How to assess liver function?
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Purpose of review
The liver comprises a multitude of parenchymal and nonparenchymal cells with diverse metabolic, hemodynamic and immune functions. Available monitoring options consist of ‘static’ laboratory parameters, quantitative tests of liver function based on clearance, elimination or metabolite formation and scores, most notably the ‘model for end-stage liver disease’. This review aims at balancing conventional markers against ‘dynamic’ tests in the critically ill.

Recent findings
There is emerging evidence that conventional laboratory markers, most notably bilirubin, and the composite model for end-stage liver disease are superior to assess cirrhosis and their acute decompensation, while dynamic tests provide information in the absence of preexisting liver disease. Bilirubin and plasma disappearance rate of indocyanine green reflecting static and dynamic indicators of excretory dysfunction prognosticate unfavorable outcome, both, in the absence and presence of chronic liver disease better than other functions or indicators of injury. Although dye excretion is superior to conventional static parameters in the critically ill, it still underestimates impaired canalicular transport, an increasingly recognized facet of excretory dysfunction.

Summary
Progress has been made in the last year to weigh static and dynamic tests to monitor parenchymal liver functions, whereas biomarkers to assess nonparenchymal functions remain largely obscure.

Keywords
acute-on-chronic liver failure, dynamic, quantitative liver function tests, static

Introduction
The liver with its pleiotropic functions not only plays a key role in host defence and acute phase response but is also a target for remote organ dysfunction in the critically ill [1]. The hepatic stress response involves not only synthesis of metabolic fuels and proteins, such as coagulation factors [2], but also removal of microbial toxins [3]. Considering solely the rise in serum bilirubin [as for instance in the Sequential Organ Failure Assessment (SOFA) score], liver dysfunction has traditionally been thought to occur rather rarely and late in multiple organ dysfunction [4–6], although prospectively collected comparative data on the various liver injury and function tests have been missing [7]. Bilirubin originates from heme degradation, as it arises from various sources such as senescent red cells and is subject to conjugation and excretion by the hepatocyte [8]. As such, bilirubin as a marker for liver dysfunction may be difficult to interpret and subject to confounding factors, for example, if turnover of heme and liver function are both altered simultaneously. Consistent with this notion, an incidence of only 1–3% of overt liver failure (SOFA 3–4) has been reported, for example, in severe sepsis, reflecting a rare impairment of the liver in this important subset of critically ill patients based on SOFA score/bilirubin levels [9,10]. Nevertheless, data collected by the Austrian Center for Documentation and Quality Assurance in Intensive Care Medicine indicated in a large cohort of mixed ICU patients that increased bilirubin upon admission without history of liver disease occurs in approximately 10% of patients and is an outstanding and independent risk factor for poor prognosis [11]. Overall, an ever growing body of evidence supports the concept that among the multiple partial functions of the liver, primarily excretory dysfunction is associated with a poor outcome.

Excretory dysfunction in critical illness: from hyperbilirubinemia to secondary sclerosing cholangitis
Sepsis-associated cholestasis is a leading cause of jaundice in hospitalized patients surpassed only by malignant
biliary obstruction [7]. The unfavorable prognosis of patients with sepsis-induced cholestasis is not necessarily related to liver dysfunction, as it rarely progresses to overt liver failure with coagulation defects and hepatic encephalopathy. Some of these patients will, however, after surviving the acute phase of critical illness, develop secondary sclerosing cholangitis with rather rapid progression to biliary fibrosis, cirrhosis and liver failure. This rare, but increasingly recognized, problem of sclerosing cholangitis is a dismal disease, resulting in death without liver transplantation in the majority of cases [12**].

The clinical consequences of hepatocellular and ductular cholestasis may be divergent with considerable variations in the time of onset after the initial insult, disease course and prognosis. Whereas hepatocellular impairment of bile formation due to alterations in hepatic blood flow and ischemia is, in principle, fully reversible, persistent damage to the bile duct epithelium can lead to a progressive, irreversible cholestasis with features of sclerosing cholangitis. Appearance of bile duct alterations mark the transition from a potentially reversible disease state into a fixed irreversible stage and are usually diagnosed only upon persisting cholestasis by histology.

**Monitoring excretory function in the critically ill: hyperbilirubinemia and plasma disappearance of indocyanine green**

Biliverdin and bilirubin are derived from degradation of heme and exert important biological functions under conditions of oxidative stress. Due to the potential toxic effects of free heme, the heme-degrading enzyme, heme oxygenase, has long been recognized as being highly inducible under conditions pertinent to critical care [8]. As such, a ‘signal-to-noise’ problem results with respect to interpretation of bilirubin levels, in particular, regarding rapid changes of liver function in the acute setting, while bilirubin is a reliable parameter in assessment of chronic liver disease.

