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Identifying a unique signature of sepsis in patients with pre-existing cirrhosis

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Abstract

Background The pre-existing diagnosis of cirrhosis is a complicating factor in the progression and prognosis of sepsis; however, the unique epidemiology, sepsis characteristics, and underlying mechanisms of immune dysregulation in sepsis among patients with cirrhosis remain incompletely understood. Our primary objective was to identify clinical outcomes and biological characteristics that differ between patients with and without cirrhosis among critically ill patients with sepsis.

Methods We analyzed data from a prospective cohort of critically ill patients presenting to single center with sepsis. Subjects were followed for 6 days for the development of acute respiratory distress syndrome (ARDS) and acute kidney injury (AKI), and 30 days for mortality. Inflammatory, endothelial, and coagulopathic proteins were measured in plasma collected at ICU admission in a subset of patients. We determined associations of cirrhosis with outcomes using multivariable logistic regression adjusting for pre-specified confounders. We tested differences in plasma protein levels by cirrhosis diagnosis using the Wilcoxon Rank-sum test.

Results We enrolled 2962 subjects, 371 (13%) of whom had a pre-existing diagnosis of cirrhosis. Patients with cirrhosis had higher severity of illness scores, were more likely to have an abdominal source of sepsis, and had more significant clinically measured coagulation abnormalities relative to patients without cirrhosis. In multivariate analysis, cirrhosis was associated with higher AKI risk (adjusted OR 1.65; 95% CI 1.21 to 2.26; P = 0.002), and 30-day mortality (adjusted OR 1.38; 95% CI 1.05 to 1.82; P = 0.022). There was no significant difference in risk for ARDS (adjusted OR 1.02; 95% CI 0.69 to 1.50; P = 0.92). Cirrhosis was associated with higher plasma levels of angiopoietin-2 (P < 0.001), von Willebrand factor (P < 0.001), and soluble thrombomodulin (P < 0.001), as well as lower levels of interleukin (IL)-10 (P < 0.001), IL-1β (P = 0.008), and IL-1RA (P = 0.036). There were no significant differences in levels of IL-6 (P = 0.30).

Conclusions We identified associations between pre-existing cirrhosis and endothelial injury, AKI, and mortality in sepsis. Patients with pre-existing cirrhosis who develop sepsis may display a unique phenotype of endothelial dysfunction that requires unique targeted approaches.

Keywords Cirrhosis, Sepsis, Acute kidney injury, Acute respiratory distress syndrome, Endothelial dysfunction

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Introduction

Sepsis, the dysregulated host response to infection that leads to life-threatening organ dysfunction [1], accounts for an estimated 250,000 deaths and $62 billion in economic costs annually in the United States [2–5]. Pre-existing cirrhosis is a common comorbitiy that has long been recognized to be associated with an increased risk of sepsis as well as poorer outcomes among patients who develop sepsis [6–9]. In patients with cirrhosis, certain characteristics including the severity of liver dysfunction based on Child–Pugh and Model for End-Stage Liver Disease (MELD) scores, gastrointestinal bleeding, and low ascites protein concentration are strongly associated with infection risk [10]. Comorbidities like cirrhosis may influence sepsis biology and host response, and thus may identify specific subgroups that benefit from a personalized approach to further improve sepsis outcomes.

Patients with end-stage liver disease exhibit chronic immune alterations that are believed to result in increased infectious risk [11]. These immune alterations, termed cirrhosis-associated immune dysfunction (CAID), are characterized by both systemic inflammation and immune deficiency. Several reasons contribute to greater infection risk in cirrhosis including impaired immune function, greater bacterial translocation due to portal hypertension, and intestinal bacterial overgrowth [12]. Prior studies have demonstrated associations between cirrhosis and higher hospitalizations from sepsis, death from sepsis, and acute respiratory failure [6–9]. However, differences in the risk of sepsis-associated organ dysfunction, particularly acute kidney injury (AKI) and acute respiratory distress syndrome (ARDS), in patients with cirrhosis has not been fully elucidated. The liver plays an especially important role in host response to infection and systemic inflammation and patients with severe liver damage are at high risk for irreversible organ dysfunction [13]. Unfortunately, patients with advanced cirrhosis are often excluded from or underrepresented in randomized controlled trials and therefore represent an understudied population at high risk for sepsis incidence, morbidity, and mortality.

