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Evaluation of CA- 125 as a prognostic marker in patients with Non-Hodgkin's lymphoma

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Abstract
Background: Non-Hodgkin lymphoma (NHL) is a heterogeneous group of blood cancers that includes all types of lymphoma except Hodgkin's lymphomas. CA-125 is a protein that in humans is encoded by the MUC16 gene. The present study was conducted to assess the role of CA- 125 in patients suffering from non- Hodgkin lymphoma.
Materials &Methods: This study was conducted from year 2011 to 2015 on the patients visiting a tertiary care hospital in north India. It included 110 patients suffering from Non-Hodgkin's lymphoma. Patients were divided into two groups. Group I with CA-125 level < 35 U/ml and group II with CA-125 level > 35 U/ml. Complete blood count (CBC) and levels of urea, creatinine, calcium, total bilirubin, lactate dehydrogenase (LDH), aspartate transaminase (AST), and alanine transaminase (ALT) were collected. Viral markers such as hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), and human T-cell lymphoma virus (HTLV-I) were also evaluated for some of the patients. Serum CA-125 level was measured using chemiluminescence. The International Prognostic Index (IPI) was calculated. Staging of NHL was also assessed.
Results: Out of 110 patients, group I (CA- 125 level <35 U/ml) had 60 patients and group II (CA- 125 level >35 U/ml) had 50 patients. Relapse rate in group I and group II was 15.8% and 33.4% respectively. The mortality rate in group I was 10% and in group II was 28%. The difference was significant (P <0.05). Group I had 34 males and 26 females and group II had 28 males and 22 females. The difference was non – significant (P = 0.25). 60% in group I and 25% in group II had low IPI score. 8.5% in group I and 12.6% in group II had high IPI score. The difference was significant (P < 0.05). 55% in group I and 25% in group II had stage I, 33% in group I and 37% in group II had stage II, 10% in group I and 24% in group II had stage III and 2% in group I and 14% in group II had stage IV. The difference was significant (P < 0.05).
Conclusion: CA- 125 is a biomarker can be useful in evaluating prognosis in Non Hodgkin lymphoma patients and their response to treatment. It is a cost effective and non-invasive marker.

Keywords: CA-125, ELISA, Lactate dehydrogenase, Non Hodgkin lymphoma

1. Introduction
WHO classifies tumors of hematopoietic and lymphoid tissues into five major groups, including one for Hodgkin's lymphoma. The four groups for NHL includes Mature B-cell neoplasms, Mature T-cell and NK-cell neoplasms, Histiocytic and dendritic cell neoplasms, and Posttransplantation lymphoproliferative disorders (PTLDs). There are over 60 specific types of lymphoma in NHLs. Different types of NHL vary in severity, from indolent to aggressive lymphomas. [1]
Mature B cell NHLs constitute more than 85% of NHLs and can be histologically classified as Diffuse large B-cell lymphoma (DLBCL), Follicular lymphoma, Chronic lymphocytic leukemia (CLL) /small lymphocytic lymphoma (SLL), Mantle cell lymphoma (MCL), Marginal zone lymphomas, Burkitt lymphoma, Lymphoplasmacytic lymphoma (Waldenstrom macroglobulinemia), Hairy cell leukemia, Primary central nervous system (CNS) lymphoma etc. Symptoms include enlarged lymph nodes, fever, night sweats, weight loss, and tiredness. Other symptoms may include bone pain, chest pain, or itchiness. Some forms are slow growing while others are fast growing. [2]
Diagnosis is by examination of a lymph node biopsy. Medical imaging is done to help with cancer staging. Prognosis of NHLs depends on the histological type, stage of the disease.
CA-125 (carbohydrate antigen 125) also known as mucin 16 or MUC16 is a protein that in humans is encoded by the MUC16 gene. CA-125 has found application as a tumor marker or biomarker that may be elevated in the blood of some patients with specific types of cancers, or other conditions that are benign. CA-125 has been suggested to be used as a prognostic indicator for non-hodgkin lymphoma (NHLs). [3]
The present study was conducted to assess the role of CA-125 in patients suffering from non- Hodgkin lymphoma.

