Incorporating dynamics for predicting poor outcome in acute liver failure patients

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Abstract
Acute liver failure (ALF), also known as fulminant hepatic failure (FHF), is a devastating clinical syndrome with a high mortality of 60%-90%. An early and exact assessment of the severity of ALF together with prediction of its further development is critical in order to determine the further management of the patient. A number of prognostic models have been used for outcome prediction in ALF patients but they are mostly based on the variables measured at one time point, mostly at admission. ALF patients rarely show a static state; rapid progress to a life threatening situation occurs in many patients. Since ALF is a dynamic process, admission values of prognostic variables change over time during the clinical course of the patient. Kumar et al developed a prognostic model [ALF early dynamic (ALFED)] based on early changes in values of variables which predicted outcome. ALFED is a model which seems to be worthwhile to test in ALF patients in other parts of the world with different aetiologies. Since the exact pathophysiology of ALF is not fully known and is certainly complex, we believe that adding promising variables involved in the pathophysiology of ALF to the dynamic approach might even further improve prognostic performance. We agree with Kumar et al that an improved dynamic prognostic model should be based on simplicity (easily to be performed at the bedside) and accuracy. Our comments presented in this paper may be considered as recommendations for future optimization of ALF prediction models.

COMMENTARY ON HOT ARTICLES
We read with great interest the recent article by Kumar et al about the derivation and validation of an early dynamic model for predicting outcome in patients with acute liver failure (ALF).

ALF, also known as fulminant hepatic failure (FHF), is a devastating clinical syndrome with a high mortality of 60%-90%, depending on the aetiology and the clinical experience of the reference center. Most frequent causes of death are brain oedema, systemic inflammatory response and multiple organ failure. In the Western world (United States and Europe) annually about 7500 patients suffer from ALF. “Spontaneous recovery” occurs in a minority of these patients. In most cases liver transplantation (LT) remains the only life saving treat-
ment of irreversible ALF. However, due to lack of sufficient donors only 20% of patients can be directly treated with LT. As a result, many patients die while on the donor waiting list.

An early and exact assessment of the severity of ALF together with prediction of its further development is critical in order to determine the further management of the patient such as (bio) artificial liver support and/or urgent LT. The timely prediction of spontaneous recovery helps to prevent LT and also the need for lifelong immunosuppressive therapy. Predicting whether the patient with ALF will require LT or will survive by only intensive medical care remains, however, challenging.

A number of prognostic models have been used for outcome prediction in ALF patients to select patients in need for LT. The most widely applied ones are the King’s College Criteria (KCC), Clichy criteria, and the Model for End-Stage Liver Disease (MELD). The models have shown inconsistent reproducibility of prognostic accuracy, and the need for a better prognostic model remains[3]. Prognostic models used in literature are mostly based on the variables measured at one time point, mostly at admission. ALF patients rarely show a static state: rapid progress to a life threatening situation occurs in many patients. Since ALF is a dynamic process, admission values of prognostic variables change over time during the clinical course of the patient.

Kumar et al[1] developed a prognostic model [ALF Early Dynamic (ALFED)] based on early changes (during first 3 d of hospitalisation) in values of variables which predicted outcome independently at admission in a prospective cohort of 244 patients with ALF (mainly caused by acute viral hepatitis) and validated it in a prospective observational study of 136 ALF patients with comparable aetiology. The model was constructed based on whether the levels of predictive variables remained persistently high or increased over 3 d of hospitalisation above the discriminatory cut-off values identified in this study. Liver transplantation was not available at their centre, and the only possible outcome was recovery or death. The authors found that early changes of prognostic markers predict outcome better than the static baseline levels. Their model consists of clearly defined and routinely available predictors. This is a worthwhile study in agreement with the concept that the use of dynamic changes over time of predictors should improve prognostic performance. This observation is supported by the systematic review of Minne et al[4,5] that underlined the association between the dynamics of the Sequential Organ Failure Assessment score with hospital mortality in the intensive care.

