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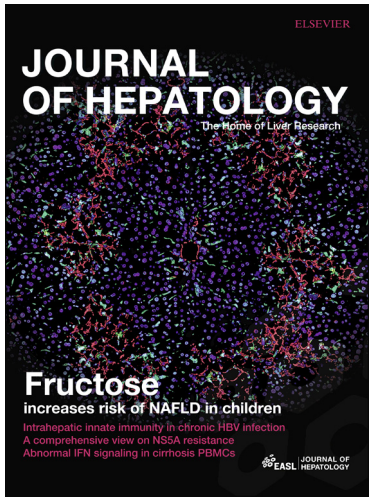

Class III obesity is a risk factor for the development of acute on chronic liver failure in patients with decompensated cirrhosis

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Class III obesity is a risk factor for the development of acute on chronic liver failure in patients with decompensated cirrhosis

Short title: Obesity and acute on chronic liver failure

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List of Abbreviations:
Acute on chronic liver failure (ACLF)
United States (US)
Liver transplantation (LT)
United Network for Organ Sharing (UNOS)
Model for end-stage liver disease (MELD)
Body Mass Index (BMI)
Nationwide Inpatient Sample (NIS)
Hepatitis C virus (HCV)
Alcoholic liver disease (ALD)
Acute kidney injury (AKI)

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Abstract

Background and Aims: Acute on chronic liver failure (ACLF) is a syndrome of systemic inflammation and organ failures. Obesity, also characterized by chronic inflammation, is a risk factor among patients with cirrhosis for decompensation, infection, and mortality. Our aim was to test the hypothesis that obesity predisposes to ACLF development in patients with decompensated cirrhosis.

Methods: We examined the United Network for Organ Sharing (UNOS) database, from 2005-2016, characterizing patients at wait-listing as non-obese (BMI < 30), obese class I-II (BMI 30-39.9) and obese class III (BMI$\geq$40). ACLF was determined based on the CANONIC study definition. We used Cox proportional hazards regression to assess the association between obesity and ACLF development at liver transplantation (LT). We confirmed our findings using the Nationwide Inpatient Sample (NIS), years 2009-2013, using validated diagnostic coding algorithms to identify obesity, hepatic decompensation and ACLF. Logistic regression evaluated the association between obesity and ACLF occurrence.

Results: Among 387,884 with decompensated cirrhosis, 116,704 patients (30.1%) were identified as having ACLF in both databases. Multivariable modeling from the UNOS database revealed class III obesity to be an independent risk factor for ACLF at LT (HR=1.24, 95% CI 1.09-1.41, p<0.001). This finding was confirmed using the NIS (OR=1.30, 95% CI 1.25-1.35, p<0.001). Regarding specific organ failures, analysis of both registries demonstrated patients with class I-II and class III obesity had greater prevalence of renal failure.

Conclusion: Class III obesity is a newly identified risk factor for ACLF development in patients with decompensated cirrhosis. Obese patients have a particularly higher prevalence of renal failure as a component of ACLF. These findings have important implications regarding stratifying risk and preventing the occurrence of ACLF.

Lay Summary: In this study, we identify that among patients with decompensated cirrhosis, class III obesity is a modifiable risk factor for the development of acute on chronic liver failure (ACLF). We further demonstrate that regarding the specific organ failures associated with ACLF, renal failure is significantly more prevalent among obese patients, particularly class III obesity. These findings underscore the importance of weight management in cirrhosis, to reduce the risk of ACLF. Patients with class III obesity should be monitored closely for the development of renal failure.

Introduction

Acute on chronic liver failure (ACLF) is a syndrome that occurs in patients with cirrhosis, characterized by acute hepatic decompensation, organ system failure, and 28-day mortality of greater than 15%.(1) The pathophysiology of ACLF has not been fully elucidated, but appears to be a consequence of a dysregulated inflammatory response, resulting in rapidly evolving organ failure and mortality.(2-6) The reported prevalence of ACLF among those hospitalized with decompensated cirrhosis approaches 30%(1) and associated healthcare costs of ACLF are as high as $1.7 billion in the United States (US).(7) Considering the high prevalence of this condition, along with the associated mortality and healthcare burden, identifying modifiable risk factors for ACLF is of high importance.

Characterized by a chronic low-grade inflammatory state, obesity has been identified as an independent risk factor for liver decompensation and infection in cirrhosis.(8, 9) Class III obesity, in particular, has been found to be a risk factor for mortality among those awaiting liver transplantation (LT), according to two recent United Network for Organ Sharing (UNOS) registry studies.(10, 11) In a recent study by Piano et al, several predictors of ACLF development were identified, including ascites, anemia, hypotension and increasing model for end-stage liver disease (MELD) score.(12) However, this study did not include obese patients, as the upper limit of body mass index (BMI) in their study population was 29 kg/m^2. Therefore, whether obesity similarly increases the risk of ACLF development, has yet to be determined.

The aim of this study was to characterize the association between obesity and ACLF, along with specific organ system failures in obese patients with ACLF, using two

US registries. We hypothesized that obesity would be an independent risk factor for development of ACLF, given the dysregulated inflammatory response characteristic to both of these conditions.

Patients and Methods

The study protocol was approved as exempt from review by the institutional review board at Cedars-Sinai Medical Center. The study and analysis of this study was performed consistent with STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines. (supplemental information) All statistical analyses were performed using the Stata statistical package (version 14, Stata Corporations, TX).

United Network for Organ Sharing (UNOS) database analysis

From the UNOS registry, we evaluated patients age 18 or older listed for liver transplantation from 2005 to 2016, using a retrospective cohort study design. Patients with acute or fulminant liver failure or who had hepatocellular carcinoma at the time of waitlist registration were excluded. We stratified patients into categories of obesity according to BMI as follows: non-obese (BMI < 30.0 kg/m^2), obese class I-II (BMI of 30.0-30.9 kg/m^2), and obese class III (BMI > 40.0 kg/m^2), per guidelines from the World Health Organization.(13) We collected data regarding patient demographics, etiology and severity of liver disease, and medical comorbidities at the time of waitlist registration.

