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Organ allocation for patients with acute-on-chronic liver failure: Time to look beyond MELD-Sodium?

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Intense research by many groups around the world into the clinical, pathophysiologic and prognostic basis of decompensated cirrhosis has led to the conclusion that acute-on-chronic liver failure (ACLF) is distinct from 'mere' acute decompensation [1]. The main clinical difference is that in patients with cirrhosis that require hospitalisation for a liver-related complication, the failure of organs, in addition to, or other than the liver, namely, coagulation, brain, kidneys, circulation and respiration are independently associated with high-risk of short term mortality. These observations imply that 'liver failure' is not necessary for the diagnosis of ACLF in patients with cirrhosis. The diagnostic criteria for ACLF was defined using the data from the CANONIC study in 2013, which is the only prospective study that was specifically performed to define ACLF [2]. This idea of the importance of the failure of extrahepatic organs, has been confirmed by 'The North American Association for End Stage Liver Disease (NACSELD)' who define the syndrome based only on the failure of extrahepatic organs [3]. From the pathophysiological perspective, ACLF is characterised by intense systemic inflammation [4] triggered by release of damage associated molecular patterns from cell death [5] and pathogen associated molecular patterns from infection and bacterial translocation [6]. Together, this culminates in mitochondrial failure, organ immunopathology and immune failure (Moreau et al. JHEP 2020; Engelmann et al. JHEP 2020; Van Der Merwe et al. Gut 2019) [6,7,8].

The limitations of Model for end stage liver disease-Sodium (MELD-Na)

MELD-Na was derived from the MELD score, which was described as a prognostic score in 2000 to try and define the outcome of patients undergoing the transjugular intrahepatic stent shunt [9]. The MELD-Na score is derived from biochemical variables that include bilirubin, INR, creatinine and sodium. It was adapted for liver transplantation and very rapidly introduced into clinical practice as a organ allocation system in 2002 and, adopted world-wide as it was shown to have a c-statistic of 0.8 in those early studies. As MELD and MELD-

Na scores were based on biochemical measurements and a risk-score, it allowed more equitable distribution of organs. It was shown to be superior to the Child-Pugh score that was open to manipulation because the score contains less accurately quantifiable signs such as encephalopathy and ascites.

Over the past 15-years or so it has become apparent that many groups of cirrhotic patients are poorly served by the MELD-Na score such as those with hepatic encephalopathy, sarcopenia, frailty, refractory ascites, hepatopulmonary syndrome, primary sclerosing cholangitis and hepatocellular carcinoma as they have a high risk of mortality but relatively low MELD-Na scores. These patients often have long waiting times as patients with higher MELD-Na scores are prioritised. Many experts have suggested that MELD score needs to be modified so that these complications are acknowledged as being relevant through grant of 'extra points'. In response, patients with hepatocellular carcinoma receive MELD-Na exception points but the other groups are treated as variant syndromes which seriously disadvantage them on the waiting list. More recently, further modification to MELD has been suggested through addition of lactate for patients presenting with acute decompensation [10].

With this background, if MELD-Na is used to allocate organs to patients with ACLF, one could hypothesize that it may not be as accurate as it is in patients with stable decompensated cirrhosis as ACLF has dintinctive prognostic features. The independent prognostic factors defining 3-month mortality of ACLF patients include organ failures not recognised by the MELD-Na score such as brain, circulation and respiration; in addition to age and white cell count [11]. Therefore, a new scoring system was derived for ACLF patients, the CLIF-C ACLF score [11]. When compared head-to-head in the CANONIC study, the MELD-Na score performed significantly worse and had a c-statistic of 0.66 in

defining the risk of death [11]. More recently, in a transplant population from the US, MELD-Na score was shown to have a c-statistic of only 0.7 [12]. Investigation of the UNOS database of transplant listed patients revealed that MELD-Na failed to identify patients with severe ACLF on the waiting list with high attendant mortality across all MELD-Na scores [13].

