ANNALS of Hepatology

HEPATOLOGY HIGHLIGHTS

July-August, Vol. 12 No.4, 2013: 356-358

Hepatology highlights

Jorge A. López-Velázquez, Justo Fernández-Rivero, Norberto C. Chávez-Tapia, Misael Uribe, Nahum Méndez-Sánchez

Liver Research Unit, Medica Sur Clinic & Foundation. Mexico City, Mexico.

Predicting the prognosis in acute liver failure: results from a retrospective pilot study using the LiMaX test

Lock, *et al.* Nowadays, acute liver failure is a major cause of short mortality with a poor prognostic. Assessment of hepatic function is crucial in the follow-up of patients with fulminant liver failure. Breath testing has been used experimentally and clinically for several years; it is based on the principle that a measurable metabolite of an ingested substrate is expelled by the respiratory system.[1] The ideal substrate would be metabolized solely by the liver and therefore selectively reflect liver metabolic function. To improve the diagnostic efficacy of these tests, several quantitative approaches have been proposed to measure metabolic liver function.[2]

The LiMaX test, a breath quantitative test that determines the absolute quantity of the cytochrome P450 1A2 (CYP1A2) system which is exclusively expressed in hepatocytes acinus and is proportional to parenchymal volume therefore that is not influenced by drugs or genetic variations.

A substance exclusively metabolized by CYP1A2 is methacetin which is transformed by demethylation and oxidation to acetaminophen in the endoplasmic reticulum of hepatocytes.[2,3]

In this study, Lock, *et al.* determine the maximal liver function capacity for predicting the prognosis of ALF. Twelve patients with ALF diagnosis caused by viral hepatitis (n = 2), toxic liver injury (n = 3) and cryptogenic liver failure (n = 7) were analyzed. Seven patients recovered from ALF and were discharged for liver transplantation, while from the non recovery group four patients died and one undergone liver transplantation. According to hepatology scores (MELD and Kings College criteria) there were no differences between both groups, meanwhile LiMAx data achieved statistical significance despite the small sample size. Results obtained were 19 ± 19 (16-62) for non-recovery *vs.* 94 ± 119 (39-378) μg/kg/h for recovery (P = 0.018). Subsequently, ROC curve analysis indicates an area under ROC of 0.94 (95% confidence interval 0.74-1.00, P < 0.019) with a best cut off of 38 μg/kg/h.

Regarding this data, the authors propose that the LiMAx test cannot only determine ALF itself, but can potentially differentiate between those patients with spontaneous recovery and those that require urgent liver transplantation. This study highlights the markedly impaired in patients with ALF which could be a prognostic value for predicting the outcome as well as the option of liver transplantation. However, bear in mind that in order to confirm and validate the results of this study, a multicenter study must be performed on a larger patient population with several degrees of damage. Therefore a period of analysis based on a rigorous and clinical evaluation of the tests would assist in investigating the clinical utility of each biochemical test.

Correspondence and reprint request: Prof. Nahum Méndez-Sánchez, MD, MSc, PhD, FACG, AGAF.
Liver Research Unit, Medica Sur Clinic & Foundation
Puente de Piedra, Núm. 150. Col. Toriello Guerra, Mexico City, Mexico.
Tel.: +5255 5424-7200 (4215). Fax: +5255 5666-4031
E-mail: nmendez@medicasur.org.mx

The size does matter in the assessment of liver fibrosis with transient elastography (FibroScan®)

Cirrhosis is the end result of many types of chronic liver injury, is characterized histologically by extensive fibrosis in association with the formation of regenerative nodules.[4] Patients with cirrhosis are at higher risk of morbidity and mortality,[5] hence the importance of early detection of fibrosis stages. The accuracy of liver biopsy in assessing fibrosis may be questioned because of sampling error and interobserver variability.[6] Non-invasive methods such as transient elastography (FibroScan®, Echosens, Paris) has been evaluated for the detection of hepatic fibrosis and cirrhosis with good results. Castera, *et al.* prospectively compared transient elastography (TE) with other noninvasive methods such as FibroTest, APRI, and liver biopsy in patients with hepatitis C virus showing an AUROC > 0.9 for F3 of METAVIR.[7]

