Associations of Fatty Liver Disease with Recovery After Traumatic Injury

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Abstract

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Fatty liver disease (FLD) is prevalent among US adults (20-30%) and associated with chronic systemic inflammation, extra-hepatic comorbidities, and socioeconomic risk factors for poor health outcomes. These factors may directly and indirectly contribute to an individual's recovery from traumatic injury. However, FLD has not been studied as a risk factor for poor outcomes in the trauma population.

We performed a retrospective cohort study of adults admitted to a level-1 trauma center in Seattle, Washington between September 2016 and December 2020, excluding those with severe head injury or cirrhosis. To classify FLD, we measured the liver-spleen attenuation difference in Hounsfield Units (HU_{L-S}) using virtual non-contrast reconstructions of CT scans performed using dual-energy: none ($HU_{L-S}>1$), mild ($-10\leq HU_{L-S}<1$), or moderate/severe ($HU_{L-S}<-10$). The primary outcomes of interest were 1) recovery from a systemic inflammatory response (SIRS), defined as SIRS <2, and 2) recovery from organ dysfunction, defined as a sequential organ failure assessment score <2. For each outcome, patients with scores <2 sustained for at least 3 consecutive days or at the time of being discharged alive were classified as recovered. We used Cox models to compare the "hazard" of recovery among those with FLD compared to the hazard of recovery among those without FLD. The secondary outcomes were hospital acquired infection, sepsis, ICU days, and discharge to a skilled nursing or long-term care facility. Relative risks (or rates) for the associations between FLD and outcomes were assessed using multivariable log-binomial and Poisson models. In an exploratory analysis, we compared nested Cox models using the likelihood ratio test to determine whether associations of FLD with the physiologic

recovery outcomes differed among patients with higher vs. lower numbers of pre-existing comorbidities or injury characteristics. All models adjusted for age, sex, alcohol use disorder, and health insurance.

Among 510 adults meeting inclusion criteria, the median age was 51 years (interquartile range 30, 69), 350 (69%) male, median injury severity score 17 (10, 24). FLD was present in 80 (16%) individuals; 51 had mild FLD and 29 had moderate/severe FLD. Among those with, compared to those without FLD, the adjusted hazard ratio of recovery from SIRS was 0.94 (95% CI 0.72, 1.23), and that for organ dysfunction was 1.08 (95% CI 0.84, 1.41). Associations of FLD with infection, sepsis, ICU days, and disposition were not statistically significant. The association of FLD with recovery from SIRS differed according to whether an individual had shock on admission (HR 0.76 (95% CI 0.55, 1.05) among those with shock, HR 1.81 (95% CI 1.43, 2.28) among those without shock, p-value for interaction = 0.039).

Fatty liver disease is common in adults hospitalized after injury. In this study, which was limited by small sample size, FLD was not associated with adverse short-term outcomes. Associations of FLD during recovery from critical illness and long-term outcomes after trauma remain unclear and warrant further study.

Introduction

As the body's main source of acute phase reactants and major orchestrator of metabolic pathways, the liver plays an important role in the body's response to physical injury.[1,2] It is well-recognized that individuals with end stage liver disease have low physiologic reserve, and thus experience high morbidity and mortality after injury.[3] However, little is known about the recovery experiences of those with a far more common form of chronic liver disease, fatty liver disease (FLD). Non-alcoholic FLD (NAFLD) is the most common form of chronic liver disease in Western countries[4] with an estimated prevalence of 20-30% among US adults.[5] Including alcohol-induced etiologies, FLD accounts for over 75% of cases of liver disease diagnosed each year.[6] Approximately 10-20% of individuals with FLD have steatohepatitis, which can progress to cirrhosis and hepatocellular carcinoma.[7] As such, FLD is anticipated to be the leading indication for liver transplant by 2030.[8]

Investigating the impact of FLD on recovery may be especially important among individuals who have sustained physical injury. FLD may directly or indirectly impact physiologic recovery after injury through pre-existing local and systemic inflammation. The biomolecular pathways involved in the development and progression of FLD are shared with those of the metabolic syndrome: insulin resistance, dyslipidemia, hypertension, and obesity.[9] These conditions result in higher circulating levels of IL-6 and TNF-a, which contribute to systemic inflammation.[9] IL-6 and TNF-a are also transiently elevated after traumatic injury, and relatively higher levels are predictive of prolonged recovery patterns (i.e., more days in an intensive care unit (ICU) and more days with organ dysfunction).[10,11] Additionally, FLD is an independent risk factor for cardiovascular disease, the leading cause of death in the United States, and thought to be mediated by a separate proinflammatory pathway.[12] It is unknown whether inflammation present at baseline among individuals with FLD contributes to inflammatory responses to injury that are associated with prolonged recovery patterns. The association of FLD with physiologic and clinical outcomes may be stronger among those who sustain multiple and/or more severe injuries, in whom the inflammatory response to injury is greater.

FLD is also associated with aberrations of the gut microbiome, namely overgrowth of bacteria in the small intestine, and increased gut permeability.[9] Intestinal permeability may worsen when its blood supply is impaired, which can occur during physiologic stress, hemorrhagic shock, hypotension in the perioperative setting, or with the use of vasoactive medications—any combination of which may be present during the acute phase of injury (first 24-48 hours). Increased gut permeability facilitates bacterial translocation into the blood, which may increase the risk for bacteremia and wound infections.[13,14] Consistent with a higher risk for complications after surgery are reports that individuals with FLD have a twofold higher risk of postoperative infections[15] and a threefold higher risk of mortality after planned liver resection.[16,17]

Given the high prevalence of FLD in the US population, its associations with extra-hepatic comorbidities, and a proinflammatory pathophysiology, FLD may be an important risk factor for complicated recovery after injury. We hypothesized that in a cohort of injured adults requiring intensive care, FLD would be associated with clinical signs of a prolonged systemic inflammatory response, prolonged organ dysfunction, and worse clinical outcomes. We also hypothesized that the associations of FLD with the outcomes in this study would be stronger among those with higher overall injury severity scores, multiple serious injuries (polytrauma), and those exposed to shock on admission.

Methods

Study Design and setting

We conducted a retrospective cohort study of adults who were admitted to the intensive care unit (ICU) at Harborview Medical Center, a level-1 trauma center in Seattle, Washington, between September 2016 through December 2020. Harborview Medical Center serves Alaska, Washington, Montana, and Idaho, and receives over 6,000 trauma admissions per year. This study was reviewed and approved by the Institutional Review Board at Harborview Medical Center in Seattle, Washington.

