Journal of Intensive Care Medicine
2016, Vol. 31(2) 104-112

DOI: 10.1177/0885066614554897
jic.sagepub.com
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Biomarkers in Hepatic Disease: A Review Focused on Critically Ill Patients

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Abstract

The ability to make a diagnosis early and appropriately is paramount for the survival of the critically ill ICU patient. Along with the myriad physical examination and imaging modalities available, biomarkers provide a window on the disease process. Herein we review hepatic biomarkers in the context of the critical care patient.

Keywords

biological markers, critical illness, ICU, intensive care unit, liver disease, serum proteins

Rationale for the Use of Biomarkers

The ability to make an early diagnosis and, hopefully, initiate therapy is paramount to the survival of critically ill patients in the intensive care unit (ICU). Although the use of physical examination skills have been and remain of critical importance in the care of the critically ill, biological molecules as markers for disease processes have efficacy for a variety of reasons including the diagnosis and prognosis of a disease state, patient classification and placement, duration of treatment, detection of pathogens, host responses, and potential enrollment in studies. Each of these is a conclusion that may be drawn from biomarker evaluation.

In hepatic disease, no one biomarker satisfies all the aforementioned criteria. An ideal molecule will be validated, easy to measure, and have precise results and an impact that is of clinical significance.

Acute liver failure (ALF) is a clinical syndrome of sudden and severe hepatic injury resultant from toxic exposure, viral etiologies, autoimmune disorder, or shock/hypoperfusion—typically associated with coagulopathy and encephalopathy—in a patient without preexisting liver disease or cirrhosis; up to 20% have no discernable cause (note 1). Most of these patients require aggressive intensive care management; transplantation remains the only reliable form of rescue therapy.[1] Hepatic dysfunction (HD) in the ICU, on the other hand, is quite variable in nature. Some patients may develop mild elevation in liver function tests (LFTs), while other may develop rapid deterioration in hepatic synthetic function, seen as ALF. Regardless, HD has been associated with multiple organ dysfunction syndrome (MODS) and is a specific and independent risk factor for poor prognosis in ICU.[2,3] Subsequently, we consider HD in critical care setting.

Biomarkers of HD

In critically ill patients with MODS, HD is often overshadowed or missed, being more insidious in its occurrence and less immediately life threatening than respiratory, cardiovascular, or renal failure.[4] This may explain the paucity of studies on biomarkers in HD as compared to acute lung injury/acute respiratory distress syndrome or acute respiratory failure. Hepatic dysfunction may be related to a reduction in blood flow relative to metabolic demand,[5] major surgery-related ischemic injury, bilirubin overproduction, cholestasis, and anesthesia-induced liver dysfunction often observed postoperatively,[6] as well as sepsis and trauma.[4,5,7] The liver is relatively protected from hypoxic injury due to its capacity to extract up to 95% of oxygen from blood; hypoxic liver injury is most frequently seen in the setting of congestive heart failure, acute cardiac failure, and/or respiratory failure.[6] Other examples such as mechanical ventilation with positive end expiratory pressure,[8] total parenteral nutrition (TPN),[9] and many medications are reported to impact hepatic function.

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Received April 20, 2014, and in revised form July 15, 2014. Accepted for publication July 17, 2014.

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Table 1. Biomarkers of Hepatic Dysfunction.