2. Materials & Methods
This study was conducted from year 2011 to 2015 on the patients visiting the hospital. It included 110 patients suffering from non hodgkin lymphoma. The old cases or patients already on treatment for NHL were excluded. All were informed regarding the study and written consent was obtained. Patient information such as name, age, gender etc was recorded.
Symptoms such as fever, sweating, and weight loss were recorded. Lymph node examination was also performed. Routine investigations like Complete blood count (CBC) and levels of urea, creatinine, calcium, total bilirubin, lactate dehydrogenase (LDH), aspartate transaminase (AST), and alanine transaminase (ALT) were collected. Viral markers

such as hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), and human T-cell lymphoma virus (HTLV-I) were also evaluated for some of the patients as viral markers have been found to be associated with some NHL.

The type and stage of NHL were determined as per World Health Organisation (WHO) criteria [5] on the basis of results of imaging, pathology, and immunohistochemistry. Serum CA-125 level was measured using chemiluminescent assay on ADVIA Centaur (Siemens, USA). The International Prognostic Index (IPI) [1] based on age, performance status, stage, extranodal involvement and LDH levels was calculated. Patients were divided into two groups, Group I with CA-125 level < 35 U/ml and group II with CA-125 level > 35 U/ml.

Results were subjected to statistical analysis by using SPSS version 16 (SPSSv.16, USA). Non-parametric Mann whitney U test was performed to determine the statistically significant difference between the means of two groups i.e. group I with CA-125 level < 35 U/ml and group II with CA-125 level > 35 U/ml. Chi square test was performed to compare categorical data. P value < 0.05 was considered significant.

3. Results

The mean value of CA 125 was found to be 78.1± 12.6 U/ml. Table I shows that out of 110 patients, group I (CA- 125 level <35 U/ml) had 60 patients and group II (CA- 125 level >35 U/ml) had 50 patients. Relapse rate in group I and group II was 15.8% and 33.4% respectively. The mortality rate in group I was 10% and in group II was 28%. The difference was significant (P < 0.05). Table II shows that group I had 34 males and 26 females and group II had 28 males and 22 females. The difference was non – significant (P – 0.25). Fig I shows that 60% in group I and 25% in group II had low IPI score. 8.5% in group I and 12.6% in group II had high IPI score. The difference was significant (P < 0.05). Fig II shows that 55% in group I and 25% in group II had stage I, 33% in group I and 37% in group II had stage II, 10% in group I and 24% in group II had stage III and 2% in group I and 14% in group II had stage IV. The difference was significant (P < 0.05).

4. Discussion

CA-125 is a glycoprotein of approximately 200KDa molecular weight. CA125 has been found to be expressed by amniotic and coelomic epithelium of fetal tissue and mesothelial cells of the pleura, peritoneum and pericardium, female genital epithelia (tubal, ovarian, endometrial, and endocervical) and mucosal epithelia of gastrointestinal tract in adult tissues. It is a product of MUC 16 gene that promotes cancer cell proliferation and inhibits anti-cancer cell immunity[4].CA125 is a tumor associated antigen that is widely used as a tumor biomarker particularly in differentiating benign from malignant and response to treatment in epithelial ovarian cancer. It is detected using monoclonal antibodies OC125 and M11 against 2 epitopes of CA125, namely, A and B, respectively [5], However, elevation in serum CA-125 levels has also been reported in other conditions including gynaecological malignancies like endometrial adenocarcinomas, fallopian tube carcinoma, other malignancies like malignant mesotheliomas, carcinomas of pancreas, colon, breast and lung, and also non-malignant conditions like pregnancy, endometriosis, benign ovarian cysts, liver cirrhosis, pelvic inflammatory diseases etc. [6].

