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EDITORIAL

From bed to bench: Which attitude towards the laboratory liver tests should health care practitioners strike?

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Abstract

There is a general consensus in re-interpreting the so-called liver function tests in the light of novel discoveries. At the same time, recent evidence favours the use of different laboratory data to assess liver damage, fibrosis or regenerative process, but this point is not always shared. Actually, balancing the need for diagnosis, prognostic evaluation and therapy response of liver disease with a good cost/benefit ratio is very difficult. New tests are probably not needed but the aim should be for better utilization of existing tests to contain the increasing cost of health care.

Key words: Laboratory liver tests; ALanine aminotransferase; Aspartate aminotransferase; Quantitative testing of liver function; Alcoholic liver disease; Non-alcoholic steatohepatitis; Hepatitis C virus

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SCENARIO

The liver being a multifunctional organ (specialized in detoxification, metabolism and defence), the reliability of a single laboratory test is relatively limited (obviously, chemistry is the first approach followed by imaging and histology, not necessarily in this order). So far, the hepatic diagnostic evaluation is based on several contextual or in sequence analyses. Different algorithms have been proposed to improve the detection, the differentiation and the severity of liver diseases. Actually, the favourable relationship between hepatologists and the clinical chemistry experts is jeopardized by an overuse of laboratory services. This attitude does not reduce mortality, does not shorten hospital stays, nor contribute to the quality of medical care. Actually, balancing the need for diagnosis, prognostic evaluation and therapy response of liver disease with a good cost/benefit ratio is quite difficult. But, is it true that those never ending reports that advice the practitioners about the clinical utility of various diagnostic tools greatly broaden the health care costs?

Until now, physicians evaluate the type and the entity of hepato-cellular damage. Generally, it is considered to appear as inflammation and colliquative necrosis. In this direction the laboratory liver tests (LLTs) moved since the discovery of the transaminases usefulness in diagnosing acute hepatitis, anciently known as "icterus catharralis", in the mid 1950s, and published some years later[1].

These tests are erroneously named as liver function tests, and alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are considered the most important. They are present in high concentration in hepatocytes, where they catalyse the transfer of amino groups from alanine and aspartate to the α-keto group of ketoglutaric acid in order to produce pyruvic acid and oxaloacetic acid, respectively. These enzymes leak into the blood when the hepatocytes cell membranes are damaged.

IS THE ROLE OF APOPTOSIS DEFINITELY UNDERESTIMATED IN EVALUATING THE ENTITY OF LIVER INJURY?

As previously stated, the hepatic damage evaluation is abundantly unbalanced toward the inflammation/necrosis process. Apoptosis may occur in the absence of significant transaminases increase as happens in hepato-cellular necrosis. Apoptosis describes the process by which damaged or senescent cells are eliminated from the organism. The expression "the falling of old leaves from trees in the autumn" clearly explains the apoptosis meaning. Apoptosis occurs by two mechanisms: death receptor or extrinsic mechanism and mitochondrial or intrinsic mechanism. Hepatocytes express different death receptors, i.e., Fas, tumor necrosis factor-receptor 1 (TNF-R1), TNF-related apoptosis-inducing ligand receptor 1 (TRAIL-R1), and receptor 2 (TRAIL-R2); stellate cells express Fas and TRAIL when are activated into myofibroblast-like phenotype and undergo apoptosis during resolution of liver injury *in vivo*. Cholangiocytes seem to be a type of

cells in which the mitochondrial mechanism to apoptotic is essential. Apoptosis has a major role in hepatic injury and subsequent progression to fibrosis as it has been well established in different hepatic diseases. In fact, apoptosis is one of the most important mechanisms leading to hepatocyte elimination in non-alcoholic fatty liver disease (NAFLD) and contribute to intensify inflammation in the same disease inducing proapoptotic protein p53 with the inhibition of antiapoptotic Bcl-2[2].