Identification of ACLF

The study population was categorized as having ACLF at the time of waitlist registration or LT based on the CANONIC study criteria (14) of having a single hepatic decompensation such as ascites, hepatic encephalopathy, variceal bleed, or bacterial infection and one of the following organ failures: single renal failure, single non-renal organ failure with renal dysfunction or hepatic encephalopathy, or two non-renal organ failures. Given the lack of necessary data to assess for organ failure at time of waitlist

removal or death, we were unable to evaluate for presence of ACLF at these time points. Regarding decompensating events, we assessed for the presence of ascites or hepatic encephalopathy, as information regarding variceal hemorrhage and bacterial infection were unavailable. Specific organ failures were determined according to the chronic liver failure (CLIF) consortium organ failures score(14) for coagulopathy, liver failure, renal insufficiency and renal failure, neurologic failure, and circulatory failure. We used mechanical ventilation as a surrogate marker for respiratory failure. (Table 1)

Statistical analysis

Comparisons across weight strata were made utilizing Chi-square testing for categorical variables and analysis of variance for continuous variables. To evaluate the association between obesity and ACLF, we performed time to event analyses on our study population. Overall probability of developing ACLF from time of waitlist registration to LT was evaluated with Kaplan Meier methods, with differences in survival probabilities among weight categories assessed by log-rank testing. Predictors of developing ACLF at the time of LT were determined with multivariable Cox proportional hazards modeling. Independent variables were selected a priori, based on hypothesized clinical significance. The final multivariable model was determined using manual backwards selection, with p-value <0.10 on univariable analysis considered significant for inclusion. Goodness of fit was determined using Cox-Snell residuals.

Nationwide Inpatient Sample (NIS) analysis

Due to the selection biases associated with evaluation the UNOS database, such as lack of information regarding organ failure at the time of death and inability to analyze data from non-transplant hospitals, we also tested our hypothesis using the

NIS, years 2009-2013.(15) The NIS is the largest publicly available inpatient database in the US, representing a 20% stratified sample of all the discharges occurring in a given year from approximately 1000 non-federal hospitals.

Study population

The study population consisted of patients age 18 or older with decompensated cirrhosis, as determined by the presence of International Classification of Diseases, Ninth Revision, Clinical Modification codes. Specifically, all patients studied were required to have a diagnostic code for cirrhosis (571.2, 571.5, 571.6), as based on a previously validated algorithm, which had a positive predictive value of 90% and negative predictive value of 87%, with 88% agreement.(16)

In addition to having a diagnostic code indicative of cirrhosis, all patients in our study population were also required to have at least one decompensating event such as ascites, hepatic encephalopathy, variceal hemorrhage, determined according to an algorithm which has an 85.7% positive predictive value for hepatic decompensation among inpatients.(17) In accordance with the CANONIC study definition of ACLF(14), a patient was also deemed to have a decompensating event if diagnosed with any of the following bacterial infections: urinary tract infection, bacteremia, pneumonia/respiratory infection, and spontaneous bacterial peritonitis,(18, 19) which are the most commonly observed bacterial infections in patients with end-stage liver disease.(20, 21)

Regarding etiology of cirrhosis, we evaluated for presence of hepatitis C virus (HCV) or alcoholic liver disease (ALD).(16) Patients were excluded if they had an associated diagnostic code indicating they were post-transplantation, as it would be uncertain whether organ system failure occurred as a complication of transplant surgery

or immunosuppression. Specific diagnostic codes used for identification of hepatic decompensation, bacterial infection, etiology of liver disease and liver transplantation are included in the supplementary document. (Supplemental tables 1 and 2)

Obesity classification

We categorized patients into the following groups according to ICD-9-CM codes that indicate obesity and body mass index (BMI): class I–II obesity (BMI 30–39.9 kg/m2) (278, 278.0, 278.00, V85.30-39) and class III obesity (BMI ≥40 kg/m2) (278.01, V85.40-45). These codes were previously validated in a study by review of records at a single center and found to have a positive predictive value of 77.8% for class I-II obesity and 85.7% for class III obesity.(9) Patients whose records did not contain ICD-9-CM codes to suggest obesity were classified as non-obese.

Identification of ACLF

To determine the presence of ACLF among our study population of decompensated cirrhotic patients, we assessed for renal failure, coagulopathy, respiratory failure, and circulatory failure, using validated coding algorithms previously studied to assess the presence of organ failure in patients with sepsis.(22, 23) (Table 1) We did not evaluate for hepatic or neurologic failure, as we believed the associated diagnostic codes for these conditions would not accurately reflect bilirubin level or grade of hepatic encephalopathy. Patients were considered to have ACLF if their record contained a diagnostic code for cirrhosis, at least one decompensating event as above, and any of the following organ failures: single renal failure, hepatic encephalopathy plus single organ failure, or two non-renal failures.(14)

Medical comorbidities

We utilized the Deyo modification of the Charlson index as a proxy for patient comorbidity, with additional adjustments for hepatic dysfunction.(24, 25) We grouped the Charlson index into three categories: Charlson category 1 (score=0), category 2 (scores 1-3), and category 3 (scores >3) to represent the degree of comorbidity. We created a separate variable for anemia, which is associated with ACLF but is not included in the Charlson index.(12) The presence of anemia considered clinically significant was determined based on having one diagnostic code representative of anemia and one procedure code indicating packed red blood cell transfusion. (supplemental table 1)

Statistical analysis

Chi-square testing was utilized to compare the distribution of categorical variables and analysis of variance with Bonferroni correction was used to compare the distribution of continuous variables between obesity categories. A p-value < 0.05 on two-tailed testing was considered significant. For our logistic regression model, variables were selected a priori based on hypothesized clinical significance. The final model was created using manual backwards selection, with incorporation of independent variables considered significant on univariable regression ($p<0.10$). As less than 5% of data was missing from the variables incorporated into our regression models, we did not impute for missing data. Goodness of fit for logistic regression modeling was evaluated using the Hosmer-Lemeshow method.

Results

UNOS database analysis

Patient characteristics at waitlist registration

We identified a total of 100,382 patients who met our inclusion criteria at the time of transplant listing. (Supplemental figure 1) In Table 2, we characterize the study population, stratified by obesity category. With regards to patient demographics, obesity class I-II were the oldest and had the greatest proportion of males. There were also a greater percentage of Caucasians among the obesity class I-II and class III categories as compared to non-obese patients.

