

## ORIGINAL ARTICLE

ASSOCIATION OF SERUM CA-125 LEVELS  
WITH NON-HODGKIN'S LYMPHOMA

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**Background:** Non-Hodgkin's lymphoma (NHL) is a common malignancy presenting to oncology out-patient departments. Several prognostic markers including lactate dehydrogenase (LDH), BCL-2 and beta-2 micro-globulin have been studied and have been found to be of significance. Serum CA-125 has been studied in the past and feeble but unclear association was found. The present study aims at finding an association between serum CA-125 levels and NHL. **Methods:** One hundred patients (90 males, 10 females) with histological diagnosis of NHL diffuse large B-cell type were enrolled in the study through convenience sampling method. After documenting the demographics (age, gender and performance status), staging investigations including bone marrow aspiration/trephine, CT scans, baseline haematology and biochemistry. Serum LDH and serum CA-125 levels were measured at diagnosis and completion of treatment. **Results:** Fifty-eight patients had normal serum CA-125 levels while 42 patients had raised levels. Patients with high CA-125 levels at baseline had higher international prognostic scores. These patients had poorer response to treatment. Raised CA-125 levels were found more frequently among patients who had ascites or pleural effusions due to lymphoma. **Conclusion:** Serum CA-125 level measurement before during and after treatment correlates with response to treatment and increasing levels following treatment completion can predict disease relapse ahead of time.

**Keywords:** Non-Hodgkin's Lymphoma, Serum CA-125, International Prognostic Index (IPI).

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## INTRODUCTION

Cancer antigen 125 (CA-125) is a 220 kDa glycoprotein expressed in normal tissues originally derived from coelomic Cancer epithelia such as peritoneum, pleura, pericardium, epithelium of the fallopian tubes, endometrium, endocervix, as well as other tissues of Müllerian origin.<sup>1,2,3</sup> Its antigenic determinant is identified by a monoclonal antibody, OC 125, raised against the epithelial ovarian cancer cell line OVCA 433.<sup>4</sup> Serum CA-125 is an established tumour marker for ovarian cancer and have been shown to be associated with disease progression or tumour recurrence.<sup>5,6</sup> They may also be elevated in other malignant and non-malignant conditions.<sup>7-9</sup>

Elevated serum CA-125 levels have been reported in patients with Non-Hodgkin's lymphoma (NHL), especially those with advanced disease.<sup>10</sup> Many prognostic factor have been established in aggressive NHL: B symptoms (fever, night sweats, and weight loss), performance status, age serum lactate dehydrogenase (LDH) level, serum  $\beta$ 2-microglobulin, tumour bulk, and number of nodal and extranodal sites of disease.<sup>11</sup> CA-125 was reported by Lazzarino *et al* to be a reliable biologic marker for the staging and restaging of patients with NHL.<sup>1</sup>

We measured serum CA-125 in patients with NHL at diagnosis, with other presenting features of the disease and with response to treatment, and to evaluate its potential role as an independent predictor of survival.

## PATIENTS AND METHODS

Between Nov 2006 and Dec 2009, 100 patients with NHL were treated in Oncology Department of Combined Military Hospital, Rawalpindi, Pakistan. All 100 underwent serum CA-125 measurement at diagnosis and upon completion of treatment. Serum CA-125 was measured by radioimmunoassay. Normal values were considered below 35  $\mu$ /ml. Patients with NHL evaluated at diagnosis were classified according to the international working formulation. All patients with diffuse large B-cell Lymphoma were included. History followed by physical examination, performance status assessment using the WHO Classification system, differential blood cell count, renal and liver function tests, CA-125 and LDH levels, iliac crest bone marrow biopsies, and chest x-rays were performed. Complete response was defined as disappearance of all clinical and radiological evidence of disease with normalization of elevated laboratory values. Partial response (PR) was defined as 50% or greater reduction in the sum of the products of the perpendicular diameters of all measurable sites of tumour. No response (NR) was defined as <50% decrease in the tumour mass or tumour growth during therapy. Patients were followed-up at median follow-up of 6 years, i.e., in May 2015, for survival.

The associations between CA-125 level and patient characteristics were assessed using either Chi-square test or a Fisher's exact test, as appropriate. Odds ratios were computed as well, and  $p \leq 0.05$  was considered significant.

