



CA-125 Significance in Cirrhosis and Correlation with Disease Severity and Portal Hypertension

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Edula *et al.*¹ in their retrospective study of 172 patients concluded that serum concentrations of cancer antigen-125 (CA-125) are elevated in cirrhotic patients with ascites. This relationship has been well known for several decades,²⁻⁶ as well as the relationship of CA-125 with pleural and pericardial effusions, among many other non-malignant conditions,^{4,5,7} because CA-125 is expressed in the coelomic epithelium.⁸ In fact, ascitic fluid concentrations of CA-125 are even higher than in serum.²

Edula *et al.*¹ said that cirrhotic patients without ascites had normal mean CA-125 concentrations, and define this observation as "a new finding". However, these observations are not new. More than 25 years ago our group published a prospective and comprehensive study of 159 patients with liver diseases, including 85 cirrhotics with and without ascites.³ In this article, cited by Edula *et al.* as their reference 14, we found the same results as Edula *et al.*¹ reported for ascitic and non-ascitic patients.¹ Moreover, our group published other articles focused exclusively on patients without ascites.^{9,10} Like Edula *et al.*,¹ we found that elevations of CA-125 concentrations in patients without ascites were uncommon, but also that these elevations were related to the degree of liver dysfunction.

Therefore, CA-125 increases markedly (even 100 times above the upper normal level) in patients with ascites, an increase that we previously found to be highly proportional to the amount of ascites as measured semiquantitatively in 5 degrees, and it decreases rapidly with the diminution of ascites. In fact, CA-125 proved to be a reliable marker of ascites (sensitivity 98.4%, specificity 95.9%, positive predictive value 93.8%, negative predictive value 98.9%, efficiency 96.9%).³

Although to a considerably lower degree, and much more infrequently, we also previously found increased CA-125 concentrations in some patients who did not have ascites, as evaluated ultrasonographically, as well as significant correlations between CA-125 and some liver function markers, such as albumin and prothrombin.⁹ Our findings suggested that, apart from the determinant role of ascites, liver dysfunction itself is also responsible for moderate increases in the serum concentrations of CA-125, probably due to a poor metabolization of this glycoprotein.^{9,10}

On the other hand, the absence of statistical significance regarding portal hypertension ($p = 0.1$) reported by Edula *et al.*¹ is surprising, considering that the differences in the CA-125 concentrations that they found were substantial (414 vs. 256 U/mL) and that portal hypertension is tightly

related to ascites. The authors evaluated portal hypertension by a history of esophageal varices. Besides the limited sensitivity of this method to detect portal hypertension, perhaps the number of patients studied was too small (Type II error). Also, the parametric tests used by the authors for statistical calculations (t -test, ANOVA) might have been inappropriate, as we found that the distribution of CA-125 was markedly non-Gaussian, and the illustrations of Edula *et al.*¹ suggest the same.

In our series, we found marked differences in CA-125 concentrations in patients with or without portal hypertension, as evaluated separately by three different methods: echography, esophageal varices and splenomegaly ($p < 0.0001$ for each).³ Even portal hypertension was associated with higher CA-125 concentrations in patients without ascites ($p = 0.049$).⁹

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Conflict of interest

The author has no conflict of interest related to this publication.

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The Author's Reply

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We would like to thank Julio Collazos for taking the time to read and critique our study. While we understand that there were several studies done in the past on the same subject, our attempt was to revive interest in the same subject as CA-125 antigen is no longer recommended as part of the diagnostic work-up in patients with ascites as per the most recent American Association for the Study of Liver Diseases (AASLD) guidelines for ascites in cirrhosis.¹ The findings of our study did lead us to comment that CA-125 could be a useful test, especially in patients with truncal obesity where clinical quantification of ascites could be challenging, and will require radiological imaging which may be more expensive and inconvenient for patients, especially when they are being followed for dose titration of diuretics.²

Our study did correlate CA-125 antigen with ascites and the model for end-stage liver disease (MELD) score in a linear regression model and concluded that there was a better statistically significant correlation with ascites as compared to the MELD score. Since the MELD score is currently used as the best objective marker for decompensation in patients with end-stage liver disease, we feel this is a significant finding in our study. This also applies to the albumin-bilirubin (ALBI) score, which is a relatively new 'kid on the block' in the evaluation of patients with cirrhosis. These findings are new and have not been reported from other previous studies.

Since our study was retrospective and relied on available data, we used esophageal varices as a marker of portal hypertension rather than other parameters. Moreover, the elevated total CA-125 in both groups of patients with and without esophageal varices (414 vs. 256 IU/mL) was significant, although the significance did not reach the threshold set for statistical significance; this finding was confounded by the fact that several of the patients in both groups had ascites from decompensated cirrhosis, which had the best correlation with elevated CA-125 antigen.

While we understand the limitations of a retrospective study and the probability of a Type 2 error, we were able to conclude that patients with cirrhosis but without ascites had normal values of CA-125 antigen, unlike in the study by Collazos *et al.*,³ who concluded that findings of elevated antigen were uncommon in the absence of ascites; moreover, their study concluded that CA-125 antigen was invalidate as a tumor marker. I would also like to highlight that our group of patients studied was homogenous and consisted of patients with cirrhosis exclusively.

Conflict of interest

The author has no conflict of interest related to this publication.

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