Apoptosis results in the extracellular release of a limited number of proteins including: cytochrome c, some caspases and cleaved cytokeratin-18 and possibly a few other proteins. Mitochondrial cytochrome c release is the key event, which is critical for the initiation of the formation of the apoptosome complex that is essential for the activation of caspase-9 and initiation of the mitochondria-dependent apoptotic cascade[3,4]. Following this pattern of speculation, a new (not completely!) marker in detecting Non-Alcoholic Steato Hepatitis (NASH)[5], has been studied.

MORE SUBTLE TESTS OF LIVER CELL DAMAGE WILL PROBABLY BECOME AVAILABLE IN THE FUTURE, BUT IN THE MEANTIME, DOES MEASUREMENT OF SERUM AMINOTRANSFERASE CONCENTRATIONS FULFILL THE PRECISION PURPOSE?

ALT is the more specific marker of hepatocellular injury because it occurs exclusively in the liver, whereas AST occurs to some extent also in heart, skeletal muscle, kidney and pancreas. AST is prevalently found in mitochondria (near 80%) and to a lesser extend in cytoplasm (20%). Meanwhile, ALT is bound to cytoplasm. It is necessary to stress that, although transaminases are sensitive indicators of hepatocyte damage, they could not be considered reliable markers. The likelihood that abnormal aminotransferase levels reflect liver disease is exponentially increased by the presence superior to six months; the association with signs or symptoms of liver disease; the high enzyme levels; the plurality of abnormal liver enzymes.

Serum ALT/AST concentrations are raised in almost all forms of liver disease, but to different degrees. Very high concentrations (> 10 × Upper limit of normality, ULN) are typical of acute viral, drug-induced hepatitis, ischemic injury to the liver. ALT/AST levels may be unexpectedly high in the early stage of biliary obstruction and, rarely, in flares of autoimmune chronic hepatitis. Those levels do not necessarily mirror the severity of hepatocyte necrosis or the patients' prognosis. This point is evident in massive hepatic necrosis, when a decreasing serum concentration signifies not recovery, but a fewness of hepatocytes from which the enzymes can leak. In the patient in state of shock, serum ALT and AST concentrations typically rise abruptly and return to normal within days after haemodynamic stability is restored. Return to previous normal values may be sufficiently rapid in drug-induced hepatitis. These laboratory abnormalities patterns contrast with those in acute viral hepatitis, in which the decrease is far more gradual. Serum ALT and AST concentrations are moderately raised (2-10 × ULN) in chronic and asymptomatic cases of acute viral or drug-induced hepatitis, autoimmune hepatitis, and alcoholic liver disease. In these disorders the enzyme concentrations generally correlate with the activity of the disease. Post-viral cirrhosis, the whole spectrum of NAFLD, cholestatic liver disease, and hepato-cellular carcinoma are characterised by slightly raised serum aminotransferase levels (< 2-3 × ULN). The serum AST/ALT ratio may help diagnose some liver diseases. In most patients with acute liver injury the ratio is 1 or less, whereas in alcoholic hepatitis it is generally about 2. Deficiency of pyridoxal-5'-phosphate, a necessary coenzyme for both aminotransferases, is common in alcoholic liver disease. This deficiency decreases hepatic ALT to a greater extent than AST, ending up in changes in serum concentrations. Although diagnostic laboratories scarcely offer measurement of AST isoenzymes, a high ratio in the serum of mitochondrial to total AST indicates mitochondrial damage and provides further evidence of alcoholic liver disease. Paradoxically, in patients suffering from liver cirrhosis of any etiology without ongoing liver injury the values may be normal.

COULD THE "MEASUREMENT LOCATION" AFFECT THE ALT AND AST ELEVATION DEGREE?