Investigator	Patient Groups	Biomarker/Summary	Analysis-cutoff values; Specificity, Sensitivity, PPV, NPV, or AUCs	Limitations
Thomsonet al.[28]	• Prospective obsv study • 263 ICU pts w/ any cause of admission	• LFT measured daily • 61% had abnormal value in at least 1 of their LFT • Abnormal LFT on admission associated w/ 30-day mortality • None was independently predictive of 30-day mortality	• AUC for GGT: 0.7, ALT: 0.67, ALP: 0.7, Bili: 0.54 evaluating predictive ability of abnormal LFT on mortality	• The enzymes are not specific to liver, therefore, the association with mortality cannot be directly correlated to liver dysfunction
Kramer et al.[2]	• Prospective multicenter cohort • 42 394 all admissions • 38 036 analyzed • 4146 (11%) w/ early HD	• Early HD = bili > 2 w/ in 48 hours of admission—independently increased mortality • RR of mortality 1.65 in pts w/early HD • Prognostic effects are equally pronounced in pts w/nonsurgical and surgical conditions	• Not estimated	• No ROC curve analysis • No bilirubin levels are measured after 48 hours
Sakka et al.[45]	• 336 surgical ICU pts	• ICG-PDR • Was low in nonsurvivors and pts with sepsis	• ICG-PDR • <8% per minute—80% mortality • > 16% per minute—80% survival • 10.3% per minute AUC of 0.815 for accuracy, AUC of 0.745 for mortality	• Retrospective study • Only surgical pts
Fuhrmann et al.[21]	• Prospective observational study • 117 pts w/ hypoxic hepatitis in medical ICU	• Peak AST, LDH, INR, and lactate higher in nonsurvivors • INR > 2 independent risk factor	• Increase in AST > 24 hours—higher in non survivors—81% specificity, 63% sensitivity • INR > 2 odds ratio: 3.25 (overall mortality)	• Small sample size • No surgical factors • Residual confounding factors

Hofer et al.[60]	• Prospective obsv study
	• 147 pts
	  • 101 severe sepsis
	  • 28 postop major abd surgery
	  • 18 healthy volunteers
		• Total and fragments of CK-18, IL-6, and sVCAM. sICAM measured
		• IL-6, sICAM higher in sepsis group
		• CK-18 highest in septic group > postop > healthy
		• Nonsurvivors w/ sepsis and HD higher total CK-18 compared to non-HD
			• Total CK-18 (1900 U/L):
			• 60, 92, -, -% AUC of 0.78
			• For early discrimination of survivors
				• Whether the presence of HD is completely responsible for the observed difference in CK-18 measurements is unclear—not explained

Koch et al.[75]	• Prospective study • 108 medical ICU pts	• Longitudinal liver stiffness measured on admission, day 3, 7, and weekly • Liver stiffness on admission • Correlated with factor VII activity, INR, pseudocholinesterase activity, GGT, bili, and ALP • On day 3 and 7, any of the findings could not be replicated • Associated w/ RF, pulmonary dysfunction, heart failure, NT-pro BNP and CVP, APACHE II and SOFA • > 17 kPA associated w/ high short-term mortality • 18 kPA discriminate best b/t ICU survivors and nonsurvivors	• Not estimated	• No confirmation with histology • Findings need to be validated in larger sample groups

Abbreviations: PPV, positive predictive value; NPV, negative predictive value; AUC, area under the curve; obs, observational; w/, with; Billi, bilirubin; b/t, between; ICU, intensive care unit; LFT, liver function test; GGT, γ-glutamyl transferase; ALP, alkaline phosphatase; HD, hepatic dysfunction; ROC, receiver operator characteristic curve; ICG-PDR, indocyanine green plasma disappearance rate; AST, aspartate aminotransferases; obsv, observational; pts, patients; NT-pro BNP, N-terminal probrain natriuretic peptide; CK, Caspase cleaved cytokeratin; IL, interleukin; APACHE II score, acute physiology and chronic health evaluation score, version II; RF, respiratory failure; sVCAM, soluble vascular cell adhesion molecule; sICAM, soluble intercellular adhesion molecule; CVP, central venous pressure; APACHE, acute physiology and chronic health evaluation II; abd, abdominal; postop, postoperative; ALT, alanine aminotransferases; RR, relative risk; LDH, lactate dehydrogenase; INR, international normalized ratio; SOFA, sequential organ failure assessment score.
Score -, -%, means that there were no values available.

Identifying the optimal measure of hepatic function that either determines or reliably correlates with outcome is difficult, in part resultant to the complex structure of the liver and the diverse array of functional pathways in which this organ participates.

