Research Article

Association of CA 125 with Degree of Fibrosis in Chronic Liver Disease with Portal Hypertension

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Abstract

Objective: To determine the association between serum CA-125 levels and degree of fibrosis in chronic liver disease with portal hypertension.

Methodology: This study was conducted at Mayo Hospital Lahore. A total of 63 patients with liver cirrhosis were enrolled, demographic, clinical and laboratory parameters were documented. Modified FIB-4 index was calculated and value of 3 or more was defined as advanced liver cirrhosis. Receiver Operating Characteristic (ROC) curve was applied to calculate cut off value for CA-125 as 50 IU/L. Pearson correlation and linear regression analysis were applied to determine the association between CA-125 and modified fib -4 index.

Results: Sixty three patients were enrolled. Mean age was 52.047±12.78. Female patients were 22(34.9%) and male patients were 41(65.1%). Regarding the clinical features, 8(12.7%) patients had jaundice, 38(60.3%) had ascites , 61(96.8%) had splenomegaly ,58(92.1%) had history of upper gastrointestinal bleed while 12(19%) had history of hepatic encephalopathy. Mean value of Modified fib-4score was 4.75±2.89SD, 43(67.2%) had value above cutoff of 3. Total of 38(60.3%) had CA-125 value above the cutoff level of 50 IU/L. CA-125 value above 50 IU/L has 63% sensitivity and 70% specificity in predicting advanced liver fibrosis and this association was statistically significant. (p value 0.024) .

Conclusion: Serum CA-125 level above 50 IU/L is associated with presence of significant liver fibrosis.

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Introduction:

Chronic liver disease has high morbidity and mortality after progression to stage of decompensation. It is one of the major contributors to chronic diseases worldwide. It accounts for 1.6% and 2.1% of the global burden regarding disability-adjusted life years and years of life lost respectively. Cirrhosis is the eleventh most common cause of death all over the world[1]. A study in Pakistan has established Hepatitis C as the commonest cause of chronic liver disease[2]. Five percent of Pakistani population suffers from hepatitis C and a lot of these patients develop progressive liver fibrosis[3].

Chronic liver disease is progressive in nature irrespective of etiology. It passes through various stages and ultimately fibrosis results in hepatic decompensation. Various parameters are used to measure fibrosis. Liver biopsy remains a gold standard, however it is an invasive procedure with certain potential complications[4]. Many noninvasive techniques and scoring systems have been developed. Techniques like transient elastography, acoustic-radiation-force impulse elastography, and real-time elastography and magnetic resonance imaging elastography are used[5]. They have the disadvantage of being expensive. Other noninvasive scoring systems in-

clude platelet count, aspartate aminotransferase/ alanine aminotransferase (AST/ALT) ratio (AAR), AST/ platelet ratio index (APRI), AAR/platelet ratio index (AARPRI), Pohl score, age-platelet (AP) index, fibrosis quotient (FibroQ), and Lok index[6].

Wang et al have developed a new scoring system and have validated it in Asian population. It is used for predicting fibrosis of the liver. It is named as modified fibrosis-4 (mFIB-4) index[6]. It has shown good sensitivity and specificity in identifying advanced stage of disease with the added benefit of being inexpensive and readily available.

CA-125 is an antigenic determinant on a high-molecular-weight glycoprotein recognized by a monoclonal antibody and it is mainly a tumor marker for ovarian cancer. Elevation of serum CA 125 may also be associated with other malignancies and benign physiological states, including pregnancy, endometriosis and menstruation[7]. The elevation of tumor makers in liver disease is considered unspecific up till now. Very few studies have addressed the relation of CA-125 levels with liver cirrhosis and degree of fibrosis[8]. Some studies explored the association of elevated CA-125 levels with ascites and found excellent sensitivity, specificity, efficiency, predictive values and likelihood ratios for detecting ascites[9]. Edula et al conducted a study that documented the prevalence of CA-125 as 85% in patients of liver cirrhosis[10]. The reason behind the elevation of CA-125 levels in liver disease remain unknown[11]. One study from Canada suggests that it's due to stretching of peritoneum and abdominal distension and in patients who got liver transplant the CA-125 levels gets normalized after transplantation[12]. However association of CA-125 levels with stage of liver disease is still unexplored. We planned a study to determine the relationship of CA125 levels with degree of fibrosis in chronic liver disease.