As expected, non-alcoholic steatohepatitis was more prevalent among obese patients, and additionally was the most common cause of liver disease among class III obesity (45.3%). Non-obese patients had a greater percentage of cirrhosis secondary to alcoholism (33.5%) and HCV (38.9%). Also as expected, obese patients of all classes had significantly greater prevalence of diabetes than non-obese individuals.

Class III obese patients were more decompensated, with a greater proportion of moderate ascites and grade 3-4 hepatic encephalopathy. Class III obesity additionally was associated with a significantly higher MELD-Na score at listing, along with higher total bilirubin and INR levels. Notably, the non-obese patients had significantly higher serum albumin level compared to all obese patient groups (3.1 vs 2.9 g/L, $p<0.001$), suggesting that an obese state is not exclusive of being malnourished.

ACLF at the time of waitlist registration was most prevalent among class III obesity patients (23.1%, $p<0.001$), as compared to class I-II (16.5%) or non-obese (15.9%) individuals.

Time to event analysis

A total of 7,630 patients had ACLF at time of LT, of which 4,688 were non-obese, 2,587 were obese class I-II and 355 were obese class III. Median time from waitlist registration to LT was 167 days (range 1-3085 days). Kaplan-Meier analysis with log-rank testing revealed class III obesity to have a significantly greater likelihood of development of ACLF ($p<0.001$). (Figure 1) Probabilities of ACLF among class III obesity at 1, 3, and 5 years were 12.8%, 19.9%, and 22.3%, respectively. (Supplemental table 3)

In table 3, we depict univariable and multivariable Cox proportional hazards regression evaluating predictors of ACLF at transplantation. Multivariable analysis demonstrated both obesity class I-II (HR=1.12, 95%CI 1.05-1.19) and obesity class III (HR=1.24, 95% CI 1.09-1.41) were significantly associated with ACLF at time of LT. Additional patient factors found to predict ACLF included increasing age (HR 1.01 per yer), hepatitis C alone (HR=1.22) or in combination with alcoholic liver disease (HR=1.18), presence of ascites and hepatic encephalopathy at listing, lower serum sodium and albumin level, and increasing MELD score. Our findings also showed that alcoholic liver disease alone was a negative predictor of ACLF at LT (HR=0.78). However, this likely reflects the effects of alcohol abstinence among patients eligible for transplantation, as opposed to the disease itself.

Organ failure at transplantation

Table 4 depicts specific organ failures among patients with ACLF at LT. A significantly greater prevalence of renal failure as a component of ACLF was found with increasing obesity class ($p<0.001$), though the development of renal insufficiency was similar among the three groups. The prevalence of liver failure as a component of ACLF

was inversely correlated with higher obesity class. Additionally, obese class I-II patients with had the greatest prevalence of coagulation failure (51.3%). No significant differences were found among the patient groups regarding prevalence of respiratory failure, circulatory failure, neurologic failure, and two organ or three organ failures.

Sensitivity Analyses

Due to the possibility that ascites can increase BMI, we performed a sensitivity analysis to assess for the association between obesity and ACLF development, excluding patients with moderate ascites at the time of listing. After exclusion of 25,458 patients with moderate ascites, multivariable Cox proportional hazards analysis revealed class I-II obesity (HR=1.12, 95% CI 1.04-1.20) and class III obesity (HR=1.31, 95% CI 1.12-1.53) to be independently associated with the development of ACLF. (supplemental table 4). Additionally, among patients who developed renal failure as a component of ACLF, we could not distinguish between those who had acute renal failure versus chronic renal parenchymal disease. We therefore performed an additional multivariable analysis (supplemental table 5) regarding the outcome renal failure as a component of ACLF, after exclusion of 10,224 patients who underwent simultaneous liver and kidney transplantation. Our analysis revealed class III obesity was associated with renal failure development (HR=1.21, 95% CI 1.03-1.43).

NIS analysis

Patient characteristics

We identified a total of 287,502 patient records with decompensated cirrhosis (supplemental figure 2), of which 109,074 were identified as having ACLF (37.9%). Stratifying our study population with decompensated cirrhosis by weight category, we

found that 258,402 were non-obese, 15,108 were obesity class I-II and 13,692 were categorized as obesity class III.

In Table 5, we describe the study population, stratified by obesity category. With regards to patient demographics, non-obese patients were the oldest and had the greatest proportion of males. There were also significantly more Caucasians and fewer African-Americans among the obesity class I-II and class III categories as compared to non-obese patients. Regarding etiology of liver disease, we found that hepatitis C and alcoholic liver disease to be more prevalent among non-obese patients, consistent with our findings from the UNOS database. When accounting for medical co-morbidities, the obesity class III group had the highest proportion of patients grouped as Charlson category 3 (22.3%, $p<0.001$), while clinically significant anemia was more prevalent among non-obese patients (18.4%, $p=0.041$).

Evaluating for decompensating events, we found the non-obese category had the highest prevalence of ascites and variceal bleeding. However, hepatic encephalopathy was significantly more common among obesity class III patients. Additionally, bacterial infection was also highest among class III obesity, consistent with findings from a prior study.(9)

Regarding the presence of ACLF, our findings indicated that ACLF was most prevalent ($p<0.001$) in class III obesity (45.1%), as compared to class I-II obesity (38.8%) or non-obese individuals (37.6%).

Decompensating events and organ failures in ACLF

Table 6 depicts the distribution of decompensating events and organ failures, among patients identified as having ACLF, according to the three weight categories.

Similar to our findings in the total population, we found that ascites and variceal bleeding were more common in the non-obese category, whereas hepatic encephalopathy and bacterial infection were more common in obese patients, with obesity class I-II having the greatest prevalence of encephalopathy (34.9%) and obesity class III having the highest proportion of bacterial infection (59.5%).

Regarding specific organ failures leading to ACLF, our analysis demonstrated increasing prevalence of renal failure with rising obesity class, consistent with our findings from the UNOS database. Additionally, we found that the prevalence of circulatory failure was inversely correlated with worsening obesity. The percentage of patients with respiratory failure and coagulopathy as a component of ACLF differed between the three groups, though no trend was seen regarding obesity and prevalence of these organ failures. 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 again no correlation was seen between increasing prevalence of two-organ and three-organ failure and worsening obesity category.