## RESULTS

The median age of the patients was 53 years (range 23–84 year). There were 90 males and 10 females. Thirty-two patients (32%) had B symptoms, liver and spleen were enlarged in 12 patients (12%) each, serum CA-125 was raised in 42 patients (42%), serum LDH was raised in 80 patients (80%), 27 patients (27%) had bone marrow infiltrated by lymphoma. Fifteen (15%) patients showed some abnormality in their chest x-rays, 47 patients (47%) had an abnormal abdominal ultrasound study. Computed tomography of the relevant area showed abnormalities in 67 patients (67%), 55 patients (55%) had ECOG PS 1, while 32 (32%) had PS 2. The IPI was 0 in 2 (2%), 1 in 25 (25%), 2 in 30 (30%), 3 in 23 (23%) and 4 in 20 patients (20%). According to Ann Arbor Staging System, 37 patients (37%) had stage IV disease, 25 (25%) had stage II, 20 (20%) had stage III while 18 patients (18%) had stage I disease.

Chi-square test was applied to the results to know about the possible association between raised CA-125 levels. Two-sided Pearson Chi-Square test revealed a positive association ( $p=0.042$ ), a positive likelihood ratio ( $p=0.032$ ), and a positive linear-by-linear ratio association ( $p=0.003$ ). Six years' follow-up showed statistically significant differences in survival among the 2 groups of patients. (Table-1, 2)

**Table-1: Patients' Characteristics**

Characteristics	
N	100
Age at diagnosis (median)	53 (range 23–84)
Gender	
Male	90
Female	10
Ann Arbor stage	
I-II	43
III-IV	57
B Symptoms	
Absent	68
Present	32
Bone marrow involvement	27
WHO performance status	
0-1	27
2-4	73
Serum LDH level(u/l)	
$\leq 300$	20
$> 300$	80
Serum CA 125 level (u/ml)	
$\leq 35$	58
$> 35$	42

**Table-2: Comparison of complete response rates after treatment and at median follow-up of 6 years**

	Normal CA-125	Raised CA-125
Complete Response after initial treatment [n (%)]	79 (79%)	52 (52%)
Survival at 6 years of follow-up (alive/contacted)	36/60 (60%)	2/18 (11%)

## DISCUSSION

Outcome of patients suffering from NHL depends upon stage, histology and burden of tumour.<sup>13</sup> CA-125 is widely used as a tumour marker for the monitoring of

epithelial ovarian cancer.<sup>2</sup> It has also been a significant prognostic factor for the complete remission and survival in patients with NHL.<sup>14</sup> High serum CA-125 levels are correlated with advanced disease, mediastinal involvement, bulky tumours, effusion and/or extra-nodal extension in patients with NHL.<sup>14-16</sup>

In the present study, serum CA-125 levels were elevated in 42% of patients with NHL. This was in concordance with previous studies who reported high values of 46%, and 43% in patients with NHL.<sup>12,14,17,18</sup> Our analysis showed significant association between CA-125 levels and other clinic-pathological features. Lokanathan *et al*<sup>11</sup> and El Gawad *et al*<sup>18</sup> also showed association between CA125 and extra-nodal involvement, advanced stage and elevated serum LDH level. CA-125 level was independently correlated to IPI score in the present study as reported by Lokanathan *et al*.<sup>11</sup>

The measurement of CA-125 during the treatment and follow-up showed strong relationship with the CA-125 level and the survival as documented by Zacharos *et al* in their study as well.<sup>19</sup> The marker normalised in all patient achieving complete responses and the levels remained high in non-responders. This finding was also documented by Bairey *et al*.<sup>20</sup> Its measurement may contribute to early detection of mediastinal and abdominal recurrence, thus can be used for monitoring of patients after chemotherapy.

Serum CA-125 levels were more frequently high among patients who had involvement of either peritoneal or pleural cavity, as found by El Gawad *et al*<sup>18</sup> and Hazarika *et al*.<sup>21</sup>

## CONCLUSION

The CA-125 is a useful prognostic marker for NHL. It can be used as a surrogate marker of response to therapy and long term survival, especially if the levels raised initially. It was more consistently associated with pleural or peritoneal effusions. Future, large scale studies could focus on such lymphomas to establish its prognostic significance.

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