Observations from Hernaez et al. [14]

The important study by Hernaez et al. [14] in the present issue of the Journal provides further validation of these earlier observations in a group of about 71,000 cirrhotic patients from 127 VA hospitals between Jan and Dec 2014 from the VA Corporate Data Warehouse. The study aimed to compare 3-month observed mortality of patients with ACLF with expected mortality based on the calculated MELD-Na score. They identified about 19,000 patients that fulfilled the criteria for having ACLF as was previously defined by the EASL-CLIF Consortium in the CANONIC study. They showed that at each ACLF Grade, mortality was significantly underestimated if MELD-Na score was used (Standardised Mortality Rate (SMR): any ACLF: 1.52; ACLF1: 1.46; ACLF2: 1.50; ACLF3: 1.66). The biggest discrepancy in SMR was in patients with low MELD-Na scores. The occurrence of ACLF-2 in those with MELD-Na 0-9 carried an SMR of 27; and in patients with MELD-Na of 10-20, the SMR for patients with ACLF-1, 2 and 3 were 6.5, 7.5 and 10.1 respectively. Importantly, they observed that only 9.1% of patients with ACLF would reach the median MELD-Na threshold of 35 that would give them priority for organ transplantation. In order to evaluate the consequences of underestimating clinical severity using MELD-Na for ACLF patients, they calculated transplant center-specific median MELD-Na at transplantation for these ACLF patients to estimate the proportion likely to receive priority for LT. They observed that depending upon the center involved, only 17% - 35% reached that threshold using the MELD-Na allocation scheme. They also tested the NACSELD criteria for ACLF confirming the inadequacy of the

MELD-Na score. However, the NACSELD criteria diagnosed only about 8000 patients with ACLF compared with the EASL-CLIF criteria, using which nearly 19000 patients were diagnosed. They interpret their data as suggesting that patients with ACLF are seriously disadvantaged in the MELD-Na based allocation system and their data support the possible superiority of the EASL-CLIF criteria for the diagnosis of ACLF compared with the NACSELD criteria.

The major limitation of studies such as this is the retrospective nature not allowing accurate characterisation of organ function, particularly respiratory failure and very importantly evolution of the disease. Although the massive number of patients included in this study provided the authors the power to discriminate the importance of diagnosis ACLF and limitation of the MELD-Na score, it is difficult to extrapolate directly to a transplant waiting list situation. Also, about 40% patients were actively drinking alcohol at the time of admission, many of who would have other contraindications to liver transplantation. Finally, it is not clear what proportion of the patients had multiple organ support in the ICU, which would be standard for patients with ACLF on the waiting list. Nevertheless, the data presented in this impressive study are robust and conclusions seem to be appropriate.

Is it time that patients with advanced ACLF had priority for organs?

The Hernaez [14] data substantially adds to the growing number of studies that further validates the argument for allocating organs to patients with ACLF outwith the MELD-Na system for decompensated cirrhosis [1]. ACLF classification and scores seem more appropriate. This suggestion is not surprising as the MELD-Na score was developed for patients with *stable* cirrhosis and has been shown to be useful for allocating organs to these patients [9]. In contrast, although ACLF occurs in patients with cirrhosis, it is clinically and pathophysiologically a distinct clinical syndrome with unique prognostic models, which have

been shown to be significantly better than the MELD-Na score [2, 11]. There is clear precedence for using unique criteria for allocation of organs in special situations such as in the case of acute liver failure.

The is now a large body of published work that individually and cumulatively provide clear evidence of transplant benefit for patients with ACLF with 5-year survival rates of about 65-70% even in those with ACLF-3 [13, 15]. Based on the arguments presented above, a pilot programme has been initiated in the UK where patients with ACLF-2 and 3 will be listed for transplantation separately and organs will be allocated to these patients as a priority immediately after the patients listed with acute liver failure. The accumulated data would suggest that similar pilots should be explored in other countries.

It is clear however, that further refinement in the prognostic models for ACLF patients will need to be made taking into account post liver transplantation outcomes such as survival, costs and quality of life. Variables such as the number and type of organ failure, severity and sort of infection present, sarcopenia, frailty, quality of organ to be transplanted and timing of transplantation need to be defined carefully. In order to achieve this aim, a large prospective, international study of liver transplantation in ACLF patients, the CHANCE study, is being intiated as a tri-partite collaboration between the European Foundation for Chronic Liver Failure (EFCLIF: www.efclif.com), European Liver and Intestinal Transplant Association (ELITA www.esot.org) and International Liver Transplantation Society (ILTS: www.ilts.org).

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