The ALFED model of Kumar et al[1] consists of four variables, which is in line with the known pathophysiology of ALF, namely hyperammonemia as a consequence of impaired hepatic urea synthesis and contributing to the development of hepatic encephalopathy (HE); hyperbilirubinemia as a consequence of impaired biliary excretion and coagulopathy as a consequence of decreased protein synthesis, especially of clotting factors, expressed by international normalized ratio (INR).

We assessed the quality of the ALFED model and its development process based on a framework for the assessment of the quality of and reporting on prognostic models[7]. Kumar et al[1] clearly describe the setting and the study population; they report the type of the study (prospective) and the number of patients and events (deaths/survivals). Based on the results of our previous work[6] we are aware that many studies often do not report the definition of the disease. Kumar et al[1] give a clear definition of ALF as well as of the variables, including their units. Furthermore it could be inferred which variables were continuous or categorical. Initial variables included routinely available factors, which were already known to be important. However, we could not find any information about whether there were missing values, and if so, where, and what was done to them. This information should not be neglected when presenting the development of a model.

Kumar et al[1] clearly report the type of the model, its intended use as well as its derivation and evaluation process and present the model’s formula which can be used to make prediction. ALFED is a logistic regression model used for predicting the outcome of ALF patients based on the prospectively collected development set. First univariate analyses were performed to determine the variables which were statistically significantly (at the 0.05 level) associated with the outcome. Next, a multivariable logistic regression model was developed with the significant predictors using a stepwise forward selection procedure. We recommend using an information criterion (such as the Akaike Information Criterion) in the (e.g., backward, stepwise) selection process instead of relying on P-values ≤ 0.05 in univariate analysis.

It is important to perform validation of the model, e.g., assess a model’s discrimination and calibration performance in order to reinforce model credibility before its use in clinical practice. Discrimination is the ability of the model to assign higher predicted probabilities of the outcome (e.g., death) in patients actually having the outcome than in those not having it. The discrimination of the ALFED model was assessed by the area under the receiver operator characteristic (AUROC) curve. Calibration measures the proximity between the predicted probabilities and the actual risk of a group of similar patients. Calibration was assessed using an observed versus predicted plot and the Hosmer-Lemeshow statistic. Kumar et al[1] report also on other statistical performance measures based on a given cut-off point, such as: sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, negative likelihood ratio and diagnostic accuracy. Kumar et al[1] performed temporal validation of the model[8], which means on a different sample collected later, but from the same population of the developmental dataset. However, the two samples significantly differed in INR, arterial pH and ammonia, mean MELD value, hepatitis E virus aetiology and mortality.

The ALFED model was also compared with the established prognostic models KCC and MELD. The results
of this comparison showed that performance of MELD and KCC criteria (based on AUROC and the above mentioned statistical performance measures determining its prognostic accuracy) was inferior to the ALFED model in the two cohorts, although no statistical testing was attempted for comparison.

Since the exact pathophysiology of ALF is not fully known and is certainly more complex than the above mentioned disturbances in ammonia (HE), bilirubin metabolism and coagulation, our hypothesis is that extending the dynamic approach to other variables involved in the pathophysiology of ALF might still improve prognostic performance. For example, biomarkers of the inflammatory response of ALF may further improve the predictive performance of such a model, for example plasma ratio of interleukin (IL)-6/IL-10[10-12]. In addition, the impaired capacity of the ALF patient to maintain metabolic homeostasis might be included by using hyperlactatemia for example. We agree with Kumar et al.[9] that an improved dynamic prognostic model should be based on simplicity (easily to be performed at the bedside) and accuracy.

Although ALFED should be still tested on patients with other aetiologies (e.g., paracetamol overdose), it seems to be a valuable step forward.

Based on our above considerations we conclude that ALFED is a well constructed and well reported model which seems to be worthwhile to test in ALF patients in other parts of the world with different aetiologies. In addition, we believe that adding promising variables involved in the pathophysiology of ALF to the dynamic approach might even further improve prognostic performance. Our comments may be considered as recommendations for future research on developing ALF prediction models.

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