Thus, xenobiotic compounds, such as bromsulphthalein or indocyanine green (ICG), have long been used to reduce confounding factors associated with the use of bilirubin in the assessment of excretory liver function. Of all the available quantitative tests to assess excretory function, the plasma disappearance rate of ICG (PDRICG) has increasingly gained attraction due to its easy bedside performance. Figure 1 summarizes confounders and information provided by bilirubin as compared with PDRICG. The PDRICG is one of a variety of ‘dynamic’ or ‘quantitative tests of liver function’ that all rely on composite assessment of perfusion together with a (sub)cellular metabolic or excretory function. Apart from PDRICG, the aminopyrine breath or monoethylglycinexilidide (MEGX) tests are important examples that provide similarly useful and complementary information attributable to diverse cellular compartments (e.g., cytosolic, microsomal, mitochondrial) and acinar regions of the liver, reflecting, for instance, resectability as well as recovery or response to treatment in hepatitis [13,14]. Consequently, these tests share not only some common information (permanent loss of parenchymal cell mass, rapid changes associated with altered blood flow) but also diverse information regarding specific pathways that might be of clinical significance [15*,16]. Due to more convenient handling and availability of the test, in particular, in the critical care unit, the PDRICG has outpaced other dynamic tests.

The organic anion ICG is an infrared absorbing, fluorescent dye, which is nearly exclusively subject to hepatobiliary elimination and does not undergo enterohepatic recirculation. Under physiological conditions and after a 0.25–0.5 mg/kg body weight bolus, the dye appears unconjugated and rapidly in the bile, that is, at least within 30 min [17]. Although measuring the clearance of the dye allows to dissect both aspects, perfusion and elimination, mere assessment of its elimination from the blood stream (PDRICG) reflects a complex measure of both sinusoidal perfusion and hepatic (cell) membrane function and, thus, reflects a functional reserve of hepatocytes that have access to perfusion [18]. As such, rapid changes primarily reflect changes in perfusion [19,20], while delayed loss of parenchymal cell mass has been observed with prolonged kinetics, for example, upon development of graft dysfunction or rejection of liver grafts [21*,22]. It is noteworthy that obstructive jaundice may substantially and reversibly impair PDRICG [23].

Major hepatobiliary [24**] as well extrahepatic surgery, including cardiac surgery [25,26*,27], remain active areas of research regarding use of the PDRICG, presumably as a surrogate for the otherwise frequently hidden impairment of gastrointestinal perfusion, a significant factor for morbidity and mortality in these patients. Liver transplantation and its associated perfusion abnormalities and potential episodes of rejection are reflected well in the PDRICG, however, with the inherent haziness regarding differential diagnosis of impaired perfusion/energy state as opposed to cell/membrane/transporter function [21*,22]. Nevertheless, normal PDRICG values render both complications unlikely, although an uncertainty of underestimated canalicular transporter dysfunction remains [28,29*].

A study published in the current review period analyzed a variety of static laboratory values, including transaminases as well as the PDRICG, in 48 severely septic patients in a prospective and comparative design. Incidence of liver dysfunction in septic patients was 42% as assessed by hyperbilirubinemia but 74% by impaired dye
excretion. Conventional markers for liver injury (transaminases), synthesis (prothrombin ratio, albumin, cholinesterase) and cholestasis [alkaline phosphatase, gamma-glutamyl transferase (γ-GT), bilirubin] failed to predict outcome, while dye excretion of less than 8% per minute predicted death with high sensitivity and specificity. Moreover, PDR_{ICG} discriminated surviving from nonsurviving patients as early as on the day of diagnosis, challenging the concept of delayed deterioration of liver dysfunction during the course of ICU treatment [29**].

Taken together, there is accumulating evidence to suggest that among the various disparate parenchymal functions, disturbances of excretion are key to understand the pathophysiology or at least suitable to predict poor outcome. These are reflected in the setting of rapid changes in the critically ill by dye excretion, while bilirubin is useful as ‘fingerprint’ of prolonged alterations in the excreatory machinery [11,29**,30**]. The significance of extrahepatic sequelae, as reflected in the ‘model for end-stage liver disease’ (MELD) score, which takes into account kidney function, is beyond the scope of this short review. It is, however, important to note that significant differences result from various assays for serum creatinine and are reflected in differences of MELD between centers that are important in the light of its use in allocation algorithms for liver grafts [31,32*].