Study population

We included adults ages 18 years and older who were admitted to Harborview Medical Center's ICU following traumatic injury—a physical injury caused by blunt or penetrating force—who had a Washington State address at the time of admission, and who underwent a CT scan of the abdomen and pelvis within 72 hours of admission on Harborview's only dual energy CT scanner (See Figure 1 for a flow diagram of inclusion and exclusion criteria). We excluded individuals with "severe", "critical", or "maximal" traumatic brain injury, defined as an abbreviated head injury severity score (AIS) of 4 or higher (scale of 0-6) because traumatic brain injury is among the strongest drivers of poor outcomes after injury, and we thought significant associations between FLD and clinical outcomes would be difficult to detect in this subpopulation. We also excluded individuals with a history of cirrhosis documented in the health record because individuals with cirrhosis have end-stage liver disease and are not representative of the target population. If a patient had more than one admission during the study period after meeting inclusion criteria, the most recent admission was selected.

Exposure

We ascertained the presence of FLD from virtual non-contrast reconstructions of abdominal CT scans performed using dual energy within 72 hours of arrival to hospital. We estimated liver fat content using the liver-spleen attenuation difference in Hounsfield Units (HU_{L-S}). We classified FLD as none ($HU_{L-S} \geq 1$), mild ($-10 \leq HU_{L-S} < 1$), or moderate/severe ($HU_{L-S} < -10$), as previously described.[18–21] We used the mean of four density measurements from the liver, and two from the spleen to calculate the liver-spleen attenuation difference. Only one CT scan per patient was used for the analysis. If more than one CT was available during the same admission, the first CT meeting criteria was used.

Protocol for Collecting Measurements from Dual Energy CT

All CT scans from patients meeting inclusion criteria were imported into a viewing application (Syngo.Via by Siemens) where liver virtual non-contrast image reconstruction was performed. Four readers (LA, DG, MW, and KS) were trained to process and read images by a board-certified radiologist (KL). Each reader collected density measurements from the liver and spleen from 50 patients, with complete overlap between readers. We assessed interrater reliability for the mean density of the liver and spleen separately using the intraclass correlation coefficient, accounting for two-way random effects, single-rater type, with measurements from a single rater being used as the basis for the actual measurement.[22] We re-assessed interrater reliability during data collection on 25 scans randomly selected to overlap between readers. We classified measurements of the ICC as "excellent" (≥ 0.90), "good" (0.75 to <0.90), "moderate" (0.50 to <0.75), or "poor" (<0.50) as previously described.[22]

Outcomes

We examined outcomes for which underlying liver disease may play a role: the duration of the initial physiologic response to injury, hospital acquired infections and sepsis, and in-hospital outcomes indicating a failed and/or prolonged recovery.

We measured the physiologic response to injury using two clinical scoring systems, the systemic inflammatory response syndrome criteria (SIRS) score[23] which captures outward signs of acute inflammation, and the modified sequential organ failure assessment score (SOFA),[24] which captures adverse effects of injury and inflammation on multiple organ systems. Components of these scoring systems are described in the supplemental content Tables S1 and S2. If a laboratory component of the scoring system was not available on a given day, we assigned a sub-score of 0 points, which aligns with the clinical practice to monitor abnormal values and not perform repeated tests on patients without signs or symptoms of abnormal physiology. Recovery from a systemic inflammatory response and recovery

from organ dysfunction were defined as a maximum daily SIRS or SOFA score of <2 that was sustained for at least three consecutive days, or a score of <2 at the time of being discharged alive. Individuals who died in hospital within three days of a recovery event were treated as failing to recover.

We defined hospital acquired infections as infections that developed after 48 hours of hospitalization.[25] Infections were identified explicitly using administrative data from the trauma registry and ICD codes, and implicitly using clinical criteria collected from the electronic health record. As previously described, implicit criteria for infection included an order for a new, non-prophylactic IV antibiotic within 48 hours of an order for body tissue culture, and antibiotic treatment sustained for at least 4 consecutive days, until discharge, or death, whichever came first.[26,27] We defined sepsis according to the 2016 international guidelines as infections (meeting implicit or explicit criteria) accompanied by worsening of organ dysfunction.[28] We defined worsening organ dysfunction as an increase in the SOFA score of at least 2 points within a +/-3 day window of the culture day.[27,28]

We also evaluated associations of FLD with the following clinical outcomes: ICU days, in-hospital mortality, and dispositions associated with increased 3-year mortality: discharge to a skilled nursing or long-term care facility (SNF/LTCF), and discharge to a location other than home without assistance (includes discharge to home with assistance, SNF/LTCF, or other location including shelters, unhoused, psychiatric or other acute care facility, and legal custody).[29]

Covariates

We constructed a directed acyclic graph[30] to guide the selection of covariates that we included in the multivariable models. Factors associated with FLD and causally linked to short-term outcomes included age, sex, alcohol use, and type of health insurance plan. We adjusted for these factors using the following rationale: FLD varies by age and the prevalence is estimated to be highest among those in their 5th and 6th decade of life.[7] The relationship between sex and FLD may change as a function of age, with females experiencing a higher incidence of FLD at older ages as compared to males.[12] Additionally, older

age and male sex are associated with excess morbidity and mortality after trauma.[29,31] Heavy alcohol use leads to fat accumulation in the liver and may be associated with ICU length of stay and discharge to subacute care facilities by way of its association with traumatic brain injury.[32] We used a documented history of alcohol use disorder in the electronic health record as an indicator of alcohol consumption that may lead to FLD. We used health insurance as a proxy for socioeconomic conditions that may increase the likelihood of developing FLD and are associated with mortality.[33–36] We defined covariates as follows: age (in years), male (yes or no), alcohol use disorder (present or absent), health insurance plan (Medicaid, Medicare only, Medicare supplemented, or Other).

Medical conditions other than alcohol use disorder which are associated with FLD could contribute to outcomes after injury and include diabetes, cardiovascular disease, and obesity. These are later manifestations of precursor conditions (insulin resistance, elevated blood pressure, dyslipidemia, elevated waist circumference) collectively referred to as the metabolic syndrome. The metabolic syndrome (unmeasured) is interrelated with the development of FLD, while diabetes, cardiovascular disease, and obesity (measured) are situated along the causal pathway between FLD and outcomes in this study. For this reason, we considered these comorbidities to be mediators and did not adjust for them in the primary analysis. However, it is possible these conditions may develop before or independent of FLD. Because onset in relation to FLD was not available from our data sources, we conducted a sensitivity analysis to compare results when the presence of pre-existing diabetes, hypertension requiring medications, and obesity (body mass index ≥30, calculated as weight in kg/height in m^2) were included the models.