Data Collection Procedure:

After ethical approval, and informed consent, sixty three patients of chronic liver disease with portal hypertension were enrolled from January 2019 to July 2019. This analytical cross sectional study was carried out in Department of Medicine Mayo Hospital Lahore. Patients were labelled as cases of chronic liver disease with portal hypertension on the basis of clinical features of portal hypertension including splenomegaly and/or ascites, presence of esophageal varices as determined on endoscopy along with radiological evidence of chronic liver disease and portal hypertension.

Patients with chronic liver disease without portal hypertension or evidence of hepatocellular carcinoma were excluded. Patients with other conditions associated with raised CA125 such as pelvic malignancies, pancreatic, colorectal, breast and lung carcinoma or benign conditions like acute pancreatitis and peritonitis were also excluded. Pregnant and lactating women were also excluded.

Demographic profiles including name, age, gender, address, contact number were recorded. Etiological evidence for viral infection such as anti HCV, HBsAg was noted. Clinical manifestations of chronic liver disease like ascites, hepatic encephalopathy and upper gastrointestinal bleed was recorded. History regarding other malignancies was taken along with specific examination where required. Liver function tests, complete blood count was performed along with abdominopelvic ultrasound and chest radiograph. Level of serum CA125 was recorded. Modified FIB 4 index was calculated to determine presence of liver fibrosis.

Data Analysis:

Data analysis were done with SPSS 24®, numerical variables like age, CA125 levels were presented as mean ± SD. Nominal variables like gender, presence of clinical manifestations of chronic liver disease were presented as frequency and percentage. Pearson corre-lation and Linear regression analysis were applied to study the relationship between serum CA 125 levels and liver fibrosis. p value ≤ 0.05 was considered significant

Results:

Sixty three patients were included. There were no drop-outs. Mean age was 52.047±12.78 (Table-1). Female patients were 22(34.9%) and male patients were 41 (65.1%) (Table-2). All patients had positive anti HCV antibodies and one patient had evidence of co infection with Hepatitis B. Regarding the clinical features, 12.7% patients had jaundice. Ascites was present in 60.3% patients, 96.8% had splenomegaly and11.1% had pedal edema. Upper gastrointestinal bleeding was the presenting symptom in 92.1% while 19% developed

Table-1: *Age*

	N	Minimum	Maximum	Mean	Std. Deviation
age	63	23.00	90.00	52.0476	12.78284
Valid N (listwise)	63				

Table-2: *Gender*

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	female	22	34.9	34.9	34.9
	male	41	65.1	65.1	100.0
	Total	63	100.0	100.0	

Table-3: *Descriptive Statistics*

	N	Minimum	Maximum	Mean	Std. Deviation
CA125	63	9.38	369.00	87.0965	75.06721
Modified_fib_4 _index	63	1.06	14.85	4.7560	2.89622
Valid N (listwise)	63				

hepatic encephalopathy. Association between CA-125 and ascites was found to be statistically significant (p= .014).

Mean score of CA125 was 87.09±75.06SD (Table-3). Regarding modified FIB-4score, mean value was 4.75±2.89SD (Table-4) and 67.2% had a value greater than cutoff level of 3. Cut off value of CA125 for predicting liver fibrosis as determined by Fib-4 was calculated as 50IU/l by applying Receiver Operating characteristic (ROC) curve (Figure-1). Area under Curve (AUC) was 0.692. Total of 60.3% patients had a CA 125 value above the cutoff level of 50 IU/L. Sensitivity of value above 50 IU/L was 63% and specificity was 70% for predicting liver fibrosis. On analysis of two variables in accordance with cut off values, association was found to have statistically significant p value of 0.024.

Table-4: *Correlations between CA-125 and modified fib-4 index*

		CA125 _cutoff	Modified FIB score_ cutoff
CA125_cutoff	Pearson Correlation	1	.283*
	Sig. (2-tailed)		.024
	N	63	63
Modified FIB score_cutoff	Pearson Correlation	.283*	1
	Sig. (2-tailed)	.024	
	N	63	63

*. Correlation is significant at the 0.05 level (2-tailed).