This point is clearly supported by some evidence. The causes of very high serum aminotransferase concentrations in a particular centre are influenced by its location, as noted in Swansea, Wales, where viral hepatitis accounts for only 3.5% of AST concentrations of over 400 U/L. Ischaemic/hypoxic liver injury accounts for a half, extrahepatic biliary obstruction for a quarter, and drug toxicity for 8.5% of the cases. This pattern reflects a highly developed community. In developing countries viral hepatitis is still prevalent, and toxic hepatitis is more likely and biliary obstruction from gallstones less likely to be encountered than they are in Swansea[6].

ARE CLUES IN THE HISTORY AND CLINICAL EXAMINATION NECESSARY TO ASSESS ALT/AST LEVELS?

A recent study sought for identifying any benefit of routine LLTs, i.e., AST, ALT, total bilirubin, or alkaline phosphatase, in 268 consecutive, chronically ill, geriatric patients presenting for acute care from a long-term care facility. All were without jaundice, right upper quadrant pain, pruritus, bruising, or evident signs of chronic liver disease. The degree of LLTs abnormality during admission was compared to the clinical diagnosis at the time of discharge. The levels normalized within two days in 26 of these patients, 25 of whom had a history of vascular disease (96%). All but one of the 268 patients were

discharged without further evaluation. Over one year of follow-up, no patient returned for a liver-related problem. Based on these findings, only those patients with LLTs levels that are twice normal and which do not normalize within two days warrant further evaluation. Authors concluded that transient LLTs abnormalities may be due to decreased liver perfusion[7].

CARDIOVASCULAR DISEASE EVALUATED BY A VINTAGE TEST

ALT is a marker of NAFLD presence (be aware of silent NASH) and predicts incident type 2 diabetes mellitus. Lately, ALT was shown to be also associated with endothelial dysfunction and carotid atherosclerosis[8].

SHOULD NEW PERSPECTIVES BE APPLIED TO THE PROGNOSIS EVALUATION OF LIVER DISEASES?

In westernized countries metabolic, alcoholic and chronic viral disease represent the major part of hepatic illnesses. The search for markers of alcohol abuse has been dynamic for the past years. Several laboratory abnormalities based on liver enzymes, metabolic substances, hormone levels and haematological characteristics have been observed to be associated with the problem of drinking.

Due to its short half life, breath, urine or blood ethanol analyses provide scarce information about the entity of alcohol drinking, being an increased tolerance possibly identified. Blood or breath alcohol levels > 1.5% without great evidence of intoxication or > 3% at any time have been reported to be the first-level criterion of alcoholism.

An elevated serum level of membrane-bound enzyme, gamma-glutamyl transpeptidase (GGT) has been widely used as a marker of alcohol abuse. The half life of elevated GGT is between two and three weeks. Unfortunately, the sensitivity of GGT in detecting alcohol abuse has been reported to greatly vary (34%-85%).

GGT does not increase after acute alcohol intake, but needs continuous alcohol consumption of 80-200 g/d for several weeks. In addition to alcohol abuse, increased GGT is frequently found in NAFLD, heart failure and in subjects using antiepileptics, anticoagulants or barbiturates.

Mean corpuscular volume (MCV) is an index of red blood cell size. Increased MCV values have been observed in 34%-89% of alcohol abusers. Increased MCV values are also found in cases of vitamin B_{12} and folic acid deficiency, chronic liver diseases, hypothyroidism, haematological disorders as well as among smokers. MCV responds slowly to abstinence and up to 40% may have an elevated MCV value even after three months of abstinence.

Other generally used markers are serum amino-transferase. These enzymes are more indicative of liver damage than of alcohol abuse. The overall sensitivity of AST has been estimated to be 35% as a marker of alcohol abuse[9]. The sensitivity for ALT is even lower. One of the modern laboratory tests for alcohol abuse is serum carbohydrate deficient transferrin (CDT). The marker consists of the asialo, mono-sialo and di-sialo isoforms of transferrin that are deficient in their terminal trisaccharides. False-positives have been reported in patients with severe liver diseases (primary biliary cirrhosis, chronic hepatitis C, hepato-cellular carcinoma) and in patients with genetic D-variant of transferrin. During abstinence, the CDT values normalize with a mean half-life of 15 d. CDT values seem to increase after one week of drinking at a level of at least 80 g ethanol per day. Obviously, the diagnosis of alcoholic liver disease (ALD) is based on alcohol consumption, physical signs and symptoms, and laboratory tests. In a recent study, the sensitivity and specificity of CDT for ALD was 93.4% and 71.9%, respectively[10].