For descriptive purposes, we also collected information on medical comorbidities which we categorized according to levels of the Charlson comorbidity index[37] (0 points, 1-2, 3-4, 5+), the injury severity score (range: 1-75) categorized as low (<18), moderate (19-25), and high (25+), head injury (by exclusion criteria AIS <4), liver injury, multiple severe injuries defined as 2 or more body regions with an AIS ≥3 (present or absent), shock on admission defined as a systolic blood pressure <90mmHg or a base deficit >6 mmol/L documented during the first 24 hours of admission (present or absent),[31] red blood cell

transfusion during the first 24 hours (transfused or not transfused), units of red blood cells transfused during the first 24 hours (number of units among those transfused), whether the patient underwent emergency laparotomy, and required invasive mechanical ventilation.

Analysis

We described patient demographics, injury characteristics, and outcomes using the median (interquartile range) for continuous variables, and count (proportion %) for discrete variables.

We applied Kaplan Meier survivor estimates and log-log transformations to compute the median time to a recovery event (resolution of SIRS or organ dysfunction) and its 95% confidence interval. We used Cox Proportional Hazards to estimate the hazard of each recovery event comparing those with FLD to those without FLD (reference), adjusting for age, sex, alcohol use disorder, and type of health insurance. For each patient, follow up began on the day of the qualifying CT scan. We checked the proportional hazards assumption visually by plotting Schoenfeld residuals over time, and formally by testing for time-varying covariates.

We used multivariable log-binomial regression with robust standard errors to estimate the adjusted relative risk and 95% confidence intervals for binary outcomes, comparing individuals with FLD to those without FLD (reference). We used Poisson regression to compare the number of ICU days per person hospital days between the two groups. In all regression models, we matched individuals according to the calendar day of their CT scan relative to their arrival day (same day, 1 day after, 2 days after) to prevent immortal time bias. In a sensitivity analysis, we repeated the multivariable Cox, relative risk, and Poisson regressions with adjustments for pre-existing diabetes, hypertension, and obesity.

We performed a post-hoc exploratory analysis to examine whether associations of FLD with time to recovery events differed by levels of FLD severity, the comorbidity index, and injury characteristics (liver injury, injury severity score, multiple severe injuries, and shock on admission). To explore these relationships visually, we fit semiparametric Cox models and plotted the subgroup-specific cumulative

hazard of recovery. We then tested for significant interactions by comparing nested models with and without interaction terms for FLD and the potential effect modifiers using the likelihood ratio test.

All hypothesis tests were two-sided using an alpha level of <0.05. We did not adjust p-values for multiple testing because outcomes were pre-specified. All data processing and statistical analyses were performed in R version 4.1.0 using statistical software packages "psych," "sandwich," "lmtest," "survival," "flexsurv," and "survminer."

Results

There were 612 patients with scans that met all inclusion criteria. However, 102 patients were excluded due to streak artifact covering the liver and/or spleen. Based on imaging findings, we suspected that patients excluded due to scan artifact were more severely injured than those included in the study. We compared the injury severity scores of the two groups using the Wilcoxon rank-sum test and found that excluded patients had significantly higher injury severity scores (ISS 24 [14, 34]) compared to those without artifact (ISS 17 [10, 24]), P <0.001.

Among the 510 patients included in the analysis, the median age was 51 years (30, 69) and 350 (69%) were male. FLD was present in 80 (16%); 51 had mild FLD and 29 had moderate/severe FLD. Compared to those with no or mild FLD, among those with moderate/severe FLD, a larger proportion were male, with obesity, diabetes, hypertension, or alcohol use disorder (Table 1). The distributions of injury characteristics were similar across the three groups excepting head injuries (all AIS <4 by exclusion criteria) which had a similar, albeit subtle, pattern as the pre-hospital characteristics: 117 (27%) no FLD, 16 (31%) mild FLD, 10 (34%) moderate/severe FLD (Table 1). In-hospital mortality for the cohort was 3% (n = 15). Given the small number of patients with moderate/severe disease, we collapsed the two FLD categories for the main analyses.

Time to recovery from SIRS and organ dysfunction were similar for patients with and without FLD. The median time to recovery from SIRS was 5 days (interquartile range 5, 7) among those with

FLD and 5 days (5, 6) for those without FLD. The adjusted hazard of initial recovery from SIRS was 6% lower among those with FLD compared to those without FLD (HR 0.94, 95% CI 0.72, 1.23), and not statistically significant $P = 0.65$, Figure 2. The median time to recovery from organ dysfunction was 4 days (3, 5) among those with FLD and 4 days (3, 4) among those without FLD. There were no significant differences in the adjusted hazard ratio of a recovery event in those with compared to those without FLD (HR 1.08, 95% CI 0.84, 1.41, $P = 0.54$), Figure 2.

FLD was not associated with adverse clinical outcomes (Table 2). There were no meaningful changes in the adjusted hazard ratios for recovery events, or in the adjusted relative risk for adverse outcomes when diabetes, hypertension, and obesity were included in the multivariable regression models (Table S3 and Table 2).

In the exploratory analyses, in which we examined whether the associations of FLD with recovery from SIRS varied by levels of the comorbidity index, liver injury, injury severity scores, multiple severe injuries, or shock on admission, patients with FLD had consistently lower cumulative hazard curves within each strata, indicating longer recovery times (Figure 3). Among patients with shock on admission, the hazard of recovery was 25% lower for those with FLD compared to those without FLD (HR 0.76 (95% CI 0.55, 1.05)); whereas among those without shock on admission, the hazard of recovery was 80% higher among those with FLD compared to those without FLD (HR 1.81 (95% CI 1.43, 2.28), p-value for interaction = 0.039). The association of FLD with recovery from SIRS did not differ significantly between strata of the comorbidity index, injury severity score, liver injury, or multiple severe injuries. The association of FLD with recovery from organ dysfunction did not vary significantly by these additional exposures (Figure 4).

Discussion

In this retrospective cohort study of over 500 injured adults, we found that FLD ascertained from dual energy CT was prevalent, but was not associated with time to resolution of an inflammatory response, organ dysfunction, or adverse short term clinical outcomes.