The primary objectives of this study were to first, determine the association of a pre-existing diagnosis of cirrhosis and the development of AKI, ARDS, and mortality among critically ill patients with sepsis, and second, determine the association of a pre-existing diagnosis of cirrhosis with early measures of plasma biomarkers selected to represent inflammation, endothelial dysfunction, and coagulation in sepsis [14–16]. Biomarkers representing these pathogenic pathways were selected as they represent potential future thereaputic targets in sepsis and are different in non-septic cirrhosis patients at baseline [17–20]. We hypothesized that patients with a pre-exiting diagnosis of cirrhosis who develop sepsis will have distinct clinical and biological characteristics characterized by a higher inflammatory, endothelial dysfunction, and coagulation markers, and higher risk for AKI, ARDS, and mortality compared to patients without a pre-existing diagnosis of cirrhosis. Our secondary objectives were to describe distinguishing demographic characteristics, physiologic and laboratory values, and infectious sources of patients with and without cirrhosis who are critically ill with sepsis.

Methods

Study design

We conducted a secondary analysis of a prospective cohort study of critically ill patients with sepsis admitted to the medical intensive care units (ICU) of the Hospital of the University of Pennsylvania, an urban quaternary referral center.

Sepsis population

The study population was comprised of patients enrolled in the Molecular Epidemiology of SepSis in the ICU (MESSI) study between 2008 and 2022 [15, 21, 22]. Patients were screened upon admission to the ICU, whether from the ED, hospital wards, or outside hospitals, and were enrolled if the primary reason for their ICU admission was sepsis with organ dysfunction, as defined by sepsis-3 criteria [1]. All enrolled patients had a confirmed or strongly suspected infection. Patients were enrolled with a waiver of timely informed consent allowing for the prompt collection of biospecimens, as approved by the Institutional Review Board of the University of Pennsylvania (Protocol #808542). Patients or their surrogates were later approached for consent and had the opportunity to withdraw consent at any time. Additional exclusion criteria included patients receiving palliative measures only, patients admitted from a long-term acute care hospital, or patients previously enrolled in the cohort.

Data collection

Research personnel trained by physician investigators in data collection methods, electronic data capture instruments, and a manual of procedures collected clinical data from the medical record, including demographics and chronic health information, and microbial origins of sepsis on standard electronic case report forms. If sepsis source was not certain, physician investigators reviewed the medical record and utilized their best expert judgement to adjudicate source of infection causing sepsis. We applied the United States National Institutes of Health standards for reporting race and ethnicity. Further data, including laboratory values, administered medications,

and ventilator variables were extracted directly from our hospital's electronic medical record data warehouse.

Exposure and outcome definition

Our primary exposure was a pre-existing history of cirrhosis recorded in subjects' medical records and extracted by study coordinators. We required a prior physician diagnosis of cirrhosis for a subject to be categorized as having cirrhosis and therefore, did not rely on suggestive imaging alone. The primary outcomes of interest were the development of ARDS or AKI within 6 days of ICU admission and 30-day mortality. We adjudicated ARDS status by the Berlin Criteria with the additional requirement for invasive mechanical ventilation. To identify ARDS, trained physician investigators reviewed all radiographs performed for clinical purposes and characterized them as consistent with ARDS, inconsistent, or equivocal based on our previous published methods [23, 24]. We than applied the partial pressure of arterial oxygen to fraction of inspired oxygen < 300 based on arterial blood gases drawn for clinical purposes. Subjects who met both the radiographic and hypoxia criteria withint 24 h of each other were classified as having ARDS. AKI was defined and staged by the Kidney Disease Improving Global Outcomes (KDIGO) creatinine and dialysis criteria, excluding those with pre-existing end-stage kidney disease (ESKD) [25]. Baseline creatinine was determined by averaging outpatient or hospital discharge creatinine values from 365 days before to 7 days before hospital admission [26, 27]. If these data were missing, baseline was defined as the lowest value within seven days before ICU admission. Our secondary outcomes included moderate to severe AKI stage and initiation of renal replacement therapy.

