Original Article

Biochemical and Hematological Features in Ovarian Cancer

Prognostic Significance of Biochemical and Hematological Features with Ca^{125} in Newly Diagnosed Patients of Ovarian Cancer

Shahida Parveen[1], Rubaida Mehmood[2] and Kainat Warraich[1]

ABSTRACT

Objective: To investigate the significance of biochemical and hematological features with Ca125 in newly diagnosed patients of ovarian cancer.

Study Design: A prospective study

Place and Duration of Study: This study was conducted at the Multan Institute of Nuclear Medicine and Radiotherapy (MINAR) from July 2018 to September 2019 for a period of one and a half year.

Materials and Methods: One hundred females patients with age ranging from 18 to >56 years with persistent malignant ovary tumor (untreated) were involved in this study. All biochemical tests were performed in (MINAR) lab. SPSS version 24.0 was used for data analysis. One way ANOVA test was used to investigate the variation among the groups (age & stage). Associations of Ca125 with CBC, LFT and RFT were assessed by Spearman correlation before checking the Normality or Normal distribution by D'Agostino test. The level of statistical significance was set at $p<0.05$.

Results: Overall results showed the strong negative association of creatinine (r=-0.47, p=0.01) and positive association of eosinophil(r=0.40, p=0.03) with CA^{125}, while in age group-II positive association of PLT (r=0.62, p=0.01) with CA^{125} was calculated. In epithelial ovarian cancer there observed a significant negative association of Ca^{125} with MCV (r=-0.48, p=0.02) and also in seniors (age group-III, r=-0.76, p=0.03). Negative association of Ca125 was observed with RDWCV (r=-0.89, p=0.02) in stage-I, in stage-III negative association with MCV(r=0.66, p=0.02) while in stage-IV RBC indices RBC (r=0.76, p=0.01), HGB (r=0.67, p=0.03) and HCT (r=0.72, p=0.02) showed significant positive association with CA125.

Conclusion: Ca125 correlates with MCV in untreated epithelial ovarian cancer at senior age group and has no association in germ cell carcinoma. MCV and RDW-CV should be considered important diagnostic and prognostic factor in different stages of ovarian cancers.

Key Words: Bio-chemical parameters, Ca^{125}, Hematological parameters, Prognostic factor, RDW-CV.

Citation of article: Parveen S, Mehmood R, Warraich K. Prognostic Significance of Biochemical and Hematological Features with Ca^{125} in Newly Diagnosed Patients of Ovarian Cancer. Med Forum 2022; 33(2):11-14.

INTRODUCTION

Cancer antigen-125 (Ca^{125}) is repeating peptide epitope of the mucin-16 (MUC-16), and commonly used tumor marker in ovarian cancer diagnosis[1]. Ca^{125} promotes cancerous cell proliferation and suppresses anti-cancer immune responses.

[1.] Department of Obstet & Gynecol, Nishtar Medical University & Hospital, Multan.
[2.] Department of Diagnostics Labs, MINAR Cancer Hospital, Multan.

Correspondence: Dr. Shahida Parveen, Assistant Professor of Ward 17, Obstetrics & Gynecology Dept. Nishtar Medical University & Hospital, Multan.
Contact No: 0300-8631216
Email: shahidawahla@hotmail.com

Received: September, 2021
Accepted: November, 2021
Printed: February, 2022

About 90% ovarian cancer associated women have elevated level of Ca^{125} in their blood serum. Its level in serum is used to monitor the disease progression in response to chemotherapy in ovarian cancer. This biomarker is highly sensitive in advanced disease and useful as a detection tool to monitor the tumor load in epithelial ovarian cancer and for diagnosis of differential pelvic masses[2].