Functional hepatocyte profiles may differ, depending on where in the hepatic lobule the cells are located, presumably as a result of differential exposure to nutrients, oxygen, inflammatory cytokines, and numerous other mediators as blood flows through the sinusoids to the central vein.[10,11] A postmortem study of 15 ICU sepsis fatalities with no preexisting liver disease demonstrated evidence of portal inflammation in 73%, centrilobular necrosis in 80%, and hepatocellular apoptosis in 67%.[12]

Additionally, the liver is integrally involved in carbohydrate metabolism and energy production, generation or metabolism of active lipid compounds, detoxification of exogenous and endogenous hormones and xenobiotics, and is the site of significant proinflammatory cytokine production, just to name a few functional aspects of this organ.[10,13] Determining the ideal hepatic function test in this complex environment has, therefore, been challenging.

There is, nonetheless, a panel of studies used in routine daily practice in ICUs throughout the world. These include the serum alanine and aspartate aminotransferases (ALT and AST), bilirubin, alkaline phosphatase (ALP), γ-glutamyl transferase (GGT), albumin, and prothrombin time (PT). These tests are often referred to as ''liver function tests''—and we continue this convention herein—although this term is somewhat misleading since most do not accurately reflect how well the liver is functioning, and abnormal values can be caused by diseases unrelated to the liver. Perhaps more importantly, these tests may be normal in patients who have advanced liver disease.[14-16]

Specific Biomarkers

Alanine aminotransferase is a transaminase enzyme, also called serum glutamic–pyruvic transaminase, which catalyzes the 2 parts of the alanine cycle (transfer of L-alanine to α-ketoglutarate), is present in the highest concentration in the liver, but is also found in skeletal muscle and myocardium, and can be elevated in myocardial infarction or other muscle trauma. Aspartate aminotransferase or serum glutamic–oxaloacetic transaminase catalyzes the reversible transfer of an α-amino group between aspartate and glutamate and, as such, is an important enzyme in amino acid metabolism and also has an indirect contribution to the urea and citric acid cycles.[17,18] It is found, in decreasing order of concentration, in the liver, cardiac muscle, skeletal muscle, kidneys, brain, the pancreas, lungs, leukocytes, and erythrocytes.[19] There are also 2 isoenzymes: GOT1/cAST, the cytosolic isoenzyme derived mainly from red blood cells and heart; whereas GOT2/mAST, the mitochondrial isoenzyme, is present predominantly in liver. These isoenzymes are thought to have evolved from a common ancestral AST via gene duplication; they share a sequence homology of approximately 45%.[20] When used in diagnostics, they are both good indicators of hepatocellular injury, although AST is less specific than ALT, as it potentially increases in conditions such as myocardial infarction, acute pancreatitis, acute hemolytic anemia, severe burns, acute renal disease, musculoskeletal diseases, and trauma.[21]

Alkaline phosphatase, a hydrolase enzyme responsible for removing phosphate groups from many types of molecules, including nucleotides, proteins, and alkaloids, is present in all body tissues but is particularly concentrated in liver, bile duct, kidney, bone, and the placenta. There are 3 isoenzymes: ALP-I—the intestinal isoform, ALP-L—the tissue nonspecific (liver/bone/kidney) isoform, and ALP-P—the placental (Regan) isozyme.[22] Therefore, ALP may be raised in conditions affecting liver, especially cholestatic disease, bone, intestine, or kidney. The tissue of origin may be determined by assaying the predominant isoform of the enzyme but this is rarely necessary in clinical practice.[23,24]

γ-Glutamyl transferase is an enzyme that transfers γ-glutamyl functional groups and plays a key role in the synthesis and degradation of glutathione, many drugs, xenobiotic detoxification,[25] and also exerts a pro-oxidant role, with regulatory effects at various levels in cellular signal transduction and cellular pathophysiology.[25] γ-Glutamyl transferase is found in many tissues, the most notable one being the liver; however, it is a highly sensitive but nonspecific marker of liver disease and is commonly interpreted in conjunction with ALP as a marker of cholestasis.[26,27]

At the present state of knowledge, attribution of liver enzyme results to the outcomes in the ICU is shown in only 1 study.[28] In this prospective evaluation of the first ICU admission of 263 patients without preexisting hepatobiliary disease, 61% demonstrated an abnormal LFT—the majority being less than twice the upper limit of normal—at the point of admission. Episodes of care requiring ventilation or hemofiltration, and hypotensive events, during the first 48 hours were associated with an abnormal ALT on day 3. The presence of an abnormal ALT, ALP, or GGT, but not bilirubin, was associated with an increased risk of death within 30 days of ICU admission, with a receiver operator characteristic area under the curve (ROC AUC) of 0.67 for ALT, 0.7 for both ALP and GGT, and 0.54 for bilirubin. When adjusted for physiology and chronic health evaluation II (APACHE II) severity of illness score, LFTs were not independent predictors of mortality.[28]