Biomarker subset

We collected residual plasma drawn for clinical testing purposes as close to ICU or ED admission as possible. Residual plasma was stored at 4° C in the clinical lab and collected by research personal with 24 h, aliquoted into cryovials, and subsequently frozen to − 80° C. We previously quantified angiopoietin-2 (Ang-2), von Willebrand factor (vWF), soluble thrombomodulin (STM), interleukin (IL)−6, IL-10, IL-1β, and IL-1 receptor antagonist (IL1-Ra) levels with available plasma using the Meso Scale Discovery (MSD) platform (MSD, Rockville, MD), a multiplex electrochemiluminescence immunoassay. These specific biomarkers were selected as they have been previously reported to be highly relevant to sepsis pathogensis and represent potential targets for future therapeutic development [14–20]. The set of inflammatory biomarkers were measured in 859 patients, while endothelial biomarkers were measured in 711 patients. As the protein markers were initially measured for separate projects, only 463 patients had measurements of both inflammatory and vascular proteins.

Statistical analyses

Patient characteristics, physiologic data, and lab values of those with and without cirrhosis were compared using Wilcoxon rank-sum for continuous variables or the Pearson $\chi 2$ test for categorical variables. We then utilized multivariable logistic regression to determine the associations between the previous diagnosis of cirrhosis with ARDS, AKI, and mortality. In secondary analyses, multivariable logistic regression models were used to determine the association of pre-existing cirrhosis with stage 2–3 AKI and initiation of renal replacement therapy. We also conducted secondary analyses of all associations excluding patients with negative cultures as well as the association between cirrhosis and ARDS excluding patients with a diagnosis of heart failure. Confounders were selected based on careful review of the literature and the generation of a directed acyclic graphs (Supplemental Fig. 1) [28]. In all models, we adjusted for the pre-specified confounders of age, sex, history of alcohol use, and severity of illness as measured by the Acute Physiology and Chronic Health Evaluation (APACHE)-III score [29, 30]. In the ARDS model, we additionally adjusted for the pre-specified confounder of pneumonia, as pulmonary sources of infection is a strong risk factor for ARDS [31]. In AKI models, subjects with pre-existing ESKD were excluded. Additionally, we conducted regression models to determine the association of peak lactate with 30-day mortality for cirrhosis patients and non-cirrhosis patients, adjusting for age, sex, and source of sepsis. Plasma biomarker concentrations were log transformed to improve model fit. We compared biomarker concentrations by cirrhosis diagnosis and outcomes using the Wilcoxon rank-sum test. We additionally fit logistic regression models within the biomarker subgroups to determine the impact of adjusting for biomarker concentration on the associations of cirrhosis with outcomes (i.e. ARDS, AKI, and mortality). Statistical analysis was performed with RStudio 4.2.2 using packages dplyr, ggplot2, haven, tidyr, and broom.

Results

We enrolled 2,962 subjects with sepsis between 2008 and 2022, of whom 371 (13%) had a pre-existing diagnosis of cirrhosis (Supplemental Fig. 2). In the overall cohort, 680 (23%) subjects developed ARDS, 1760 (59%) developed AKI, and 1312 (44%) died by 30-days. Confounder variables were missing in < 2% of subjects.