Risk factors for ACLF

Multivariable logistic regression analysis (Table 7) demonstrated that when compared to patients who were non-obese, obesity class III was associated with ACLF (OR=1.30, 95% CI 1.25-1.35). Additional factors associated with ACLF included age greater than 40 years (OR=1.07-1.12), African-American race (OR=1.37), alcoholic cirrhosis (OR=1.14), anemia (OR=1.76), presence of ascites (OR=1.89), and Charlson category 2 (OR=1.53) or 3 (OR=3.13).

Discussion

As ACLF is a significant cause of mortality among patients with cirrhosis it is important to identify potential risk factors for this condition, particularly those that can be modified or used to stratify risk. In our study of 387,884 patients with decompensated cirrhosis and 116,704 patients with ACLF across two US registries, several novel findings were made. We describe for the first time that obesity class III is independently associated with ACLF development. Secondly, we demonstrate that among patients with ACLF, renal failure is significantly more prevalent in obese individuals, particularly those with class III obesity.

Our analyses of both databases demonstrate that obesity class III is associated with significantly increased risk of ACLF. It is possible that this population may be more prone to develop organ failures leading to ACLF due to a higher prevalence of the metabolic syndrome, leading to chronic end-organ damage(26) and heightened risk of organ failure in the setting of an acute inflammatory response. However, we believe this possibility to be less likely for two reasons. First, we demonstrated an association between obesity and ACLF in our analysis of the NIS after adjusting for non-hepatic comorbidities via the Charlson index, which accounts for diabetes, chronic kidney disease, cardiovascular disease, and lung disease. Secondly, it is unlikely that the patients with ACLF in the UNOS database analysis would have severe underlying cardiovascular or respiratory dysfunction, as they would probably not have been offered LT.

Instead, we propose that the link between class III obesity and increased risk of ACLF is due to an obesity related chronic inflammatory state. The hallmark of ACLF

pathophysiology is excessive systemic inflammation, described as an acute exacerbation of existing systemic inflammation in decompensated cirrhosis.(4, 27) This "inflammatory storm" is characterized by elevation in white blood cell count and C-reactive protein, along with increased production of pro-inflammatory cytokines, including IL-6, IL-10 and TNF-α.(5) Obesity is also characterized by an elevated inflammatory state, as adipocytes mount an adaptive immune response secondary to overnutrition, leading to production several pro-inflammatory cytokines, such as IL-6 and TNF-α,(28) promotion of NF-κB signaling via Toll-like receptor (TLR)-4, and immune activation secondary to signaling from damage-associated molecular proteins.(29) We suggest additional prospective studies to delineate these pathways, in order to prognosticate ACLF risk and identify novel therapeutic targets.

With regards to specific organ failures as a component of ACLF, we identified in both the UNOS and NIS databases, a greater prevalence of renal failure among patients with obesity, especially class III obesity. This finding has important implications. Given the heightened risk of renal failure among obese patients with cirrhosis, we suggest particularly careful management of this fragile population regarding diuretic usage, avoidance of nephrotoxic agents, and administration of an adequate albumin challenge in the setting of acute kidney injury (AKI). Furthermore, prospective studies may be warranted regarding aggressive management of AKI in the obese cirrhotic patient, such as the early use of albumin with somatostatin analogues, terlipressin, or norepinephrine..

The association between obesity and AKI is not unique to patients with cirrhosis, and is in fact an increasingly recognized phenomenon in critical care settings,(30) with

studies demonstrating obesity to yield a greater risk of AKI(31) and requirement for renal replacement therapy in critically ill patients.(32) The connection between obesity and AKI is likely multifactorial in nature, with contributions from obesity-related glomerulopathy,(33) renal hypoperfusion,(34) and endothelial dysfunction from obesity associated oxidative stress.(30) Although the exact physiologic mechanism for AKI cannot be elucidated from this study, additional investigations are needed.

Given the high mortality and healthcare burden associated with obesity,(1, 2, 7, 14) along with its rising prevalence among patients with cirrhosis (35), we suggest an even greater emphasis on weight reduction among cirrhotic patients with class III obesity. Although patients who are overweight are typically counseled regarding lifestyle changes, early implementation of a regimented weight loss program, such as that as outlined by Heimbach et al,(36) should be considered in those with compensated cirrhosis and a BMI above 40 kg/m^2. For patients unable to reach their weight loss goals via lifestyle modifications alone, bariatric surgery may be an effective preventative measure.(37) It should be noted, however, that obese patients may also be sarcopenic, (38, 39) and weight loss strategies should be implemented in conjunction with an assessment of nutritional status, to avoid worsening protein calorie malnutrition.

Our findings need to be interpreted in the context of the study limitations. The UNOS registry has certain advantages for this investigation, particularly the availability of granular patient data to assess BMI, severity of liver disease, and organ system failures. However, several limitations exist regarding our analysis of this database. First, given the lack of necessary data, development of ACLF was assessed only at LT. Therefore, certain patients with ACLF may not have been captured since they may not

have survived to or been offered LT. However, we do not believe this limitation impacts our main conclusion for two reasons. First, we demonstrate that patients with class III obesity also have a significantly greater prevalence of ACLF at waitlist registration, suggesting that the transplant cohort represents the listing cohort. Secondly, considering the unique peri and post-transplant complications associated with obesity (37), we expect that centers would be less inclined to transplant a patient with both class III obesity and ACLF. Therefore, the hazard ratio for class III obesity and ACLF development may in fact be underestimated, since class III obesity patients would be underrepresented in the cohort with ACLF at transplantation.

The UNOS database analysis additionally excludes patients with ACLF who did not present to a hospital included in the UNOS registry, such as those who died at a non-transplant hospital. We attempted to address this limitation, by confirming our findings utilizing the NIS, which encompasses 20% of US hospitals and contains a significantly larger sample size. The NIS also has limitations, however, due to reliance on diagnostic codes to determine obesity category and identify organ system failures. Although our coding algorithms were externally validated, there is still a possibility of misclassification. Additionally, neither registry contains medication information, so we cannot account for the effects of prophylactic antibiotics or beta-blockers. Finally, arguments can be made that BMI may not measure obesity as accurately as waist circumference or visceral adiposity index. However, such information is not available in public registries. Furthermore, Berzigotti et al.'s study demonstrating obesity as predictor of liver decompensation used BMI to determine weight category, supporting the notion that BMI can be used as a surrogate in this regard.(8) The presence of

ascites may also affect the accuracy of BMI measurement, and neither database allows for adjustment of BMI for ascites. However, we assessed for the confounding effects of ascites in our sensitivity analysis, and demonstrated a significant association between class III obesity and ACLF.