The prevalence of FLD observed in this study (16%) is lower than the estimated prevalence of FLD in the US (typically diagnosed using laboratory parameters, ultrasound, and confirmed by MRI or liver biopsy) which is estimated to range from 20% to over 50% in some populations.[12,38] This likely reflects the low sensitivity of CT to identify liver fat less than 30% (FLD is defined by fat infiltration >5%).[39] Our finding that older age, male sex, diabetes, obesity, and hypertension were proportionally higher among patients with lower values of the liver-spleen attenuation index is consistent with findings from prior studies which identified these same risk factors were associated with biopsy-proven NAFLD.[38] In addition to metabolic risk factors for NAFLD, a documented history of alcohol use disorder was also more prevalent among patients with FLD in this study (35%), and was higher than the estimated contribution of alcohol to FLD in the US (~10%). This is likely explained by alcohol being a risk factor for accidental injury. Although we were interested in FLD as a prognostic biomarker regardless of etiology, the distinction between NAFLD and alcohol associated FLD may be important to consider in future studies.

We examined whether FLD was associated with time to recovery from a post-injury systemic inflammatory response and organ dysfunction. Prior studies found that among adults with acute pancreatitis, those with NAFLD were more likely to meet SIRS criteria and subsequently develop multiple organ dysfunction during the course of disease.[40,41] Unlike acute pancreatitis, traumatic injury is not caused by biologic disease and thus is a unique setting to study the relationship of FLD with an acute inflammatory process. Although FLD was not associated with significantly increased recovery times from SIRS or organ dysfunction in the main analyses, the exploratory analyses suggested FLD may contribute to longer recovery times in the context of other conditions. As anticipated, recovery times

were markedly longer among patients with higher indices of injury severity (ISS, multiple injuries, shock) and may be partially explained by danger-associated molecular patterns released from damaged tissue which contribute to SIRS after injury.[42] The mediators of this process may persist in the setting of chronic low grade hepatic and systemic inflammation in patients with FLD,[42–44] which could explain the lower curves (suggesting longer recovery times) among those with FLD within each subgroup. Another mechanism which could explain an additive or synergistic effect of FLD and shock on outward signs of systemic inflammation is intestinal permeability, which has been shown to acutely increase after severe injury and contribute to SIRS.[45] It's possible this process becomes exaggerated for individuals with FLD, who have increased intestinal permeability at baseline related to changes in the intestinal microbiome.[46] To determine whether these findings are merely subclinical or carry importance for long-term recovery outcomes such as chronic critical illness, functional recovery, and 1-year mortality requires further study, ideally in patients who are more critically ill and at higher risk for adverse outcomes.

Although FLD was not associated with adverse short-term outcomes in this study, further work is needed to understand the prognostic implications of FLD after injury. Fatty livers are vulnerable to ischemia-reperfusion injury,[47,48] which may place those with FLD who sustain liver injury at higher risk for liver necrosis and its associated infectious complications. This may be an important consideration when balancing the risks and benefits of angioembolization and post-injury surveillance practices.[49] Another motivation to study long term outcomes among injured patients with FLD comes from prior work on sarcopenia, an indicator of frailty, in which decreased skeletal muscle mass ascertained from abdominal CT scans in older trauma patients was not associated with short-term outcomes (e.g., ICU lengths of stay, disposition), but was strongly associated with 1-year mortality.[50] Although FLD affects patients over a broader age range than sarcopenia, FLD has also been associated with indicators of frailty, food insecurity, and other measures of low socioeconomic status which may also increase the risk for long term mortality after injury.[35,51–53] Finally, there is growing evidence that acute physiologic stress may accelerate the progression of FLD towards the higher risk subtype NASH and irreversible fibrosis.[54,55] Although the development and progression of FLD after burn injury has been reported,[1] it is

unknown whether the inflammatory response to blunt or penetrating trauma is associated with an accelerated progression of pre-existing FLD and whether these patients would benefit from more frequent surveillance and/or intervention.

This study had some limitations. First, we sourced data from a single center and results may not generalize to other care settings. Second, the liver-spleen attenuation index from virtual non-contrast reconstructions was likely insensitive to milder fat infiltration (5%-30%) and these individuals may have been misclassified as not having FLD. However, this is unlikely to change the interpretation of our results because we suspect that lower levels of liver fat are less likely to have clinical manifestations. Third, alcohol consumption sufficient to cause FLD was likely under-ascertained. As such, our results may have been biased by residual confounding from factors associated with alcohol consumption and study outcomes. Fourth, this study was likely underpowered to detect significant associations of FLD with short-term outcomes, as these may be relatively weak compared to those for longer-term outcomes (e.g., 1-year mortality) or compared to those reported for end-stage severe liver disease (e.g., cirrhosis), for example. Finally, patients included in this study were on average less severely injured compared to those excluded due to the presence of streak artifact from external leads, shrapnel, bullets, hemostatic agents (embolic beads), and external fixation devices across the liver or spleen. This finding may be useful for future studies as strategies to reduce artifact during CT image acquisition and during data processing may be underutilized in the trauma setting. As dual energy technology becomes more widely available along with automated methods to measure fat content from solid organs, there may be opportunities to re-assess FLD in larger, more severely injured cohorts.

Conclusion

Fatty liver disease, as detected by dual-energy CT, is common in adult trauma patients. In this study, which was limited by small sample size, FLD was not associated with adverse short-term outcomes. Associations of FLD during recovery from critical illness and long-term outcomes after injury remain unclear and warrant further study.

