



CA-125 Significance in Cirrhosis and Correlation with Disease Severity and Portal Hypertension: A Retrospective Study

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Abstract

Background and Aims: To evaluate the prevalence and significance of elevated cancer antigen-125 (CA-125) levels in patients with cirrhosis being treated in a tertiary care liver center and its correlation with objective markers of disease severity.

Methods: We retrospectively reviewed medical records of 172 adult patients with cirrhosis (due to any etiology) after obtaining CA-125 serum analysis. Demographics, etiology of cirrhosis, model of end-stage liver disease (MELD) score, Child's Turcotte-Pugh classification, albumin bilirubin (ALBI) score, degree of ascites, presence of esophageal varices, serum CA-125 level and various other parameters were collected. Statistical analysis was performed using SPSS software and descriptive statistics. **Results:** Elevated CA-125 levels were noted in 147 patients (85%) of the study population. Higher MELD score was associated with higher CA-125 levels ($p = 0.001$). Statistically significant correlation was observed between elevated CA-125 levels and degree of ascites ($p < 0.001$), ALBI score ($p < 0.001$) and Child's Turcotte-Pugh class ($p < 0.001$). No correlation was observed with presence or absence of esophageal varices. Near-normal CA-125 levels were noted in patients with cirrhosis but undetectable ascites on ultrasound imaging. No differences were observed in mean values between male and female patients ($p = 0.207$). Regression analysis confirmed that CA-125 levels had a better correlation with degree of ascites than MELD score or ALBI score. **Conclusions:** Elevated CA-125 levels were noted in 85% of patients with cirrhosis at our center. Our study establishes that the more advanced the degree of decompensation based on MELD score, Child's Turcotte-Pugh classification and ALBI score, the higher the elevation in CA-125. Absence of ascites was associated with normal CA-125 level, with a direct correlation between high levels and worsening ascites, but there was no statistically significant correlation with esophageal varices, indicating that elevated CA-125 levels could be related to mechanical stretch of the peritoneum rather than portal hypertension itself. Further multi-centered studies are required to confirm and validate these findings.

Keywords: Portal hypertension; Ascites; Esophageal varices; MELD score; Child's Turcotte-Pugh classification.

Abbreviations: ALBI, albumin-bilirubin; CA-125, cancer antigen-125; CTP, Child's Turcotte-Pugh; HCC, hepatocellular cancer; MELD, model for end-stage liver disease; NASH, nonalcoholic steatohepatitis.

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Introduction

Serum cancer antigen-125 (CA-125) has long been used as a tumor marker for the preoperative diagnosis and monitoring of ovarian malignancy and may be a prognostic indicator for this disease. CA-125 is a peptide epitope of the mucin glycoprotein called MUC16.¹ The function of MUC16 is unclear but the distribution of the antigen CA-125 suggests that it may have a physiological role.² It is expressed by the coelomic and the Müllerian epithelium³ and can be elevated in various benign and malignant conditions, including pregnancy, menstruation, ovarian cancer, endometriosis, pelvic inflammatory disease, chronic renal failure, cirrhosis of liver, congestive heart failure, pleural effusion, colorectal and pancreatic cancer.^{2,4–9}

Cirrhosis of liver is one of the most common disorders associated with increased levels of CA-125. Several studies have shown that in patients with cirrhosis, the presence of ascites appears to play a major role for increase in CA-125 levels.^{10–13} This led to the suggestion that CA-125 could be used as a marker for detection of ascites.^{14,15} Other studies with small sample sizes have demonstrated that there is a direct correlation between elevated levels of CA-125 and objective markers of disease severity like model for end-stage liver disease (MELD) score and Child's Turcotte-Pugh (CTP) classification.^{16–21} To date, no study has demonstrated the correlation between CA-125 and esophageal varices, which is an important marker of portal hypertension and is associated with significant morbidity and mortality as a result of variceal hemorrhage.