Ovarian cancer is the 8th most common cancer in women, causing 152,000 deaths annually around the globe[3]. Only 20% ovarian cancers are diagnosed in early stage while majority of cases are diagnosed at advanced stages (III and IV stages) and their 5-year survival rate is only 3–19%, while stage-I and stage-II patients have 5-year survival rates of 40–90%[4]. The poor survival rate due to late stage diagnosis, most cancerous patients remain asymptomatic until disease has metastasized[5]. Early stage detection of ovarian cancer is need for further treatment, which requires high sensitivity and precision screening tools. Ovarian cancer detection sensitivity could be improved via

hematological parameters studied through immunological serum marker Ca^{125}. CBC parameters are easily measured and inexpensive tool which can be potentially used in the diagnosis, prognosis, recurrence rates, and metastases in various types of cancer[6]. Recently published studies showed that inflammatory markers and some CBC parameters panel might have relationship with epithelial ovarian cancer[7]. Ovarian cancer patients have cellular abnormalities[8]. Hematological markers including white blood cells (WBCs) count is considered as prognostic factor for clinical outcomes and elevated platelets level, neutrophils and lymphocytes or neutrophils to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR) and thrombocytosis has been reported in epithelial ovarian cancer[9].

Previous studies showed that renal insufficiency is not always associated with elevated level of Ca^{125} during treatment for ovarian cancer. Impaired renal functions parameters at the diagnostic stage of malignant diseases have been linked with postoperative morbidity and impair survival. Serum creatinine considered as prognostic factor in colorectal cancer, urothelial, liposarcoma and multiple myeloma[10].

Through this study we are able to evaluate the association of Ca^{125} (tumor marker) level with CBC, LFT and RFT parameters in age-wise and stage-wise groups of ovarian cancer. The correlation of Ca^{125} with CBC and biochemical parameters can be recommended as important diagnostic and therapeutic tool at highest risk of treatment toxicity.

MATERIALS AND METHODS

This prospective study after the approval of a local ethical committee was carried out at Multan Institute of Nuclear Medicine and Radiotherapy (MINAR) from July 2018 to September 2019. One hundred females patients with age ranging from 18 to >56 years (mean age=45.31±12.28) having completed structured form concerning demographic characteristics with persistent malignant ovary tumor (untreated) and after informed consent were included in this study. Patients during treatment or chemotherapy and after surgery were not involved in this study. Further exclusion criteria patient not supplemented with other medications which affect ovary gland.

All blood samples of patients were taken in K2-EDTA vials (BD-Vacutainers for CBC analysis) and red top vials (for LFTs and RFTs parameters). Ca125 was measured with an electrochemiluminescence immunoassay (Hitachi Modular E411; Roche Diagnostics, Mannheim, Germany), routine hematology testing was performed on the MEK9100 Celltac G Hematology Analyzer and LFTs and RFTs were performed on chemistry analyzer (P-500 Diatron, Hungary).

SPSS version 24.0 (SPSS Inc., Chicago, IL, USA) was used for data analysis. One way Anova test was used to investigate the variation among the groups (age & stage). Associations of Ca^{125} with CBC, LFT and RFT were assessed by Spearman correlation before checking the Normality or Normal distribution by D'A gostino test. The level of statistical significance was set at $p<0.05$.

RESULTS

Total hundred (100) patients of un-treated ovarian cancer age ranging from 18 to >56 years, mean age ±SD (45.31±12.28) were involved in the study, and their Serum tumor marker (Ca^{125}), Hematological parameters (WBC, RBC, HGB, HCT, MCV, MCH, MCHC, PLT, RDW, PCT, MPV, and PDW), Liver function test (ALP, ALT, AST& Total Bill.), renal function tests (Urea &Creatinine) were monitored.

The comprehensive results of Ca^{125}, CBC, LFT and RFT parameters are shown in table 1. The significance of the differences between the groups was assessed by one-way ANOVA. Significant difference were observed in Creatinine (p=0.00) in age-wise groups. Whereas, significant difference were observed in MCV (p=0.01), MCH (p=0.04), PLT (p=0.03), PDW (p=0.03) and NEA (p=0.04) in the stage-wise groups.

Table No. 2 indicates the correlation of serum tumor marker Ca^{125} with CBC, LFT, and RFT parameters in overall patients, age-wise groups and stage-wise groups. In overall results of the patients, significant positive correlation was observed in EO (r=0.40, p=0.02). There was no significant association found in age group-1 (18-36 years). In age group-2 (36-56 years) strongly significant positive correlation was assessed in PLT (r=0.62, p=0.01), while in age group-3 (>56y) strong negative correlation was observed in MCV(r=-0.76, p=0.02).