TE was validated by Foucher, *et al.* in different etiologies of chronic liver disease such as hepatitis C virus or hepatitis B virus infection, alcohol, and non-alcoholic fatty liver disease (NAFLD).[6] Obesity is a common and well-documented risk factor for NAFLD,[8] the prognosis depends of histological severity. Wong, *et al.* evaluated the accuracy of TE for the diagnosis of fibrosis and cirrhosis in patients with NAFLD establishing a high negative predictive value to exclude advanced fibrosis.[9] Liver stiffness measurement (LSM) has limitations. LSM failure [defined as an interquartile range (IQR)/LSM ratio above 0.30, a success rate below 60% or a number of successful acquisitions less than 10] was reported in 11.6 to 18.4%.[10] Failure is associated independently with body mass index (BMI) > 30 kg/m^2 (OR 7.5) emphasizing the need for technological improvements in this group of patients.[10]

Myers, *et al.*[11] evaluate the feasibility and diagnostic performance of the FibroScan XL probe for LSM in overweight and obese patients with chronic liver disease. Compared with the M probe, the FibroScan XL probe reduced the TE failure (1.1 *vs.* 16%) and facilitates reliable LSM (73 *vs.* 50%) in patients with BMI > 28 kg/m^2, with comparable accuracy. Similar findings were reported by de Lédinghen, *et al.*;[12] a strong correlation between M and XL values, proposing the use of M probe as a first step for LSM, with a comparable diagnostic accuracy between M and XL probe in overweight and obese patients in 91.2% of the cases.

In this number of *Annals of Hepatology* Lai-Hung, *et al.* evaluate the cut-off values of M probe to XL probe for diagnosis of advanced fibrosis in a large prospective, multicenter cohort of overweight and obese patients who underwent LSM by TE. Cut-off values were established by discretized LSM-M probe, and use of LSM-XL probe to predict ranges. The overall accuracy was 89% for < 4.8 kPa or > 10.6 kPa, in patients with BMI 25-30 kg/m^2 that was subsequently validate in a subgroup of patients who underwent liver biopsy. The XL cutoffs at 4.8 kPa and 10.7 kPa were the best estimate of 6.0 kPa and 12.0 kPa of M probe for patients with overweight. Obese patients might use M probe cutoffs for XL probe.[13] The change in cut-off values has important clinical implications. The reduction of these values will move more patients to increased risk of liver fibrosis. In the validation cohort the new cut-off values put out from no fibrosis 19% of patients, and 13% were moved to the gray zone, and 6% goes to advanced fibrosis. This change was similar in the exploratory cohort reducing the non fibrosis 16%, and increasing the gray zone 12%, and advanced fibrosis 4%. This change is very similar for obese and non-obese group in the exploratory cohort.

There is no doubt about the importance of the adjustment of LSM, and the validation of this proposal in other obese and non-obese population. But also we need remark the implications for the practitioner, which will face an important clinical question. How to manage more patients in the grey zone of TE? Further research is necessary to answer this, and the contribution of these cut-offs will raise new questions.

Acute phase proteins for the diagnosis of bacterial infection and prediction of mortality in acute complications of cirrhosis

Lazzarotto, *et al.* Decompensated liver cirrhosis is characterized by the presence of several conditions with a poor prognosis such as bacterial infections that in consequence precipitate liver failure and cause death in most cases. Spontaneous bacterial peritonitis, urinary tract infections, respiratory infections and bacteraemia are the most frequent infective complications in cirrhosis.[14,15]

There has also been an interest in finding a test that would identify patients at high risk of infection

as well as the prognosis. These patients could then be followed more closely, and infection could perhaps be detected and treated at an earlier more survivable stage. In this context, the aim of the present study was to evaluate the performance of two inflammatory serum markers C reactive protein (CRP) and procalcitonin (PCT) for the diagnosis of bacterial infection in patients with decompensated liver cirrhosis, and to investigate the association between theses biomarkers and short-term mortality.

In a group of 64 cirrhotic patients and a total of 81 admissions due to clinical complications of the disease were analyzed in the prospective study. Results from present study show that were estimated the sensitivity and specificity by measuring area under ROC curves of CRP and PCT for the diagnosis of infection. CRP levels > 29.5 exhibited sensitivity of 82% and specificity of 81% for the diagnosis of bacterial infection. By the other hand, PCT levels > 1.10 showed sensitivity of 67% and specificity of 90%. Interestingly higher levels of CRP (P = 0.026) and PCT (P = 0.001) were observed among those who died within three months after admission.