Bilirubin, a catabolic product of hemoglobin metabolism, exerts important biological functions under conditions of oxidative stress. Measurement of hepatic purification is partly expressed by bilirubin,[21] and hepatocyte dysfunction causes reduction in bilirubin uptake, intrahepatic processing, and canalicular excretion in sepsis.[6] It is a key component of prognostic scores for patients with chronic liver disease[29] and cirrhosis[30]—including the Child-Pugh classification and the Model of End Stage Liver Disease (MELD) score—and also of prognostic models in patients with ALF. Bilirubin levels are used in scoring algorithms for assessing prognosis in critically ill patients, such as sequential organ failure assessment score

(SOFA), mortality probability model, and simplified acute physiology score (SAPS) scores. Low-grade hyperbilirubinemia often goes unnoticed in patients not presenting with clinically evident jaundice. Since clinical jaundice tends to develop only several days after hepatic injury, HD is traditionally considered a late event in sepsis and multiorgan failure.[31] Nevertheless, there is evidence to suggest that low-grade hyperbilirubinemia with mild hepatic enzyme increase associated with liver injury[32,33] may be as frequent as renal and lung dysfunction,[34] and is associated with increased mortality.[7,33,35] Surgical patients with mild hyperbilirubinemia (more than 2.0 mg/dL) manifest a higher mortality rate than patients without hyperbilirubinemia,[33] and septic patients with billirubin levels greater than or equal to 2.0 mg/dL have a mortality rate that approximates 60%.[35] In a prospective study of heterogeneous critically ill patients, in which HD was defined as serum bilirubin levels greater than or equal to 2.0 mg/dL, lasting for at least 48 hours, Brienza and colleagues[3] showed that HD occurrence was associated with moderate and severe shock, sepsis, mechanical ventilation in which end expiratory pressure was used, major surgery, and gram-negative infections; HD had an incidence of 31% with a median onset of 3 days from ICU admission. In a similar study setting, with a larger cohort of 4146 patients, Kramer and colleagues[2] accepted the same definition as "early" HD and found an 11% incidence in critically ill patients. Early HD independently increased mortality with odds ratio of 1.86 and, more interestingly, exceeded the mortality effects of all single extrahepatic organ dysfunctions. Even a slight increase in bilirubin was found to be associated with a marked reduction of survival, and both studies suggested that liver dysfunction was more closely related to the risk of death than APACHE II Severity of Illness score. In both studies, surgical patients represented the largest proportion of patients with HD, but logistic regression analysis in the latter study showed no direct effect of surgery on the development of early HD. It has also been emphasized that hyperbilirubinemia may precede positive blood cultures in more than one-third of patients with sepsis,[35] and an otherwise unexplained increase in bilirubin should be prompt to exclude latent sepsis. Finally, jaundice in critically ill patients may occur due to reduction in hepatic excretory capacity, but a rise in bilirubin can also occur due to nonspecific factors such as sepsis, drug metabolism, side effects of TPN and, to a smaller extent, of enteral nutrition (EN), or factors unrelated to hepatocellular function, such as biliary obstruction and hemolysis. Parenteral nutrition-associated hepatobiliary disease—such as hepatic steatosis and cholestasis—which presents with increased liver enzymes and bilirubin within 2 to 4 weeks of TPN/EN therapy and returns to normal even when PN is continued,[6,36] may be seen in the ICU setting with frequent TPN/EN use. Chronic liver disease, however, is generally unexpected in this setting,[36] except that the patient exposed to long-term TPN (> 6 months) may progress to steatohepatitis and micronodular cirrhosis.[6] Finally, while in the acute setting, in which rapid changes in liver function occurs, interpretation of bilirubin levels may be problematic, the bilirubin level is a reliable parameter in the assessment of chronic liver disease.[37] A significant exception to the worsened outcome in hyperbilirubinemia is seen in the inherited Gilbert syndrome, which presents with elevation of unconjugated bilirubin in stressful situations as a result of defective uridine diphosphoglucuronate-glucuronosyltransferase 1A1.

