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Biochemistry

ASSOCIATION OF CA-125 LEVELS WITH SEVERITY OF LIVER CIRRHOSIS AND ASCITES

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ABSTRACT **Background:** Elevated serum CA-125 levels have been used as pre-operative diagnostic and prognostic marker for ovarian malignancy, which may increase in certain non-gynaecological disorders also. Many cases of liver cirrhosis may be mis diagnosed as ovarian carcinoma due to combination of elevated CA125 and ascites.

Aim– To determine association between elevated serum levels of cancer antigen (CA) 125 and severity and prognosis of patients presenting with liver diseases.

Material and Methods – A total of 80 patients were enrolled in this study. There were 34 patients of acute liver disease, 12 patients of compensated cirrhosis and 34 patients of decompensated cirrhosis with ascites. Fasting LFT and CA -125 levels were measured in all patients. Ultrasound abdomen was carried out to assess severity of ascites. Statistical analysis was carried out on SPSS. P-value less than 0.05 was taken as significant

Results- The mean CA-125 levels in patients of acute liver disease (n=34) was 8.39±4.83 U/mL, in patients of compensated cirrhosis (n=12) was 9.74±3.39 U/mL and 286.28±219.71 U/mL in patients of decompensated cirrhosis with ascites (n=34). Mean CA-125 levels were significantly higher in patients with ascites. A significant positive correlation was observed between serum CA-125 levels and severity of ascites ($p < 0.001$).

Conclusions – Serum CA-125 levels have high predictive value for determining severity and progression of liver disease.

KEYWORDS : CA =Cancer antigen, ALD= Acute liver disease, CLD= Chronic liver disease

INTRODUCTION

Cancer antigen (CA) -125 is peptide epitope of high molecular weight Mucin glycoprotein (MUC 16) produced both by ovarian cancer cells and tissues derived from coelomic epithelium during embryonic development [1, 2]. It is expressed by coelomic and Mullerian epithelium and is used as a tumor marker. It can be identified by murine monoclonal antibody against epithelial ovarian tumors [2, 3]. CA- 125 levels are frequently increased in patients with epithelial ovarian cancer where its levels are used to monitor disease progression and assess efficacy of treatment. However, CA -125 levels may be increased in benign gynecological diseases and other non gynecological malignancies [4, 5]. Some of the earlier studies have demonstrated a direct correlation between objective markers of end-stage liver disease (MELD) and elevated levels of CA-125 [6]. High CA -125 levels have been reported in patients with liver disease but this phenomenon is not widely appreciated by the clinicians [7,8]. This ignorance can lead to mistaken diagnosis of ovarian malignancy and patients can unnecessarily undergo diagnostic laparotomy.

The purpose of this study was to evaluate the levels of CA-125 in different stages of liver disease and probable relation between the high levels and the amount of ascites.

METHODS

The study was carried out in 80 patients of age >18 years, admitted to the Gastroenterology Department of Himalayan Institute of Medical Sciences , Dehradun , India with liver diseases. Patients were selected in three groups, - 34 patients with acute liver disease, 12 patients with compensated cirrhosis, 34 patients with decompensated cirrhosis.

Structured study formats and subject proformas (questionnaires / case reporting forms and investigations) were developed, and used to generate data for the study.

Fasting CA -125 levels and liver function tests were measured in serum of 80 patients admitted to Gastro-enterology Department. Prior approval from ethical committee was obtained and written informed consent of all the patients was taken. In patients of decompensated cirrhosis, CA-125 levels were re-assessed at the time of discharge and patients were followed up for 30 days for recurrence of ascites.

Patients with hepatocellular carcinoma or any other malignancy (excluded by ultrasound of abdomen), any other cause of ascites like tuberculosis, cardiac disease, renal failure , Inflammatory conditions of GIT (peritonitis , pancreatitis) were excluded from the present study.

