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CHI3L1 Overexpression In Different Types Of Ovarian Cancer

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Abstract : *Epithelial ovarian cancer contributes to a large proportion of mortality among all cancer in women due to late diagnosis at an advance stage. The present study was done on 40 ovarian cancer patients which include 35 patients wuth epithelial tumor, 3 patients with germ cell tumor, 2 patients with sex chord stromal tumor and 8 healthy controls. Objective was to test the usefulness of CHI3L1 for diagnosis of ovarian cancer at an early stage. CHI3L1 level (80.0-414.2 ng/ml) was significantly higher in ovarian cancer patients as compared control group (24.8-123.4 ng/ml). CHI3L1 level was also tested in different ovarian cancer types, histological subtypes of EOC and in different stage. Plasma levels of CHI3L1 was elevated in all histological sub types as 88% serous tumor patients, 80 % mucinous tumor patients and 60% undifferentiated tumor patients have elevated marker level. With increasing stage, percentage of patients having elevated CHI3L1 value also increased as it was elevated in 67% of patients in early stage whereas 85% of patients in advance stage have elevated CHI3L1 value.*

Keywords: *Biomarker, CHI3L1, Gynaecological malignancy, Ovarian Cancer, glycoprotein*

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I. Introduction

Ovarian cancer is the most common cause of cancer death associated with gynaecological malignancy. More than 70% of patients diagnosed with EOC had stage III or IV and the five year survival rate among these patients was approximately 30% [1]. The overall annual incidence of ovarian cancers is 17 cases per 10,000 women [2]. The proportion of ovarian cancer varied from 1.7 % to 8.7% of all female cancer in India during the period 2004 -2005, in various urban and rural population based registries operating under the network of the National Cancer Registry Program of Indian Medical Council Research [3].

CHI3L1 is a inflammatory glycoprotein and a member of mammalian chitinase like protein. It is produced by human embryonic stem cells. High CHI3L1 protein expression at cellular level was observed in embryonic tissue characterised by fast proliferation and differentiation. CHI3L1 is secreted by a type of human nonmalignant cells, including monoctes, macrophages and synovial cells [4,5]. CHI3L1 was highly expressed in many tumors such as breast cancer [6], cervical cancer [7], endometrial cancer [8], recurrent ovarian cancer [9], and epithelial ovarian cancer [10].

As high mortality in ovarian cancer is due to late diagnosis when tumor is in advance stage. So there is need of effective biomarker which can diagnose ovarian cancer at an early stage to reduce mortality. The present study has been conducted to analyse efficiency of CHI3L1 as biomarker for screening ovarian cancer at an early stage so that proper treatment can be followed.

II. Materials And Methods

2. Patients

Present study has been conducted on forty patients of ovarian cancer diagnosed from the Department of pathology, Pt. B.D Sharma university of health sciences, Rohtak. A written informed consent was obtained from patients before study entry which was approved by Institutional Human Ethical Committee. Out of 40 patients diagnosed, there were 35 cases of epithelial tumor, 2 cases of Sex chord stromal tumor and 3 cases of Germ cell tumor. The healthy control group consisted of 8 healthy female without cancer or joint, liver or endocrine disease. These patients were analysed for age, histological type and tumor stage.

2.2. Blood collection and plasma preparation

Five ml blood was taken in EDTA vacutainer from patients as well as from healthy controls, and centrifuged at 4 °c for 15 min at 1500 rpm. The plasma was then subdivided in to small aliquots and stored at -70ºc.

2.3. Analysis of CHI3L1 level

CHI3L1 concentration in plasma was determined using CHI3L1 ELISA kit (Thermo fisher scientific) according to manufacturers instructions. The standard curve was generated by plotting standard CHI3L1 conc. (ng/ml) on horizontal x axis and average absorbance on y axis. The protein CHI3L1 concentration were determined as absorbances using the Multiskan FC Microplate reader (Thermo fisher scientific). The mean, standard deviation and standard error of mean was calculated using microsoft excel. Box and whisker plot showing median,1st quartile, 3rd quartile and inter quartile rangewas generated using web tool R. Plasma CHI3L1 concentration was also classified as normal elevated.