Indocyanine green (ICG) is an infrared absorbing fluorescent dye. The ICG-plasma disappearance rate (ICG-PDR) has been suggested as an alternative measure of hepatic excretory function and has long been used to reduce confounding factors associated with the use of bilirubin, although relatively expensive and not in common use at this time. After injection into the circulation, ICG is nearly completely eliminated unchanged by the liver into the bile without enterohepatic recirculation. In principle, elimination of the ICG from the blood into the bile is determined by hepatic blood flow, cellular uptake and excretion, and suggestively controlled by 2 polar surfaces of human hepatocytes: while the basolateral transporter protein regulates the disappearance of bile/ICG from the blood, the canalicular transporter protein regulates excretion of bile/ICG into the bile.[38] In sepsis, upregulation of genes encoding the basolateral transporters and downregulation of canalicular transporter genes suggest maintained uptake of ICG from sinusoidal blood but impairment of bile/ICG canalicular transport.[39] Under physiological conditions, after a 0.25 to 0.5 mL/kg body weight bolus, the dye appears within about 30 minutes in an unconjugated form in the bile; the bedside assay is relatively simple to perform.[40] It is a noninvasive method and measured by a transcutaneous system adapted from pulse oximetry[41,42]; the results can be obtained within 6 to 8 minutes. Although measuring clearance of the dye allows analysis of both perfusion and elimination, simple assessment of its elimination from the blood stream reflects a complex measure of both sinusoidal perfusion and hepatic membrane function and, thus, reflects a functional reserve of perfused hepatocytes.[43] It is noteworthy that obstructive jaundice may substantially and reversibly impair ICG-PDR.[44]

In a retrospective study of 336 critically ill patients, ICG-PDR was found to be significantly lower in nonsurvivors. The ROC AUC as a measure of accuracy was 0.815 with a cutoff value less than or equal to 10.3% per minute when using the lowest ICG-PDR in each patient. When ICG-PDR was compared to scores of severity of illness such as APACHE II and SAPS II, the ROC AUCs were 0.745 for ICG-PDR and 0.680 and 0.755 for APACHE II and SAPS II scores, respectively.[45] In another retrospective study of 40 patients with sepsis in the ICU, ROC AUC was 0.765 for ICG-PDR and 0.692 for APACHE II scores. Mortality was 80% in patients with ICG-PDR below 8% per minute, and survival was approximately 89% in patients with ICG-PDR above 24% per minute.[46] In a prospective, comparative study analyzing a variety of static laboratory values, including transaminases as well as the ICG-PDR in 48 patients with severe sepsis, the incidence of HD was 42% as assessed by hyperbilirubinemia, but 74% by impaired dye excretion. Conventional markers of liver injury (transaminases), synthesis (prothrombin ratio and albumin), and cholestasis (ALP, GGT, and bilirubin) failed to predict

outcome, while dye excretion of less than 8% per minute predicted death with a sensitivity of 81% and specificity of 70%. Moreover, ICG-PDR discriminated surviving from nonsurviving patients as early as the day of diagnosis, challenging the concept of delayed deterioration of liver function during the course of ICU treatment.[38]

Prothrombin time and albumin are used to evaluate the liver's biosynthetic activity/capability. On average, the adult liver synthesizes approximately 15 g per day (200 mg/kg/d). Hypoalbuminemia is not always a sign of hepatic synthetic dysfunction, since a variety of other conditions may be responsible, including systemic inflammation, the nephrotic syndrome, and malnutrition.[47] Prothrombin time, the recalcification time of citrated plasma in the presence of a tromboplastin reagent,[48] is used to assess the extrinsic pathway of clotting and the biosynthetic function of the liver, since both vitamin K-dependent and vitamin K-independent clotting factors are reduced in liver failure. A prolonged PT, however, is also not specific for liver disease, as it may result from various congenital or acquired conditions, including consumption of clotting factors—such as disseminated intravascular coagulation or severe gastrointestinal bleeding—and certain drugs, such as warfarin. When these conditions have been excluded, a prolonged PT usually reflects either a deficiency of vitamin K—which may be caused by inadequate dietary intake, prolonged obstructive jaundice, malabsorption, or the administration of antimicrobials that alter the gut flora—or poor utilization of vitamin K due to advanced parenchymal liver disease. In the former setting, the PT typically returns to normal within 24 hours after a single parenteral injection of vitamin K—this response is particularly helpful diagnostically when evaluating patients with jaundice—whereas in the latter, vitamin K supplementation is generally ineffective.[49-52]