Our study has several strengths, however, including a large sample size and utilization of two databases, which complement each other's limitations. In particular, the UNOS registry contains granular patient information, whereas the NIS yields a larger sample size and is more nationally representative study population. In this setting, we based our study conclusions only on findings that were demonstrated in both databases, specifically the association of class III obesity with ACLF and the greater prevalence of renal failure as a component of ACLF among obese patients, particularly class III obesity. We suggest caution in drawing conclusions from findings that were discrepant between the two registries.

In conclusion, class III obesity is identified as an independent risk factor for development of ACLF and prevalence of renal failure is especially high in this population. These findings highlight the importance of weight management in obese patients with cirrhosis, especially among those with class III obesity, and suggest vigilance regarding development of ACLF and renal failure in this population. Additional studies are necessary to elucidate the pathophysiologic basis for the association between class III obesity and ACLF.

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Figure 1. Probability of developing acute on chronic liver failure, stratified by obesity category

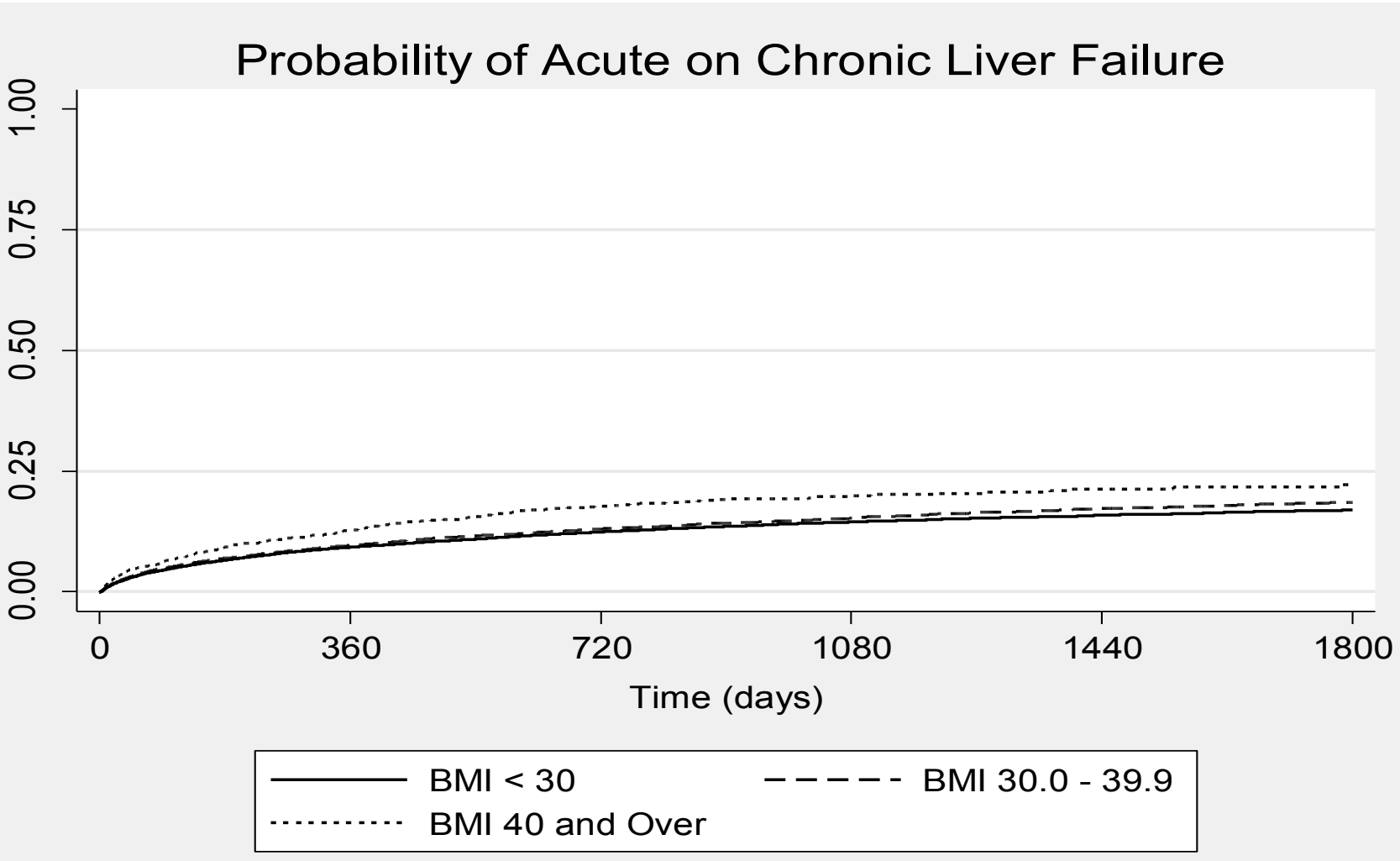

Probability of Acute on Chronic Liver Failure
0.00
0.25
0.50
0.75
1.00
0
360
720
1080
1440
1800
Time (days)
BMI < 30
BMI 30.0 - 39.9
BMI 40 and Over

Table 1. Criteria to determine presence of organ dysfunction/failure

Organ failure	UNOS database analysis	NIS database*
Liver	Total biluribin > 12 mg/dL	Not assessed
Renal	Insufficiency: creatinine 2-<3.5 mg/dL Failure: creatinine > 3.5 mg/dL or hemodialysis	584, 580, 585, 39.95 (renal failure only)
Coagulopathy	INR > 2.5	286.2, 286.6, 286.9, 287.3-5
Neurologic	grade 3-4 encephalopathy	Not assessed
Circulatory	requirement of vasopressors	458.0, 785.5, 785.51, 785.59, 458.0, 458.8, 458.9, 796.3
Respiratory	requirement of mechanical ventillation	518.81, 581.82, 518.85, 786.09, 799.1, 96.7