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Tables and Figures

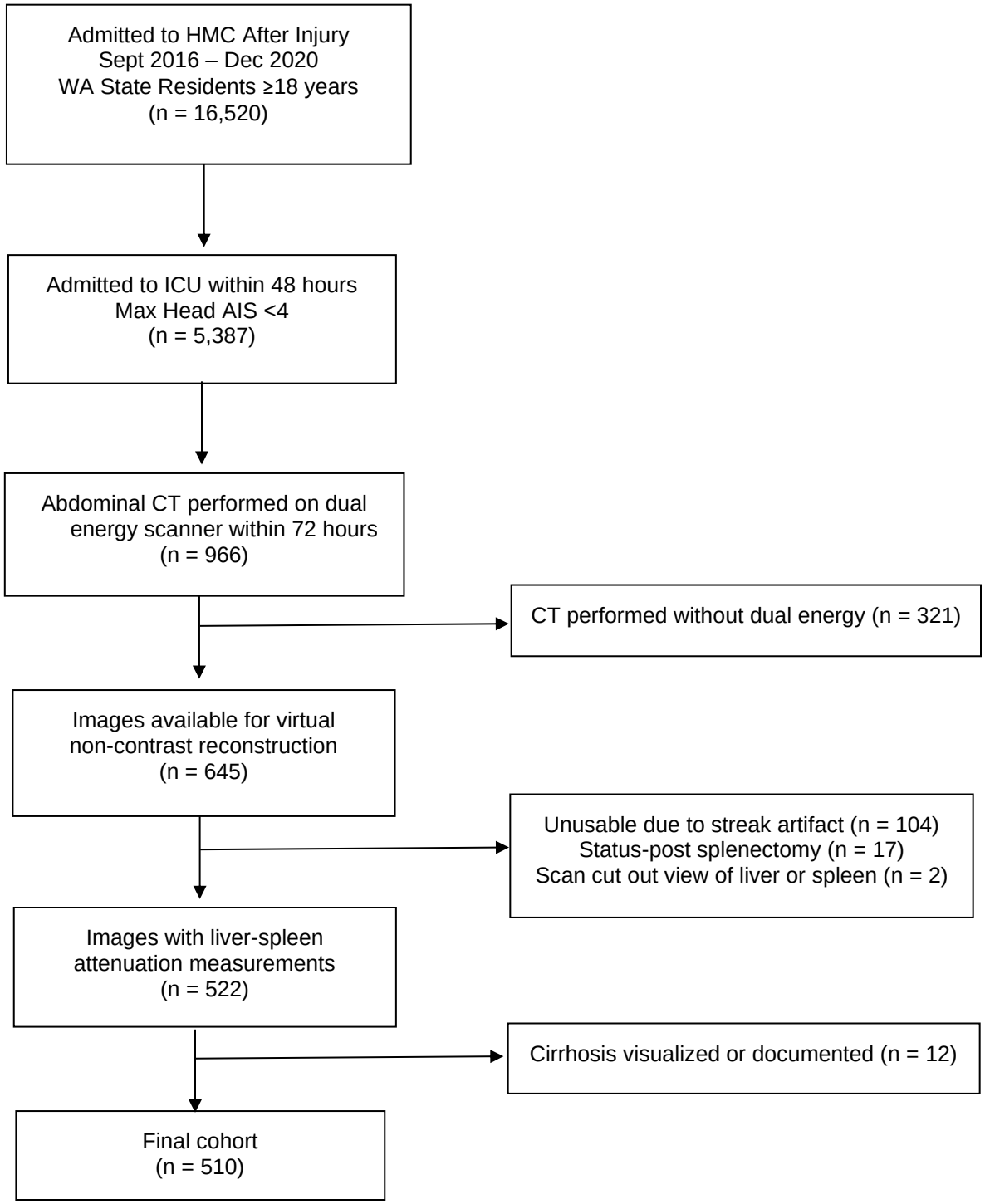

Figure 1. Study Inclusion and Exclusion Criteria Applied to Trauma Admissions to Harborview Medical Center's (HMC) Intensive Care Unit (ICU) from September 2016 through December 2020.
Abbreviations: computerized tomography (CT)

Table 1. Characteristics and Outcomes Among Injured Adults Admitted to the Intensive Care Unit of a Level 1 Trauma Center (September 2016-December 2020) Who Underwent Dual Energy CT-Scan of the Abdomen, Stratified by Estimated Liver Fat Content

	Estimated Liver Fat (Liver-Spleen Attenuation Difference (HU))		
Characteristic	None (≥1 HU), N = 430	Mild (-10 to <1 HU), N = 51	Moderate/Severe (<-10 HU), N = 29
Age	48 (29, 69)	48 (34, 65)	56 (34, 64)
Male	287 (67%)	39 (76%)	24 (83%)
Obesity (BMI ≥30 kg/m^2)	55 (14%)	14 (28%)	9 (33%)
Missing	6%	2%	7%
Diabetes	33 (8%)	6 (12%)	4 (14%)
Hypertension	94 (22%)	13 (25%)	12 (41%)
Charlson Comorbidity Index			
0	213 (50%)	27 (53%)	10 (34%)
1-2	94 (22%)	12 (24%)	14 (48%)
3-4	58 (13%)	4 (8%)	3 (10%)
5+	65 (15%)	8 (16%)	2 (7%)
Alcohol use disorder[a]	71 (17%)	15 (29%)	13 (45%)
Insurance Plan			
Medicaid	190 (44%)	23 (49%)	15 (52%)
Medicare only	37 (9%)	7 (15%)	1 (3%)
Medicare supplemented	73 (17%)	3 (6%)	2 (7%)
Other[b]	130 (30%)	18 (35%)	11 (38%)
Injury & Admission Physiology			
Mechanism			
Blunt	282 (66%)	37 (73%)	19 (66%)
Penetrating	148 (34%)	14 (27%)	10 (34%)
Injury Severity Score	17 (10, 24)	14 (10, 21)	14 (6, 26)
0-16	195 (46%)	27 (55%)	16 (55%)
17-24	126 (30%)	13 (27%)	5 (17%)
25+	105 (25%)	9 (18%)	8 (28%)
Head Injury[c]	117 (27%)	16 (31%)	10 (34%)
Liver Injury	42 (10%)	5 (10%)	2 (7%)
Two or more body regions with AIS≥3	39 (9%)	3 (6%)	2 (7%)
Shock on Admission[d]	139 (32%)	15 (29%)	11 (38%)
Received RBC transfusion first 24 hours	88 (20%)	9 (18%)	7 (24%)
RBC units transfused first 24 hours	2 (1, 4)	2 (1, 3)	2 (2, 3)
Emergency Laparotomy	28 (7%)	3 (6%)	1 (3%)
Outcomes			
Hospital Acquired Infection[e]	56 (13%)	9 (18%)	4 (14%)
Hospital Acquired Sepsis[f]	19 (4%)	2 (4%)	2 (7%)
ICU Days	3 (2, 4)	2 (2, 4)	3 (2, 4)
Invasive Mechanical Ventilation	172 (40%)	29 (57%)	14 (48%)
Ventilator Days ≥3	54 (13%)	5 (10%)	3 (10%)
In-Hospital Mortality	14 (3%)	0	1 (3%)
Discharged to SNF or LTCF	78 (19%)	10 (20%)	8 (29%)
Discharged home without assistance	255 (59%)	28 (55%)	16 (55%)

Characteristic	Estimated Liver Fat (Liver-Spleen Attenuation Difference (HU)) None (≥1 HU), N = 430	Mild (-10 to <1 HU), N = 51	Moderate/Severe (<-10 HU), N = 29