Alcoholism plays a key role in worsening any other liver disease! An up-to-date research using population-based mortality data to investigate whether heavy drinking affected the age of death among individuals with HCV was analyzed a total of 7263163 death records in the United States between 2000 and 2002. This study provided evidence to establish heavy alcohol consumption as one of the key risk factors contributing to premature deaths from HCV in the United States. Still, it pointed out that alcohol consumption affects men and women differently in HCV mortality[11].

From a similar point-of-view, laboratory tests reflecting the "metabolic co-factor" linked to HCV-related chronic hepatitis should not be neglected.

WHICH LIVER DISEASE IS UNRAVELLED BY CHRONIC ABNORMAL ALT LEVELS?

Near 10% of the patients with chronically abnormal ALT levels show no evident relationship with any illness. The prognosis of this finding, the link with liver fibrosis and the need for a liver biopsy are largely unknown. The aim of a recent retrospective study in 67 patients with accidentally detected chronically elevated ALT levels, who had a liver biopsy, was to evaluate the prevalence of NASH, and the biological factors associated with this entity. Fibrosis scores were: F0, 37.3%; F1, 32.8%; F2, 26.9%; F3, 1.5%; and F4, 1.5%. NASH was absent in 59.7% and present in 40.3%. Significant differences were observed between $F < 2$ and $F \geqslant 2$ fibrosis patients for AST and ALT and between patients with NASH or without for body mass index. The prevalence of $F \geqslant 2$ fibrosis and NASH in patients with unexplained chronic abnormal ALT were 30% and 40%, respectively. Since the risk of $F \geqslant 2$ fibrosis was significantly increased in patients with AST > N and/or ALT > 2N, liver biopsy, concluded the Authors, should be performed only in patients with AST > N or ALT > 2N[12].

WHICH IS THE NORMAL RANGE OF ALANINE-AMINOTRASFERASE?

The ULN of serum ALT was in these years challenged, because patients diagnosed with liver diseases may have 'normal' or near-'normal' ALT levels, and because possible modulators are often ignored in determining normal range. Some researchers reviewed medical records of subjects aged 15-90, who underwent standard panels of laboratory tests, including serum ALT, over 6 mo at a

central laboratory. Three groups were defined: Group 1, comprised total study population (n = 272). Group 2 (n = 87) comprised total study population, excluding those receiving potentially hepatotoxic drugs, or diagnosed with liver disease, or had any abnormal laboratory test results other than for triglycerides, cholesterol, glucose, or HbA1c. Group 3 (n = 17) the 'healthy' population, from whose ALT values we established the new ULN, comprised Group 2 subjects with normal triglycerides, cholesterol, glucose, and HbA1c levels. The results were intriguing. The 95th percentile ALT values, corresponding to the ULN, in groups 1, 2, and 3 were 50.1, 40, and 37.5 U/L, respectively. 6.2% of subjects whose ALT was below ULN listed by the test manufacturer (52 U/L), had ALT level above in their new ULN. Linear and logistic-regression analyses showed that ALT levels were significantly modified by gender, age, glucose, cholesterol, triglycerides, and overweight/obesity diagnosis[13].

