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Hepatology Highlights

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Serum cystatin C: a non-invasive marker of liver fibrosis or of current liver fibrogenesis in chronic hepatitis C?

Ladero, et al. Progression of fibrosis is an important prognostic factor in chronic hepatitis C. Factors associated with accelerated fibrosis include age at infection, alcohol consumption and co-infection with either HIV or hepatitis B.[1] To determine level of fibrosis, liver biopsy has been considered the gold standard for many years. It is not a perfect test, however, as sampling error and interobserver variation have been observed.[2] Additionally, there is a risk of bleeding, pneumothorax and biliary peritonitis when performed percutaneously, which is lowered when performed with the transjugular approach.[3,4] With this in mind, various non-invasive tests, including serum markers and transient elastography, have been studied as possible alternatives to liver biopsy. No single test has proven superior, but results have been improved when used in combination, leading to the development of various diagnostic algorithms to assess liver fibrosis.[5]

In this study, Ladero, *et al.* study the role of cystatin C, a cysteine protease inhibitor, as a potential non-invasive marker for liver fibrosis in patients with treatment naïve chronic hepatitis C and normal renal function. Patients with creatinine > 1.20 mg/dL, HIV, hepatitis B, hepatocellular carcinoma and ethanol ≥ 50 g daily were excluded. Patient serum cystatin C was compared to same day liver biopsy, with fibrosis graded using METAVIR scoring by a single pathologist. Additionally, serum cystatin levels were obtained from a small group of well-compensated cirrhotics (Child A).

One hundred patients (M = 56, F = 44) were in the first group and sixteen in the cirrhotic group. Cystatin C levels were seen to increase significantly from stage 0-2 but noted a non-significant decline in stage 3 and plateau in stage 4. The authors propose that this may be related to decreased TGFβ levels, a cytokine involved in active fibrogenesis, in patients with advanced fibrosis. TGFβ may be the primary stimulus for cystatin C production, but this relationship was not directly assessed in this study. The authors report that cystatin C levels were directly related to necroinflammatory grade, suggesting a possible marker of fibrogenesis. Cystatin C levels were seen to increase in the well-compensated cirrhotic group, possibly indicating early reduction in glomerular filtration rate not reflected by serum creatinine as the cystatin C has also been proposed as a marker of renal function.

This study highlights the complex pathophysiology of progressive liver fibrosis and the challenge in finding an optimum non-invasive test to replace liver biopsy. Interestingly, its use in cirrhosis to detect early changes in glomerular filtration rate should be studied further in the context of predicting development of the hepatorenal syndrome.

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Liver transplantation in the critically ill: donation after cardiac death compared to donation after brain death grafts.

Burcin Tanner, et al. Over the past thirty years, great strides in liver transplantation have been made to improve survivorship from liver cirrhosis and hepatocellular carcinoma, which is a minimum 63-67% at five years[6,7] and, in most cases of non-hepatitis C, non-malignant disease, much higher. One challenge has been meeting the demand for donor organs, resulting in attempts to expand the supply pool through donation post-cardiac death (DCD) and live donor. The early 21st century saw an increase in DCD, but early studies suggest increased graft failure relating to hepatic artery anastomoses and biliary strictures,[8-10] Current studies are ascertaining whether populations exist where DCD may be a feasible option, leading us into the article from this issue of the journal, where critically ill patients are the population in focus.

In this study, Burcin Taner, *et al.* report their experience from the Mayo Clinic in Jacksonville, Florida, in a cohort study comparing short and long term outcomes in critically ill patients who received liver transplantation post-brain death (DBD) or DCD. Over a five- year period (2003-2008), 1,215 liver transplants were performed, with 50 recipients in the intensive care unit. Forty-two patients were in the DBD and 8 in the DCD groups, respectively. Baseline characteristics, including MELD, APACHE, vasopressor, ventilation and renal replacement requirements were similar in both groups. Graft cold and warm ischemia times did not differ, but DCD operative time was significantly higher ($p = 0.037$). Donor risk index scores (DRI) were also higher in the DCD group ($p = 0.030$). Despite these differences, total stay in the ICU and hospital stay were similar. Also, non-significant differences in graft and overall survival were seen at 4 month and 1 year post-transplant but survival rates were similar at 3 years.

This is a single centre study with significant experience with transplantation post-cardiac death and with liver transplantation in general, with over 200 DCD cases performed in a 5 year period. Additionally, there were non-significant differences in graft and overall survival at 4 months and 1 year, raising concern regarding the quality of grafts post-cardiac death. This study was underpowered to detect such a difference. We agree with the authors that donation post-cardiac death may be an important method to increase organ availability in their centre but more centres should publish outcomes to assess whether this statement can be applied universally.

Does the size of the needle influence the number of portal tracts obtained through percutaneous liver biopsy?

Sporea, et al. Given the problems associated with liver biopsy (including sampling error as a liver biopsy samples only 1/50,000 of the volume of the liver, an organ which is the approximate size of an American football, risk of bleeding, pain, etc.) and the recent explosion of papers studying non-liver biopsy modalities of assessing liver fibrosis (i.e. transient elastography, or Fibrotest, acoustic radiation force impulse, or ARFI, and laboratory algorithms such as Fibrotest/Fibroscan), one can be excused for assuming that the liver biopsy is soon to be obsolete. On the contrary, although liver biopsies may be of suboptimal utility for the sole purposes of fibrosis staging, in those patients with a secure diagnosis of their liver disease, in many cases, the clinical and laboratory diagnosis of the specific liver disease may be equivocal and definitive diagnosis will be dependent on the histologic findings. Likewise, in liver transplantation, the grade and severity of acute graft rejection as well as the distinction between graft rejection and primary disease recurrence (i.e. hepatitis C), depends on examining a liver biopsy, as post-transplant liver biochemistry alone is notoriously non-specific.

The study by Sporea, *et al.*, from Romania, reports their retrospective analysis of the number of portal tracts obtained after liver biopsy with a 1.4 mm Menghini needle compared to a 1.6 mm needle. At their centre, all patients underwent ultrasound guided liver biopsy (the ultrasound "marked the spot" followed by a liver biopsy) and the standard of care was to obtain two biopsy samples. Not surprisingly, the 1.6 mm needle biopsy obtained more portal tracts for histologic examination compared to the 1.4 mm needle. In terms of suboptimal/inadequate liver biopsy samples, both needles performed similarly – 2.7-3.7% had less than 8 portal tracts. The inadequacy of liver biopsy samples was speculated to be related to patient specific factors such as obesity, rather than the fault of the needles themselves. Reassuringly, of the 596 study patients reviewed, there

were no complications, confirming that liver biopsies, although associated with material risks, are generally safe. Although this study confirms that "size matters" when it comes to selecting Menghini needles for biopsy, the study also confirms that, in the era of rapid technological advancement in medicine, the "old fashion" liver biopsy, still remains relevant.

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