Patient characteristics

Comparisons of patient characteristics by cirrhosis status are provided in Table 1. A higher percentage of patients with cirrhosis were male and were of younger age. The median MELD score among patients with cirrhosis was 24 (interquartile range 18–32), reflecting relatively advanced liver disease. Patients with cirrhosis were less likely to have a history of cancer, ESKD, hypertension, or CHF. They were also about twice as likely to have abdominal/GI sources of sepsis, and were slightly less likely to have a pulmonary source of sepsis. Correspondingly, there was a significantly greater rate of positive respiratory cultures in non-cirrhosis patients (Supplemental Table 1). Patients with cirrhosis were more likely to have a documented history of alcohol use (48%) as compared to those without cirrhosis (9%), and more likely to have a history of smoking. Patients with cirrhosis had higher APACHE-III scores, sequential organ failure assessment (SOFA) scores, and poorer outcomes. Figure 1 represents the distribution of SOFA scores for cirrhosis and non-cirrhosis patients, which is further summarized in Supplemental Table 2. Cirrhosis patients had markedly higher SOFA scores ($P < 0.001$), notably driven by higher scores in coagulation and liver categories, which correspond to lower platelet counts and higher bilirubin levels, respectively.

Cirrhosis is associated with higher risk of AKI and mortality

In multi-variable analysis, cirrhosis was associated with AKI risk during the first 6 days of enrollment (adjusted OR, 1.65; 95% CI, 1.21 to 2.26; $P = 0.002$) and 30-day mortality (adjusted OR, 1.38; 95% CI, 1.05 to 1.82; $P = 0.022$) (Supplemental Table 3). We did not identify significant difference in ARDS risk within the first 6 days between cirrhosis and non-cirrhosis patients in adjusted analyses (adjusted OR, 1.02; 95% CI, 0.69 to 1.50; $P = 0.92$) (Supplemental Table 3), nor did we identify differences in ARDS risk excluding patients with pre-existing heart failure (Supplemental Table 4). Figure 2 shows the standardized risks of AKI, ARDS, and 30-day mortality by cirrhosis diagnosis adjusted for prespecified confounders. Cirrhosis was also associated with Stage 2–3 AKI (adjusted OR 1.60, 95% CI 1.22–2.10; $p < 0.001$) and the receipt of kidney replacement therapy (adjusted OR 1.79, 95% CI 1.34–2.38; $P < 0.001$) (Supplemental Table 5). Excluding patients without a positive culture did not change our results (Supplemental Table 6). Peak lactic acid was similarly associated with 30-day mortality in patients with cirrhosis (OR 1.25; 95% CI 1.15–1.36; $P < 0.001$) and patients without cirrhosis (OR 1.20; 95% CI 1.16–1.24; $P < 0.001$).