Continuous data are presented as the median (IQR); discrete data are presented as number (%)
Missing values greater than 5% are reported
[a]Explicit or implicit criteria documented in the medical health record consistent with the American Psychiatric Association DSM 5 definition
[b]Includes private insurance, employer-based, or other governmental insurance plan
[c]Includes head injuries with AIS scores <4 (head AIS ≥4 were excluded during patient selection)
[d]Systolic blood pressure <90mmHg or a base deficit ≥6mmol/L within 24 hours of arrival
[e]Culture-proven infection or clinically suspected infection between hospital days 3-14
[f]Culture-proven or clinically suspected infection and an increase in the sequential organ failure assessment score of at least 2 points within +/- 3 days of the culture
Abbreviations: abbreviated injury severity score (AIS), body mass index (BMI), computerized tomography (CT), Hounsfield units (HU), intensive care unit (ICU), long term care facility (LTCF), red blood cell (RBC), skilled nursing facility (SNF)

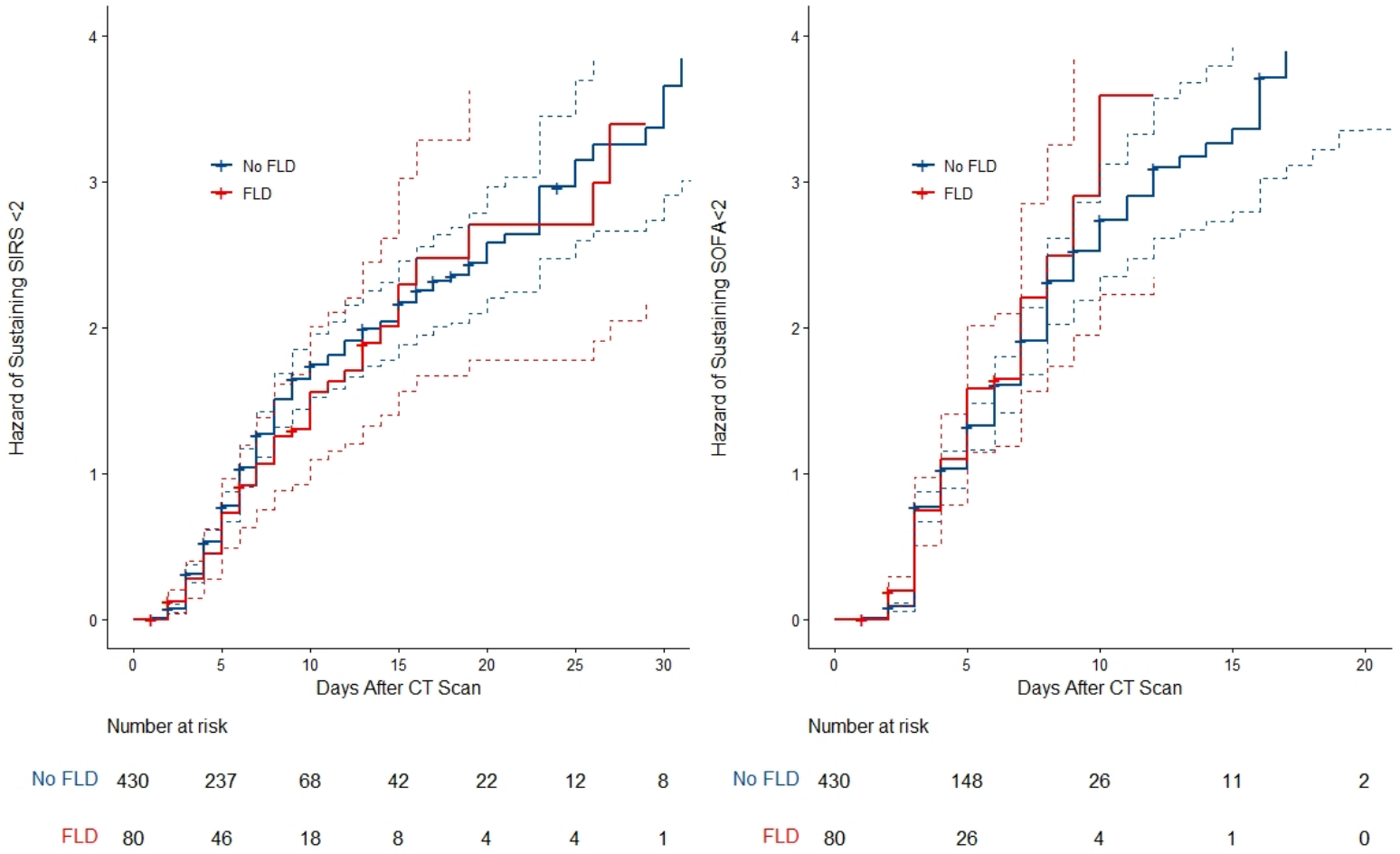

Figure 2. Cumulative Hazard of Initial Recovery from a Systemic Inflammatory Response Syndrome (Left) and Recovery from Organ Dysfunction (Right) Among Hospitalized, Injured Adults (n=510) With and Without Fatty Liver Disease (FLD). Dashed lines represent 95% confidence intervals.

Table 2. Associations of Fatty Liver Disease with Clinical Outcomes Among Injured Adults Admitted to the Intensive Care Unit of a Level-1 Trauma Center and Underwent Dual Energy CT of the Abdomen

			RR (95% CI)	
Outcome	**FLD No. (%)**	**No FLD No. (%)**	**Model 1**	**Model 2**
Hospital Acquired Infection	13 (16%)	56 (13%)	1.35 (0.75, 2.40)	1.37 (0.76, 2.46)
Hospital Acquired Sepsis	4 (5%)	19 (4%)	0.90 (0.30, 2.71)	0.84 (0.29, 2.40)
ICU Days[a]	2 (2, 4)	3 (2, 4)	0.85 (0.65, 1.11)	0.86 (0.60, 1.24)
Discharge to Skilled Nursing or Long-Term Care Facility	18 (22%)	78 (18%)	1.32 (0.84, 2.06)	1.32 (0.84, 2.09)
Discharge to Home Without Assistance	44 (55%)	255 (59%)	0.91 (0.73, 1.13)	0.89 (0.71, 1.12)