*organ failure determined by presence of validated ICD-9-CM codes (21, 22)

Table 2. Baseline characteristics for study population from the UNOS cohort, classified by BMI category

Characteristic **N (%)**	**Non-obese** **(BMI < 30.0)** (n=63,712)	**Obesity class I-II** **(BMI < 30.0 – 39.9)** (n=32,605)	**Obesity class III** **(BMI >= 40.0)** (n=4,065)	**p-value**
Age (mean +/- SD)	53.10 +/- 11.0	54.6 +/- 8.9	52.6 +/- 9.1	< 0.001
Male	40,105 (62.9)	20,805 (63.8)	2,181 (53.7)	< 0.001
Caucasian	45,802 (72.6)	24,192 (75.2)	2,974 (74.2)	< 0.001
African-American	5,609 (8.9)	2,534 (7.9)	334 (8.3)	< 0.001
Hispanic	8,885 (14.1)	4,946 (15.4)	658 (16.4)	< 0.001
Asian	2,775 (4.4)	509 (1.6)	41 (1.0)	< 0.001
Etiology of Liver Disease				
NASH	5,993 (14.8)	8,047 (31.7)	1,437 (45.3)	< 0.001
HCV	15,752 (38.9)	8,435 (33.3)	875 (27.6)	< 0.001
ALD	13,545 (33.5)	6,149 (24.2)	652 (20.6)	< 0.001
HCV/ALD	5,209 (12.9)	2,732 (10.8)	206 (6.5)	< 0.001
Diabetes Mellitus	12,422 (20.2)	9,707 (31.1)	1,353 (34.7)	< 0.001
Ascites				
None	15,408 (24.2)	6,361 (19.5)	719 (17.7)	< 0.001
Slight	32,533 (51.1)	17,889 (54.9)	2,012 (49.5)	< 0.001
Moderate	15,771 (24.8)	8,353 (25.6)	1,334 (32.8)	< 0.001
Hepatic Encephalopathy				
None	25,311 (39.7)	10,799 (33.1)	1,289 (31.7)	< 0.001
Grade 1-2	34,353 (53.9)	19,597 (60.1)	2,440 (60.0)	< 0.001
Grade 3-4	4,048 (6.4)	2,207 (6.8)	336 (8.3)	< 0.001

MELD-Na (mean +/- SD)	18.3 +/- 8.4	18.9 +/- 8.7	21.6 +/- 9.8	< 0.001
Total bilirubin (mean +/- SD)	6.3 +/- 8.9	6.1 +/- 8.7	8.1 +/- 10.3	< 0.001
INR (mean +/- SD)	1.3 +/- 0.8	1.7 +/- 0.9	1.8 +/- 0.9	< 0.001
Albumin (mean +/- SD)	3.1 +/- 0.7	2.9 +/- 0.7	2.9 +/- 0.7	< 0.001
Sodium (mean +/- SD)	135.9 +/- 4.9	135.9 +/- 4.8	135.8 +/- 4.8	0.012
ACLF	10,152 (15.9)	5,377 (16.5)	940 (23.1)	<0.001

*Chi-square testing to compare categorical variables and Analysis of variance with Bonferonni correction to compare continuous variables

Table 3. Cox proportional hazards model analysis of the UNOS database, regarding predictors of ACLF at time of LT

	Univariable			**Multivariable**		
	Hazard ratio	95% CI	p-value	Hazard ratio	95% CI	p-value
Obesity Categories						
Non-obese	1.00	Reference	-	1.00	Reference	-
Obesity class I-II	1.07	1.02 - 1.12	0.007	1.12	1.05 - 1.19	< 0.001
Obesity class III	1.42	1.28 - 1.59	< 0.001	1.24	1.09 - 1.41	< 0.001
Male	1.07	1.02 - 1.12	0.004	1.05	0.98 - 1.11	0.155
Race/Ethnicity						
White	1.00	Reference	-	1.00	Reference	-
Black	1.24	1.14 - 1.34	< 0.001	0.90	0.81 - 1.01	0.075
Hispanic	1.08	1.01 - 1.15	0.017	1.01	0.94 - 1.09	0.827
Asian	0.90	0.79 - 1.02	0.109	0.97	0.80 - 1.19	0.802
Age	1.00	0.994 - 0.998	0.001	1.01	1.00 - 1.01	0.037
Etiology of Liver Disease						
NASH	1.00	Reference	-	1.00	Reference	-
HCV	1.08	1.00 - 1.17	0.037	1.25	1.16 - 1.35	< 0.001
ALD	1.02	0.94 - 1.10	0.679	0.78	0.72 - 0.85	< 0.001
HCV/ALD	1.20	1.09 - 1.32	< 0.001	1.18	1.06 - 1.30	0.002
Ascites						
None	1.00	Reference	-	1.00	Reference	-
Slight	1.57	1.47 - 1.67	< 0.001	1.49	1.32 - 1.68	< 0.001
Moderate	3.27	3.06 - 3.50	< 0.001	2.00	1.76 - 2.27	< 0.001

Hepatic Encephalopathy						
None	1.00	Reference	-	1.00	Reference	-
Grade 1-2	1.44	1.38 - 1.51	< 0.001	1.73	1.47 - 2.03	< 0.001
Grade 3-4	3.36	3.04 - 3.71	< 0.001	2.16	1.78 - 2.62	< 0.001
Sodium	0.91	0.90 - 0.91	< 0.001	0.96	0.95 - 0.96	< 0.001
Albumin	0.46	0.44 - 0.48	< 0.001	0.76	0.72 - 0.79	< 0.001
Diabetes Mellitus	1.00	0.95 - 1.06	0.889	-	-	-
MELD-Na at listing	1.19	1.18 - 1.19	< 0.001	1.22	1.21 - 1.23	< 0.001

*Analysis performed using univariable and multivariable Cox proportional hazards regression

Table 4. Decompensating events and organ failure among patients with ACLF at the time of LT, according to the UNOS database