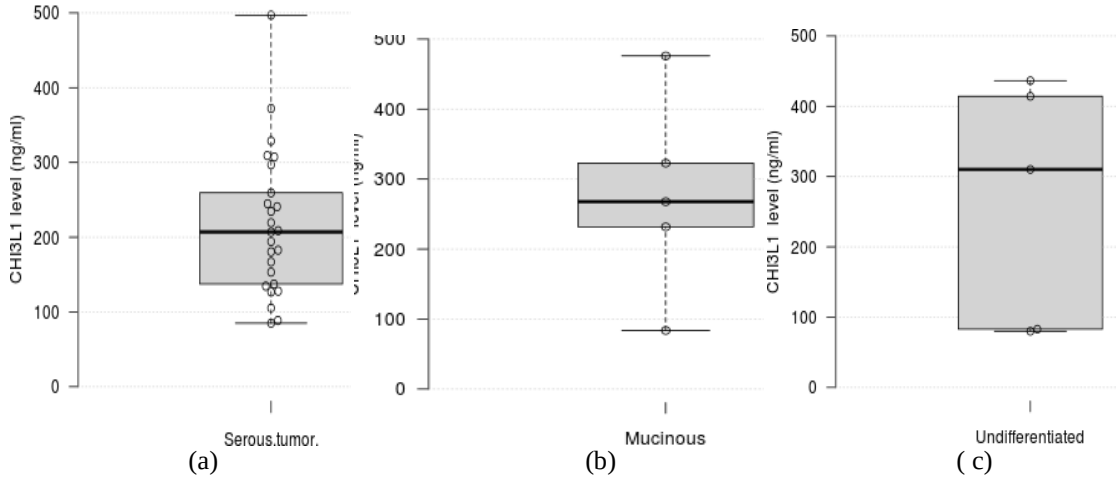
III. Results

Forty patients of ovarian cancer were studied in the present investigation, out of which 35(87.5%) cases of epithelial tumor, 3(7.5%) cases of germ cell tumor, 2(5%) cases of sex chord stromal tumor reported by histopathological analysis. Among the epithelial tumors , serous tumor were the most frequent 71%,followed by 14% mucinous and 14% undifferentiated carcinoma. Fifty eight percent patients were above 60 years of age (Table-1).

Table: 1. Ovarian cancer patient characterstics.

		N = 40	Percentage (%)
Age distributio	30-40	3	7
	41-50	5	13
	51-60	9	22
	61-70	13	33
	71-80	10	25
Histopathologic distribution	Epithelial tumors	35	87.5
	Germ cell tumors	3	7.5
	Sex chord stromal tumors	2	5
Epithelial ovarian cancer subtypes	Serous carcinoma	25	71.4
	Mucinous carcinoma	5	14.2
	Undifferentiated carcinoma	5	14.2

The First and third quartile for serous (Q1= 136, Q3 = 278.2), mucinous (Q1= 157.8, Q3 = 399.4) and undifferentiated were Q1= 81.45, Q3 = 425.3 and its interquartile range was 142.2 for serous, 241.6 for mucinous and 343.8 for undifferentiated (Fig-1). In case of epithelial ovarian cancer Q1, Q3 and IQR were 134.6, 309.2 and 174.6 where as in case of controls were 27.55, 105.3 and 77.8 (Fig-2).



(a) (b) (c)

Fig 1 Box and whisker plots showing median levels and the interquartile range (box) for histological subtypes of Epithelial ovarian cancer. The dots represent each individual patient plasma CHI3L1 values.