CA-125 in the serum samples was estimated by a 2-step enzyme immunoassay sandwich method with a final fluorescent detection Enzyme Linked Immunofluorescent Assay (ELFA). Normal values were defined as less than 35 U/ml.

Ascites was graded as Grade I (Mild), Grade II (Moderate) and Grade III (Severe) based on criteria defined by Moore etal [9]. Severity of ascites was also verified by estimating Total Abdominal Ascites on Ultrasonogram. The maximum diameters of ascites pools/ pockets in longitudinal and transverse planes were measured and volume of each pocket was calculated. The volumes of all pockets was then added to find out total abdominal ascites [TAA]. Ascites was classified as mild/ Grade I (if TAA <500 ml), Moderate/ Grade II (if TAA >500 ml upto 2000ml) and Severe/ Grade III (if TAA >2000 ml)

Interpretation and statistical analysis was done using SPSS software 20.0 Version and Microsoft Excel Software. Data is presented as mean ± Standard Deviation. The statistical analysis of difference of means/proportions for baseline characteristics (age and sex) and serum CA-125 levels was carried out by using parametric tests (unpaired 't' test). Pearson's correlation coefficient was applied to test the positive/ negative correlation between various test variables. *p* value < 0.05 was considered as significant.

RESULTS

Age wise distribution of liver diseases shows that the patients of acute liver disease were more in the age group between 21-30 and 31-40 years with a mean age of 48.26±13.43 years, whereas chronic compensated patients were more in the age group of 31-40years with a mean age of 37.4±13.83 years. Majority of decompensated patients were in the age group between 41-50 years with mean age of 42.16±15.22 years (Table 1).

Table 1: Distribution of study subjects by their age-groups.

Age groups (in years)	Acute liver disease	Compensated cirrhosis (CLD without ascites)	Decompensated Cirrhosis(CLD with ascites)
	(n=34)	(n=12)	(n=34)
21-30	10	4	3
31-40	9	5	7
41-50	5	1	12
51-60	6	1	7
61-70	4	1	5
Mean age±SD (years)	48.26±13.43	37.4±13.83	42.16±15.22

Table 2. Gender distribution of subjects:-

Sex	Severity			Total
	Acute	Compensated cirrhosis	Decompensated cirrhosis	
Male	19	7	30	56
Female	15	5	4	24
Total	34	12	34	80

It can be seen from table 2, that the number and proportion of males were considerably more than females in all the three forms of liver disease [19 (23.75%), 7(8.75%) and 30 (37.5%) respectively]. Number and proportions of female were less ,15(18.75%), 5(6.25%) and 4 (5.0%) in comparison to that of males.

Table 3 summarizes the mean serum CA-125 levels in three group of patients. The mean CA-125 levels in patients of acute liver disease (n=34) was 8.39±4.83 U/mL, whereas the mean CA-125 levels in patients of compensated cirrhosis (n=12) was 9.74±3.39 U/mL. In patients of decompensated cirrhosis (n=34) the mean CA-125 levels was 286.28±219.71 U/mL. The difference between the mean values of CA-125 in acute and chronic compensated liver disease was statistically insignificant (p=0.59) whereas the difference between acute and decompensated liver disease was statistically significant (p<0.001). It was also found that the difference in mean values between chronic compensated and chronic decompensated group was highly significant (p<0.001).

Table 3: CA 125 levels in different types of liver diseases

Types of liver disease	CA- 125 levels				
	N	Mean	Std. Deviation	Minimum	Maximum
Acute liver disease	34	8.394	4.83	1.3	20.3
Compensated cirrhosis	12	9.74	3.339	4.9	15.3
Decompensated cirrhosis with ascites	34	286.283	219.717	12.66	600

A highly significant correlation was observed between CA 125 levels and total abdominal ascites (r=0.789, P<0.001) (Table 4). Mean CA 125 levels in the mild ascites group were 69.73 ±43.74 U/ml, whereas in moderate / Grade II ascites group the levels were 422.33±138.01 U/ml and in severe / Grade III ascites group , the values were 598.10±2.70 U/ml (p<0.001).

