Comorbidity Burden May Be Associated with Increased Mortality in Patients with Severe Acute Liver Injury Referred for Liver Transplantation

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Background: Severe acute liver injury (S-ALI) can lead to acute liver and multisystem failure, with high mortality and need for liver transplantation (LT); however, the burden and impact of liver disease and comorbid conditions are unknown.

Material/Methods: We assessed liver disease and Charlson Comorbidity Index (CCI) in adults without cirrhosis evaluated for LT at our center for S-ALI between 2004 and 2017. The study endpoints were 30-day death or LT and 90-day mortality (with LT as a competing risk).

Results: A total of 136 patients with S-ALI were included; 13% had underlying liver disease and a higher Model for End-stage Liver Disease score than those without liver disease. Sixty patients (41%) died or underwent LT within 30 days. They were older and more frequently female and had disease of autoimmune, viral, or indeterminate etiology. Transplant-free survival was associated with acetaminophen injury. The mean CCI was higher in patients with 30-day mortality or LT (1.5±2.4) *vs.* LT-free survivors (0.8±1.2), (*P*=0.03). Beyond severity of illness, CCI was associated with increased 90-day mortality (subhazard ratio 1.17, 95% confidence interval, 1.01–1.35) but not 30-day mortality or LT in the risk-adjusted analyses.

Conclusions: Comorbidity burden may be an important modifier of transplant-free survival in patients with S-ALI, but further studies are needed to validate these findings.

MeSH Keywords: Comorbidity • Liver Diseases • Liver Failure, Acute

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Background

Acute liver injury, when severe, can lead to acute liver failure (ALF) and multisystem failure with high short-term risk of mortality and need for liver transplantation (LT) [1–3]. Medical comorbidity is associated with increased mortality in acute and chronic medical conditions, such as acute coronary syndrome and congestive heart failure [4–6]. Beyond Model for End-stage Liver Disease (MELD), comorbidity burden is also independently associated with increased risk of 6-month mortality in patients with suspected drug-induced liver injury, highlighting an important interplay of severity of liver injury and comorbidity burden [7]. Patients with less severe liver injury but significant comorbidities had higher short-term mortality than patients with more severe liver injury but no or mild comorbidities [7]. These findings were also observed in the subset of patients with underlying liver disease in that study. Underlying liver disease was associated with more severe liver injury in a prospectively studied cohort of patients with drug-induced liver injury [8]. The impact of comorbidity burden and underlying liver disease (which contributes to comorbidity burden) on outcomes in other forms of acute liver injury are not well described, but they may be most pertinent in patients with severe acute liver injury (S-ALI) and may inform clinical management and prognostication. There is no universally accepted definition of S-ALI; however, Koch et al. [1] have described criteria to define S-ALI that were associated with death or need for LT in 23% of cases in their study. Therefore S-ALI appears to be clinically important, and understanding the factors that can impact outcomes in this context would be meaningful. We hoped to build on our prior observations that, in addition to the severity of liver injury, comorbidity burden affected 6-month mortality in patients with suspected drug-induced liver injury but in a broader context of patients with S-ALI and consideration of LT. Chronic liver disease is an integral component of comorbidity burden scores [9,10], but it can also predispose to more severe liver injury for a given insult with worse outcomes. While patients with underlying cirrhosis sustaining S-ALI with ALF are commonly captured and studied in acute-on-chronic liver failure (ACLF) literature with particularly poor outcomes [11,12], patients with mild liver disease are generally excluded from study of acute liver injury and ALF [1,13]. The aim of this study was to test the hypothesis that underlying liver disease and comorbidity burden may adversely affect short-term transplant-free survival in patients with S-ALI in the absence of underlying cirrhosis.

The management of the most severe forms of acute liver injury leading to ALF is predicated on early referral to centers with LT services. We examined this hypothesis in a cohort of patients hospitalized for S-ALI, with or without ALF, and who were consequently referred for LT.

Material and Methods

The study was approved by the Indiana University Institutional Review Board. We derived the study cohort through a search of our center's transplant database for *all patients who were referred for LT due to acute liver injury or failure between 2004 and 2017*. This institutional electronic health care database includes all patients referred for LT at our institution with recorded United Network for Organ Donation diagnostic codes. These codes were used to identify patients considered to have fulminant liver failure or acute hepatic necrosis. Chart review was performed on all referred patients, who were screened for inclusion and exclusion criteria.

We included adult patients with S-ALI with or without ALF. For the descriptive purposes of the study we defined patients as having S-ALI based on the laboratory criteria described by Koch et al. [1], but we did not exclude patients with noncirrhotic underlying liver disease, including (i) coagulopathy (international normalized ratio [INR] ≥2) (ii) alanine transaminase ≥10 times upper limit of normal, and (iii) hyperbilirubinemia (total bilirubin ≥3 mg/dL) in patients with non-acetaminophen (APAP)-related liver injury and no bilirubin criterion in patients with APAP-related liver injury. ALF was defined as INR ≥1.5 and hepatic encephalopathy (HE) in patients without underlying cirrhosis [14].

