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Invited Editorial to Baldessare M, Naldi M, Zaccherini G, Bartoletti M, Antognoli A, Laggetta M, et al. Determination of effective albumin in patients with decompensated cirrhosis: clinical and prognostic implications. *Hepatology*. In press.

The 'Alter Ego' of Albumin in Cirrhosis

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<FNTX>Abbreviations: ACLF, acute-on-chronic liver failure; eALB, effective albumin concentration; HAS, human albumin solution; MELD, model for end-stage liver disease; nAlb, native albumin; tALB, total albumin concentration

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Albumin is a globular, multifunctional protein that is highly conserved in nature. Alpha-fetoprotein, Vitamin D and E binding proteins are part of the albumin family and these are produced exclusively in the liver. Albumin is negatively charged and this gives it the oncotic properties it is well known for. More recently, it has become clear that albumin has clinically significant effects on antioxidant status, immune and endothelial function, capillary permeability, organ function, and metabolic homeostasis.<sup>(1)</sup> These non-oncotic properties of albumin are attributable to its free cysteine residue, binding sites for a host of metabolites including metals, drugs, and circulating toxins. Importantly, studies have confirmed that albumin is taken up by a variety of cells including endothelial cells and inflammatory cells and has an impact on limiting the deleterious effects of a variety of toll-like receptor ligands.<sup>(2,3)</sup> It is also important to note that albumin can be oxidized and the function of the binding sites is reduced in disease states.<sup>(1)</sup> Thus, simply measuring the concentration of albumin is unlikely to provide an insight into its biology and function.

The actual measured albumin levels is the total albumin concentration (tALB) and the functional albumin levels is referred to as the effective albumin concentration (eALB), a concept that was first described by Jalan and Bernardi.<sup>(4)</sup> However, how eALB is quantitated was not elaborated. The functional status of albumin can be quantified by using different methods that provide an insight into the function of the different domains.<sup>(1)</sup> For example, the oxidation status of albumin is measured using high performance liquid chromatography to quantify the redox status of the Cysteine 34 residue of albumin. The reduced form is called human mercaptalbumin. Human non-mercaptalbumins 1 and 2 describe the two forms of oxidised albumin that accumulate in patients with liver failure and their levels have been shown to correlate with risk of mortality.<sup>(5)</sup> Albumin also contains a metal binding domain, the function of which can be assessed using cobalt binding. The altered form is referred to as ischemia-modified albumin and its levels also correlate with mortality.<sup>(6)</sup> The function of the binding sites are assessed using electron paramagnetic resonance spectroscopy and this provides information about binding efficiency and transport function of albumin.<sup>(6)</sup>

Baldessare et al.<sup>(7)</sup> build on this body of work by examining albumin structure and function in a cohort of hospitalized patients with acute decompensation of cirrhosis, of whom a proportion had acute-on-chronic liver failure (ACLF), as well as stable cirrhotic outpatients and healthy controls. Albumin structure was characterized by mass spectrometric approaches to identify native (*nAlb*) and damaged albumin and, standard routinely used commercial Kit (Bromocresol Method) to measure total albumin (*tAlb*). Consistent with previous work, they identified several specific isoforms with oxidative or non-oxidative alterations in AD patients, with modification at Cysteine 34 being the most common. Effective albumin concentration (*eAlb*) was defined as the circulating concentration of unaltered, native albumin, calculated from the product of the total concentration of albumin and the proportion of native albumin on mass spectrometry. In this cohort, *eAlb* was a better discriminator of mere AD from ACLF than *tAlb*, and was also more closely correlated with model for end-stage liver disease (MELD) and other scores of disease severity. Additionally, *eAlb* and disease severity scores were independent predictors of 30-day incidence of ACLF and 90-day mortality on multivariate analysis, unlike *tAlb*. Further, they examined albumin function using electron paramagnetic resonance spectroscopy, specifically addressing a number of aspects of fatty acid binding efficiency and detoxification efficiency.

This study has important implications.

- The first is that *eALB* is an efficacious prognostic tool that may have translational utility if a scalable method of measurement can be found. Of course, scalability of the mass spectrometric or EPR methodology used by Baldessare et al.<sup>(7)</sup> is not currently feasible and is a major barrier to the translation of this work. Alternative markers such as ischemia-modified albumin can be measured using FDA-approved rapid assays and could therefore be widely scaled. Additionally, the rapid advances in nanopore proteomics may also be of relevance in the near future.
- A second, timely implication is whether *eAlb* can be used to guide albumin therapy in a more effective way than *tAlb*. Although albumin replacement for indications such as spontaneous bacterial peritonitis, prophylaxis of post-paracentesis syndrome, and treatment of hepatorenal syndrome has a firm evidence base, the wider use of albumin in cirrhotic patients has yielded mixed results. The ANSWER study evaluated the use of

administration of human albumin solution (HAS) in patients with decompensated cirrhosis over a long period and showed that this resulted in improved patient survival.<sup>(8)</sup> In contrast, the MACHT study, which included sicker patients and administered lower doses of albumin, showed no beneficial clinical effect of HAS in a similar outpatient study.<sup>(9)</sup> The INFECIR studies that targeted cirrhotic patients with AD and aimed to reduced risk of new infection did not meet this end point.<sup>(10)</sup> More recently, the ATTIRE study has been published, which assessed the role of HAS in cirrhotic patients with AD and low albumin levels. Again, there was no beneficial effect of albumin in reducing the risk of infection, renal dysfunction, or short- term mortality.<sup>(11)</sup> It is interesting to hypothesise that the lack of demonstrable efficacy of HAS in patients with acutely decompensated cirrhosis and infection may be partially due to the inclusion of a heterogenous group of patients with widely variable risk of death. As such, the work of Baldessare et al.<sup>(7)</sup> suggests that measurement of effective rather than total albumin concentration, either as a biomarker for inclusion or as goal-directed therapy, may improve the use of HAS in cirrhosis and the design of future trials.

In order to evaluate the potential effect of HAS to correct eALB, the authors performed two crucially important experiments. First, they studied the percentage of nALB in commercially available HAS preparations and, disappointingly, found levels to be lower than in healthy controls and cirrhotic outpatients suggesting that infusion of this HAS may not correct the low eALB. Second, they explored whether the infusion of HAS would impact on eALB in stable cirrhosis patients. Expectedly, there was no sustained change in albumin function in stable cirrhotic outpatients who received a single infusion of 60 g 20% HAS. Taken together, these data and that of others suggests that, as much of the commercially available albumin is already modified, there is enormous opportunity in further improving the functional status of the bottled HAS. This would make HAS more effective and reduce costs by allowing greater effect despite administration of lower volumes.

As the authors acknowledge, the major limitation of this work is the lack of a validation cohort, which is important to qualify eALB as a possible biomarker. More importantly, given the

complexity of the measurements, it will be necessary to develop more user-friendly measures of albumin function that can be readily used in hospital laboratories. Additionally, as the authors also comment, the predominant viral aetiology is a further limitation and not representative of modern cirrhosis cohorts. Nevertheless, there are important implications of this work, particularly at a time when albumin therapy is being re-explored more as a 'drug' rather than as a fluid. It seems that the next part of this journey may be one for the 'native' alter-ego, effective albumin.

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