Non-Hodgkin's lymphomas (NHLs) are group of lympho proliferative malignant disorders. Various prognostic indicators based on tumor's growth and invasive potential, patient's clinical condition and response to therapy etc. have been used. [7] However, determination of a reliable serum biomarker is still not validated in NHL. CA 125 has been shown to be elevated in NHL by some studies and it is proposed that cytokines released by lymphoma cells activate mesothelial cells to secrete this glycoprotein. [8]

The present study was conducted to assess the role of CA-125 in patients suffering from non- Hodgkin lymphoma. The subjects were divided into two groups taking CA 125 value of 35U/ml as cut-off. In the present study, group I had 60 patients and group II had 50 patients. Relapse rate in group I and group II was 15.8% and 33.4% respectively. This is in accordance to Dilek *et al.* [9] who also showed CA 125 as a poor prognostic marker. IPI score in both groups were also compared. It was found that 60% in group I and 25% in group II had low IPI score. 8.5% in group I and 12.6% in group II had high IPI score. Similar finding were obtained in study by Memar *et al.* [6] In present study, the NHL stage was also evaluated. It was observed that 55% in group I and 25% in group II had stage I, 33% in group I and 37% in group II had stage II, 10% in group I and 24% in group II had stage III and 2% in group I and 14% in group II had stage IV.

In 2003, Bairey *et al.* [10] also showed that CA- 125 can be used as a reliable marker for staging and assessing tumor activity in NHL. However, contrary to the present study, a study by Bonnet *et al.* [11] showed limited usefulness of CA-125 in the prognosis of NHL

Zacharose [12] and colleagues showed an association of CA-125 with treatment failure and relapse. In another study by Brigen *et al.* [13], they showed return of elevated CA 125 levels after successful treatment.

5. Conclusion

CA- 125 as a biomarker can prove to be a reliable, cost effective, noninvasive method for evaluating prognosis in Non Hodgkin lymphoma patients and their response to treatment. It can help in determining the aggressiveness of NHL in conjunction with other clinical and pathological parameters.

Table 1: Distribution of patients

	Total – 110		
	Group I	**Group II**	**P value**
CA- 125 level	<35 U/ml	>35 U/ml	
Number	60	50	
Relapse rate	15.8%	33.4%	< 0.05
Mortality rate	10%	28%	

Table 2: Gender wise distribution

Group I		**Group II**		**P value**
Male	**Female**	**Male**	**Female**	
34	26	28	22	0.25

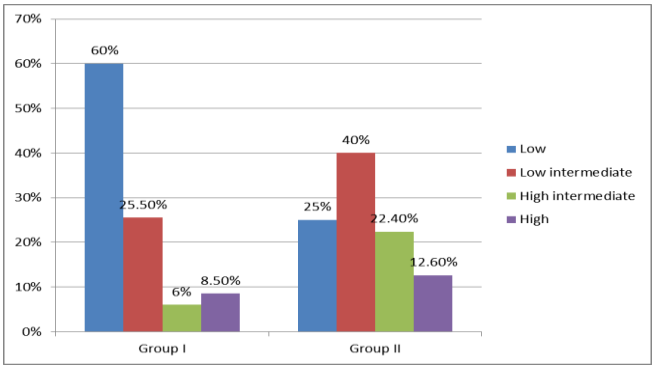

Fig 1: IPI scores

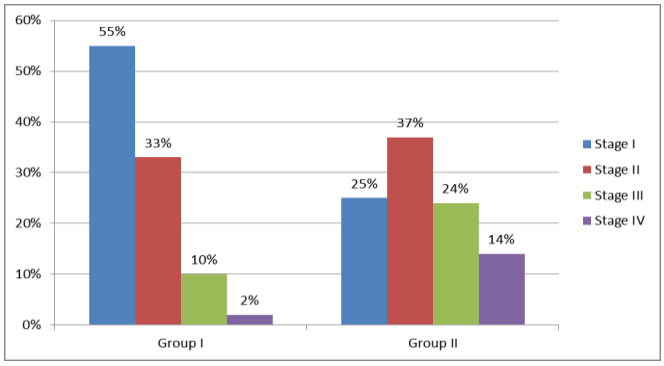

Fig 2: NHL staging

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