Children (age <18 years) and patients with prior LT or underlying cirrhosis were excluded

Demographic and clinical data were collected on admission and throughout hospitalization, including the etiology of liver injury and any documented contraindications for LT candidacy. The presence of underlying liver disease and cirrhosis was determined by review of clinical documentation and imaging data in all cases and by liver biopsy data when available [15]. Comorbidity burden was measured using the Charlson Comorbidity Index (CCI), a well-known and validated measure (Supplementary Table 1) [9]. The CCI is an aggregate of weighted scores for malignancy (solid and or hematologic), liver disease, diabetes mellitus, renal disease, atherosclerotic disease, congestive heart failure, rheumatologic disease, AIDS, peptic ulcer disease, and dementia. Underlying liver disease is an important component of CCI, but it could also directly contribute to worse outcomes of liver injury in the cohort. Consequently, we examined both CCI and underlying liver disease in the study cohort and in the analysis of study endpoints. The CCI was determined based on only pre-existing conditions and not acute illness in the context of S-ALI. The study endpoint included 30-day mortality or LT to reflect very short-term combined endpoints commonly examined in ALF literature, as well as 90-day mortality more inclusively, with LT as a competing risk.

Similar to our previous work, we assessed the severity of liver injury using MELD (7), which has also been shown to predict transplant-free survival in patients with ALF (16). King's College Criteria (KCC) were determined in all cases as high or low risk, according to APAP and non-APAP etiology of liver injury [3]. We also examined organ failure scoring using the CANONIC study Chronic Liver Failure Sequential Organ Failure Assessment (CLIF-SOFA) score (12). The seminal CANONIC study described ACLF in 1343 hospitalized patients with cirrhosis and demonstrated increased short-term mortality [12]. In contrast, the Asia Pacific Association for the Study of the Liver does not require underlying cirrhosis to define ACLF in liver failure developing in patients with chronic liver disease [17,18]. In the current study, we defined ACLF as ALF developing in patients with underlying (noncirrhotic) liver disease and examined their outcomes.

In the descriptive analysis, 30-day transplant-free survivors were compared with patients who died or underwent LT within 30 days of S-ALI. We assessed the impact of underlying liver disease and CCI on outcomes using 2 complementary regression analyses, in which MELD was used as the primary measure of liver injury severity. Logistic regression was used to assess the predictors of 30-day mortality or LT. Since LT is lifesaving, this combined endpoint may attenuate the impact of underlying liver disease or CCI on mortality. To assess the risk of short-term mortality, a competing risk regression analysis was performed to assess the predictors of 90-day mortality, with LT being analyzed as a competing risk. As a means of sensitivity testing, we repeated these analyses by modeling underlying liver disease and CCI while adjusting separately for non-MELD prediction or severity of illness scores, including CLIF-SOFA, the recently described risk score by the Acute Liver Failure Study Group (ALFSG), and the KCC score as calculated at presentation [3,12,13]. The ALFSG risk score incorporates hepatic encephalopathy grade, etiology of liver failure, vasopressor use, and log transformations of bilirubin and INR on admission in predicting transplant-free survival in patients with ALF. Factor V levels were not available to analyze the factors of interest while adjusting for the Clichy Criteria (19). While the disease severity scores used in our analyses are described in patients with ALF, little is known about their performance in predicting short-term outcomes in patients with acute liver injury. We performed area under the receiver operator curve (AUROC) analyses of MELD, CLIF-SOFA, ALFSG, and KCC and 30-day mortality or LT in the study cohort and in the subset of patients developing ALF. All analyses were performed using Stata SE 14 (College Station, TX), and tests were 2-sided with a significance threshold of *P*<0.05.

Results

During the study period, 154 adults hospitalized with S-ALI were referred for LT. We excluded 6 patients for underlying cirrhosis, and 12 for acute liver injury not meeting all the laboratory criteria for S-ALI. Among the 136 included patients, mean age was 37±13 years, 78% were women, and 78% were white. The leading cause of liver injury was APAP (58%), followed by autoimmune hepatitis (7%), ischemic hepatitis (7%), viral hepatitis (6%), idiosyncratic drug-induced liver injury (5%), and other etiologies (6%). The etiology of liver injury was undetermined in 10% of cases. Among the study cohort, 18 patients (13%) had underlying liver disease. The mean CCI was 1.2±0.2, with a distribution of scores as follows: 0 in 55%, 1 in 18%, 2 in 12%, 3 in 7%, and >3 in 9%.

During the follow-up period, 60 (44%) patients met the combined endpoint of 30-day mortality or LT. They included 41 patients (30%) who died and 19 patients (14%) who underwent LT within 30 days. Among the 42 patients who died without LT, 35 deaths (85%) were liver related. We also observed 3 early post-LT death (within 30 days of presentation). Patients who died or underwent LT within 30 days were older, more frequently women, and less frequently had APAP liver injury (Table 1). These patients also presented with worse laboratory parameters and MELD and CLIF-SOFA scores, and were more likely to have liver, respiratory, renal, and circulatory failure compared with 30-day transplant-free survivors (Table 1). These patients also had more frequent underlying liver disease, but this difference did not reach statistical significance. They also had significantly higher CCI, 1.5±2.4 *vs.* 0.8±1.2, (=0.03), respectively (Figure 1). Between 30 and 90 days, 2 patients underwent LT and 4 patients died. Patients who died without LT or those undergoing LT within 90 days tended to be older than survivors, with higher CCI and higher MELD and CLIF-SOFA scores. They also had relatively less frequent APAP-related liver injury than survivors (Supplementary Table 2).

Non-APAP liver injury was more common in women (44%) compared with men (30%), mainly due to higher autoimmune (8% *vs.* 3%), drug-induced liver injury (7% *vs.* none), and indeterminate liver injury (12% *vs.* none), (*P*=0.09), respectively. Otherwise, women and men had similar mean MELD scores (31±13 *vs.* 31±13), CLIF-SOFA scores (11±4 *vs.* 11±4), and CCI (1.2±2 *vs.* 0.9±1) at presentation.

