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MELD–Na as a prognostic score for cirrhotic patients: Hyponatremia and ascites are back in the game ☆

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Hyponatremia and mortality among patients on the liver-transplant waiting list. Kim WR, Biggins SW, Kremers WK, Wiesner RH, Kamath PS, Benson JT, Edwards E, Therneau TM.

***Background*: Under the current liver policy, donor organs are offered to patients with the highest risk of death.**

***Methods*: Using data derived from all adult candidates for primary liver transplantation who were registered with the Organ Procurement and Transplantation Network in 2005 and 2006, we developed and validated a multivariable survival model to predict mortality at 90 days after registration. The predictor variable was the Model for End-Stage Liver Disease (MELD) score with and without the addition of the serum sodium concentration. The MELD score (on a scale of 6–40, with higher values indicating more severe disease) is calculated on the basis of the serum bilirubin and creatinine concentrations and the international normalized ratio for the prothrombin time.**

***Results*: In 2005, there were 6769 registrants, including 1781 who underwent liver transplantation and 422 who died within 90 days after registration on the waiting list. Both the MELD score and the serum sodium concentration were significantly associated with mortality (hazard ratio for death, 1.21 per MELD point and 1.05 per 1-unit decrease in the serum sodium concentration for values between 125 and 140 mmol per liter; $P < 0.001$ for both variables). Furthermore, a significant interaction was found between the MELD score and the serum sodium concentration, indicating that the effect of the serum sodium concentration was greater in patients with a low MELD score. When applied to the data from 2006, when 477 patients died within 3 months after registration on the waiting list, the combination of the MELD score and the serum sodium concentration was considerably higher than the MELD score alone in 32 patients who died (7%). Thus, assignment of priority according to the MELD score combined with the serum sodium concentration might have resulted in transplantation and prevented death.**

***Conclusions*: This population-wide study shows that the MELD score and the serum sodium concentration are important predictors of survival among candidates for liver transplantation. 2008 Massachusetts Medical Society.**

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For several decades now, the severity of cirrhosis has been scored using the Child–Pugh system [1]. Use of this score became widespread because of its simplicity and its good correlation with long-term outcome in cirrhotic patients. The Mayo End-stage Liver Disease score (MELD) was initially employed to determine the prognosis of cirrhotic patients treated by means of a transjugular portacaval shunt (TIPS) [2]. This more recent score comprises three variables: bilirubin levels, INR and creatinine levels. However, the latter variable is not included in the Child–Pugh scoring system. MELD is a quantitative tool with scores ranging from 5 to 40, a

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maximum score being indicative of the most severe stage. The popularity of this more recent score has arisen firstly, from its linear correlation with a quantitative value and a risk of death within 3 months [3], and secondly because of the decision by the US health authorities in 2002 to allocate liver grafts as a function of cirrhosis severity. This new system of allocating grafts to more severe patients evaluated using the MELD score resulted in a dramatic decrease in waiting list mortality without significantly impairing post-transplant outcome [4]. It has also resulted in a reduction in the number of less severely affected patients being placed on the transplant waiting list. In addition, it has been suggested that patients in the US with a MELD score lower than 15 have a greater risk of death at one year as a result of the transplant procedure itself rather than not undergoing transplantation, suggesting that these patients should not be put on the waiting list [5]. The problem with this affirmation is that it only takes survival at one year and no further into account. Thus most countries have now decided to apply a similar system for graft allocation; this is based on the MELD score or on a composite score that includes the MELD. Unfortunately, this graft allocation system has several major drawbacks: it only applies to patients with cirrhosis; those with hepatocellular carcinoma on compensated cirrhosis, sclerosing cholangitis, metabolic disease or various other rare conditions that are not classified accurately by the MELD score and their access to liver transplantation is problematic [6]. For this reason, an artificial MELD score was developed for HCC patients, taking into account the risk of drop out from the waiting list by these patients [7]. For other patients, such as those with metabolic disease, refractory ascites or recurrent encephalopathy despite a low MELD score, the only means of ensuring their access to transplantation was to request their prioritization by an expert committee. Returning to cirrhotic patients, several authors raised the point that the Child–Pugh score also takes account of the presence of ascites, low albumin levels and encephalopathy, and that these three features are absent from the MELD score. Because the volume of ascites is a subjective sign, it was suggested that Na values should be added to the MELD score in order to allow for the presence of refractory ascites or hepatorenal syndrome (HRS) [8–10]. Indeed, hyponatremia is associated with a higher risk of complications with ascites and the onset of HRS [11]. In view of these arguments, Kim et al. analyzed the prognostic value of hyponatremia at levels between 125 and 140 Meq/l. They built a model that considered the prognostic value of both hyponatremia and MELD, and developed a new scoring system called MELD–Na. Calculation of this score was based on data concerning patients placed on the US waiting list in 2005, as follows: $\text{MELD–Na} = \text{MELD} - \text{Na} - [0.025 \times \text{MELD} \times (140 - \text{Na})] +$ 140. They then applied this new score to the cohort of cirrhotic patients placed on the US liver transplant waiting list in 2006. They showed that MELD and hyponatremia were correlated with the mortality risk, and also demonstrated that the MELD–Na score was more predictive of the risk of death in more severe patients, and particularly those with a MELD score of between 20 and 39 [12]. The presence of hyponatremia thus adds points to the current MELD score, so that a patient with hyponatremia will have a higher MELD–Na score than the same patient with normal serum sodium levels. As a result, refractory ascites has recovered indirectly its importance to scoring, as suggested by the Child–Pugh score.