The international normalized ratio (INR), standardization of PT measurement based upon characteristics of the thromboplastin reagent used in the laboratory, is often used to express the degree of anticoagulation in patients receiving warfarin. It is frequently used to evaluate the synthetic function of the liver as well.[21] Although realization of variations in thromboplastin responsiveness in patients on vitamin K antagonist therapy led to the development of a standardization of PT reporting as the international sensitivity index (ISI)—a variant of the INR—similar standardization has not yet been established in patients with liver failure.[53] Therefore, its use in hepatic failure may not provide the best expression of coagulation derangement, especially if the same thromboplastin reagents are not consistently used for measurement.[49,50] This was illustrated in 27 patients with chronic and ALF, by evaluating various expressions of the PT (seconds above control, ratio to control, activity percentage, and INR) and comparing to controls.[50] Only the activity percentage expression, obtained by a saline dilution curve constructed with normal pooled plasma and the patient's results expressed as the percentage of normal plasma yielding the same PT in seconds, eliminated variability in the PT results in individual patients when using different thromboplastin reagents.[50] This observation implies that only when the same thromboplastin reagent is used is the interpretation of changes in the INR accurate in an individual patient with liver failure. Furthermore, to evaluate the degree of biosynthetic liver function, validity of comparing different INR values measured in different centers remains controversial.[54,55]

In keeping with this observation, Bellest et al and Tripodi et al[53,56] suggested a new INR standardization method—the ISI—specific for liver disease (INR-LD). Using samples from patients with liver disease instead of plasma from patients on oral anticoagulants in the same calibration process and testing 5 and 7 different thromboplastins, respectively, both groups showed reduced variability when the INR-LD was used for calculation of the MELD score.

Two studies are of particular note in the context of the INR's role in evaluation of hypoxic hepatitis, a frequent cause of acute hepatocellular damage in the ICU. In a prospective study of 117 patients with hypoxic hepatitis, Fuhrman and colleagues found that peak AST, INR, lactate dehydrogenase, and lactate were higher in nonsurvivors; an INR over 2, septic shock, and a SOFA score more than 10 were risk factors of increased mortality.[21] This finding was replicated by Raurich et al in a retrospective study of 7674 patients with hypoxic hepatitis. These investigators also found that the need for renal replacement therapy was a risk factor for death, along with prolonged INR and presence of septic shock.[57] So, while both albumin and PT may be, and are, used in the evaluation of chronic liver disease as well as in prognostic models—such as Child-Pugh and MELD—they are relatively poor choices in the critically ill ICU patients. The use of the INR, ISI, among others, appears to be more appropriate.

Carbamoyl phosphate synthase1 (CPS-1), a soluble enzyme localized in the mitochondrial matrix, catalyzes the first step of the urea cycle; its expression is tightly restricted to the liver and intestinal mucosa. Two studies investigated CPS-1 levels in septic animal models, finding that its levels increased dramatically within 24 hours of onset of sepsis, remained elevated at 48 hours, and normalized by 6 days.[58,59] In the first study,[58] abnormalities of liver mitochondrial morphology and signs of oxidant stress, defined as an imbalance between oxidant production and removal of potentially reactive oxygen species—with attendant hazardous effects on hepatic cellular function—coincided with increased plasma CPS-1 levels. In contrast to CPS-1, plasma ALT levels did not track temporally with these mitochondrial events; while ALT elevation was evident within 8 hours of sepsis onset and peak concentrations were not observed until 48 hours after the onset of sepsis, that is, 24 hours after mitochondrial depletion was first detected. This mismatch is not surprising, given that ALT is primarily localized in the cytosol.[58] The second study,[59] evaluating patients with sepsis along with a septic baboon model, found that CPS-1 correlated moderately with AST and to a lesser extent with ALT and bilirubin levels. These studies show that outcome studies in humans are still required to determine the usefulness of this assay.