Underlying liver disease

Patients with underlying liver disease had similar age (38±12 *vs.* 36±13) and sex (72% *vs.* 79% women) compared with patients without underlying liver disease. They had higher MELD (35±9 *vs.* 30±10; *P*=0.01) and CLIF-SOFA (12.2±3.5 *vs.* 10.6±4.3; *P*=0.09) scores at presentation compared with patients without underlying liver disease, respectively. They also had more frequent autoimmune (17% *vs.* 6%), viral (11% *vs.* 5%), and indeterminate (22% *vs.* 8%) etiology of S-ALI but less frequent APAP-related liver injury (28% *vs.* 64%) compared with

Table 1. A comparison of demographic and clinical characteristics of patients surviving hospitalization *vs.* dying or undergoing liver transplantation within 30 days of hospitalization for acute liver injury. Data are shown as mean±standard deviation or number (percentage).

	All patients N=136	Hospitalization or 30-day survivor n=76	Died or transplant within 30 days n=60	P-value
Age	37±13	34±13	40±14	0.02
Gender (Female) n(%)	106　(78)	55　(72)	51　(85)	0.08
Race (%)				
Caucasian	106　(78)	62　(82)	44　(73)	
Black	20　(15)	9　(12)	11　(18)	
Hispanic	4　(3)	2　(3)	2　(3)	0.4
Asian	5　(4)	2　(3)	3　(5)	
Unknown	1　(1)	1　(1)	None	
Etiology of liver injury n (%)				
Acetaminophen injury	80　(58)	57　(75)	23　(38)	
Autoimmune hepatitis	10　(7)	1　(1)	9　(15)	
Drug-induced liver injury	7　(5)	2　(3)	5　(8)	<0.001
Ischemic hepatitis	10　(7)	6　(8)	4　(7)	
Viral	8　(6)	2　(3)	6　(10)	
Undetermined	13　(10)	2　(3)	11　(18)	
Other	8　(6)	6　(8)	2　(3)	
Underlying liver disease n(%)	18　(13)	7　(9)	11　(18)	0.12
Charlson Comorbidity Index	1.1±1.8	0.8±1.2	1.5±2.4	0.03
International normalized ratio	4.3±3	3.3±1.7	5.7±3.7	<0.001
Bilirubin mg/dL	7.2±7.8	4.5±5	10.8±9.3	<0.001
Creatinine mg/dL	1.7±1	1.7±1.5	1.8±1.4	0.7
Clinical presentation n (%)				
Hepatic encephalopathy	112　(82)	54　(71)	59　(98)	<0.001
Jaundice	94　(69)	47　(62)	47　(78)	0.04
Ascites	40　(29)	17　(22)	23　(38)	0.04
Renal failure	93　(68)	46　(60)	47　(78)	0.03
Received N-acetyl cysteine n (%)	105　(77)	67　(88)	38　(63)	0.001
Received steroids n (%)	15　(11)	4　(5)	11　(18)	0.02
Admitted to intensive care unit n (%)	120　(90)	62　(83)	58　(98)	0.003
Mechanical ventilation n (%)	83　(63)	28　(38)	55　(93)	<0.001
Renal replacement therapy n (%)	52　(42)	17　(24)	35　(66)	<0.001
Vasopressors n(%)	51　(58)	15　(21)	36　(71)	<0.001
Model for End-stage Liver Disease	30.7±9.9	26.8±9.1	36.3±8.2	<0.001
CLIF-SOFA	10.8±4.2	9.2±3.8	12.8±3.9	<0.001
Met high risk Kings College Criteria n (%)	38　(28)	15　(20)	23　(39)	0.02
Developed ALF at any time n (%)	114　(84)	55　(72)	59　(98)	<0.001

ALF – acute liver failure; CLIF-SOFA – Chronic Liver Failure Sequential Organ Failure Assessment

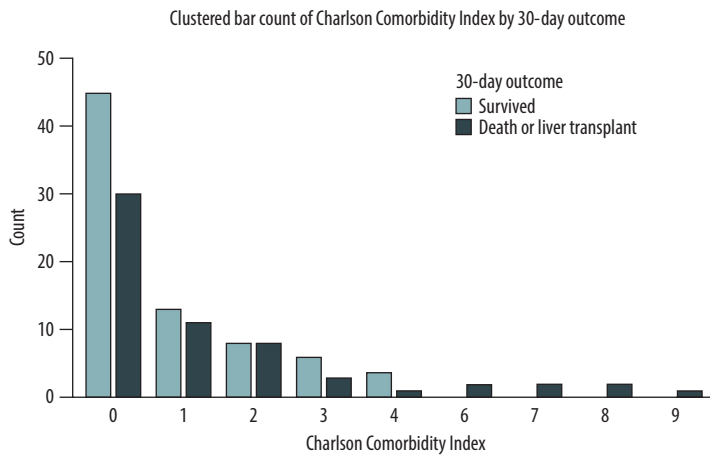Clustered bar count of Charlson Comorbidity Index by 30-day outcome

Figure 1. A comparison of Charlson Comorbidity Index scores in patients surviving hospitalization *vs.* dying or undergoing liver transplantation within 30 days of acute liver injury.

Table 2. Underlying liver disease in patients surviving hospitalization *vs.* dying or undergoing liver transplantation within 30 days of hospitalization for acute liver injury. Data are shown as number (percentage).