This new score needs to be validated in additional independent cohorts, and it will be interesting to determine whether it will benefit the more severely affected patients only, or the entire cohort of cirrhotic patients. We should acknowledge the constant efforts of our US colleagues to improve prognostic scoring systems for cirrhotic patients, so that the more severe amongst them will benefit from better access to transplantation. However, it is also important to apply this new score to a variety of cirrhotic patient cohorts and to different etiologies of the disease, and to determine the prognostic value of the MELD–Na score not only in the short-term but also in the medium and longer terms. We need to decide whether this new score should be implemented for allocation by organ-sharing organizations, and clarify how it might impact waiting list mortality and post-transplant outcome.

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Are pigs more human than mice? ☆

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Disruption of the CFTR gene produces a model of cystic fibrosis in newborn pigs. Rogers CS, Stoltz DA, Meyerholz DK, Ostedgaard LS, Rokhlina T, Taft PJ, Rogan MP, Pezzulo AA, Karp PH, Itani OA, Kabel AC, Wohlford-Lenane CL, Davis GJ, Hanfland RA, Smith TL, Samuel M, Wax D, Murphy CN, Rieke A, Whitworth K, Uc A, Starner TD, Brogden KA, Shilyansky J, McCray PB Jr, Zabner J, Prather RS, Welsh MJ.

Almost two decades after CFTR was identified as the gene responsible for cystic fibrosis (CF), we still lack answers to many questions about the pathogenesis of the disease, and it remains incurable. Mice with a disrupted CFTR gene have greatly facilitated CF studies, but the mutant mice do not develop the characteristic manifestations of human CF, including abnormalities of the pancreas, lung, intestine, liver, and other organs. Because pigs share many anatomical and physiological features with humans, we generated pigs with a targeted disruption of both CFTR alleles. Newborn pigs lacking CFTR exhibited defective chloride transport and developed meconium ileus, exocrine pancreatic destruction, and focal biliary cirrhosis, replicating abnormalities seen in newborn humans with CF. The pig model may provide opportunities to address persistent questions about CF pathogenesis and accelerate discovery of strategies for prevention and treatment.

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In the era of molecular genetics we tend to think that once we have discovered the gene that is responsible for a monogenetic disease, we will understand the pathogenetic mechanisms of this disease. For this purpose, we "simply" make a knockout mouse for this gene, which we believe will always solve the problem. Alas, in many cases this is far from true. Just as an example: Niemann-Pick C disease is an inherited storage disorder characterized by cholesterol accumulation in the lysosomes; the gene (*NPC1*) mutated in this disease was identified in 1997 [1] and mice with a defect in the *Npc1* gene were available at that time. In spite of intense research for two decades by many groups, the function of this gene is still unsolved.

The situation is only slightly better for cystic fibrosis. The responsible gene, the cystic fibrosis transmembrane regulator (CFTR), was identified in 1989 [2] and knockout mice have been available since 1993 [3]. CFTR is known as a cAMP-regulated chloride channel, but various other functions have been attributed to this protein as well. Cystic fibrosis as a disease has many appearances and few of them are well understood. A complicating factor is that the $Cftr^{-/-}$ mouse as a disease model is far from a phenocopy of this multi-organ disease.

Cystic fibrosis is a common, potentially fatal genetic disorder affecting about 1 in 3000 live births [4]. Seventy percent of the patients carry the ΔF508 mutation in which the amino acid phenylalanine at position 508 is deleted. This mutant protein is not properly folded and largely broken down in the endoplasmatic reticulum. The high frequency of this genetic disorder suggests that heterozygotes for *CFTR* mutations may have some selective advantage. It has been proposed that carriers are more resistant towards cholera toxin-induced diarrhoea. Cystic fibrosis is a devastating disease that affects many tissues, including lungs, pancreas, intestine and liver. Thickened mucus is the hallmark of this disease leading to secretory failure of these organs. Meconium

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