Caspase cleaved cytokeratin 18 (CK-18) is a structural protein of the intermediate filament group present in most simple

epithelial and parenchymal cells. Both CK-18 and uncleaved CK-18, 2 novel noninvasive high-sensitivity markers of cell death, were evaluated by Hofer and colleagues[60] for the prediction of clinical outcome in sepsis. These investigators showed significantly increased levels of total CK-18 and CK-18 fragments in patients having sepsis with impaired liver function, in comparison with patients with sepsis and preserved liver function. In patients with severe sepsis and HD, a cutoff value of 1900 U/L for total CK-18 at the onset of sepsis revealed an ROC AUC of 0.78, sensitivity of 92%, and specificity of 60% for early discrimination of survivors and nonsurvivors. In this study, apoptosis and necrosis were identified differentially: in healthy volunteers, the mode of cellular turnover was primarily apoptotic, whereas in patients with severe sepsis, both apoptotic and necrotic cell death were present; patients with severe sepsis and HD showed a necrotic picture. In these patients, hepatocyte necrosis—not apoptosis—is an early predictor of disease outcome in sepsis with liver dysfunction. This work also suggests some potential for therapeutic efficacy of caspase inhibitors, at least in patients having sepsis with liver dysfunction.[60]

Hyaluronan (hyaluronic acid, HA), synthesized by fibroblasts or other matrix-producing cells, is abundantly found in healthy individuals[61] and at low concentrations in circulation as it is rapidly cleared from bloodstream by the liver sinusoidal endothelial cells.[62] Since circulating HA levels are increased with liver dysfunction, it has been suggested as a potential biomarker for fibrotic liver diseases, especially as its concentration has been found to correlate with the degree of fibrosis in patients with chronic liver diseases.[63] Increased levels of HA due to impaired clearance by liver sinusoidal endothelium have also been demonstrated in sepsis.[64] Yagmur and colleagues,[65] evaluating 164 critically ill patients in the ICU—of whom 12 had hepatic cirrhosis—showed that HA levels were significantly elevated in those with preexisting cirrhosis as compared to noncirrhotic critically ill patients. Additionally, there was demonstrated a significant correlation between HA levels and the SOFA score.[65] Nevertheless, the correlation of HA with liver dysfunction alone, as well as with contributing sepsis, remains uncertain.

C-reactive protein (CRP), a significant marker of infection with ROC of 0.72, secreted in increased amounts within hours of an acute inflammatory stimulus, is only synthesized by the liver.[66,67] In sepsis, the liver is the main source of inflammatory mediators but also, at the same time, a target organ for the effects of these mediators.[68,69] For example, in fulminant hepatic failure (FHF), synthetic capacity of liver is impaired secondary to the severe liver damage.[67] Thus, the CRP levels may be decreased despite sepsis-induced clinical deterioration. In a prospective study, with 7 patients having sepsis with acute FHF, CRP levels were found to be decreased significantly, to normal levels, despite clinical deterioration.[70] In another study, Izumi et al demonstrated, in 50 patients with FHF, serum CRP levels that were significantly lower than that expected despite severe inflammatory factors.[67] Overall, in the presence of FHF, decreased levels of CRP may be used as a marker of severe liver dysfunction but are not appropriate to follow as a marker of infection/inflammation. Silvestre et al[70] found an association between low CRP level and factor V activity in patients with FHF. In patients with these low levels, careful monitoring of mental status is warranted in concern for the development of FHF.