	All patients N=18	Hospitalization or 30-day survivor n=7	Died or transplant within 30 days n=11	P-value
Underlying liver conditions n (%)				
Alcohol	6 (33)	5 (71)	1 (9)	
Viral	7 (39)	2 (29)	5 (45)	
Autoimmune	3 (17)	None	3 (27)	0.04
Fatty liver	None	None	None	
Other	2 (11)	None	2 (18)	

patients without liver disease (*P*=0.03). Although there were no sex differences in the presence of pre-existing liver disease, the type of underlying liver diseases differed by sex. We observed more frequent underlying viral (46% *vs.* 20%) and autoimmune (23% *vs.* none) conditions among women *vs.* men with pre-existing liver disease (*P*=0.07).

ALF developed in 17 (94%) of 18 patients with underlying liver disease, compared with 97 (82%) of 118 patients without liver disease (*P*=0.2). In other words, almost all patients with underlying liver disease, albeit nonadvanced, developed ACLF per the study definition. Hence the analysis of the impact of underlying liver disease in this cohort largely reflected the impact of ACLF as well. The underlying liver conditions that were more frequently observed in patients who died or underwent LT within 30 days included viral and autoimmune disease, which were more common in women. In contrast, the liver condition observed more frequently in 30-day transplant-free survivors was alcohol related (Table 2). In aggregate, these observations point to potential sex-based differences in relation to outcomes, predominantly related to favorable 30-day transplant-free survival with APAP-related injury and in men *vs.* women (81% *vs.* 53%; *P*=0.06). The respective outcomes

were similar for men and women with non-APAP-related liver injury (25% *vs.* 32%, respectively).

Comorbidity conditions in CCI

The most common comorbid conditions contributing to CCI in the cohort included underlying liver disease (13%), diabetes mellitus (14%), peptic ulcer disease (12%), chronic obstructive pulmonary disease (11%), and solid tumors (6%). Of these, only solid tumors were significantly more frequent in patients who died or underwent LT within 30 days (Table 3).

LT evaluation and outcomes

The clinical records were scrutinized for documented contraindications to LT, and these were compared in patient who died or underwent LT within 30 days *vs.* 30-day transplant-free survivors (Table 4). Although the number of contraindications were similar between the groups, the types of contraindications differed. Substance abuse and psychiatric disease were more frequent contraindications in 30-day survivors, whereas being too sick to undergo a transplant was a more frequent contraindication in those who died within 30 days. Outcomes of LT

Table 3. A comparison of individual comorbidities in patients surviving hospitalization *vs.* dying or undergoing liver transplantation within 30 days of hospitalization for acute liver injury. Data are shown as number (percentage).

	Overall N=136	Hospitalization or 30-day survivor n=76	Died or transplant within 30 days n=60	P-value
Diabetes without complications n (%)	13 (10)	8 (10)	5 (8)	0.9
Diabetes with complications n (%)	6 (4)	3 (4)	3 (5)	
Peptic ulcer disease n (%)	16 (12)	7 (9)	9 (15)	0.3
Chronic pulmonary disease n (%)	15 (11)	11 (14)	4 (7)	0.15
Liver disease (mild) n (%)	28 (13)	7 (9)	11 (18)	0.12
Solid tumor – localized n (%)	6 (4)	None	6 (10)	0.02
Solid tumor – metastatic n (%)	2 (1)	1 (1)	1 (2)	
Stroke n (%)	6 (4)	5 (7)	1 (2)	0.2
Congestive heart failure n (%)	6 (4)	3 (4)	3 (4)	0.8
Myocardial infarction n (%)	6 (4)	5 (7)	1 (2)	0.2
Connective tissue disease n (%)	6 (4)	2 (3)	4 (7)	0.3
Renal disease (moderate to severe) n (%)	1 (1)	1 (1)	None	0.4
Lymphoma n (%)	1 (1)	None	1 (2)	0.3
Acquired immunodeficiency syndrome n (%)	1 (1)	None	1 (2)	0.3

No patients had leukemia, hemiplegia, dementia or peripheral vascular disease.

evaluation were examined for descriptive purposes. Among a small subset of 30-day survivors who were listed for LT, more than half improved without LT.

Factors associated with mortality and LT

Twenty-one survivors had less than 30-day follow-up (mean age 30±13, median CCI 0 [interquartile range, 0, 0], 92% APAP-related S-ALI, mean follow-up 8±5 days). These patients were excluded from the logistic regression analysis of 30-day mortality or LT. However, they were included in the time to event (competing risk) analysis of mortality within 90 days.

We examined the association of clinical factors at presentation with 30-day combined endpoint of mortality or LT with simple and multiple logistic regression. The factors associated with increased risk on simple logistic regression included MELD score, while APAP-related liver injury was associated with reduced risk (Table 5). Factors not associated with the endpoint included underlying liver disease, race, and treatments of S-ALI or ALF (N-acetyl cysteine or steroids). The multiple logistic regression was controlled for age, sex, and APAP-*vs.* non-APAP-related liver injury. Severity of liver injury (MELD score) was associated with 30-day mortality or LT. The CCI was not associated with the endpoint on the risk-adjusted analysis. APAP-related liver injury was associated with reduced 30-day mortality or LT. The findings were similar with introduction of interaction terms between sex and APAP-related liver

injury. A post hoc power analysis indicated that the sample size was only 35% powered to detect the observed differences in 30-day mortality or LT in patients with and without underlying liver disease.

We examined the association of baseline clinical factors at presentation with 90-day mortality, but with LT as a competing risk. Factors not associated with the 90-day mortality in the univariable analysis included age, race, underlying liver disease, and treatment for S-ALI or ALF. The factors associated with 90-day mortality in the risk-adjusted analysis included CCI and MELD score (Table 6). Sensitivity analyses were performed to assess the risk-adjusted associated of CCI with mortality in the competing risk regression using 30 day (subhazard ratio 1.2, 95% confidence interval [95% CI] 1.05–1.38; P=0.009), 180 day (subhazard ratio 1.2, 95% CI 1.05–1.38; P=0.009), or time unrestricted analyses (subhazard ratio 1.2, 95% CI 1.04–1.38; P=0.01). APAP-related liver injury was not associated with 90-day mortality, but the other findings were similar when we included interaction terms between sex and APAP-related liver injury.