Elevated liver enzymes are infrequent in patients with Hepatitis C virus (HCV) infection undergoing chronic hemodialysis (HD), suggesting that ALT is a poor predictor of hepatocellular damage in this population. The objective of this research was to establish a more appropriate cut-off value of ALT to identify biochemical activity due to HCV infection in HD patients. A total of 217 patients, with an average age of 51.2 years, were evaluatedin in a single year; 130 were males (60%). Serum ALT was measured by a kinetic method in five consecutive monthly blood samples, from which an average was obtained and divided by ULN. The cut-off value of ALT was obtained from a ROC curve. Within the 217 patients, 18 (8.3%) were anti-HCV-positive, 17 (7.8%) of whom were also HCV-RNA-positive. Genotype distribution was: 1a = 47%; 1b = 18%; 3a = 35%. Mean ALT/ULN (0.77 +/- 0.57) of the 18 anti-HCV-positive cases was higher than the negative group (0.38 +/- 0.23). The mean ALT/ULN (0.81 +/- 0.57) of the 17 HCV-RNA-positive cases was also higher than the negative cases (0.37 +/- 0.23). The cut-off value of ALT to distinguish the anti-HCV-positive from negative patients was 0.50% or 50% of the ULN (sensitivity = 67%; specificity = 83%). According to the HCV-RNA, the cut-off value of ALT was 0.45% or 45% of the ULN (sensitivity = 71%; specificity = 80%). The Authors concluded that reducing the cut-off of ALT by half, enabled a better identification of biochemical activity in patients with HCV infection on chronic HD[14].

ALT activity is the most widely used laboratory test for the recognition of liver disease. As aforementioned, normality limits for values of serum ALT activity have been questioned lately. One reason for this recent uncertainty may be an unrecognized decline in aminotransferase levels in the aging population. To verify such hypothesis a cross-sectional evaluation of the association between age and ALT activity was performed. Laboratory data of residents in single home for the aged and of adult subjects in three general practice clinics in Israel were reviewed, excluding subjects with known liver disease. One hundred and twenty-eight individuals from the home for the aged and 207 individuals from three family practices were included. The study ended up in finding out that ALT activity regressed with age creating an inverted U curve with a peak at 40-55 years, (polynomial regression). According to age groups, serum ALT level was 19 +/- 13 U/L in those under 40 year, 25 +/- 19 U/L in 40-55 year olds, 22 +/- 10 U/L in 56-72 year olds, 17 +/- 9 U/L in 73-83 year olds, and 13 +/- 5 U/L in 83-100 year olds. Gender also showed different levels for ALT, i.e., 22 +/- 15 U/L in men, and 17 +/- 11 U/L in women. Multiple regression analysis including age, gender revealed that age and gender retained association with ALT activity but not interestingly BMI. No such associations were noted for AST activity. These data suggest a significant inverted-U-like association between age and serum ALT activity. Thus, when interpreting the laboratory results of a subject suspected of liver disease, age should probably be taken into account[15].

Despite the association between elevated ALT levels and liver diseases, the entity of the ALT elevation does not always correlate with the extent of liver cell damage. Accordingly, the ALT levels are of scarce prognostic value. It is noteworthy to stress that, currently, measurement of serum ALT levels is the most frequently used test to identify patients with liver diseases.

Other reports have questioned whether established values to define normal ALT/AST range are accurate and have suggested that the upper limit of normal should be revised. A study by Prati[16], screening 6835 first-time blood donor candidates, demonstrates that ALT activity was independently related to body mass index (BMI) and to laboratory indicators of abnormal lipid or carbohydrate metabolism, as well as to sex. Still, the authors calculated "healthy" ranges for serum ALT level in 3927 donors who had a normal BMI and normal levels of serum glucose, cholesterol, triglyceride, and who were not taking medications. The upper limit of normal for ALT level decreased from 40 U/L to 30 U/L in men and from 30 U/L to 19 U/L in women. The new normal ranges increased the sensitivity for detection of patients with liver injury from 55% to 76% but decreased the specificity from 97% to 88%. But, should these more realistic values for normal ALT levels be widely adopted? Probably yes, because this would sensibly increase the number of asymptomatic patients with abnormal ALT values and would identify far more patients with NAFLD and clinically mild or occult HCV infection[17].