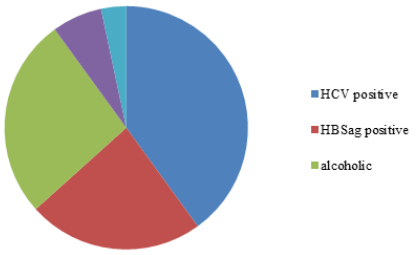
Table 4 : Correlation of CA-125 levels with the amount of ascitic fluid

USG findings	N	Mean CA-125 levels	Minimum	Maximum
Mild Ascites (TAA <500 ml)	14	69.73 ± 43.74	12.66	164.6
Moderate Ascites (>500 ml upto 2000 ml)	16	422.33± 138.02	169.07	598.1
Severe Ascites	4	598.1± 2.71	595	600

The etiology of de compensated chronic liver disease was evaluated and correlated with CA-125 levels. No significant correlation of CA-125 levels was observed with the etiology of de compensated chronic liver disease. The distribution of patients of de compensated liver disease by etiology is shown in Figure 1.

The major cause of liver disease in the study subjects was HCV- related hepatitis (15 subjects) followed by alcoholic liver disease and HBsAg –related hepatitis (8 each) Other causes were autoimmune hepatitis (2 subjects) and cryptogenic cirrhosis (1 subject).

Figure 1: Distribution of patients of decompensated chronic liver disease (n=34) by etiology



In patients with de compensated cirrhosis, CA-125 levels were re-assessed at the time of discharge when ascites had settled. The patients were followed up for recurrence of ascites within 30 days of discharge.

Table 5: CA-125 as an indicator of recurrent ascites in de compensated patients

			Recurrence	
			Recurrence of ascites	Non recurrence
CA-125 levels	>35	Count	16	4
		%	80 %	20 %
	<35	Count	3	11
		%	21.5%	78.5%
Total		Count	19	15
		%	55.9%	44.1%

Out of 34 patients admitted in the hospital, 20 patients had CA-125 levels more than 35 U/ml at discharge, with a mean of (73.47±21.52 U/ml), out of which 16 had recurrent episode of ascites and the remaining 4 did not have recurrent episode, whereas remaining 14 patients had levels less than 35 U/ml with a mean of (17.67±8.96 U/ml) out of which 3 had recurrent episode and 11 had no episode of recurrence. The difference between the two groups was statistically significant (p =0.01). The positive predictive value of elevated CA-125 levels in predicting recurrence of ascites was 80% in the present study.

DISCUSSION

In the present study, most of the patients with acute liver disease and compensated liver cirrhosis were in younger age group, whereas most of the patients with decompensated liver cirrhosis were in the age group 41-50 years. Liver has a remarkable capacity of regeneration, however with increasing age, susceptibility of fibrotic responses to liver injury increases and it is associated with poor prognosis of various liver diseases including nonalcoholic fatty liver disease, alcoholic liver disease, hepatitis C, and liver transplantation [10].

Proportion of males was found to be higher than the females in all the groups. The reasons for this gender disparity are complex, however they may result from differences in behavioral risk factors (HBV & HCV infection, alcohol use), metabolic factors, and treatments received [11]. For both HBV and HCV, there is evidence that female gender confers a protective effect as estrogen decreases IL-6 mediated hepatic inflammation and viral production [12-13].

Elevated serum CA-125 levels were observed in patients with de compensated liver cirrhosis with ascites in the present study (Table 3), whereas the patients with acute liver diseases and compensated liver cirrhosis had CA-125 levels within normal biological reference range. In patients with de compensated liver cirrhosis, CA-125 levels showed a strong positive correlation with the degree of ascites but there was no association with liver function parameters.