Additional sensitivity analyses were performed to assess how different models of severity of liver injury or illness, beyond MELD, might influence the association of CCI or underlying liver disease with 30-day and 90-day outcomes (including CLIF-SOFA, ALFSG, and KCC in lieu of MELD-based modeling). The CCI was not associated with 30-day mortality or LT on multiple

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Table 4. Evaluation and contraindications for liver transplant candidacy in patients surviving *vs.* dying or undergoing liver transplantation within 30 days after acute liver injury. Data are shown as number (percentage).

	Overall N=136	Hospitalization or 30-day survivor n=76	Died or transplant within 30 days n=60	P-value
Result of liver transplant evaluation n (%)				
Denied/not candidates	56 (41)	36 (47)	20 (33)	
Died before completing evaluation or listing	10 (7)	None	10 (17)	<0.001
Improved	35 (26)	33 (43)	2 (3)	
Listed	35 (26)	7 (9)	28 (47)	
*Contraindications for liver transplantation n (%)	35 (26)			
Substance abuse	23 (17)	25 (33)	10 (17)	0.03
Psychiatric disease	7 (5)	18 (24)	5 (8)	0.02
Poor compliance	6 (4)	5 (7)	2 (3)	0.4
Inadequate social support	4 (3)	4 (5)	2 (3)	0.6
Malignancy	3 (2)	1 (1)	3 (5)	0.2
Cardiac	5 (4)	1 (1)	2 (3)	0.4
Too sick to be listed	1 (1)	None	5 (8)	0.01
Lack of insurance		None	1 (2)	0.3
Comorbidity impacted candidacy in course of evaluation n (%)	9 (7)	2 (3)	7 (12)	0.04
Total number of contraindications n (%)				
None	75 (55)	38 (50)	37 (62)	
1	40 (29)	24 (32)	16 (27)	0.4
2	19 (14)	12 (16)	7 (12)	
3	2 (2)	2 (3)	None	
Result of listing n (%)	N=35	n=7	n=28	
Died	8 (23)	1 (14)**	7 (25)	<0.001
Improved	4 (11)	4 (57)	None	
Transplanted	23 (66)	2 (29)**	21 (75)	

* Patients could have multiple contraindications; ** Death or liver transplant more than 30 days after presentation

logistic regression analysis while adjusting for (i) CLIF-SOFA, (ii) the ALFSG risk score, or (iii) the KCC (Supplementary Table 3). However, the CCI was associated with 90-day mortality on the competing risk analysis (significantly or trend) while adjusting for (i) the CLIF-SOFA (subhazard ratio 1.13, 95% CI 0.97–1.31; *P*=0.10), (ii) the ALFSG risk score (subhazard ratio 1.19, 95% CI 1.03–1.037; *P*=0.014), or (iii) the KCC (subhazard ratio 1.15, 95% CI 0.99–1.3; *P*=0.054).

The regression analyses were repeated in the 114 patients who developed ALF (55 survived without LT, and 59 died or underwent LT within 30 days). The CCI was not associated with 30-day mortality or LT in models based on MELD, CLIF-SOFA, ALFSG, and KCC. However, CCI was associated with a trend for increased 90-day mortality in the competing risk model based on MELD and ALFSG scores, but not CLIF-SOFA or KCC (Supplementary Table 4).

The AUROCs (95% CI) for predicting 30-day mortality or LT in all patients (S-ALI with or without ALF) were MELD, 0.74 (0.65–0.84); CLIF-SOFA, 0.73 (95% CI 0.63–0.82); ALFSG, 0.69

(95% CI 0.58–0.79); and KCC, 0.57 (95% CI 0.5-0.66). The AUROCs (95% CI) for the same endpoint only in patients developing ALF were MELD, 0.72 (0.61–0.83); CLIF-SOFA, 0.69 (0.58–0.8); ALFSG, 0.65 (0.54–0.77); and KCC, 0.56 (0.46–0.65), respectively.

Discussion

Our examination of all adults evaluated for LT for S-ALI demonstrated that approximately 1 in 8 patients had underlying liver disease, and roughly half carried some comorbidity as measured by the CCI. Notably, by definition CCI incorporates a severity-adjusted component for underlying liver disease. In this cohort, underlying liver disease had a limited contribution to differences in comorbidity burden as measured by CCI (1 point for mild liver disease, and cirrhosis was excluded). All models were adjusted for the presence of underlying liver disease. Overall comorbidity burden independently affected 90-day transplant-free survival, but not combined 30-day mortality or LT. Although the analysis of the latter endpoint was limited

Table 5. The logistic regression analysis of predictors of 30-day mortality or liver transplantation in patients with severe acute liver injury referred for liver transplantation.

Variable	Simple logistic regression		Multiple logistic regression		
	Odds ratio (95% confidence interval)	P-value	Odds ratio (95% confidence interval)		P-value
CCI	1.18 (0.96–1.46)	0.1	*1.17	(0.9–1.5)	0.3
Underlying liver disease	1.5 (0.6–4.3)	0.4	*0.4	(0.1–1.7)	0.2
Age	1.03 (0.99–1.06)	0.07	*0.99	(0.96–1.04)	0.9
MELD	1.11 (1.06–1.17)	<0.001	*1.14	(1.07–1.2)	<0.001
Female gender	2.1 (0.8–5.4)	0.1	3	(0.8–10.4)	0.09
APAP etiology	0.1 (0.1–0.5)	0.001	0.2	(0.07–0.54)	0.002

APAP – acetaminophen; CCI – Charlson Comorbidity Index; MELD – model for endstage liver disease. * The results were similar when the multiple logistic regression was controlled for interactions of gender and APAP etiology of liver disease.