The mechanism of elevated CA-125 in ascites is not fully understood. Peritoneal stretching could be a relevant explanation, as some studies have shown that peritoneal mesothelial cells shed five times more CA-125 than ovarian cancer cells²² and that serum CA-125 falls rapidly after paracentesis.²³ One theory proposes that the antigen enters the blood via lymphatic absorption of ascites.²⁴ In patients with cirrhosis, low clearance of CA-125 by the liver could be another factor¹⁴ and in those with malignant ascites, infiltration of the peritoneal membrane could contribute to elevated levels.²⁵

The aim of our study was to retrospectively evaluate the prevalence of elevated CA-125 levels in patients with cirrhosis (due to any etiology) being treated at a tertiary level liver center, in order to determine its correlation with objective

markers of disease severity, which included ascites, MELD score, CTP classification, albumin-bilirubin (ALBI) score, esophageal varices, serum sodium and renal function. Whether CA-125 is a marker of onset of portal hypertension or it purely represents a physiological increase due to mechanical stress of the peritoneum from ascites based on its correlation with clinical markers of portal hypertension was evaluated in our study.

Methods

Materials

We retrospectively reviewed electronic medical records of 172 adult patients presenting to our center between December 2013 to June 2015 for evaluation and management of cirrhosis.

Ethics approval

This study was approved by the institutional review board. Since this was a retrospective low-risk study, subject approval was not required.

Selection of patients

All study subjects were diagnosed with cirrhosis (due to any etiology) and confirmed by imaging and initial evaluation by a hepatologist at our center.

Inclusion criteria

This study included adult patients between ages 18–85 and with availability of CA-125 tumor marker data obtained prospectively and randomly once a diagnosis of cirrhosis was confirmed clinically and based on imaging studies performed at our center.

Study population

The study included patients with a diagnosis of cirrhosis followed in the out-patient setting and patients admitted to our center for management of complications related to cirrhosis. Patients with current or previous history of gynecological malignancy, those without clear documentation of degree of ascites based on radiological criteria and inability to clearly determine CTP classification status were excluded from the study.

Standard-of-care was implemented in the care of all patients with regards to management of cirrhosis-related complications, including use of diuretics, paracentesis, if deemed necessary based on American Association for the Study of Liver Diseases and institutional guidelines. Since several of these patients were either in the process or listed for liver transplant in the United Network of Organ Sharing waiting list and had a history of ascites from decompensated cirrhosis, a decision to perform paracentesis was determined by the hepatologist taking care of the patient based on current guidelines. Several of these patients had refractory ascites requiring frequent changes in the diuretics regimen and paracentesis on a regular basis at the time of study inclusion.

Methods

All patients had CA-125 serum level analyzed at our center once the diagnosis of cirrhosis was confirmed and they had been included in the study if they met the inclusion criteria.

Patients with history of intraabdominal malignancies were excluded, except for those with hepatocellular cancer as a complication of cirrhosis. The reference range of CA-125 was 0–35 units/mL and any result greater than the upper limit of normal was considered abnormal. Lab analysis was performed at our center using standard enzyme-linked immunosorbent assay developed by Abbott Diagnostics (IL, USA).

Data on demographics, etiology of cirrhosis, MELD score, CTP classification at the time of analysis, ALBI score, degree of ascites (classified as absent, mild (perihepatic ascites) or moderate (diffuse ascites)) based on ultrasound or computerized tomography findings performed at our center, serum CA-125 measurement, history of esophageal varices and hepatocellular cancer were collected. Other lab parameters, including but not limited to serum sodium, creatinine, glomerular filtration rate, total bilirubin, albumin, international normalized ratio, complete liver function tests, thyroid profile, lipid profile, hemoglobin A1C, iron profile, ferritin, hepatitis C genotype and viral load, were collected and stored in a password-protected Microsoft Excel file for final analysis.

Statistical analysis

Statistical analysis included linear regression, one-way ANOVA and Student's *t*-test, all of which was performed using SPSS software and descriptive statistics. A *p*-value of <0.05 was considered statistically significant.