Breath and blood pentane, a product of reactive oxygen species-mediated lipid peroxidation, has been suggested as a potential marker of oxidative stress in hepatic injury and was tested in the presence of propofol,[71] a molecule which inhibits lipid peroxidation. Free radical-mediated lipid oxidation is known to be rapidly increased in ischemia–reperfusion (IR) injury.[72,73] In a hepatic IR animal model, 20 male swine were divided into 2 groups based on anesthesia: propofol ($n = 10$) and chloral hydrate ($n = 10$); peak exhaled and blood pentane concentration in the propofol group were significantly less than that of the chloral hydrate group ($P < .05$); the latter (chloral hydrate) group also demonstrated significantly higher plasma AST levels and more profound histopathological changes in liver injury, as well as a lower survival rate (30% vs 100%). The authors concluded that exhaled pentane, a noninvasive technique, may be a useful biomarker to evaluate the severity of hepatic IR injury and possible adverse outcomes of this injury in liver.[71] Since, to our best knowledge there are no extant human studies on this matter, its applicability as a biomarker of hepatic injury remains suggestive.

Miscellaneous Assays

In a prospective, observational study in which the amino acids glutamate and glutamine were compared to the standard studies of hepatic function, the plasma glutamate/glutamine ratio was consistently lower in nonsurvivors compared to survivors, and both parameters were good predictors of outcome with ROC AUC of 0.75 and 0.82, respectively. Glutamate concentration was an independent and stronger risk factor for mortality as compared to the standard studies of hepatic function.[74]

Hepatic stiffness. Koch and colleagues,[75] in a prospective study, investigated hepatic stiffness, measured by a novel method of transient elastography (fibroscan), as a potentially useful tool for early detection of patients with hepatic deterioration and risk stratification with respect to short- and long-term mortality in critically ill patients. There is a strong association between hepatic stiffness and degree of hepatic fibrosis,[76,77] and hepatic stiffness is a well-known tool to detect hepatic fibrosis in patients, especially those with chronic liver disease, and also in those with acute liver diseases. Hepatic stiffness is measured by propagation of an elastic shear wave induced by low amplitude and frequency vibrations followed by pulse-echo ultrasonographic acquisitions to measure the velocity of the shear wave propagation.[76] Koch, et al showed that critically ill patients without known liver disease had significantly elevated liver stiffness, reaching levels commonly observed in advanced hepatic disease. Upon admission to the ICU, hepatic stiffness

was found to be closely related to hepatic damage, but the course of ICU treatment, presence of fluid overload—due to renal failure or volume therapy—and increased central venous pressure were also major factors determining hepatic stiffness. Hepatic stiffness values above 18 kPa upon ICU admission were associated with increased ICU stay and long-term mortality.[75]

Summary

Synthesis of the findings noted in the above sections (Table 1) suggests that HD does not occur late in the course of MODS, as previously thought. Yet the importance of HD seems underestimated although there is evidence suggesting that HD is an early predictor of poor outcome in the ICU. This underestimation may be a result of the availability of well-known and commonly used biomarkers, and the fact that no therapeutic approach exists to improve the HD, other than treating the underlying cause, most commonly septic shock. Nevertheless, the implications of HD suggest that broader studies should be designed and biomarkers found to be useful in ALF should be studied in ICU patients without preexisting liver disease.

While the identification of HD is of significance, there are limited treatment options available to us even when it is so recognized. For example, the recently introduced extracorporeal albumin dialysis—in one of its iterations, single-pass albumin dialysis or molecular adsorbent recycling system—is an investigational option in this situation.[78] These supportive methodologies may be used to bridge patients to liver transplantation[79,80] or until hepatic recovery occurs in ALF and acute-on-chronic liver failure.[79]

Alanine aminotransferase, AST, GGT, and bilirubin are presently biomarkers that make up "The Liver Panel," used to assess HD/failure; the panel may be strengthened in its sensitivity and specificity by adding ICG-PDR, especially in patients with sepsis. Other, newer biomarkers, such as hyaluronan, blood pentane, and CPS-1, are promising, but human studies are needed to assess their utility in humans. It is our best sense that the determination of HD/failure is optimally estimated by utilization of ALT, AST, GGT, bilirubin, and CRP plus factor V, complemented by ICG-PDR.

Authors' Note

Doctor Kubilay was a visiting scholar in the Department of Critical Care Medicine. Doctor Erturk Sengel is a distance research scholar in the Department of Critical Care Medicine.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Note

1. http://www.aasld.org/practiceguidelines/Documents/Bookmarked%20Practice%20Guidelines/acute%20liver%20failure.pdf accessed 4 June, 2014.

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