Table No.1: Comprehensive Results (Age and stage wise parameters)

	Age-wise Groups				Stage- wise groups				
Parameters	**Group- 1 (18-35y)**	**Group- 2 (36-54y)**	**Group- 3 (55-69y)**	**P-value**	**Stage-1**	**State-2**	**Stage-3**	**Stage-4**	**P-value**
MCV	83.8±6.93	80.71±8.32	84.58±10.3	0.53	89.5±9.07	90.46±1.30	78.36±5.74	80.36±8.45	0.01
PLT	300.8±85.89	409.66±135.84	345.6±165.2	0.20	253.5±64.55	322.66±62.16	366.90±140.99	449.1±140.4006	0.03
PDW	17.85±1.27	17.84±0.93	17.98±1.34	0.95	18.61±1.16	17.6±0.72	18.24±0.92	17.18±0.98	0.03
NEA	59.01±13.09	63.30±9.16	65.51±13.88	0.54	55.98±8.74	54.93±8.83	69.57±9.6	62.08±11.93	0.04
CREAT	0.78±0.12	0.92±	1.155±0.21	0.00	1.09±0.31	1.05±	0.89±0.16	0.93±0.21	0.33
Ca125	1022.7±1616.2	307.36±	121.3±185.9	0.12	766.3±181.9.3	104.16±	205.92±442.36	556.52±627.08	0.57

Table No.2: Correlation Table of Ca-125 with CBC, LFT'S and RFT

Parameters	Overall results	Age-wise groups (Ca-125)			Stage-wise groups (Ca-125)			
		Group 1 (18-35y)	Group 2 (36-54y)	Group 3 (55-69y)	Stage 1	Stage 2	Stage 3	Stage 4
RBCs	0.10(0.59)	-0.46(0.29)	0.21(0.44)	0.31(0.45)	0.14(0.78)	-0.86(0.33)	-0.25(0.45)	0.75*(0.01)
HGB	-0.00(0.98)	-0.17(0.70)	-0.15(0.57)	0.21(0.61)	0.71(0.11)	-0.86(0.33)	-0.37(0.259)	0.67*(0.03)
HCT	-0.05(0.77)	0.09(084)	-0.24(0.37)	0.00(1.00)	0.42(0.39)	-0.86(0.33)	-0.45(0.16)	0.72*(0.01)
MCV	-0.28(0.12)	0.25(0.58)	-0.46(0.08)	-0.76*(0.02)	0.14(0.78)	-0.86(0.33)	0.66*(0.02)	-0.17(0.62)
RDWCV	0.13(0.46)	0.00(1.00)	0.38(0.15)	0.38(0.35)	-0.88*(0.01)	-0.86(0.33)	0.10(0.77)	0.16(0.65)
PLT	0.25(016)	0.46(0.29)	0.62*(0.01)	-0.12(0.77)	0.48(0.32)	-0.86(0.33)	0.07(0.82)	0.09(0.80)
EO	0.40*(0.02)	0.34(0.45)	0.3.5(0.26)	0.67(0.06)	0.81(0.05)	-0.50(0.66)	0.08(0.80)	0.59(0.06)
Creatinine	-0.465*(0.01)	0.37(0.468)	-0.43(0.104)	-0.51(0.192)	-0.60(0.285)	-0.866(0.333)	-0.34(0.297)	-0.49(0.150)

Significant negative correlation of Ca^{125} with RDW-CV (r=-0.88, p=0.01) was found in the stage-1. There was no significant correlation found in stage-2. At the stage-3 positive significant association was found in MCV (r=0.66, p=0.02), whereas in stage-4, strong positive correlation was observed in RBC (r=0.75, p=0.01), HGB (r=0.67, p=0.03) and HCT (r=0.72, p=0.01).