Results

A total of 172 adult patients with a confirmed diagnosis of cirrhosis and availability of CA-125 level, MELD score, CTP classification of cirrhosis, ALBI score and degree of ascites based on radiological criteria (ultrasound and computerized tomography) were included in the final analysis.

Baseline characteristics

The majority of patients were men ($n = 110$, 64%) and the most common etiology of cirrhosis was alcohol ($n = 56$, 32.5%) followed by hepatitis C ($n = 47$, 27.3%), nonalcoholic steatohepatitis ($n = 18$, 10.4%), cryptogenic ($n = 18$, 10.4%), hepatitis C plus alcohol ($n = 14$, 8.1%), with hepatitis B, PBC and PSC accounting for the rest. The majority of subjects were Caucasian ($n = 85$, 49.4%), followed by Hispanics ($n = 45$, 26.1%), African Americans ($n = 20$, 11.6%), Arab ($n = 11$, 6.4%) and Asian ($n = 11$, 6.4%). Elevated CA-125 levels were noted in 147 patients (85%) of the study population (Table 1).

Sex and CA-125

There was no statistically significant difference in elevated mean CA-125 level between male (411 U/mL) and female (324 U/mL) patients ($p = 0.207$) (Fig. 1).

Association between objective markers of hepatic decompensation and CA-125

Patients with higher MELD score had a higher CA-125 level ($p = 0.001$), as noted in the linear regression model analysis (Fig. 2). Subjects without ascites had a mean CA-125 level of 36 U/mL, mild ascites of 218 U/mL and moderate ascites of 534 U/mL ($p < 0.001$) (Fig. 3). Ascites was graded based on

Table 1. Patient characteristics and etiologies of cirrhosis

Characteristics	Patients
Sex	
Male	110 (64.0%)
Female	62 (36.0%)
Race	
Caucasian	85 (49.4%)
Hispanic	45 (26.1%)
African American	20 (11.6%)
Arabic	11 (6.4%)
Asian	11 (6.4%)
Etiology of cirrhosis	
Alcohol	56 (32.5%)
Hepatitis C	47 (27.3%)
Nonalcoholic steatohepatitis	18 (10.4%)
Cryptogenic	18 (10.4%)
Hepatitis C plus alcohol	14 (8.1%)
Hepatitis B	9 (5.8%)
Autoimmune hepatitis	7 (4%)
PSC	2
PBC	1

ultrasound or computed tomography findings from scans performed at our center. A similar trend was noted with CTP classification. Child's-A showed a mean CA-125 level of 59 U/mL, Child's-B showed 324 U/mL and Child's-C showed 509 U/mL ($p < 0.001$). Although MELD score had a statistically significant correlation with CA-125 independently, when combined with ascites in a regression model, ascites appeared to be the main player for elevated CA-125 ($p < 0.0001$) when compared to MELD score ($p = 0.375$) (Fig. 4).

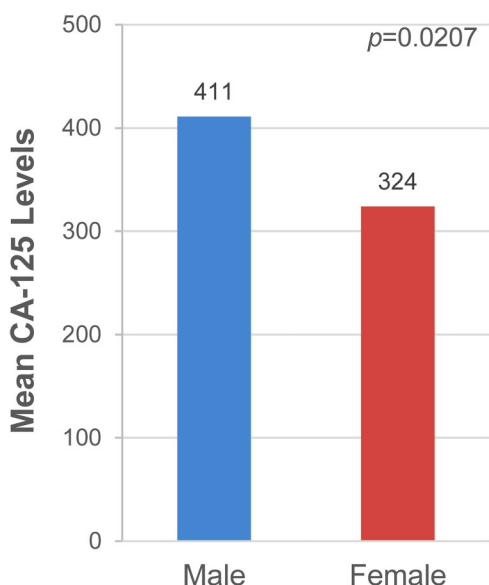


Fig. 1. CA-125 correlation with sex among the study cohort.