Regarding these data serum CRP and PCT may be used as sensitive screening tools for detecting the presence of current bacterial infection and predicting subsequent outcomes in this kind of patients. Perhaps as the authors mention, the small size sample was similar to most studies in this field, however the data observed require external validation by prospective studies with a bigger number of patients, especially with regard to the chosen cutoffs of both inflammatory markers. This tool could be worked into an orchestrated care plan for patients with cirrhosis. Actually in hepatology, it is very well known that many useful biomarkers have been described and are being used clinically to help make decisions regarding patient care. With the new era of validated and tested biomarkers for bacterial infections in decompensated cirrhosis will make more sense to use to guide duration of antibiotic treatment as well as to involve in other risk factors that endanger the clinical condition of these patients.[16]

REFERENCES

1. Ilan Y. Review article: the assessment of liver function using breath tests. *Aliment Pharmacol Ther* 2007; 26: 1293-302.
2. Stockmann M, Lock JF, Riecke B, Heyne K, Martus P, Fricke M, Lehmann S, et al. Prediction of postoperative outcome after hepatectomy with a new bedside test for maximal liver function capacity. *Ann Surg* 2009; 250: 119-25.
3. Afolabi P, Wright M, Wootton SA, Jackson AA. Clinical utility of 13C-liver-function breath tests for assessment of hepatic function. *Dig Dis Sci* 2013; 58: 33-41.
4. Lefton HB, Rosa A, Cohen M. Diagnosis and epidemiology of cirrhosis. *Med Clin North Am* 2009; 93: 787-99, vii.
5. Bosch FX, Ribes J, Cleries R, Diaz M. Epidemiology of hepatocellular carcinoma. *Clin Liver Dis* 2005; 9: 191-211, v.
6. Foucher J, Chanteloup E, Vergniol J, Castera L, Le Bail B, Adhoute X, et al. Diagnosis of cirrhosis by transient elastography (FibroScan): a prospective study. *Gut* 2006; 55: 403-8.
7. Castera L, Vergniol J, Foucher J, Le Bail B, Chanteloup E, Haaser M, et al. Prospective comparison of transient elastography, Fibrotest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C. *Gastroenterology* 2005; 128: 343-50.
8. Chalasani N, Younossi Z, Lavine JE, Diehl AM, Brunt EM, Cusi K, et al. The diagnosis and management of non-alcoholic fatty liver disease: practice guideline by the American Gastroenterological Association, American Association for the Study of Liver Diseases, and American College of Gastroenterology. *Gastroenterology* 2012; 142: 1592-609.
9. Wong VW, Vergniol J, Wong GL, Foucher J, Chan HL, Le Bail B, et al. Diagnosis of fibrosis and cirrhosis using liver stiffness measurement in nonalcoholic fatty liver disease. *Hepatology* 2010; 51: 454-62.
10. Castera L, Foucher J, Bernard PH, Carvalho F, Allaix D, Merrouche W, et al. Pitfalls of liver stiffness measurement: a 5-year prospective study of 13,369 examinations. *Hepatology* 2010; 51: 828-35.
11. Myers RP, Pomier-Layrargues G, Kirsch R, Pollett A, Duarte-Rojo A, Wong D, et al. Feasibility and diagnostic performance of the FibroScan XL probe for liver stiffness measurement in overweight and obese patients. *Hepatology* 2012; 55: 199-208.
12. de Ledinghen V, Wong VW, Vergniol J, Wong GL, Foucher J, Chu SH, et al. Diagnosis of liver fibrosis and cirrhosis using liver stiffness measurement: comparison between M and XL probe of FibroScan(R). *J Hepatol* 2012; 56: 833-9.
13. Wong GL, Vergniol J, Lo P, Vincent Wai-Sun Wong, Juliette Foucher, Brigitte Le Bail, Paul Cheung-Lung Choi. Non-invasive assessment of liver fibrosis with transient elastography (FibroScan®): applying the cut-offs of M probe to XL probe. *Ann Hepatol* 2013; 12: 402-412.
14. Navasa M, Rodés J. Bacterial infections in cirrhosis. *Liver Int* 2004; 24: 277-80.
15. Papp M, Vitalis Z, Altorjay I, Tornai I, Udvardy M, Harsfalvi J, Vida A, et al. Acute phase proteins in the diagnosis and prediction of cirrhosis associated bacterial infections. *Liver Int* 2012; 32: 603-11.
16. Tsiakalos A, Karatzaferis A, Ziakas P, Hatzis G. Acute phase proteins as indicators of bacterial infection in patients with cirrhosis. *Liver Int* 2009; 29: 1538-42.