Table 1 Patient characteristics by cirrhosis diagnosis

	No cirrhosis (n = 2591)	Cirrhosis (n = 371)	p-value
Demographics			
Male sex	1412 (55%)	240 (65%)	<0.001
Race			<0.001
White	1460 (56%)	245 (66%)	
Black	916 (35%)	94 (25%)	
Asian and Pacific Islander	104 (4%)	15 (4%)	
Native American	6 (< 1%)	0 (0%)	
Other/unknown	105 (4%)	17 (5%)	
Hispanic ethnicity	72 (3%)	21 (6%)	
Age, years	63 (52, 72)	59 (52, 66)	<0.001
Body mass index (kg/m^2)	26 (22, 30)	27 (23, 30)	0.31
Medical history			
Cancer	574 (22%)	371 (12%)	<0.001
Chronic kidney disease	461 (18%)	81 (22%)	0.070
End-stage renal disease	178 (7%)	33 (9%)	0.19
Hypertension	1466 (57%)	182 (49%)	0.02
Diabetes mellitus	797 (31%)	125 (34%)	0.46
HIV	24 (1%)	2 (1%)	0.71
Congestive heart failure	433 (17%)	48 (13%)	0.08
Severity			
APACHE-III	86 (64, 114)	99 (78, 128)	<0.001
SOFA score	8 (4, 12)	12 (8, 15)	<0.001
Admission source			
Source			<0.001
ED	1315 (51%)	130 (35%)	
Other hospital ward	1009 (39%)	184 (50%)	
Outside hospital	267 (10%)	57 (15%)	
Substance use history			
History of alcohol use			<0.001
Never	1557 (61%)	156 (39%)	
Former	668 (26%)	38 (10%)	
Current	233 (9%)	177 (48%)	
Unknown	133 (5%)	10 (3%)	
History of smoking			<0.001
Never	1235 (48%)	139 (38%)	
Former	999 (39%)	158 (43%)	
Current	246 (10%)	59 (16%)	
Unknown	111 (4%)	15 (4%)	
Sepsis source			
Source			<0.001
Genitourinary	237 (9%)	30 (8%)	
Abdominal/GI	373 (14%)	119 (32%)	
Pulmonary	1426 (55%)	145 (39%)	
Head/neck	26 (1%)	1 (< 1%)	
Blood	250 (10%)	31 (8%)	
Skin/soft-tissue/bone	84 (3%)	13 (4%)	
Gynecologic	2 (< 1%)	0 (0%)	
Unknown	193 (7%)	32 (9%)	
Therapeutics day 0			
Systemic steroids	938 (36%)	103 (28%)	0.002
Vasopressors	1271 (49%)	220 (59%)	0.001

Table 1 (continued)

Continuous variables are expressed as median (IQR) and categorical variables are number (%). P values obtained using the Wilcoxon rank-sum or the Pearson χ2 test

Cirrhosis is associated with biomarkers of endothelial activation in sepsis

The subgroup of patients with and without biomarker data were largely similar (Supplemental Table 7). Cirrhosis patients were marked by significantly higher