Esophageal varices and CA-125

Although patients with evidence of esophageal varices identified during an upper endoscopy had higher mean CA-125 level (414 U/mL) compared to those without varices (256 U/mL), there was no statistical significance for the difference ($p = 0.102$). There was also no correlation between glomerular filtration rate and CA-125 levels ($p = 0.900$).

Hepatocellular cancer and CA-125

The group included 27 (16%) patients with hepatocellular cancer (HCC) at the time of analysis. Those with HCC had a mean CA-125 level of 617 U/mL versus 335 U/mL for those without HCC ($p = 0.001$). Since the number of subjects with HCC was a very small fraction of the total study population, we are unable to draw a meaningful conclusion from this result. This could also be confounded by the fact that the more advanced the liver disease, the higher the risk of HCC.

Serum sodium and CA-125

Since hyponatremia is associated with cirrhosis, especially at the time of decompensation, as a result of volume expansion from fluid retention,²⁶ we correlated serum sodium with CA-125 but found no statistically significant difference ($p = 0.333$).

ALBI score and CA-125

ALBI score, a relatively new prognostic marker in patients with end-stage liver disease, also appeared to have a statistically significant correlation with elevated CA-125 ($p < 0.001$). When combined in a regression model with ascites, the p -value appeared to be more significant for ascites ($p < 0.001$) as compared to the ALBI score ($p = 0.023$) (Figs. 5 and 6).

Other parameters

Statistical significance was observed with serum albumin ($p = 0.013$), total bilirubin ($p = 0.002$) and international normalized ratio ($p = 0.003$), which are markers of decompensated cirrhosis, further supporting our hypothesis of increased levels of CA-125 with further decompensation of cirrhosis based on severity of ascites, MELD score, ALBI score and CTP classification. These parameters are objective markers of decompensated cirrhosis and traditionally used to prognosticate patients with end-stage liver disease. The etiology of cirrhosis did not correlate with elevated CA-125 ($p = 0.889$).

Discussion

Elevated CA-125 levels were noted in 85% of patients with cirrhosis (due to any etiology) at our center. Our study establishes that the more advanced the degree of decompensation based on MELD score, ALBI score and CTP classification, the higher the degree of elevation of CA-125. Absence of ascites is associated with near-normal CA-125 levels and there is a direct correlation between high levels of CA-125 and worsening ascites, supporting the theory that CA-125 elevation may have a physiological role related to mechanical stretch of the peritoneum due to ascites. This theory is also strengthened by the fact that CA-125 level elevation correlated more with ascites than with MELD score and ALBI score in a multivariate regression model. There was no statistically significant correlation

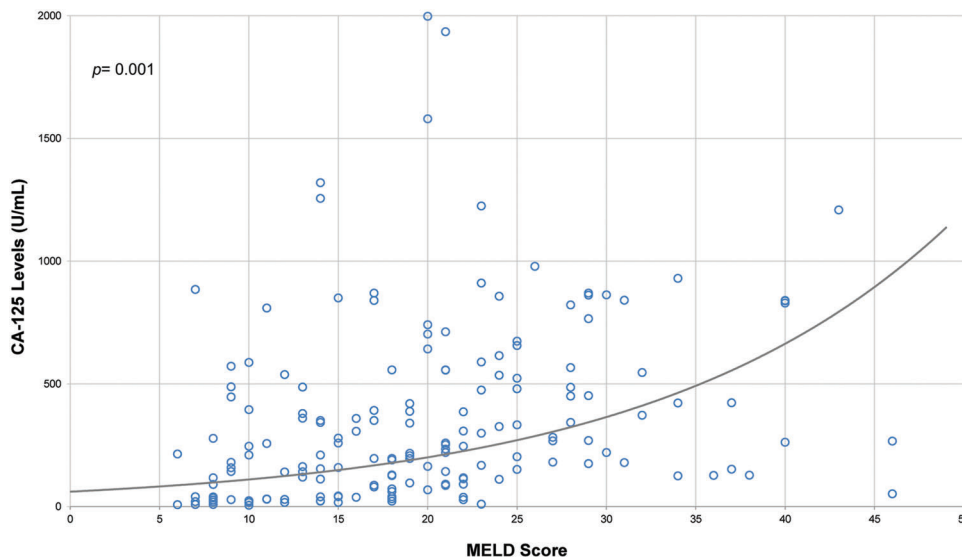


Fig. 2. Scatter plot of linear regression analysis of MELD score and CA-125 antigen. Abbreviation: MELD, model for end-stage liver disease.

identified between male and female patients. 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.