Table 6. The competing risk regression analysis of predictors of mortality within 90 days, with liver transplantation as a competing risk, in patients with severe acute liver injury referred for liver transplantation.

Variable	Univariable analysis		Multivariable analysis	
	Sub-hazard ratio (95% confidence interval)	P-value	Sub-hazard ratio (95% confidence interval)	P-value
CCI	1.18 (1.03–1.35)	0.014	*1.17 (1.01–1.35)	0.037
Underlying liver disease	0.9 (0.4–2)	0.8	*0.4 (0.1–1.1)	0.07
MELD	1.05 (1.02–1.08)	<0.001	*1.07 (1.03–1.1)	<0.001
Female gender	2.5 (0.99–6.1)	0.05	2.8 (1.04–7.7)	0.04
APAP etiology	0.6 (0.3–1.02)	0.06	0.7 (0.4–1.4)	0.3

APAP – acetaminophen; CCI – Charlson Comorbidity Index; MELD – model for endstage liver disease. * The results were similar when the multivaraible competing risk regression was controlled for interactions of gender and APAP etiology of liver disease.

by a smaller sample size, it is possible that CCI may not predict the need for LT *per se* and affects outcomes mainly through increased mortality risk. The focus on comorbidity burden in this context, as quantified by CCI, was relatively novel. This helped quantify the risk associated with comorbidity burden for the outcomes of interest in this population. In addition, modeling the severity of liver injury by MELD, CLIF-SOFA, or ALFSG or KCC scores, as a means of sensitivity analysis, did not obviate the association of comorbidity burden with increased short-term mortality. If validated, these findings could significantly improve prognostic models used in determining mortality risk in patients presenting with S-ALI. The comparison of MELD, CLIF-SOFA, ALFSG, and KCC in the prediction of 30-day death or LT using AUROC in patients with S-ALI was also of interest. While MELD and CLIF-SOFA performed the best in S-ALI or ALF, these scores are not specifically validated for outcomes in acute liver injury as defined by this study; however, these data support their use as a measure of disease severity in this cohort.

The inclusive definition of the study cohort allowed us to describe and assess the impact of underlying noncirrhotic liver disease, an entity that would otherwise be excluded in a strict definition of ALF or acute liver injury [1,13]. We observed underlying liver disease in approximately 1 in 8 patients with S-ALI, with a numerically higher frequency of underlying liver disease in patients with 30-day mortality or LT. Although this finding was not statistically significant, a post hoc power analysis indicated that the study cohort was not sufficiently powered to detect the observed higher rate of death or LT within 30 days in that subset of patients. The presence of any underlying liver disease was associated with higher MELD and CLIF-SOFA at presentation and all but one of these patients developed ALF, and hence ACLF, signifying clinical importance despite the statistical limitations. Outcomes also differed by the types of underlying liver diseases due to increased frequencies of viral and autoimmune liver disease in patients who died or underwent LT. Here we observed sex-based differences. Specifically,

women had more autoimmune and viral liver disease and experienced more autoimmune and indeterminate etiologies of S-ALI, but they had less frequent APAP-related S-ALI. In addition, men had more favorable outcomes even with APAP-related injury, as others have reported [20]. All these factors were associated with relatively worse outcomes in the descriptive analysis and are supported in part by previous reports on the impact of etiology of liver injury and sex on outcomes in ALF [21–25]. Taken together these findings suggest that larger studies are needed in S-ALI occurring in patients with pre-existing noncirrhotic liver disease given the high rates of ACLF and potential sex-based interactions.

In this cohort, CCI emerges as an important modifier of outcomes in patients with S-ALI, but that association was attenuated and lost statistical significance when analyzed only in patients developing ALF by strict definition. This result may be related to a true lack of association in patients with more severe liver injury, in which the liver injury is the overwhelming determinant of mortality or need for LT. However, it may also be related to sample size limitations and the need for a larger cohort to adequately power the analysis. Interestingly, the subhazard ratio values for CCI in the competing risk models for 90-day mortality adjusting for MELD, CLIF-SOFA, ALFSG, and KCC (and underlying liver disease in all models) were relatively uniform despite the lack of statistical significance. These findings suggest that larger studies are needed to better elucidate the impact of CCI on mortality or need for LT in patients with acute liver injury and ALF.

The inclusion of patients with both acute liver injury and ALF in our study brought up an interesting observation. Although not all patients referred to our center for LT consideration had or developed ALF, even the transplant-free survivors were demonstrably severely ill, justifying transplant referrals in the course of care. We also briefly examined the 12 excluded patients with acute liver injury without cirrhosis but not meeting the laboratory criteria that we used to define S-ALI. Interestingly 3 (25%) of the 12 died or underwent LT within 30 days, similar to rates reported by Koch et al. [1] in strictly defined S-ALI (23%). This suggests that a definition of S-ALI may be more inclusive and remains undetermined. It also underscores the merits of understanding the determinants of outcomes in patients with S-ALI in clinical practice, even in the absence of established ALF.