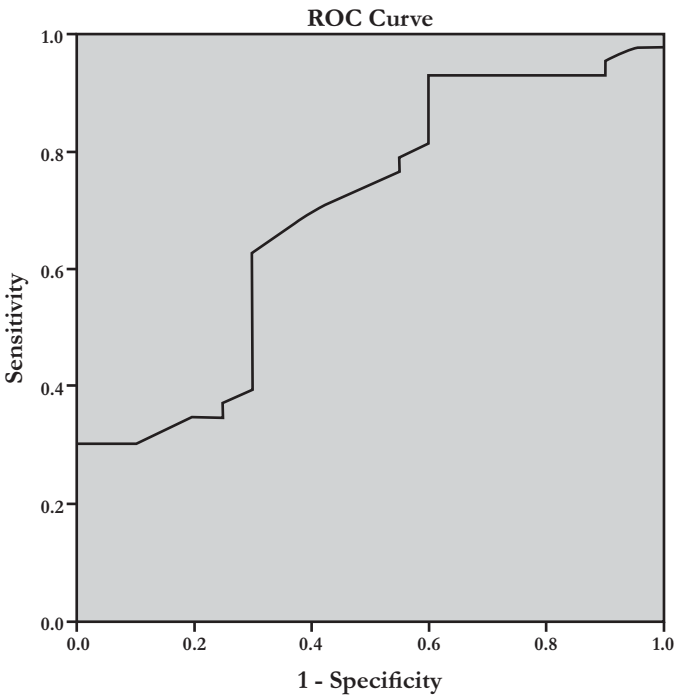

Figure-1: *A receiver operating characteristic curve for the diagnostically of CA125.*

Discussion:

Chronic liver disease with portal hypertension is one of the common causes of hospital visits. Various markers have been studied to evaluate the clinical presentation of portal hypertension. Peritoneal stretch due to ascites has been linked with higher values of CA 125. Zucker-

man et al concluded that CA125 was significant marker to detect ascites in such patients. Serum CA125 had significant correlation with amount of ascites ® =0.78)[13]. In our study, the association was also found to be statistically significant (p=.014). Another study demonstrated moderate correlation between CA 125 and degree of ascites[14].

In another study by Edula et al, 85% of cirrhotic patients had elevated value of CA 125. Authors took value above 35 IU/L as abnormal[12]. Value of CA 125 was compared with degree of ascites. They also established the association with degree of decompensation. In our study, we calculated cut off value at 50 IU/L and 60.3% patients had value above this level, we analyzed the association with degree of fibrosis. This association is significant at the calculated cut off value for CA 125.

A study of eighty patients was carried out in Iran to assess the presence of tumor markers in patients of chronic liver disease. CA 125 was found to have statistical significance (p=0.02) in patients with Hepa-titis C infection. They concluded that CA 125 is related to cirrhosis[15]. Similarly, our study also showed significant association with higher degree of fibrosis.

Modified FIB-4 has been proposed as simple noninvasive test to assess the severity of fibrosis by Wang et al[6]. Its diagnostic performance has also been applied to predict the development of hepatocellular carcinoma (HCC) in cirrhotic patients. The index demonstrated the highest performance for predicting HCC development at 3 years (AUROC = 0.71, 95% confidence interval [CI]: 0.64–0.78) in a study by Kim et al[16]. Thus, the index has been established as reliable measure for degree of fibrosis in chronic live disease. We have applied modified fib-4 index proposed by Wang et al that was found to be significantly associated with CA 125. Another modified FIB-4 index that included FIB-4, Gamma glutamyl transferase levels and body mass index has been developed with high accuracy (AUC =0.86) by Cepeda et al[17]. Thus, research is being done to develop inexpensive and easy to apply tools to assess fibrosis. Small sample was the main limitation of our study. Determination of a significant correlation between degree of cirrhosis and elevated CA-125 is the main strength of the study, as this inexpensive tool can be used to determine degree of cirrhosis in a resource depleted country like ours.

Conclusion:

CA 125 has significant correlation with fibrosis of liver at a cut off value of 50 IU/L.

More studies with larger sample size are needed to provide evidence regarding the significance of tumor marker and degree of fibrosis, and to evaluate the reason for high CA-125 in cirrhotic patients. Use of relatively less expensive noninvasive tool can prove to be beneficial in patients of cirrhosis.

Ethical Approval: Given
Conflict of Interest: The authors declare no conflict of interest.
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