All models matched patients according to the day of the CT scan
Model 1 included adjustment for age, sex, history of alcohol use disorder, health insurance plan, and day of CT
Model 2 included covariates from model 1 and history of diabetes, hypertension, and obesity
[a]ICU days are presented as median (interquartile range); estimate is the number of ICU days per person-hospital days comparing those with FLD to no FLD
Abbreviations: computerized tomography (CT), confidence interval (CI), fatty liver disease (FLD), intensive care unit (ICU), relative risk (RR)

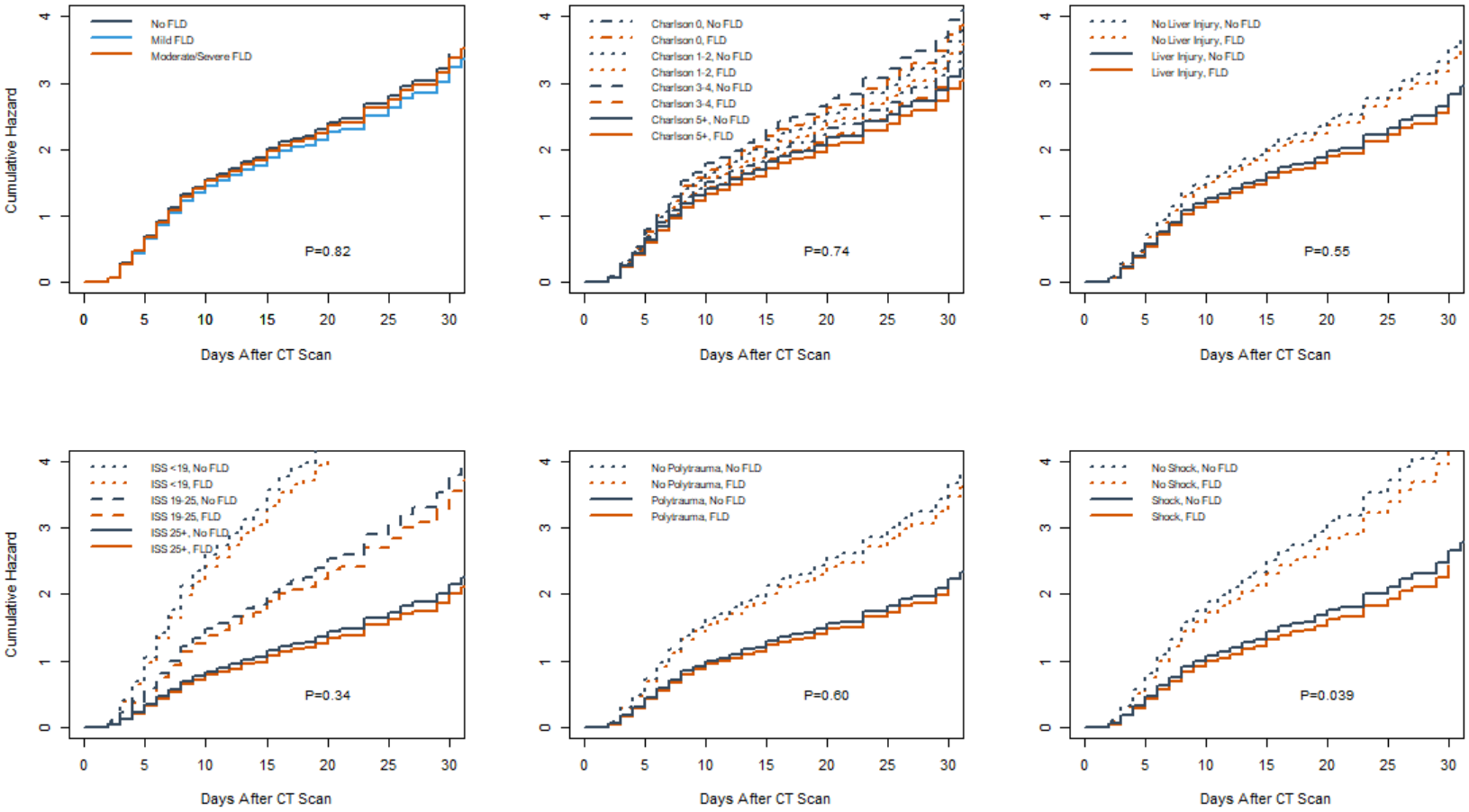

Figure 3. Associations of Fatty Liver Disease (FLD) With Time to Recovery from the Initial Systemic Inflammatory Response (SIRS) After Injury Among Adults Admitted to the Intensive Care Unit of a Level 1 Trauma Center. The recovery event was defined as maximum daily SIRS score <2 sustained for at least 3 days or until discharge alive with a score <2. Plots compare the semiparametric, subgroup-specific hazard curves for groups defined by FLD severity, levels of the Charlson Comorbidity Index, presence of liver injury, injury severity score, multiple serious injuries (polytrauma), shock on admission.

