Obesity and acute-on-chronic liver failure

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Acute-on-chronic liver failure (ACLF) and obesity are two topics that have garnered considerable interest within the hepatology community over recent years. The syndrome of ACLF occurs in patients with cirrhosis and is characterized by the development of acute hepatic decompensation, organ failure and a high rate of 28-day mortality (1). Consortia from the United States and Europe have published extensively on multiple aspects associated with this syndrome (2). The epidemic of obesity has resulted in a myriad of adverse health consequences that impact all aspects of medicine—from public health policy to the development of novel endoscopic techniques for its treatment. Many obese patients have non-alcoholic fatty liver disease (NAFLD), which is now a leading indication for liver transplantation (LT) worldwide (3). Obese LT recipients had worse survival than non-obese patients in pooled analysis of studies which had similar causes of liver disease (4). In their recent publication, Sundaram *et al.* sought to determine if there was an association between obesity and ACLF and to characterize the specific organ system failures in obese patients with ACLF (5).

From a pathophysiology perspective, inflammation may link ACLF and obesity. The former has been associated with a dysregulated inflammatory response producing a "storm" of cytokines that drive the development of organ failure (6). Obesity has been characterized as a chronic low-grade inflammatory state (7). Earlier publications reported that obesity was an independent risk factor for hepatic decompensation (8). The analysis by Sundaram *et al.* is therefore timely and instructive (5). They interrogated two large clinical registries, the United Network for Organ Sharing (UNOS) and the Nationwide Inpatient Sample (NIS) databases, to conduct their analysis. Various laboratory, clinical and coding data were utilized based on the CANIONIC criteria for ACLF (2). In the UNOS dataset, laboratory and clinical findings at time of listing for transplant were analyzed (5). While extremely useful given the large numbers of patients it contains, the UNOS registry is limited by the specific data that are collected and the bias that only patients listed for transplant are included. To address some of these limitations, including the lack of information regarding organ failure at time of death and no data from non-transplant hospitals, Sundaram *et al.* also queried the NIS database. This is the largest publicly available inpatient database in the United States (US), representing a 20% stratified sample of all discharges in a given year from approximately 1,000 non-federal (i.e., non-veterans-affairs) hospitals. Specific ICD-9-CM codes at the time of hospital discharge within the NIS were studied. This clearly requires experience in using the database and confidence that the coding used for individual patient events is valid (9).

In their analysis of 387,884 patient records, Sundaram *et al.* identified 116,704 patients (30%) as having ACLF in both databases (5). Through multivariate modeling from the UNOS database, class III obesity [body mass index (BMI) greater than 40.0 kg/m^2] was found to be an independent risk factor for ACLF at LT, with a hazard ratio of 1.24 (95% CI, 1.09–1.41, P<0.01). Analysis of the NIS confirmed this finding (odds ratio 1.30; 95% CI, 1.25–1.35; P<0.001). When specific organ failures were analyzed, there was an increasing prevalence of renal failure with rising obesity class. When accounting for medical co-morbidities by means of the Charslon index in the NIS, the obesity class III group had the highest proportion of patients grouped as Charlson category 3 (22.3%, P<0.001). The Charlson index was calculated from diagnostic codes so it also relied on the accuracy of coders to document all predetermined

co-morbidities (10). Hepatic encephalopathy (HE) and bacterial infections were more common among obesity class III patients. When evaluating for multi-organ failure, obesity class III patients had the highest prevalence of two-organ (14.7%) and three-organ failure (3.2%), though no correlation was seen between increasing prevalence of two-organ and three-organ failure and worsening obesity category.

Sundaram *et al.* recognized that using BMI as the means to determine the degree of obesity had limitations given the possibility of fluid retention (5,11). They therefore performed an analysis excluding patients with moderate ascites at time of listing for LT—when doing so, they found class III obesity remained independently associated with the development of ACLF (HR 1.31; 95% CI, 1.12–1.53).

Since only patients who are listed for LT are in the UNOS registry, we can presume that they will have undergone some degree of evaluation for co-morbidities prior to listing by the respective transplant centers. While no testing is mandatory, there are well established guidelines in assessing patients' suitability for LT (12). However, the UNOS registry contains no information concerning the thoroughness of the evaluation performed. There are indicators within the UNOS data that the obese group included particularly high risk candidates for transplantation—more morbidly obese patients had ACLF at the time of listing for transplant (23% versus 15.9% for non-obese individuals). In the NIS, the obesity class III group had the highest proportion of patients with co-morbidity using the Charlson index as a proxy. One could argue that the transplant community has evolved significantly over the last decade, proceeding to list these very sick patients for transplant irrespective of the presence of obesity, given that class III obesity has been deemed a relative contraindication to LT (12).

A striking observation in the CANIONIC study was that about 40% of patients developed ACLF on the first episode of acute decompensation of their liver disease (13). Late referral may preclude a patient with ACLF from transplantation due to the usual rapid evolution of ACLF (14). In my opinion, the report by Sundaram *et al.* emphasizes the need for considering LT evaluation early in the disease course of morbidly obese patients with cirrhosis, given the specter of ACLF.

The finding of a greater prevalence of renal failure in both the UNOS dataset and NIS provides additional evidence regarding the importance of this complication in ACLF. The most common cause of acute kidney injury (AKI) in hospitalized patients with decompensated cirrhosis is pre-renal impairment (2). Infections are an important precipitant of intra-renal AKI (15). Obesity was previously noted to be an independent risk factor for the development of infections in patients with cirrhosis (16). Based on the limitations in each of the datasets, we cannot be certain as to the specific causes of renal failure. However, bacterial infections were more common in the obese cohort in the NIS dataset. Prompt identification of the precipitant of AKI, paying particular attention to an infectious etiology, along with appropriate treatment of renal failure in hospitalized cirrhotic patients should be a priority.

Single center and collaborative multicenter efforts through clinical studies and protocols will help define the optimal management of obese patients with decompensated cirrhosis and ACLF. In their retrospective analysis of registry data, Sundaram *et al.* found that morbidly obese individuals with cirrhosis had a greater likelihood of ACLF. Renal failure is of particular concern in these patients as it inevitably will result in additional morbidity and mortality, as well as increase the cost of care. The analysis did not determine a level of obesity too sick to transplant, or a point of futility in the care of morbidly obese patients with ACLF. The authors highlighted the need to address weight reduction among cirrhotic patients with class III obesity (5). Requiring morbidly obese patients with cirrhosis to lose weight is particularly difficult. They may be very limited in their ability to exercise by deconditioning and HE. Overly restrictive diets may exacerbate sarcopenia which can be present in obese cirrhotics (17). Waiting to address obesity at the time of or after transplantation may be too late (18). The work by Sundaram *et al.* adds further impetus to develop new strategies in treating obese patients with medical co-morbidities prior to the onset of decompensated disease and ACLF.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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