65-72.

10 Murthy NS, Shalini S, Suman G — Changing trends in incidence of ovarian cancer- the Indian scenario. *Asian PAC J Cancer Prev* 2009; **10:** 1025-30.

11 Al-Musalhi k, Al-Kindi M, Ramadhan F, Al-Rawahi T, Al-Hatali K, Mula-Abed WA — Validity of cancer antigen -125(CA-125) and risk of malignancy index (RMA) in the diagnosis of ovarian cancer. *Oman Med J* 2015; **30(6):** 428-34.

12 Wu J, Fu Z, Liu G, Xu P, Xu J, Jia X — Clinical significance of plasma D-dimer in ovarian cancer: A meta-analysis. *Medicine (Baltimore)* 2017; **96(25):** e7062.

13 Sakurai M, Satoh T, Matsumoto K, Michikami H, Nakamura Y, Nakao S, *et al* — High pretreatment plasma D-dimer Levels areassociated with Poor Prognosis in Patients with Ovarian Cancer Independently of Venous Thromboembolismand Tumour Extension. *Int J Gynecol Cancer* 2015; **25(4):** 593-8.

14 Vahid Dastjerdi M, Ahmari S, Alipour S, Tehranian A — The comparison of plasma D-dimer levels in benign and malignant tumours of cervix,ovaryand uterus. *Int J Hematol Oncol Stem Cell Res* 2015; **9(3):** 107-11.