Localized solid tumors were observed in 4% of patients but were more frequent in patients who died within 30 days, and they were identified as barriers to LT candidacy in most of those cases. Otherwise, medical contraindications to LT candidacy were not directly related to a specific comorbid condition captured by the CCI and affected a limited number (7%) of patients. The majority of contraindications to LT were related to psychosocial and behavioral factors, which predominated in patients with APAP-related liver injury, which in turn

was associated with significantly better transplant-free survival. This finding may explain why contraindications to LT candidacy did not affect outcomes in the study cohort.

Limitations

We acknowledge a number of limitations of the study, including the small sample size, retrospective design, and lack of an accepted definition of S-ALI. Sample size specifically limited our ability to assess the impact of underlying liver disease on mortality and LT. These limitations were unavoidable, despite the high volume (1961) of primary liver transplants performed at our center during the study period. Since the study patients were referred to our center for LT, the actual start date of S-ALI could not be reliably determined, and using the admission date as the reference for 30-day outcomes could have affected the related analyses. However, we believe that these patients would have had a high priority for admission, and we suspect there would have been little if any delay in admission to the study center after referral. A referral bias for more severe cases of acute liver injury may also affect our cohorts' characteristics and analysis results in the context of LT referral. We also did not have laboratory data such as Factor V to calculate additional ALF criteria scores [19]. Thirty-day follow-up was also missing for some patients who were discharged to home. The majority of those patients were young with CCI=0 and rapidly resolving APAP-related liver injury at the time of discharge, and they would have been expected to recover from S-ALI. They were included in the competing risk analysis of 90-day mortality. The use of the 30-day time point for mortality or LT missed 10% of overall events (occurring after 30 days). However, this time frame allowed the optimal balance of capturing the majority of patients with these endpoints while maintaining a critical sample size of evaluable patients with documented follow-up for the logistic regression analysis.

Conclusions

In summary, nonadvanced underlying liver disease and medical comorbidity burden are prevalent in patients with S-ALI referred for LT. Underlying liver disease is associated with more severe liver injury, while severity of injury and overall comorbidity burden are associated with decreased 90-day transplant-free survival. These findings warrant further investigation, and if validated, incorporating comorbidity scores could improve the accuracy of prognostic models available to patients and clinicians and guide earlier referral to LT centers in patients with S-ALI.

Ethical statements

This study was approved by the Indiana University Institutional Review Board (IRB protocol number 1804254172).

Supplementary Data

Supplementary Table 1. The conditions composing the Charlson Comorbidity Index as described by Charlson et al. [9].

Charlson Comorbidity Index comorbid conditions (score weight)	Clinical scenarios
Acquired Immune Deficiency Syndrome (6)	Not just HIV positive, includes patients with HIV, CD4 count <200, or the presence of AIDS-defining condition regardless of the CD4 count (opportunistic infections or malignancies)
Metastatic solid tumor (6)	Clinical review
Non-metastatic solid tumor (2)	Exclude if >5years from dx, Exclude non-melanoma malignant neoplasm of skin
Lymphoma (2)	Includes lymphosarcoma, Hodgkins Waldenstrom's, macroglobulinemia, myeloma, and other lymphomas
Leukemia (2)	Includes acute or chronic myelogenous or lymphocytic leukemia, and polycythemia vera
Moderate or severe renal disease (2)	– Mild includes serum creatinine of 2–3 mg – Moderate includes serum creatinine of >3 mg – Severe renal disease includes patients on dialysis, those who had a transplant, and those with uremia
Hemiplegia or paraplegia (2)	Clinical diagnosis
Diabetes with end organ damage (2)	With end-organ damage includes Retinopathy, neuropathy, nephropathy or brittle diabetes
Diabetes without complications (1)	Without end-organ damage includes all others treated with insulin or oral hypoglycemics, but not diet alone
Liver disease, moderate to severe (3)	Moderate: cirrhosis with portal hypertension without variceal bleed Severe: Cirrhosis with variceal bleed
Liver disease, mild (1)	Mild: chronic hepatitis, no portal hypertension
Peptic ulcer disease (1)	Includes patients who have required treatment for peptic ulcer disease, including those who have bled from ulcers
Connective tissue disease (1)	Systemic lupus erythematous, polymyositis, mixed connective tissue disease, polymyalgia rheumatic, rheumatoid arthritis, etc
Chronic obstructive pulmonary disease (1)	Clinical review and not based on spirometry testing
Dementia (1)	Includes patients with chronic cognitive deficits
Cerebrovascular disease or transient ischemic attack (TIA) (1)	Includes patients with a history of stroke with minor or no residua and TIA
Peripheral Vascular disease (1)	Includes patients with intermittent claudication or those who had a bypass for arterial insufficiency, those with gangrene or acute arterial insufficiency, and those with untreated thoracic or abdominal aortic aneurysm (6 cm or more)
Congestive heart failure (1)	Clinical review and includes patients who have had exertional or paroxysmal nocturnal dyspnea and who have responded symptomatically (or on physical exam) to digitalis, diuretics, or afterload reducing agents
Myocardial infarction (1)	Includes patients with one or more definite or probable Myocardial infarctions. These patients had been hospitalized and had ECG and/or enzyme changes. Not just ECG changes only

Supplementary Table 2. A comparison of salient demographic and clinical characteristics of patients who survived, underwent liver transplantation, or died within 90 days of presenting with severe acute liver injury. Data are shown as mean±standard deviation or number (percentage).