A statistically significant correlation was identified between the various chemical markers of decompensation such as bilirubin, albumin and international normalized ratio, further supporting our hypothesis. Serum sodium, which if low is believed to be a harbinger of onset of ascites and hepatorenal syndrome in cirrhotic patients and often indicates grave prognosis,²⁷ did not appear to have a correlation with the CA-125 serum levels.

The presence or absence of esophageal varices did not correlate with the CA-125 levels, further supporting the above

hypothesis of potential physiological stress-related release of the antigen. No correlation was observed between elevated level of CA-125 and impaired renal function. Since clinical detection of ascites may not always be accurate due to body habitus or presence of negligible amount of perihepatic ascites, we suggest that CA-125 could be used as an alternative marker for detecting and suspecting ascites in a patient with cirrhosis. In particular, it could potentially be used to monitor obese cirrhotic patients with history of ascites on treatment with diuretics, as clinical detection of ascites can often be difficult due to truncal obesity. This is further supported by previous studies which have clearly demonstrated that CA-125 levels drop rapidly with removal of ascitic fluid.²³ Our study has shown that patients without ascites have near normal CA-125 levels.

Serum CA-125 antigen measurement could potentially be used as a marker for the presence or absence of ascites and guide us in the management of patients with decompensated liver cirrhosis due to any etiology. Although there were few studies in the past, with limited numbers of patients but

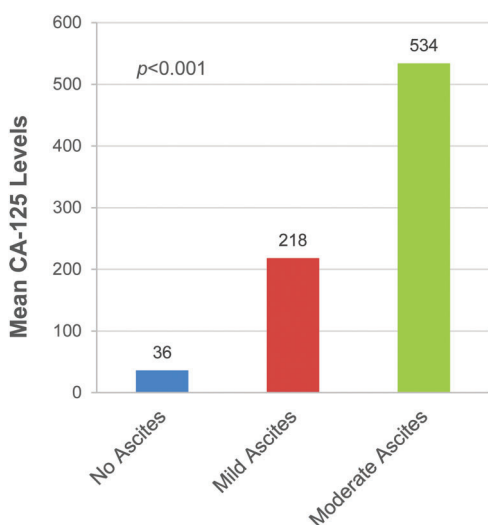


Fig. 3. CA-125 correlation with degree of ascites based on imaging criteria.

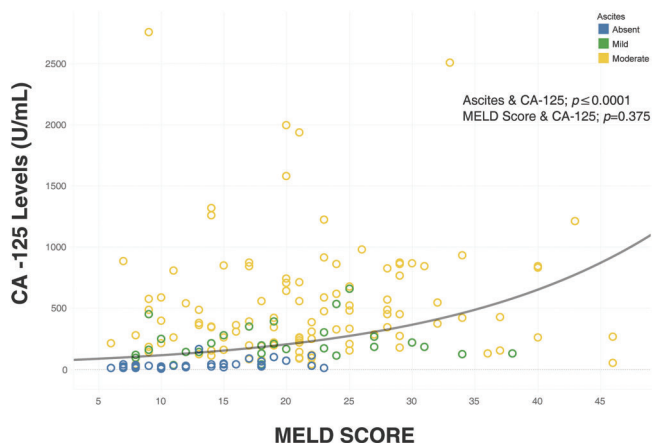


Fig. 4. Linear regression analysis of CA-125 with MELD and degree of ascites. Abbreviation: MELD, model for end-stage liver disease.