**Scores in liver cirrhosis: search for the Holy Grail**

Scoring systems were introduced to better predict course and outcome of liver cirrhosis, especially in the light of shortage of grafts for liver transplantation. The Child-Turcotte-Pugh (CTP) score consists of liver laboratory markers [bilirubin, international normalized ratio (INR) and albumin] and clinical abnormalities (ascites, hepatic encephalopathy). Due to the subjective assessment of the latter, the MELD score, which is based on bilirubin, INR and creatinine, as a marker for remote
organ dysfunction, is recently more commonly used for graft allocation, for example, by the United Network for Organ Sharing (UNOS) and Eurotransplant, although studies [33,34] in the review period continue to suggest limitations.

Numerous studies [35,36,37] have been published comparing the scores in different patient populations with conflicting results, and the search continued during the review period. Different modifications have been proposed in the last years, and improvement of estimating short-term prognosis has been reported, for example, with additional points for more severe alterations of bilirubin, albumin and INR in the CTP score increasing the maximum score to 18 and introducing a CTP class D, or by assessing changes of MELD and CTP scores over a time period [38].

The most common and best evaluated modification is the implementation of serum sodium levels in the MELD score (MELDNa). In a large cohort of almost 7000 adult candidates for liver transplantation for the year 2005, MELD score and serum sodium concentrations were associated with 90-day mortality with an increased impact of hyponatremia in patients with lower MELD scores. Multivariable Cox regression analysis revealed equation of a new MELDNa score, which was validated with the 2006 registrants (again about 7000 patients) and demonstrated better prediction of mortality than the original MELD score [39**]. Another recent study [37*] also supported the notion that serum sodium concentration included in the equation of the MELD score improves prognostic accuracy.

However, especially in the light of graft allocation, there remain concerns on the ‘objective’ and ‘reliable’ parameters used in the MELD and the MELDNa score. Xiol et al. [32*] measured parameters of the MELD and MELDNa scores in 70 patients who were waiting for a liver transplant. Blood samples were processed in three different university laboratories. They found significant differences for all four parameters, that is, bilirubin, creatinine, INR and sodium, between the laboratories, leading to different scores in 64 patients for MELD and 61 patients for MELDNa. Resulting calculated scores differed sometimes for more than 3 points [32*].

### Monitoring nonparenchymal liver functions: the blind leading the deaf

Although parenchymal liver functions are beyond a comprehensive approach, assessment of the diverse pool of pathophysiologically highly significant nonparenchymal cells and functions is almost not explored at present. These include, but are not restricted to, clearance of pathogens and their associated patterns, release of

*Figure 2 Evidence for activation of mediator cascades associated with altered function of sinusoidal cells in patients with acute or acute-on-chronic liver failure*

![Graph](image)

Biomarkers representing vasoactive mediators are dramatically increased in the majority of patients with acute or acute-on-chronic liver failure indicating that vasoactive and vasoconstrictive systems are substantially activated at the same time, thereby explaining the common changes in macrocirculation and sinusoidal microcirculation in these patients. CT-proAVP, C-terminal proarginin vasopressin (copeptin); CT-proET1, C-terminal proendothelin-1; MR-proADM, midregional proadrenomedullin; MR-proANP, midregional pro-A-type natriuretic peptide. Modified from [40].
inflammatory mediators or antigen presentation. On the basis of a multitude of experimental studies, sinusoidal perfusion abnormalities can be considered a hallmark of ‘activation’ of the nonparenchymal cell pool, reflecting release of inflammatory and vasoactive mediators, which might, in turn, deteriorate parenchymal function in a vicious circle. Biomarkers representing these alterations in vasoregulatory control are dramatically increased in the majority of patients with acute or acute-on-chronic liver failure [40] (Fig. 2).

Conclusion

Monitoring ‘liver function(s)’ poses significant problems regarding the diverse parenchymal metabolic functions. As such, rapid and repeated assessments of surrogates for more global ‘liver function’ in the critically ill are difficult to achieve, and conventional ‘static’ parameters, most notably bilirubin and transaminases, are, in general, too sluggish to meet this demand. They are, however, either alone or as a part of more complex scores such as MELD, useful to monitor deterioration of chronically impaired liver function in cirrhosis. Useful surrogates for global ‘liver function’, as they reflect functional parenchymal cell mass with access to perfusion, are the ‘dynamic’ or quantitative tests of liver functions. They rely on clearance, elimination or metabolite formation and respond more rapidly to changes associated with critical illness than static or conventional parameters such as bilirubin and transaminases. They are, however, associated with an inherent diagnostic fuzziness regarding discrimination of perfusion to function abnormalities. Among these tests, the PDRICG has the advantage of easy bedside assessment, low rates of side effects and a wealth of data regarding clinical utility in a broad spectrum of patient populations.