The normal range for ALT/AST levels was set a half century ago and has never changed since then!

PROFILING THE OLD CUMBERSOME TESTS ON A NEW LIGHT: A RIGHT CHOICE?

An occurrence could be by the following study implanted to investigate if and to what extent antiviral therapy influenced a broad panel of quantitative testing of liver function (QTLF). Fifty patients with chronic hepatitis C were either treated with interferon, interferon/ribavirin or peg-interferon/ribavirin. QTLF, including aminopyrine breath test (ABT), galactose elimination capacity (GEC), sorbitol clearance (SCl) and indocyanine green clearance

(ICG) was performed before and 3 mo after initiation of antiviral therapy. After three months of antiviral treatment, 36 patients showed normal transaminases and were negative for HCV-RNA, 14 patients did not respond to therapy. ABT and GEC as parameters of microsomal and cytosolic liver function were reduced in all patients before therapy initiation and returned to normal values in the 36 therapy responders. Parameters of liver perfusion (SCl and ICG) were not affected by antiviral therapy. In the 14 non-responders, no changes in QTLF values were observed during the treatment period. Early determination of ABT and GEC may differentiate responders from non-responders to antiviral treatment in hepatitis C[18].

An effort to simplify the "real" liver function tests, favouring their application on a large scale, at least in advanced forms, was present-day made by evaluating the TOSCA[19].

SHOULD LABORATORY LIVER TESTS BE PERFORMED AFTER THE IMAGING RESULTS?

Some Authors speculated about the association between the severity of liver steatosis and MS in apparently healthy Korean adults. They examined 1022 men and women, aged 30-79 years, who participated in a health screening test. A standard interview, anthropometrics, biochemical studies, and abdominal UltraSonography (US) were conducted for each participant. Metabolic syndrome (MS) was defined according to the National Cholesterol Education Program Adult Treatment Panel Ⅲ, lightly modified. The severity of liver steatosis was evaluated using liver US, and AST, ALT, and GGT levels were determined. The results clearly evidenced that the MS showed a stronger association with the severity of US steatosis than with the serum liver enzyme levels. The researchers advised that the degree of fatty infiltration detected on US could be used as an indicator of liver dysfunction attributable to metabolic abnormalities[20].

IS GAMMA-GLUTAMYL TRANSPEPTIDASE A SERUM MARKER OF CHOLESTASIS/ ALCOHOL-INDUCED DAMAGE/ ENZYMATIC INDUCTION ONLY?

Oxidative stress plays a crucial role in a variety of clinical settings including atherogenesis, and mediates many pathways linked to inflammation. GGT, an enzyme responsible for the extracellular catabolism of antioxidant glutathione, may directly take part in atherogenesis and evolve as a potential biochemical risk indicator of cardiovascular morbidity and mortality. Classically, GGT has been thought of as a diagnostic tool for hepatobiliary disorders and alcohol abuse. More recently, growing body of data points out that serum GGT levels can aid detection of individuals at high risk for subsequent cardiovascular events, and thus have an application in primary and secondary prevention of cardiovascular disease. Although several investigations have shown that some drugs are effective in decreasing both serum lipids and GGT, and concomitantly the incidence of subsequent cardiovascular disease (CVD). Based on current experimental and epidemiological studies, Turgut postulates that GGT present in the serum, even within its laboratory reference intervals regarded as physiologically normal, is a promising biomarker for cardiovascular risk[21].

An increase in serum GGT predicts onset of MS, incident CVD, and death suggesting that GGT is a marker of metabolic and cardiovascular risk[22]. An unchanged or increased GGT level over time, even when GGT is in the normal range, is correlated with increasing insulin resistance and is associated with a risk of incident type 2 diabetes in both sexes, independently of baseline GGT, which is itself a diabetes risk factor[23]. Also for other Authors, the role of GGT is different. In fact, it has been proposed that elevated serum GGT is an independent marker of the activation of systemic inflammation and increased oxidative stress, independent of their relationship to MS, and that the presence of MS and elevations of this liver enzyme may additively worsen the atherogenic state[24].