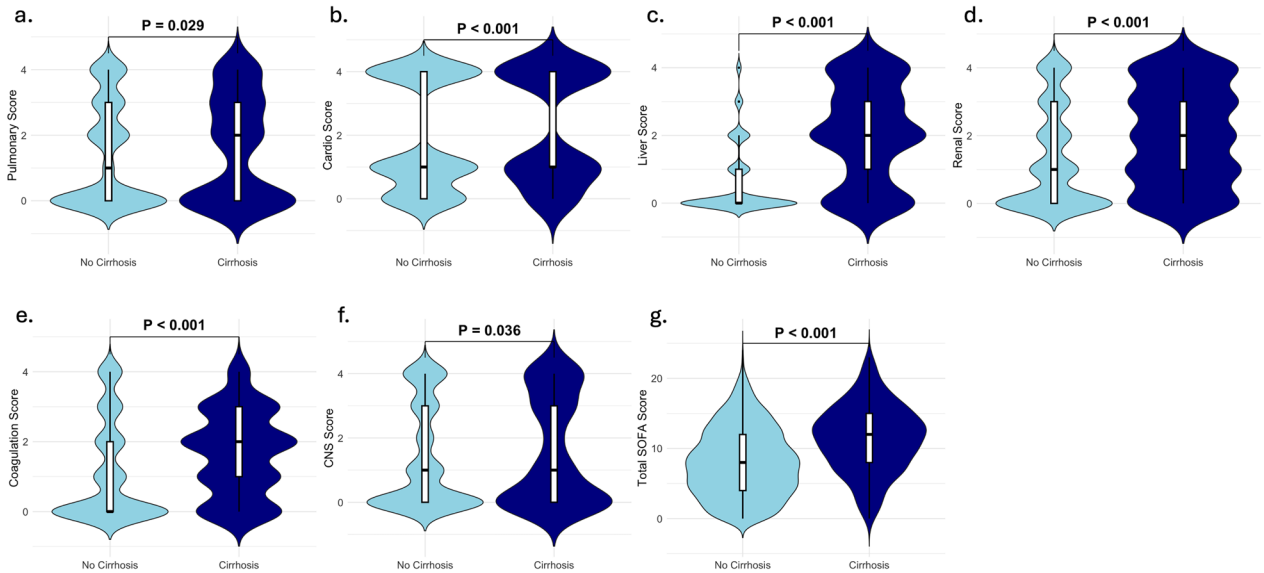

Fig. 1 Sequential organ failure assessment scores by cirrhosis diagnosis. Violin plots displaying the distribution of Sequential Organ Failure Assessment (SOFA) scores across different organ systems, for non-cirrhosis (n = 2591) and cirrhosis (n = 371) patients. The solid lines within the plots represent the median score, while the spread of the plots reflects the overall variability in organ dysfunction among the patient groups. **a** Pulmonary, **b** Cardiac, **c** Liver, **d** Renal, **e** Coagulation, **f** Central nervous system, **g** Total SOFA score

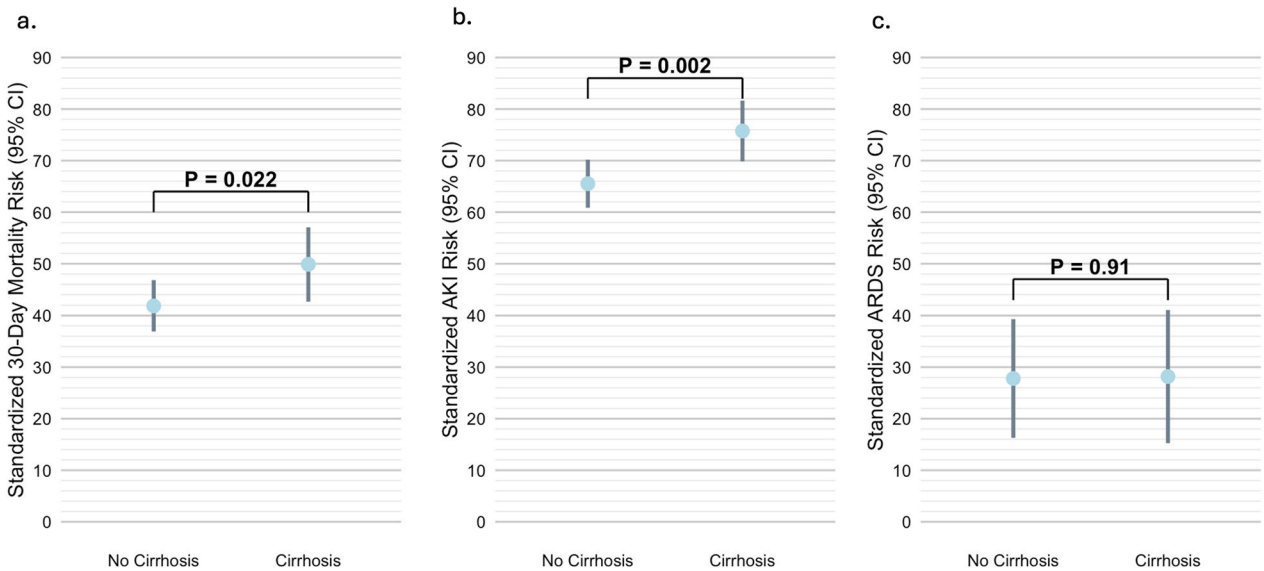

Fig. 2 Standardized risk of mortality, acute kidney injury, and acute respiratory distress syndrome by cirrhosis diagnosis. Standardized risk of 30-day mortality (**a**), 6-day AKI (**b**), and 6-day ARDS (**c**) by cirrhosis. For panels a and b, the dot represents the standardized risk of AKI and 30-day mortality, respectively, when adjusted for age, sex, APACHE-III score, and history of alcohol use. For panel c, the dot represents the standardized risk of ARDS when adjusted for age, sex, source of sepsis, APACHE-III score, and history of alcohol use. The bars represent the 95% CI around the standardized risk