	Survived without LT n=71	Underwent LT n=21	Died without LT n=44	P-value
Age	34±12	40±11	39±15	0.049
Gender (Female) n (%)	52 (73)	15 (71)	39 (89)	0.11
Race (%)	57 (80)	11 (52)	38 (86)	0.1
Caucasian	9 (13)	6 (29)	5 (11)	
Black				
Etiology of liver injury n (%)	55 (77)	5 (24)	20 (45)	<0.001
Acetaminophen injury	1 (1)	5 (24)	4 (9)	
Autoimmune hepatitis	2 (3)	3 (14)	2 (4)	
Drug-induced liver injury	5 (7)	2 (9)	3 (7)	
Ischemic hepatitis	2 (3)	2 (9)	5 (9)	
Viral	2 (3)	3 (14)	8 (18)	
Undetermined	4 (6)	1 (5)	3 (7)	
Other				
Underlying liver disease n (%)	7 (10)	6 (29)	5 (11)	0.08
Charlson Comorbidity Index	0.8±1.2	1.2±1.9	1.6±2.5	0.07
Model for End-stage Liver Disease	26.7±9.1	36.9±7.8	35.1±9	<0.001
CLIF-SOFA	9.3±3.7	11.1±4.5	13±4	<0.001
Developed ALF at any time n (%)	50 (70)	21 (100)	44 (100)	<0.001

ALF – acute liver failure; CLIF-SOFA – Chronic Liver Failure Sequential Organ Failure Assessment.

Supplementary Table 3. The association of the Charlson Comorbidity Index with 30-day mortality or liver transplantation by multiple logistic regression, and 90-day mortality by multivariable competing risk regression analyses when modeled with different severity of illness scores.

Model covariates	*MELD model		*CLIF-SOFA model		ALFSG model		Kings College Criteria model	
Multiple logistic regression	*,# Odds ratio (95% confidence interval)	P-value	*,# Odds ratio (95% confidence interval)	P-value	Odds ratio (95% confidence interval)	P-value	Odds ratio (95% confidence interval)	P-value
Charlson Comorbidity Index	1.17 (0.9–1.5)	0.3	1.06 (0.8–1.3)	0.7	1.2 (0.9–1.6)	0.06	1.14 (0.9–1.4)	0.2
Underlying liver disease	0.4 (0.1–1.7)	0.2	0.5 (0.2–2.7)	0.7	0.9 (0.3–3.2)	0.9	1.4 (0.5–4)	0.5
Multivariable competing risk regression	* Sub-hazard ratio (95% confidence interval)	P-value	* Odds ratio (95% confidence interval)	P-value	Sub-hazard ratio (95% confidence interval)	P-value	Sub-hazard ratio (95% confidence interval)	P-value
Charlson Comorbidity Index	1.17 (1.01–1.35)	0.037	1.13 (0.97–1.31)	0.1	1.19 (1.03–1.37)	0.014	1.15 (0.99–1.3)	0.054
Underlying liver disease	0.4 (0.1–1.1)	0.07	0.7 (0.3–1.6)	0.3	0.7 (0.2–1.8)	0.4	0.7 (0.3–1.7)	0.5

ALFSG – Acute Liver Failure Study Group; CLIF-SOFA – chronic liver failure-sequential organ failure assessment; KCC – Kings College Criteria; MELD – model for endstage liver disease. * Analyses were controlled for gender and APAP etiology of liver injury based on their impact in the non-adjusted analysis (p-value ≤0.1). The results were similar when the multiple logistic regression was controlled for interactions of gender and APAP etiology of liver disease. # Analysis was controlled for patient age based on its impact in the unadjusted analysis (p-value ≤0.1).

Supplementary Table 4. The association of the Charlson Comorbidity Index with 30-day mortality or liver transplantation by multiple logistic regression, and 90-day mortality by multivariable competing risk regression analyses when modeled in the 114 patients with acute liver failure with different severity of illness scores.

Model covariates	*MELD model		*CLIF-SOFA model		ALFSG model		Kings College Criteria model	
Multiple logistic regression	*,# Odds ratio (95% confidence interval)	P-value	*,# Odds ratio (95% confidence interval)	P-value	Odds ratio (95% confidence interval)	P-value	Odds ratio (95% confidence interval)	P-value
Charlson Comorbidity Index	1.14 (0.9–1.5)	0.3	1.03 (0.8–1.3)	0.8	1.19 (0.9–1.5)	0.16	1.08 (0.9–1.3)	0.5
Underlying liver disease	0.5 (0.1–2.1)	0.3	0.9 (0.3–3.2)	0.9	0.9 (0.3–3.5)	0.9	1.4 (0.5–4.2)	0.6
Multivariable competing risk regression	* Sub-hazard ratio (95% confidence interval)	P-value	* Odds ratio (95% confidence interval)	P-value	Sub-hazard ratio (95% confidence interval)	P-value	Sub-hazard ratio (95% confidence interval)	P-value
Charlson Comorbidity Index	1.14 (0.98–1.33)	0.08	1.11 (0.96–1.3)	0.16	1.14 (0.98–1.32)	0.07	1.11 (0.97–1.3)	0.13
Underlying liver disease	0.4 (0.1–1.2)	0.11	0.7 (0.3–1.6)	0.4	0.7 (0.3–1.8)	0.4	0.7 (0.3–1.6)	0.4

ALFSG – Acute Liver Failure Study Group; CLIF-SOFA – chronic liver failure-sequential organ failure assessment; KCC – Kings College Criteria; MELD – model for endstage liver disease. * Analyses were controlled for gender and APAP etiology of liver injury based on their impact in the non-adjusted analysis (p-value ≤0.1). The results were similar when the multiple logistic regression was controlled for interactions of gender and APAP etiology of liver disease. # Analysis was controlled for patient age based on its impact in the unadjusted analysis (p-value ≤0.1).

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