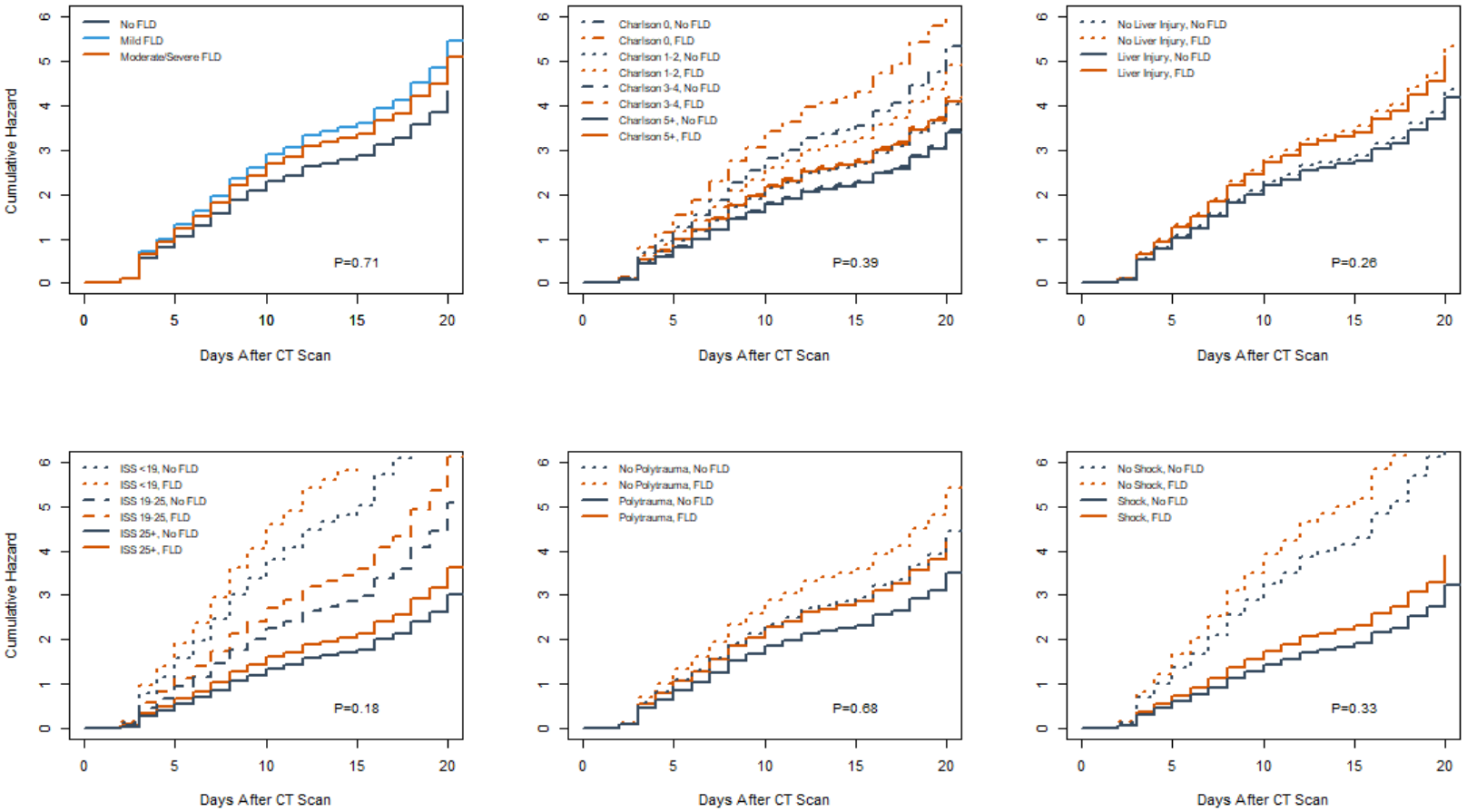

Figure 4. Associations of Fatty Liver Disease (FLD) With Time to Recovery from Organ After Injury Among Adults Admitted to the Intensive Care Unit of a Level 1 Trauma Center. The recovery event was defined as maximum daily SOFA score <2 sustained for at least 3 days or until discharge alive with a score <2. Plots compare the semiparametric, subgroup-specific hazard curves for groups defined by FLD severity, levels of the Charlson Comorbidity Index, presence of liver injury, injury severity score, multiple serious injuries (polytrauma), shock on admission.

Supplemental Content

Table S1. Systemic Inflammatory Response Syndrome (SIRS) Criteria

Component	Heart rate (beats per minute)	Respiratory rate (breaths per minute) or $PaCO_2$	Temperature (degrees Celsius)	White blood cell (count $x10^9$ per L)
Value	>90	>20 or $PaCO_2$>32mmHg	>38 or <36	>12 or <4
Points	1	1	1	1

SIRS criteria met when the sum of points is at least 2
Abbreviations: arterial partial pressure of carbon dioxide (PaCO2)

Table S2. Sequential Organ Failure Assessment (SOFA) Score

Respiratory - PaO2 (mmHg) to FiO2 ratio				
>400	300-399	200-299	≤199* or 100-199	<100 and mechanically ventilated
0	1	2	3	4
Cardiovascular – mean arterial pressure (MAP) in mmHg or vasopressors				
No hypotension	MAP <70mmHg	Dopamine ≤5 or Dobutamine any dose	Dopamine >5, Epinephrine≤0.1, or norepinephrine≤0.1	Dopamine >15, epinephrine >0.1 or norepinephrine >0.1
0	1	2	3	4
Hematologic - Platelet count (x10^3 per uL)				
≥150	100-149	50-99	20-49	<20
0	1	2	3	4
Renal - Serum creatinine (mg/dL)				
<1.2	1.2-1.9	2.0-3.4	3.5-4.9	≥5.0
0	1	2	3	4
Hepatic - Total serum bilirubin (mg/dL)				
<1.2	1.2-1.9	2.0-5.9	6.0-11.9	≥12
0	1	2	3	4

*If not mechanically ventilated
Abbreviations: arterial partial pressure of oxygen (PaO2), fraction of inspired oxygen (FiO2), mean arterial pressure (MAP), millimeters of mercury (mmHg)

Table S3. Associations of Fatty Liver Disease with Time to First Recovery from a Systemic Inflammatory Response and Time to First Recovery from Organ Dysfunction Among Adults Hospitalized After Injury (2016-2020)

	Model 1		**Model 2**	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
Recovery from SIRS (SIRS <2)	0.94 (0.72, 1.23)	0.65	0.94 (0.69, 1.30)	0.72
Recovery from Organ Dysfunction (SOFA <2)	1.08 (0.84, 1.41)	0.54	1.01 (0.75, 1.35)	>0.9

All models matched patients according to the day of their CT scan
Model 1 included age in years, sex, history of alcohol use disorder, health insurance plan, and day of CT
Model 2 included covariates from model 1 and adjusted for history of diabetes, hypertension, and BMI $\geq 30 kg/m^2$
Abbreviations: Hazard ratio (HR), confidence interval (CI), systemic inflammatory response (SIRS), sequential organ failure assessment score (SOFA)

Table S4. Interrater Reliability of Liver and Spleen Attenuation Measurements from Dual Energy CT

	No. Readers	No. Scans	ICC (95% CI) Mean Liver Density (HU)	ICC (95% CI) Mean Spleen Density (HU)
Training 1	4	25	0.91 (0.86, 0.95)	0.80 (0.70, 0.88)
Training 2	4	25	0.91 (0.85, 0.95)	0.83 (0.74, 0.90)
Interim	2	25	0.75 (0.56, 0.87)	0.71 (0.48, 0.84)

Abbreviations: Computerized tomography (CT), Hounsfield Units (HU), intraclass correlation coefficient (ICC)

Table S5. Comparison of Injury Severity Scores Among Patients Excluded Due to Imaging Artifact Compared to Those Without Imaging Artifact

	Useable Scans (n = 510)	Excluded due to artifact (n = 102)	p-value
Injury Severity Score, median (interquartile range)	17 (10, 24)	24 (14, 34)	<0.001
Abdomen AIS ≥3, %	78 (15%)	32 (31%)	<0.001

Results from Wilcoxon rank-sum test and Pearson's Chi-squared test
Abbreviations: Abbreviated injury severity score (AIS)