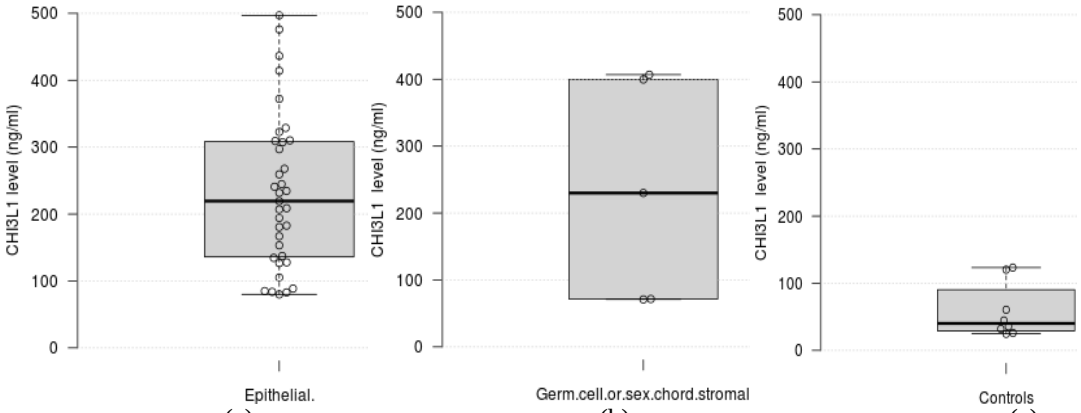


Fig 2 Box and whisker plots showing median levels and the interquartile range (box) for histological subtypes of ovarian cancer. The dots represent each individual plasma CHI3L1 values.

The mean and median CHI3L1 level in controls was 51 ng/ml and 58.1 ng/ml (range, 24.8 to 123.4 ng/ml) whereas in ovarian cancer mean and median value was 232.3 ng/ml and 214.0 ng/ml (range, 71.0 to 497 ng/ml) (Table-2).

Table: 2. Range of CHI3L1 plasma level in different groups.

	Subgroup	Size	Min (ng/ml)	Max (ng/ml)	Range	Mean
Controls		8	24.8	123.4	98.6	51.0
Patients	Epithelial	35	80.0	497	417	231.8
	Germ cell	3	71.0	399.7	328.7	653.3
	Sex chord	2	71.6	406.8	335.2	275

The CHI3L1 90th percentile value was 120.3 ng/ml for normal control group. The range of CHI3L1 for serous, mucinous, undifferentiated and control were 85-497, 83.8-476, 80-436.4 and 24.8-123.4 ng/ml. The standard deviation was 97.2, 142.4 and 173.9 for serous, mucinous and undifferentiated tumors whereas in controls is 32.4 (Table-3).

Table: 3. Descriptive statistics of CHI3L1 plasma level in different groups.

	Serous	Mucinous	Undifferentiated	All ovarian cancer	Controls
Size	25	5	5	40	8
Range	85-497	83.8-476	80-436.4	80-414.2	24.8-123.4
Mean	216.4	276.4	264.7	247.1	51.0
Median	207	267.8	310.2	454.2	58.1
90th percentile	328.8	476	436.4	414.2	120.3
SD	97.2	142.4	173.9	236.3	32.4
SEM	19.4	63.6	77.8	167.1	11.4

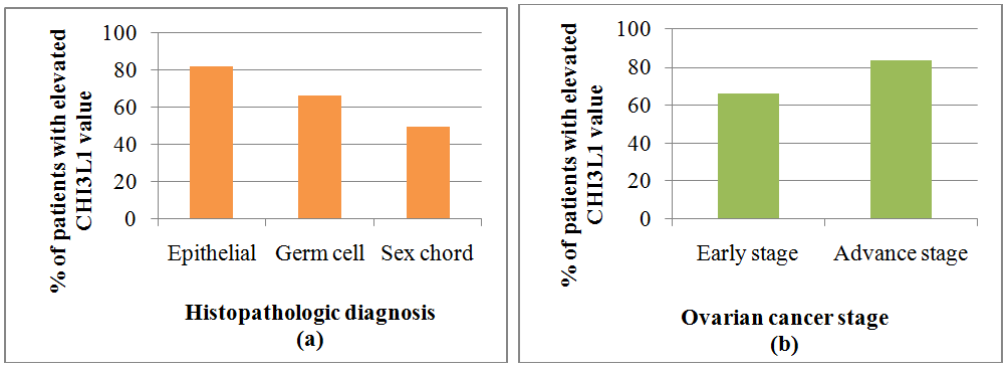


Fig 3: Percentage of patients having elevated CHI3L1 value in (a) epithelial, germ cell, sex chord stromal tumor types & (b) ovarian cancer stage