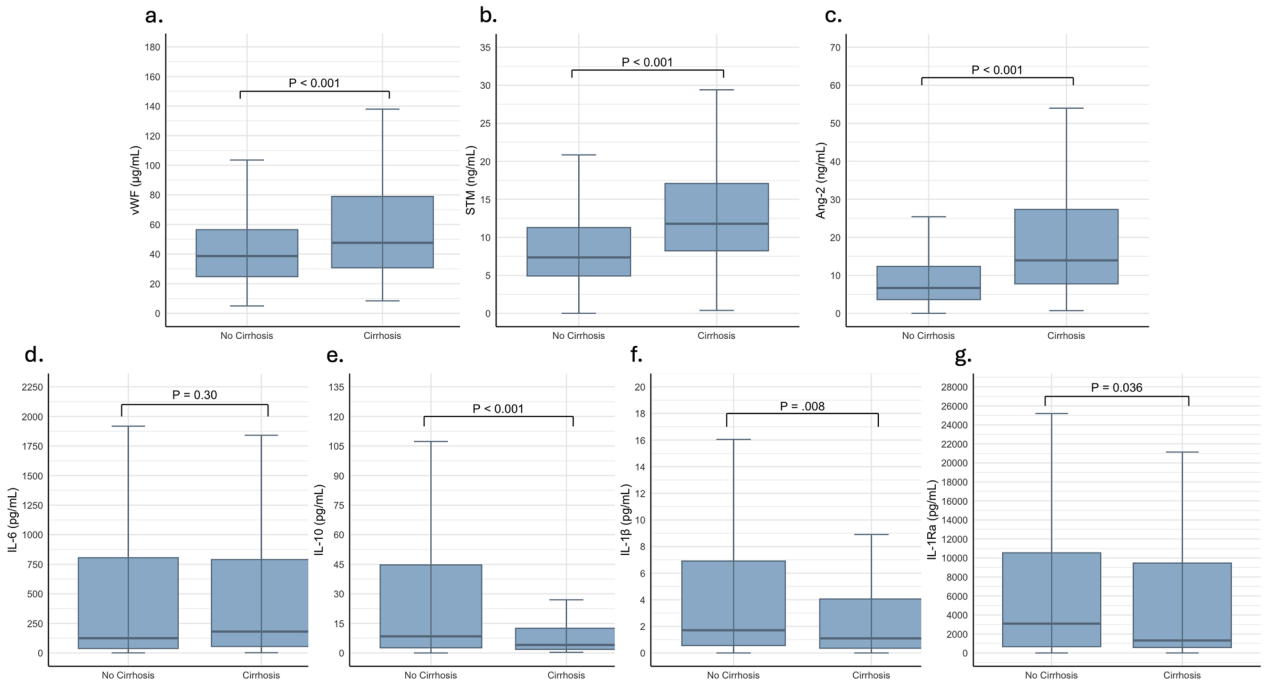

Fig. 3 Plasma protein concentrations by cirrhosis diagnosis. Panels demonstrate plasma concentrations of **a** von Willebrand factor (vWF), **b** soluble thrombomodulin (STM), **c** angiopoietin-2 (Ang-2), **d** interleukin-6 (IL-6), **e** interleukin-10 (IL-10), **f** interleukin-1β (IL-1β), and **g** interleukin-1 receptor antiagonist (IL-1RA) by cirrhosis diagnosis. The box-and-whisker plots display the median value as a line within the boxes, the bounds of the box representing the IQR, and the whiskers representing the range of the data. P values are for the unadjusted comparison of cirrhosis and non-cirrhosis patients using the Wilcoxon rank-sum test. Sample sizes for endothelial biomarkers (**a, b**, **c**) are 105 cirrhosis and 606 non-cirrhosis patients. Sample sizes for inflammatory biomarkers (**d**, **e**, **f**, **g**) are 124 cirrhosis and 735 non-cirrhosis patients