ARE THERE ANY INTERESTING MARKERS ON THE EDGE?

A recent study, zeroing in on novel parameters, assessed the role of transforming growth factor-beta1 (TGF-beta1, as anti-apoptotic marker) and vascular endothelial growth factor (VEGF, as angiogenetic factor) in the pathogenesis of fibrosis associated with HCV-related chronic hepatitis and evaluated the influence of the antiviral therapy on above parameter levels depending on the treatment results[25]. This research showed that a complete response in these patients is associated with significant changes in TGF-beta1 and VEGF.

FIBROSIS MARKERS: ARE THEY REALLY USEFUL?

Liver fibrosis is the excessive deposition and redistribution of extracellular matrix (ECM) in this organ induced by chronic injury. It leads to ultimately cirrhosis, characterized by progressive liver insufficiency/portal hypertension, and hepato-cellular carcinoma. There is a certain need for reliable, non-invasive, repeatable markers of fibrosis and fibrogenesis to substitute the invasive method (liver biopsy, which is burdened by a high degree of sampling error). A systematic literature search, using relevant papers, was timely performed to weigh the usefulness of non-invasive biomarkers of liver fibrosis[26].

Serum biomarkers are differentiated in those reflecting ECM turnover (fibrogenesis and fibrolysis) and/or fibrogenic cell changes, mainly of Ito cells. They are procollagen peptides, hyaluronan, and laminin. The remainders are based on algorithmic evaluation of commonly observed liver alterations that do not necessarily reflect ECM metabolism or fibrogenic cell changes. Several numerical scores or indices are reported for parameters,

which are mostly routine laboratory tests and frequently multiparametric, e.g., panels. In good substance, although several serum markers and panels offer the opportunity to noninvasively assess the extent of liver fibrosis and spare some patients the risks associated with percutaneous liver biopsy, only a few of them allow the determination of different stages of fibrosis on a continuum similar to that achieved with liver biopsy[27].

Indeed, hyaluronic acid is considered an accurate variable for the severity of hepatic inflammation and fibrosis[28].

Conclusively, the impact of both classes of biomarkers for diagnosis and monitoring of fibrosis, fibrogenesis, and fibrolysis is limited. They cannot replace needle biopsy even though some of them, generally expensive, might be complementary in follow-up studies. Transient elastography could be a valid alternative choice.

FINAL CONSIDERATION

Unfortunately, it is true that new reports that advice the practitioners about the clinical utility of various diagnostic tools, when embraced, make the health care costs increase without expanding the diagnostic-prognostic horizon, with very few exceptions.

To make the hepatologists' life a little more complicated, some computations have been advanced. For example, the model of end-stage liver disease (MELD) score has gained acceptance over the Child-Pugh (C-P) score in predicting survival in patients with decompensated cirrhosis, although it is more sophisticated. A suggestive research compared the predictive values of MELD, C-P and creatinine-modified C-P scores in decompensated cirrhosis. The areas under the receiver operating characteristic curves did not differ significantly among the four scores. In Cox regression analysis, all four scores were significantly associated with survival, while MELD and creatinine-modified C-P scores had better predictive values than C-P score. Adjustment for GGT (*de novo*!) levels increased the predictive values of all systems. Thus, MELD compared to the C-P classification does not appear to offer a clear advantage in predicting survival in patients with decompensated cirrhosis in daily clinical practice[29].

Still, the MELD model is only slightly superior to the Child-Pugh classification for the prediction of long-term survival in TIPS patients[30].

The "ancient" serum total bilirubin, present in MELD as well as in C-P scores, offers the best single prognostic factor in evaluating liver cirrhosis progression, except for patients suffering from Gilbert syndrome.

Prothrombin activity (expressed in time or percentage or as INR) should be regarded as a clue of disseminated intravascular coagulation.

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