EDITORIAL

C-Reactive Protein and Model for End-Stage Liver Disease Score: Have We Found the Fifth Element?

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Received March 2, 2015; accepted April 1, 2015.

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The natural history of cirrhosis varies from patient to patient, depends on a number of factors, and is largely unpredictable. The transition from the compensated phase to the decompensated phase is dictated on one hand by the loss of liver cell mass and on the other hand by the development of complications of portal hypertension.[1] Many studies have confirmed that the Model for End-Stage Liver Disease (MELD) is highly accurate for assessing the degree of hepatic insufficiency and short-term prognosis (90 days) in patients with cirrhosis in both transplant and nontransplant settings.[2] However, approximately 15% to 20% of candidates for liver transplantation are not well served by MELD. A few years ago, our group showed that the addition of serum sodium to the MELD formula significantly increased its efficacy. The replacement of MELD by MELD-Na will allow earlier access to liver transplantation, especially for patients with severe portal hypertension and ascites but with relatively well-preserved liver function and normal serum creatinine.[3,4] Serum sodium thus became the fourth element of MELD.[5] The transition to the decompensated stage of cirrhosis is usually a slow and gradual process evolving over months or even years. However, the natural course of cirrhosis is often complicated by acute episodes of decompensation triggered by a precipitating event. The outcome and reversibility of decompensation vary according to the nature and severity of the acute hepatic insult and according to the degree of dysfunction of extrahepatic organ systems.[6] Recent studies have shown that in acutely ill patients with cirrhosis, systemic inflammatory response syndrome (SIRS), with or without a documented bacterial infection, is an independent predictor of survival and is also associated with the development of portal hypertension–related complications.[7,8] Liver function appears not to be the main determinant of outcome in patients with cirrhosis who experience multiorgan failure. Therefore, the negative impact of systemic inflammation in this scenario may be poorly predicted by MELD.[9] Conventional parameters for diagnosing SIRS lack sensitivity and specificity in patients with advanced cirrhosis because of hypersplenism, hyperventilation associated with encephalopathy, hyperkinetic circulation, or the use of beta-blockers. C-reactive protein (CRP) is considered a surrogate marker for acute or chronic systemic inflammation and bacterial infection, although elevated levels have been described in many other conditions, such as acute alcoholic hepatitis, malignant tumors (including hepatocellular carcinoma), tissue necrosis, and bacterial translocation.[10] In a series of 148 consecutive patients with predominantly alcoholic cirrhosis and a Child-Pugh status $\geq$ B8, Cervoni et al.[11] found that CRP was a statistically significant predictor of death [area under the receiver operating characteristic curve (AUROC), 0.63] and SIRS (AUROC, 0.73). The prognostic value of CRP was independent of SIRS, bacterial infection, and alcoholic hepatitis. Interestingly, the majority of patients with

Abbreviations: AUROC, area under the receiver operating characteristic curve; CRP, C-reactive protein; MELD, Model for End-Stage Liver Disease; SIRS, systemic inflammatory response syndrome.

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DOI 10.1002/lt.24140
View this article online at wileyonlinelibrary.com.
LIVER TRANSPLANTATION.DOI 10.1002/lt. *Published on behalf of the American Association for the Study of Liver Diseases*

elevated CRP did not present with any of these events. According to baseline and day 15 levels, patients were allocated to 3 groups, and those with persistent systemic inflammation (elevated CRP at baseline and day 15) had a worse prognosis. On the basis of a multivariate Cox analysis, the authors developed a prognostic model, including a high MELD score, extrahepatic comorbidities, and persistent elevation of CRP (>29 mg/L). The 3-variable model was a good predictor of 6-month survival with an AUROC of 0.80 versus 0.67 for MELD.[11]

In this issue of *Liver Transplantation*, Di Martino et al.[12] extend this investigation by assessing the efficacy of their prognostic model in an independent cohort of 214 consecutive patients with cirrhosis, 149 of whom were hospitalized for decompensation (Child-Pugh ≥ B7) and constituted what the authors call the validation group. Again, patients were allocated to 3 arms according to the values of CRP at the baseline and on day 15. Overall, baseline CRP levels were significantly higher in patients who died versus those who survived, with little or no overlap between these 2 groups (40.0 ± 6.7 versus 17.5 ± 2.4 mg/L). Baseline CRP was a good predictor of death in the whole population (AUROC, 0.783) and to a lesser degree in the validation cohort with a Child-Pugh status ≥ B7 (AUROC, 0.635). Both in the whole group (cutoff value of >10 mg/L) and in the validation group (cutoff value of 32 mg/L), survival was significantly lower for patients with a persistent elevation of CRP (baseline and day 15) versus those whose CRP normalized during the observation period or who had normal values at the baseline. The AUROC of the 3-variable model for predicting 3-month survival was significantly higher than that of MELD in the validation group (0.789 versus 0.734; $P < 0.05$) but not in the whole population (0.895 versus 0.876). Results did not vary when patients with bacterial infections or alcoholic hepatitis were removed from the analysis. In addition, no correlation was found between MELD and CRP. The authors concluded that their model combining MELD and CRP may better sort the candidates for liver transplantation than MELD alone.

The interesting results obtained by Cervoni et al.[11] and Di Martino et al.[12] raise the question whether CRP may become the fifth element of MELD and, more importantly, whether their model could be used to improve liver organ allocation. Similarly to the international normalized ratio, total bilirubin, serum creatinine, and serum sodium, CRP is a quantitative, objective, reproducible, easily available, and inexpensive laboratory test and is thus attractive to be incorporated into the mathematical formula of MELD. In addition, baseline CRP was significantly higher in patients who died and in the whole population was quite effective at predicting by itself the risk of death at 3 months of follow-up. The CRP-based model proposed by Di Martino et al. has a number of limitations and uncertainties. To start, the authors recalculated the cutoff values of CRP and, therefore, did not use the exact model proposed in the original publication. Consequently, the so-called validation cohort was not truly a validation group. Second, the CRP-based model marginally improved the performance over MELD alone (by 5%) and only in patients with severe cirrhosis. Expressing a quantitative variable such as CRP in a qualitative way (presence or absence of a sustained elevation) and using different cutoff values according to the severity of cirrhosis are methodological challenges for any predictive model. Finally, the need for 2 measurements of CRP from samples obtained 15 days apart renders the model more complex and perhaps inadequate for determining candidacy for liver grafting in a timely fashion. Although an active bacterial infection is largely regarded as a contraindication for liver transplantation, a 15-day mandatory delay may be inappropriately long for patients with a rapid resolution of the infection or those with adequate antibiotic coverage for nonbacteremic infections caused by easily treatable organisms. The 3-variable model was developed from a series of patients with cirrhosis who were predominantly alcoholic (88% in the study by Cervoni et al.[11]). Therefore, their results may not be reproducible for patients with cirrhosis of other etiologies.

The most practical strategy for increasing justice in liver organ allocation today is to improve the efficacy of MELD. When they were analyzed together, no correlation was found between MELD and CRP, and this suggests that CRP may rescue some patients who are not prioritized by MELD. This appears to be the strongest message of the study by Di Martino et al.[12] Although their model is unlikely to be implemented for organ allocation, it will encourage investigators worldwide to design additional studies to answer the question of whether CRP should become the fifth MELD element.

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