In a nutshell, excretory function is of the essence to monitor impaired ‘liver function’ in the critically ill, both in the absence and presence of preexisting liver disease. Its assessment is best achieved by bilirubin and MELD in the cirrhotic patient and by quantitative tests of liver function, most notably PDRICG, in the absence of chronic liver disease. Validated biomarkers to monitor nonparenchymal enzymes, which are considered to be of outstanding significance in deterioration of liver function in the critically ill, are currently not available.

References and recommended reading

- Papers of particular interest, published within the annual period of review, have been highlighted as:
  - of special interest
  - of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 178).


The authors nicely review ‘secondary sclerosing cholangitis’, an underrecognized chronic cholestatic biliary disease, characterized by inflammation, obliteration fibrosis of the bile ducts, sticture formation and progressive destruction of the biliary tree, which may complicate sepsis-associated cholestasis, resulting in a rapidly progressive disease with poor outcome.


Peptiderferon/ribavirin, for eradication of chronic hepatitis C, is associated with early improvement of anisopropyine breath test and galactose elimination capacity as parameters of microsomal and cytosolic liver function, while sorbitol and ICG clearance require 1 year of treatment before returning to normal levels, indicating that diverse ‘dynamic’ liver function tests provide potentially additive information.


PDRICG, with a cut-off level of 12.85% per minute in the early postoperative course (days 0–5) after liver transplantation, is predictive for serious complications. Sequential changes differentiate two groups: patients with early complications (primary graft nonfunction, sepsis and hepatic artery thrombosis) with consistently low values (8.8 ± 4.5% per minute) and patients with acute rejection displaying a profound secondary decrease of PDRICG.

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25 In a cohort of 1017 patients who underwent hepatic resection for hepatocellular carcinoma (HCC), age, liver cirrhosis, MELD score and duration of surgery were risk factors for mortality, whereas ICG retention rate at 15 min, blood loss, CTP score and duration of surgery were risk factors for morbidity. Morbidity and mortality rates were 30.7 and 1.9%, respectively. These data underscore the complementary nature of MELD and PDCR, to assess chronic disease progression and rapid changes of liver perfusion/function in the periprocedural setting.


28 This study in 60 patients who underwent cardiac surgery with cardiopulmonary bypass, prolonged ICU treatment was associated with decreased PDCR as early as 1 h postoperatively, indicating its usefulness as a surrogate for gastrointestinal/liver perfusion abnormalities. Preoperative values did not differ, and haemodilutional anaemia had no influence on PDCR.


32 This article is the first to prospectively assess a broad spectrum of parameters for liver injury, synthesis and excretory function as they relate to prognosis. Furthermore, potential mechanisms for dysfunction are assessed revealing that, although injury excretion is superior to bilirubin to assess excretory dysfunction, it still underestimates the impaired canalicular transport machinery as the primary target of dysfunction in the critically ill.


34 In this study, comparing MELD and bilirubin with PDCR in cirrhotic patients, MELD/bilirubin was superior to PDCR in predicting both 90-day survival in non-ICU patients and 30-day survival in ICU patients, supporting the concept of better reflection of chronic disease in the composite MELD. The cut-off for optimal discrimination of survivors and nonsurvivors was at least 22 for MELD and 5.3, or less for PDCR Area under the receiver operating characteristic curve (AUC-ROC) was 0.89 vs. 0.71 for MELD vs. PDCR, respectively.


37 In this study, in 70 patients who were waiting for a liver transplant, blood samples were drawn to measure parameters of the MELD and MELDNa scores. Blood samples were processed in three different university laboratories. For all four parameters, that is, bilirubin, creatinine, INR and sodium, there were significant differences between the laboratories, leading to different scores in 64 patients for MELD and 61 patients for MELDNa. Resulting calculated scores differed sometimes by more than 3 points.


43 Two different calculations of a modified MELD score, in which serum sodium concentrations were incorporated in the calculation, demonstrated better mortality prediction than the original MELD score.


46 This study demonstrates a better prediction of 90-day mortality with a modified MELD score in a large cohort of patients who were waiting for a liver transplant, which incorporates serum sodium levels. This is important in the light of current discussions regarding graft allocation based on scores, and their potential improvement as score-based allocation has led to lower survival rates compared with waiting list. MELD score and serum sodium levels were significantly associated with mortality. The hazard ratio for death was 1.05 per 1-unit decrease in serum sodium concentration for values between 126 and 140 mEq/l.