Similar results were reported in a recent study by Edula R GR etal (2018) where elevated CA-125 levels were noted in 85% of patients with cirrhosis (due to any etiology). Absence of ascites was associated with near- normal CA-125 levels. In the same study it was observed that the degree of elevation of CA-125 was associated with more advanced the degree of decompensation based on MELD score, ALBI score and CTP classification [14]. In the same study, direct correlation was observed between high levels of CA-125 and worsening ascites [14]. Since the elevation in CA-125 levels correlated more with ascites

as compared to changes in MELD and ALBI score , it was concluded that rise in CA-125 levels was probably due to stretch of peritoneum due to ascites [14].

In a landmark study by Zuckermann and colleagues [15], CA-125 levels were evaluated in 170 patients of different liver diseases. In this study, only 9 out of 123 subjects with liver disease (without ascites) had raised CA-125 levels whereas 46 out of 47 patients with ascites had elevated CA-125 levels. The mean serum CA 125 concentration in the patients with ascites (group II) was significantly higher than patients without ascites (group I) ($p< 0.001$) [16]. They concluded that CA-125 is a highly sensitive marker to detect ascites in patients with liver cirrhosis and it may be a useful marker to detect small to moderate amounts of ascitic fluid in cirrhotic patients when physical examination is difficult or equivocal for ascites.

In a study by Deschenes etal mean pre-transplant CA-125 levels were 352 ± 549 U/ml as compared to post-transplant levels of 46 ± 49 U/ml in 57 cirrhotic patients which included 67% men [17]. The findings of this study clearly indicate that elevation of CA-125 levels can be majorly attributed to decompensated cirrhosis and ascites.

In contrast to the above studies where elevated CA-125 levels were observed only in decompensated cirrhosis, Devarbhavi et al. [18] reported elevated serum CA-125 levels in all forms of liver disease irrespective of the stage of disease.

In our study, the elevation in CA-125 levels did not show any correlation with derangement in Liver function tests. The findings of our study are unlike Devarbhavi etal [18] and Collazos etal [19] who found good correlation and suggested that CA-125 elevation in liver cirrhosis is due to liver dysfunction

In the present study we could not demonstrate elevation of CA 125 levels in patient with acute hepatitis and patients of chronic compensated liver disease without ascites. In fact none of the patients in these two groups showed rise in CA 125 levels. This may be due to smaller sample size in our study group.

The mechanism of raised serum CA- 125 in ascites is still under speculation. Data from several research articles, support the theory of release of CA-125 by peritoneal mesothelial cells. In cell cultures, five times more CA-125 are shed by peritoneal mesothelial cells than ovarian cancer cells [20]. Physiological release of CA-125 may occur in response to stretch of peritoneum due to ascites, since CA- 125 falls rapidly after paracentesis [8]. In patients with cirrhosis an additional factor could be low clearance of CA- 125 by the liver[18] ; and in those with malignant ascites, infiltration of the peritoneal membrane could contribute to elevation of CA-125.

Clinicians including physicians, gastroenterologist, hepatologist , gynecologist, oncologist and liver transplant specialist should be aware of this association of raised serum CA-125 levels in patients with liver disease so that patients especially female patients with raised levels of CA 125 can be screened for hepatic dysfunction if their pelvic ultrasound is normal. This may be a significant finding as elevated levels in females with cirrhosis often leads to unnecessary and expensive evaluation for ovarian cancer in the community, even though the incidence of ovarian cancer is very low, thereby contributing significant psychological and financial burden to patients.