DISCUSSION

The ovary is an endocrine gland that is found in female reproductive system that produces ovum. Ovaries also produce female reproductive hormones (estrogen and progesterone) that play important role in the regulation and development of uterus. Ovarian cancer develops when errors occur in ovarian cells growth due to genetic abnormalities (mainly in NF1, BRCA1, BRCA2, and CDK12 genes) that cause them to grow excessively[11]. The production of excessive cells often forms a mass of tissue or tumor that start covering the outer lining of the ovaries however, some may form at the Fallopian tubes. Ovulatory dysfunction and excessive secretion of androgen and testosterone hormones may affect bone marrow cells[12]. Some tumor marker Ca125 protein released by some ovarian cancers, it circulates in the blood that may affect hematological and biochemical parameters. It is also important to evaluate the relationship between Ca^{125} with CBC, liver and renal functions affected by malignant ovarian cancer.

Our comprehensive results indicate that creatinine level increases significantly with the increase in age of ovarian cancer patients, as Lafleur et.al in 2018 proved that elevated serum level is associated with patient age, creatinine level increases as patient age increases[10]. He also proved that creatinine is very important bio-chemical parameter in ovarian cancer patients, it act as a prognostic factor of ovarian cancer.

PLT also positively correlated with age group-2 (36-56y). This interaction involves platelet adhesion, platelet activation and degranulation and antagonistic signals for the ovarian cancer that can potentially promote ovarian cancer cell metastasis[13]. Neutrophil counts may be considered as systemic inflammation markers in cancer[14]. Our results also confirmed that neutrophil level increase significantly with stage of disease in untreated ovarian cancer patients similar to *Wang et al*[15]. PDW correlates with patient survival, and is an independent risk factor in cancer patients and MCH, RBC and MCV value deceases with the increase of disease stage in untreated patients similar to the study of Antonio et al[16].

Our results showed that Ca^{125} significantly positively correlate with EO and negatively correlate with creatinine in overall patients as shown in figure 2. Eosinophil are important blood circulating granulocytes residing in blood and tissues in the breast, gastrointestinal (GI) and reproductive systems that are capable of phagocytosis associated with parasitic infections, inflammation and allergic reactions and previous studies observed that eosinophil level increased in oral squamous, prostate, colorectal, breast, cervical and ovarian cancer[17-18] . There also have been proved that Eosinophil is higher in malignant tumors as compared to benign. In this study, it has been proven that creatinine has a strong negative association with Ca125 conversely, a study proved that in female dialysis patients Ca125 have no association with creatinine levels although Ca^{125} act as an important parameter in dialysis patients. However they correlate their parameter with Ca125 in dialysis patients whereas we correlate clinical parameters with Ca125 in untreated ovarian cancer patients[19].

CONCLUSION

The correlation of Ca125 with different hematological and bio-chemical parameters in all groups age-wise along with different stages is recommended as an important diagnostic tool in untreated ovarian cancer patients. The strongly significant negative association of RDW-CV with Ca^{125} at stage-I should be considered as novel diagnostic and prognostic marker for the detection of ovarian cancer in early stages.

Acknowledgements: The authors acknowledge with thanks to MINAR Cancer Hospital (Multan, Pakistan) in order to conduct study in the hospital and provide instrumental assistance for performing CBC and others Biochemical tests.

Author's Contribution:

Concept & Design of Study: Shahida Parveen

Drafting:	Rubaida Mehmood,
Data Analysis:	Kainat Warraich
Revisiting Critically:	Shahida Parveen, Rubaida Mehmood
Final Approval of version:	Shahida Parveen

Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

1. Zhang M, Cheng S, Jin Y, Zhao Y, Wang Y. Roles of CA125 in diagnosis, prediction, and oncogenesis of ovarian cancer. Biochimica et Biophysica Acta (BBA)-Rev Cancer 2021:188503.
2. Zhang L, Chen Y, Wang K. Comparison of CA125, HE4, and ROMA index for ovarian cancer diagnosis. Cur Probl Cancer 2019;43(2):135-44.
3. Shin KH, Kim HH, Kwon BS, Suh DS, Joo JK, Kim KH. Clinical usefulness of cancer antigen (CA) 125, human epididymis 4, and CA72-4 levels and risk of ovarian malignancy algorithm values for diagnosing ovarian tumors in Korean patients with and without endometriosis. Annal Lab Med 2020;40(1):40-7.
4. Rosen DG, Wang L, Atkinson JN, Yu Y, Lu KH, Diamandis EP, et al. Potential markers that complement expression of CA125 in epithelial ovarian cancer. Gynecol Oncol 2005;99(2):267-77.
5. Sabatier R, Calderon B, Lambaudie E, Chereau E, Provansal M, Cappiello MA, et al. Prognostic factors for ovarian epithelial cancer in the elderly: a case-control study. Int J Gynecol Cancer 2015; 25(5).
6. Bakacak M, Serin S, Ercan Ö, Köstü B, Bostancı MS, Bakacak Z, et al. Utility of preoperative neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios to distinguish malignant from benign ovarian masses. J Turkish German Gynecol Assoc 2016;17(1):21.
7. Chen X, Yao G, Liu J. Prognostic value of pre-operative NLR, d-NLR, PLR and LMR for predicting clinical outcome in surgical colorectal cancer patients. Chinese J Immunol 2015; 1(10):1389-93.
8. Kim HS, Choi HY, Lee M, Suh DH, Kim K, No JH, et al. Systemic inflammatory response markers and CA-125 levels in ovarian clear cell carcinoma: a two center cohort study. Cancer research and treatment: Official J Korean Cancer Assoc 2016; 48(1):250.
9. Koulis TA, Kornaga EN, Banerjee R, Phan T, Ghatage P, Magliocco AM, et al. Anemia, leukocytosis and thrombocytosis as prognostic factors in patients with cervical cancer treated with radical chemoradiotherapy: a retrospective cohort study. Clin Transl Radiat Oncol 2017;4:51-6.
10. Lafleur J, Hefler-Frischmuth K, Grimm C, Schwameis R, Gensthaler L, Reiser E, Hefler LA. Prognostic Value of Serum Creatinine Levels in Patients with Epithelial Ovarian Cancer. Anticancer Res 2018;38(9):5127-30.
11. Jayson GC, Kohn EC, Kitchener HC, Ledermann JA. Ovarian cancer. Lancet 2014;384(9951): 1376-88.
12. Ucakturk A, Demirel F, Tayfun M, Tepe D, Elmaogullari S, Kara O. Complete Blood Count Parameters in Girls with Polycystic Ovary Syndrome. ESPE Abstracts 2014;4: 82.
13. Egan K, Crowley D, Smyth P, O'Toole S, Spillane C, Martin C, et al. Platelet adhesion and degranulation induce pro-survival and pro-angiogenic signalling in ovarian cancer cells. PloS one 2011;6(10):e26125.
14. Agarwal A, Hiral MP, Raychaudhuri S, Agarwal C, Bajaj A, Menia R. Hematological Inflammatory Parameters: Can They Play a Role as Cancer Biomarkers? Inter J Health Sci Res 2020;10(1): 18-23.
15. Qin Y, Wang P, Huang Z, Huang G, Tang J, Guo Y, et al. The value of red cell distribution width in patients with ovarian cancer. Med 2017;96(17).
16. Ma X, Wang Y, Sheng H, Tian W, Qi Z, Teng F, et al. Prognostic significance of thrombocytosis, platelet parameters and aggregation rates in epithelial ovarian cancer. J Obs Gynaecol Res 2014;40(1):178-83.
17. Jacobsen EA, Taranova AG, Lee NA, Lee JJ. Eosinophils: singularly destructive effector cells or purveyors of immunoregulation? J Allerg Clin Immunol 2007;119(6):1313-20.
18. Davis BP, Rothenberg ME. Eosinophils and cancer. Cancer Immunol Res 2014;2(1):1-8.
19. Wijayaratne D, Muthuppalaniappan VM, Davenport A. Serum CA125 a potential marker of volume status for peritoneal dialysis patients? Inter J Artific Org 2021;5:03913988211016862.