CHI3L1 plasma levels was elevated in all histologicsubtypes. It was elevated in 82% of patients with epithelial tumor, 66% of patients with germ cell tumor and 50% of patients with sex chord tumor [Fig 3(a)]. CHI3L1 plasma level have increased with increasing stage [Fig 3(b)]. CHI3L1 was above cut off level in 83.8% of advance stage patients whereas it was elevated in 66.6 % of early stage patients. Thirty five (87.5 %)

of the 40 patients in the study had epithelial ovarian tumor. CHI3L1 was elevated in 22 (88 %) of 25 patients with serous tumor and in 4 (80 %) of 5 patients with mucinous tumors. Sixty six percent patients of undifferentiated tumors have elevated CHI3L1 value [Table–4].

Table: 4. Preoperative serum CHI3L1 values for epithelial ovarian cancer histologic subtypes

Type of ovarian cancer	Total number of patients	Number of patients having elevated CHI3L1 value	Percentage of patients having elevated CHI3L1 value
Serous	25	22	88
Mucinous	5	4	80
Undifferentiated	5	3	60

IV. Discussion

It has been shown from various studies that incidence of ovarian cancer increase with increasing age [11]. In present study 56% patients were above 60 years of age. Sixty eight percent patients have been diagnosed in post menopausal study. As per literature most of patients diagnosed were in advance stage due to lack of effective early screening. Approximately 70% of ovarian cancer patients have advance stage at diagnosis [12]. In the present study 83% of patients were in advance stage.

CHI3L1 has been regarded as "cancer biomarker" for detecting malignant tumors [6,13]. This Human chitinase-like glycoprotein is known to be expressed in several types of solid tumors that include breast, colon , kidney, ovarian, prostate, endometrial cancer, malignant melanoma, glioblastoma, and hodgkin's lymphoma [14]. Level of circulating CHI3L1 is increased in many malignancies, including cancers involving the lung, prostate, colon, rectum, ovary, kidney, breast, glioblastomas, and malignant melanoma. Numerous studies have correlated elevated serum levels of CHI3L1 with poor prognosis and low survival in patients suffering from these malignancies [14]. Furthermore, in breast and colon cancer it was shown that increased CHI3L1 levels correlate with tumor grade and poor differentiation of cancer cells [15,16]. CHI3L1 plays an important role in prostate cancer progression [17]. Quantitatively, serum concentration of CHI3L1 have been reported to be increased by approximately 50 ng/ml in stageI/II and 200 ng/ml in stage III/IV colon cancer, respectively, compared to healthy controls [18]. The present study, CHI3LI was elevated in 80% of ovarian cancer patients, whereas only12% of controls have elevated CHI3L1. Plasma CHI3L1 values were elevated in all histological subtypes. It was elevated in 88% patients with serous tumor, 80% patients with mucinous tumor and 60% patients with undifferentiated tumor in the present study. Ubiquitous expression of CHI3L1 in a range of solid tumors, as indicator of early dissemination and lower overall survival, may at least partially be due to CHI3L1 - positive circulating tumor cells (CTCs). Therefore it should be investigated whether CHI3L1 constitutes a general CTC-associated marker and whether CTC counts parallel the plasma concentrations of this glycoprotein.

V. Conclusion

Ovarian cancer is leading cause of death from gynecological malignancy due to lack of effective screening marker at an early stage. Most of the ovarian cancer patients were diagnosed late when the disease is in advanced stage. So there is need to search effective biomarker which can detect it in early stage. CHI3L1 has good senstivity as it was elevated in 67% of early stage ovarian cancer patients. As CHI3L1 alone may not be independent factor therefore further research is required for combination of marker for diagnosis of early stage ovarian cancer .

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