Organ failure, n (%)	**Non-obese (BMI < 30.0)** (n=4,688)	**Obesity class I-II (BMI < 30.0 – 39.9)** (n=2,587)	**Obesity class III (BMI >= 40.0)** (n=355)	**p-value**
Respiratory failure	521 (11.1)	242 (9.4)	36 (10.1)	0.062
Circulatory failure	780 (16.7)	400 (15.5)	65 (18.3)	0.245
Renal insufficiency	639 (23.2)	349 (20.9)	37 (20.9)	0.648
Renal failure	1,793 (38.3)	1,076 (41.6)	177 (49.9)	<0.001
Coagulation failure	2,158 (46.0)	1,327 (51.3)	172 (48.5)	< 0.001
Neurologic failure (grade 3-4 encephalopathy)	1,043 (22.3)	591 (22.8)	78 (22.0)	0.824
Liver failure	2,627 (56.2)	1,215 (47.1)	162 (45.9)	< 0.001
Two organ failures	2,007 (42.9)	1,073 (41.5)	157 (44.2)	0.389
Three organ failures	747 (16.0)	408 (15.8)	66 (18.7)	0.372

* Chi-square testing to compare categorical variables

Table 5. Characteristics of patients with decompensated cirrhosis from the NIS study population, categorized by obesity category

Demographic characteristic N (%) or Median (IQR)	Non-obese (n=258,402)	Obese Class I-II (n=15,108)	Obese class III (n=13,692)	p-value
Mean age, y (SD)	59.8 ± 12.2	57.8 ± 10.7	57.5 ± 12.4	<0.001
Male (%)	158,109 (61.2)	7,816 (51.7)	6,399 (46.4)	<0.001
Caucasian (%)	156,141 (60.4)	9,549 (63.2)	9,285 (67.8)	<0.001
African-American (%)	25,617 (9.9)	1,065 (7.0)	799 (5.8)	<0.001
Hispanic (%)	42,159 (16.3)	2,751 (18.2)	2,102 (15.4)	0.003
Etiology of cirrhosis:				
HCV	76,990 (29.8)	3,602 (23.8)	3,078 (22.5)	<0.001
ALD	130,838 (50.6)	5,797 (38.4)	4,127 (30.1)	<0.001
Charlson Index (%)				
Category 1	86,310 (33.4)	3,217 (21.3)	2,366 (17.3)	<0.001
Category 2	131,546 (50.9)	8,911 (58.9)	8,272 (60.4)	<0.001
Category 3	40,546 (15.7)	2,980 (19.7)	3,054 (22.3)	<0.001
Anemia	47,462 (18.4)	2,675 (17.7)	2,283 (16.7)	0.041
Ascites	164,632 (63.7)	6,305 (41.7)	7,096 (51.8)	<0.001
Hepatic encephalopathy	49,055 (18.9)	3,202 (21.2)	3,122 (22.8)	<0.001
Variceal bleed	28,455 (11.0)	1,356 (8.9)	823 (6.0)	<0.001
Bacterial infection	105,801 (40.9)	6,612 (43.8)	7,187 (52.5)	<0.001
ACLF	97,032 (37.6)	5,866 (38.8)	6,176 (45.1)	<0.001

* Chi-square testing to compare categorical variables and Analysis of variance with Bonferonni correction to compare continuous variables

TABLE 6: Decompensating events and organ failures from the NIS among patients with ACLF, grouped by obesity category

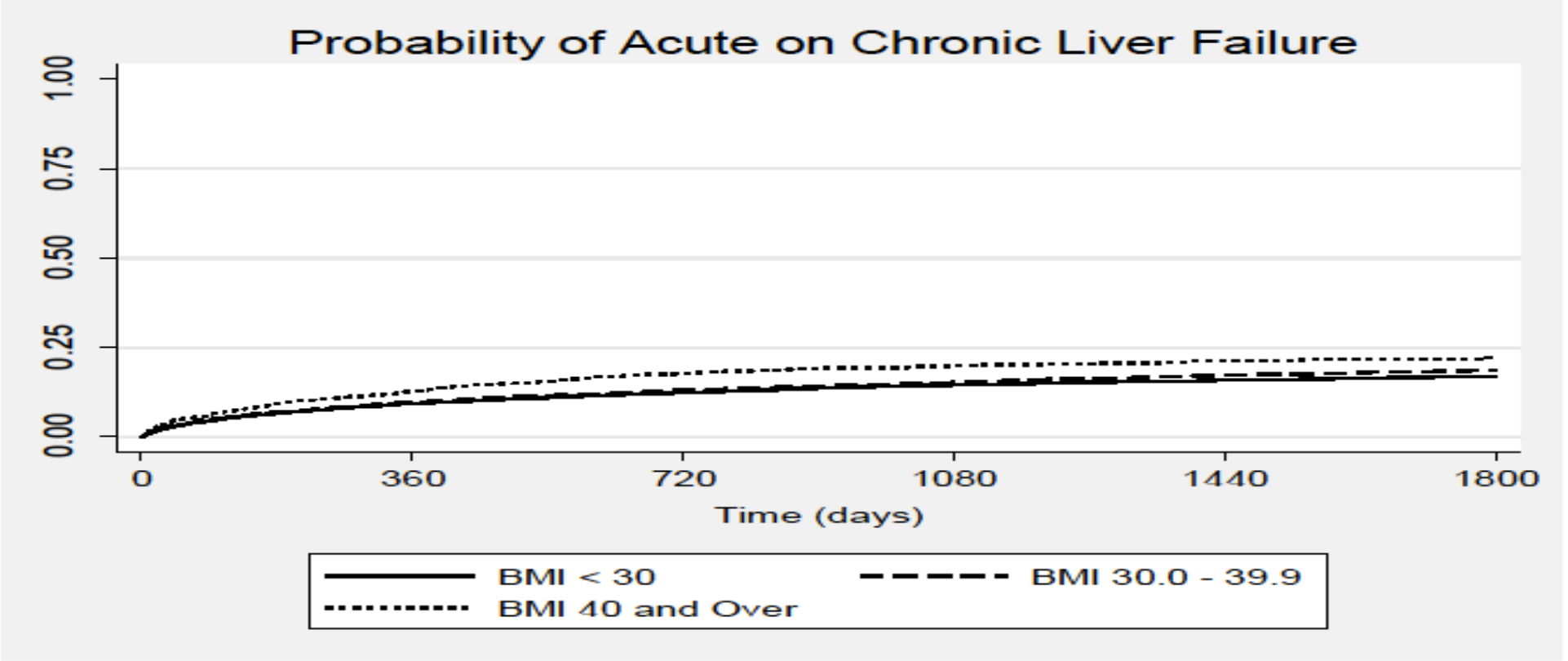
	Non-obese (n=97,032)	**Obese Class I-II (n=5,866)**	**Obese Class III (n=6,176)**	**P-value**
Ascites	60,427 (63.3)	3,296 (56.2)	3,054 (49.5)	<0.001
Hepatic encephalopathy	30,649 (31.6)	2,048 (34.9)	2,091 (33.9)	<0.001
Variceal bleed	9,040 (9.3)	441 (7.5)	328 (5.3)	<0.001
Bacterial infection	49,093 (50.6)	2,913 (49.7)	3,673 (59.5)	<0.001
Organ failure				
Respiratory (%)	23,285 (24.0)	1,286 (21.9)	1,582 (25.6)	0.004
Circulatory (%)	18,876 (19.5)	1,043 (17.8)	946 (15.3)	<0.001
Renal (%)	46,192 (47.6)	3,411 (58.1)	4,054 (65.6)	<0.001
Coagulation (%)	42,255 (43.6)	2,722 (46.4)	2,639 (42.8)	0.027
Two-organ failure (%)	59,785 (12.3)	3,772 (11.9)	4,048 (14.7)	<0.001
Three-organ failure (%)	13,583 (2.8)	227 (2.5)	868 (3.2)	<0.001