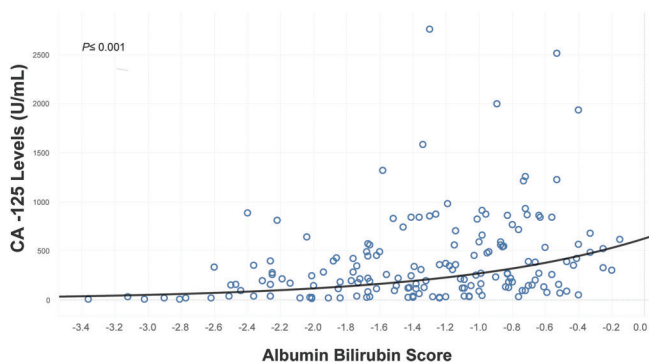


Fig. 5. Scatter plot of the linear regression model between CA-125 and ALBI score. Abbreviation: ALBI, albumin-bilirubin.

showing similar results, our large cohort study not only confirms the observed findings but also concludes that CA-125 is in the normal range in subjects with compensated cirrhosis but without detectable ascites, which is a new finding. We also demonstrated that presence or absence of esophageal varices does not correlate well with CA-125 level and this finding further strengthens the theory of peritoneal stretching from ascites leading to increased secretion of the antigen from peritoneal mesothelial cells.²² Since high MELD score and advanced CTP class are prognostic markers of liver decompensation, the observed finding of elevated CA-125 as these scores worsen can be explained by the fact that most of these patients have developed significant ascites by the time they get to this level of decompensation. With the evolution of new agents in the treatment of hepatitis C, there is hope for cure on the horizon to prevent decompensation of chronic liver disease in the near future.^{28–32} With the explosion of nonalcoholic fatty liver disease in the United States,^{33–36} we expect to see a continuing rise in the incidence of decompensated liver disease over the next decade or two, mandating the need for more research in the field.

As we strive to identify new tools for the management and treatment of these complex patients, a simple old serological test for CA-125 might be viewed as an additional diagnostic assay that can be used to identify and manage patients with decompensated liver disease, especially ascites, which cannot always be quantified accurately by clinical examination and

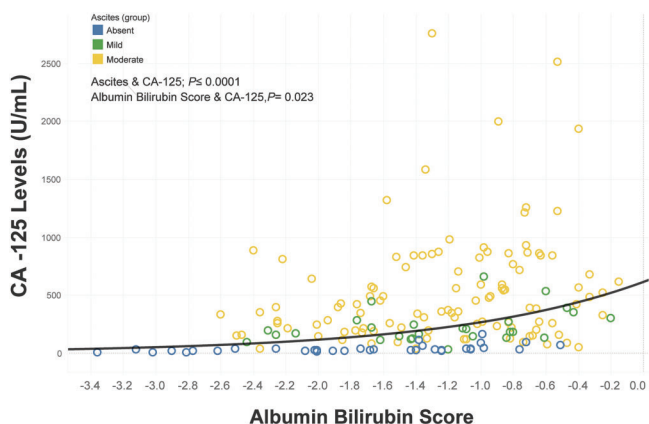


Fig. 6. Linear regression model of CA-125 with ALBI score and degree of ascites. Abbreviation: ALBI, albumin-bilirubin.

requires radiological imaging for quantification. More importantly, elevated CA-125 level in a cirrhotic female with ascites should not lead to unnecessary investigations for gynecological malignancies, unless clinically indicated. Although this abnormality is a known finding from previous studies, our study involving a large cohort of mostly decompensated cirrhotic patients not only confirms the findings but also suggests that elevated CA-125 is probably not a marker of portal hypertension but more an indicator of physiological stress as a result of peritoneal stretching from ascites.

Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Study concept, design, data collection, analysis & interpretation, drafting manuscript & critical revision (RGRE), analysis & interpretation of data, drafting manuscript (SuM), data collection (SeM, VL, PF), statistical analysis and interpretation (YW), study, concept, design, critical revision of manuscript and support (NTP).

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