REFERENCES

1. Hussain SF, Camilleri P. Elevation of tumour marker CA-125 in serum & body fluids: interpret with caution. Indian J Med Res. 2007;125(1):10-12.
2. Duraisamy S, Ramasamy S, Kharbanda S, Kufe D. Distinct evolution of the human carcinoma-associated transmembrane mucins, MUC1, MUC4 AND MUC16. Gene. 2006; 373: 28–34.
3. Bast RC Jr, Feeney M, Lazarus H, Nadler LM, Colvin RB, Knapp RC. Reactivity of a monoclonal antibody with human ovarian carcinoma. J Clin Invest. 1981; 68:1331-1337.
4. Lehtovirta P, Apter D, Stenman UH. Serum CA 125 levels during the menstrual cycle. Br J Obstet Gynaecol. 1990; 97:930- 933.
5. Haga Y, Sakamoto K, Egami H, Yoshimura R, Mori K, Akagi M. Clinical significance of serum CA125 values in patients with cancers of the digestive system. Am J Med Sci. 1986; 292: 30-34.
6. Singhal A, Lander E, Karachristos A, Daly E, Dowling P, Patel V etal. Elevation of CA-125 and CA 19-9 in patients with end-stage liver disease. Int J Biol Markers 2012; 27: e 147-e151.
7. Molina R, Filella X, Bruix J, et al. Cancer antigen 125 in serum and ascitic fluid of patients with liver diseases. Clin Chem. 1991; 37:1379-1383.
8. Zuckerman E, Lanir A, Sabo E, et al. CA-125 as a marker for detection and quantitation of ascites in liver cirrhosis [abstract]. Hepatology. 1995; 22(4, pt 2):163A.
9. Moore K P, Wong F, Gines P, Bernardi M, Ochs A, Salerno F, etal. The Management of Ascites in Cirrhosis: Report on the Consensus Conference of the International Ascites Club. Hepatology. 2003; 38: 258-66.
10. Kim H, Kisseleva T, Brenner DA. Aging and liver disease. Curr Opin Gastroenterol 2015; 31 (3): 184-191.
11. Wu EM, Wong LL, Hernandez BY, Ji JF, Jia W, Kwee SA, Kalathil S. Gender differences in hepatocellular cancer: disparities in nonalcoholic fatty liver disease/steatohepatitis and liver transplantation. Hepatoma Res 2018; 4: 66.
12. Di Martino V, Lebray P, Myers RP, Pannier E, Paradis V, et al. Progression of liver fibrosis in women infected with hepatitis C: long-term benefit of estrogen exposure. Hepatology 2004;40:1426-33.
13. Liu WC, Liu QY. Molecular mechanisms of gender disparity in hepatitis B virus-associated hepatocellular carcinoma. World J Gastroenterol 2014;20:6252-61.
14. Edula RGR , Muthukuru S, Moroianu S, Wang Y, etal. CA-125 Significance in Cirrhosis and Correlation with Disease Severity and Portal Hypertension: A Retrospective Study. J Clin Transl Hepatol 2018; 6(3): 241–246.
15. Zuckerman E, Lanir A, Sabo E, et al. Cancer Antigen 125: A senstive marker of ascites in patients with liver cirrhosis. Am J Gastroenterol 1999;94:1613– 8.
16. Kouris NT, Zacharos ID, Kontogianni DD, Goranitou GS, Sifaki MD, Grassos HE. The significance of CA-125 levels in patients with chronic congestive heart failure. Correlation with clinical and echocardiographic parameters. Eur J Heart Fail 2005; 7: 199-203.
17. Deschenes M, Michel RP, Alpert E, Barkun JS,et al. Elevation of CA-125 is due to abdominal distension in liver transplant candidates. Transplantation 2001 ; 72 : 1519-22
18. 15. Devarbhavi H, Kaese D, Williams A W, Rakela J, Klee GG, Kamath PS. Cancer Antigen 125 in Patients With Chronic Liver Disease. Mayo Clin Proc. 2002; 77:538-541
19. Collazos J, Genolla J, Ruibal A. CA 125 serum levels in patients with non-neoplastic liver diseases. A clinical and laboratory study. Scand J Clin Lab Invest 1992 May;52(3):201-206.
20. Zeimet AG, Offner FA, Marth C, et al. Modulation of CA 125 release by inflammatory cytokines in human peritoneal mesothelial and ovarian cancer cells. Anticancer-Res 1997;17: 3129-31