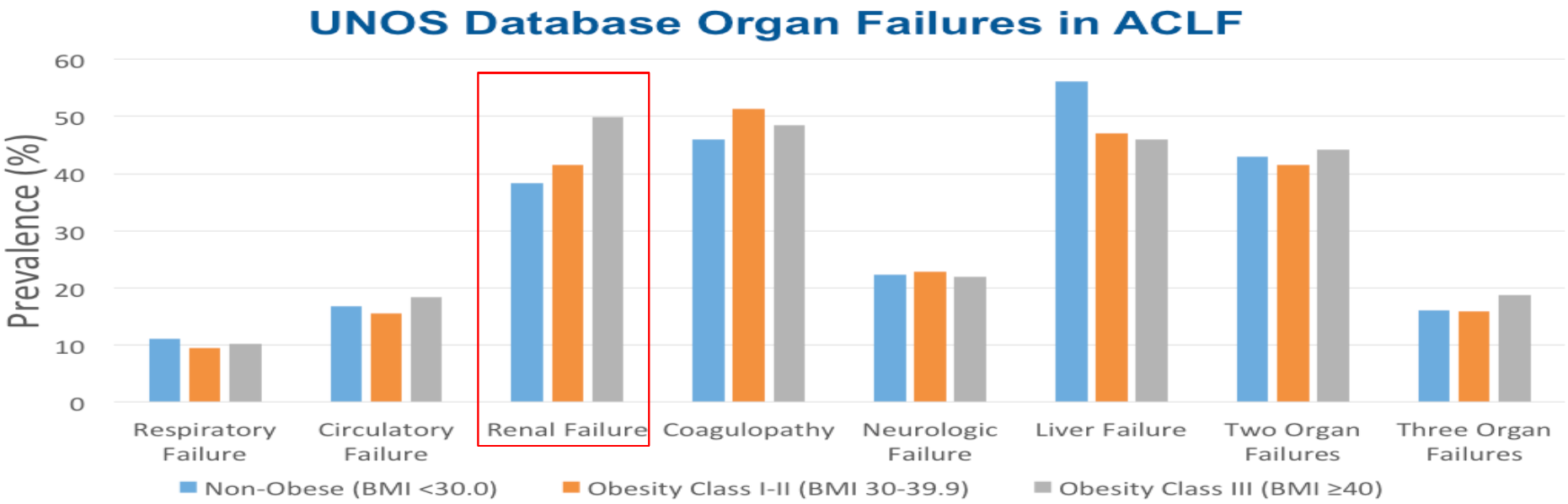
* Chi-square testing to compare categorical variables

TABLE 7: Logistic regression of the NIS regarding independent variables associated with ACLF among patients with decompensated cirrhosis

	Univariable			**Multivariable**		
Variable	Odds Ratio	p-value	95% CI	Odds Ratio	p-value	95% CI
Obesity category						
Non-obese	1.00			Reference		
Class I-II	1.03	0.057	0.98 - 1.08	0.98	0.415	0.94 – 1.02
Class III	1.36	<0.001	1.32 – 1.41	1.30	<0.001	1.25 – 1.35
Race/ethnicity						
Caucasian	1.00			Reference		
African-American	1.45	<0.001	1.42 – 1.49	1.37	<0.001	1.34 – 1.41
Hispanic	1.05	<0.001	1.02 – 1.07	1.02	0.028	1.00 – 1.05
Male	1.10	<0.001	1.08 – 1.12	1.11	0.001	1.09 - 1.13
Age category						
Age < 40	1.00			Reference		
Age 40-65	1.19	<0.001	1.15 – 1.24	1.12	0.001	1.07 – 1.17
Age > 65	1.35	<0.001	1.30 – 1.40	1.07	0.035	1.03 – 1.12
Alcoholic cirrhosis	1.21	<0.001	1.17 – 1.28	1.14	<0.001	1.12-1.16
HCV cirrhosis	0.078	<0.001	0.77 – 0.80	0.78	<0.001	0.77-0.80
Charslon category						
Category 1	1.00			Reference		
Category 2	1.48	<0.001	1.45 – 1.51	1.53	<0.001	1.50 – 1.56
Category 3	2.94	<0.001	2.88 – 3.01	3.13	<0.001	3.04 – 3.21
Anemia	1.72	<0.001	1.68 – 1.75	1.76	<0.001	1.73 – 1.81
Ascites	1.91	<0.001	1.89 – 1.93	1.89	<0.001	1.88 – 1.91

*Analysis performed using univariable and multivariable logistic regression analysis





Study highlights

- Class III obesity is an independent risk factor for acute on chronic liver failure
- Renal failure as a component of acute on chronic liver failure was increasingly prevalent with worsening obesity category
- Management of the obese patient with cirrhosis should involve a strong emphasis on weight loss and careful use of diuretics and nephrotoxic medications