admission plasma concentrations of endothelial dysfunction biomarkers Ang-2 (P < 0.001), vWF (P < 0.001), and STM (P < 0.001) (Supplemental Table 8, Fig. 3). Cirrhosis patients had significantly lower levels of anti-inflammatory IL-10 (P < 0.001) and IL-1Ra (P = 0.004), (Supplemental Table 8, Fig. 3). Cirrhosis patients also had significantly lower IL-1β (P = 0.008) levels compared to patients without cirrhosis. When we repeated these analyses in the subset of patients with all markers measured (n = 463), as detailed in Supplemental Table 9, significance was reduced but findings were consistent. In our cohort, Ang-2, vWF, STM, and IL-6 were associated with AKI; Ang-2, sTM, and IL-10 were associated with ARDS, and Ang-2, vWF, and STM were associated with mortality (Supplemental Table 10). These associations were largely consistant in the subgroup of patients with and without pre-existing cirrhosis; however, sample size in these subgroups was more limited (Supplemental Table 10). In the endothelial biomarker subset, the association between cirrhosis with AKI and 30-day mortality was attenuated by adjusted for Ang-2 and STM (Supplemental Table 11). In the inflammatory biomarker subset, the association between cirrhosis with AKI and 30-day mortality was not attenuated by adjusting for any of the inflammatory biomarkers (Supplemental Table 11).

Secondary outcomes

Table 2 details physiologic and lab values by cirrhosis diagnosis during the subjects' ICU courses. Cirrhosis patients had significantly higher peak bilirubin, and creatinine levels, although there were no differences in albumin levels between the two populations. Supplemental Table 12 details components of the MELD score for both cirrhosis and non-cirrhosis patients. Supplemental Table 13 details differences in coagulation profiles. Cirrhosis patients manifested a higher degree coagulopathy as expected, including more severe thrombocytopenia (P < 0.001), prolonged INR (P < 0.001), prolonged PTT (P < 0.001), and more severe hypofibrinogenemia (P < 0.001), though INR and fibrinogen were often missing based on clinical testing patterns.

Discussion

Our study identified unique characteristics, outcomes, and biomarker profiles in sepsis patients with a diagnosis of cirrhosis compared to those without cirrhosis. Patients with pre-existing cirrhosis had more severe

Table 2 Physiologic data and lab values from day of ICU admission

	No cirrhosis (n = 2591)	Cirrhosis (n = 371)	p-value
Peak HR (bpm)	116 (100, 133)	109 (95, 124)	<0.001
Lowest MAP (mmHg)	64 (56, 73)	60 (54, 68)	<0.0001
Peak respiratory rate (breaths/min)	33 (27, 40)	31 (25, 38)	<0.001
Highest white blood cell count (THO/μL)	11 (5.4, 18)	12.6 (7.3, 19)	0.001
Lowest albumin (g/dL)	2.5 (2.1, 3.1)	2.6 (2.1, 3.1)	0.61
Peak bilirubin (mg/dL)	0.9 (0.5, 1.7)	4.5 (1.7, 10.1)	<0.001
Peak sodium (mmol/L)	139 (136, 143)	138 (134, 143)	<0.001
Hyponatremia (Na < 135 mmol/L)	907 (35%)	180 (49%)	<0.001
Peak creatinine (mg/dL)	1.3 (0.82, 2.4)	2.1 (1.3, 3.5)	<0.001
Peak lactic acid (mmol/L)	1.9 (1.2, 3.5)	2.8 (1.6, 5.4)	<0.001

Continuous variables are expressed as median (IQR) and categorical variables are number (%). P values obtained using the Wilcoxon rank-sum or the Pearson $\chi 2$ test

illness (as determined by APACHE-III score) and were more likely to have an abdominal source of sepsis. Cirrhosis was also associated with a higher risk of AKI and mortality relative to patients without the diagnosis of cirrhosis. We did not identify a relationship between cirrhosis and increased risk of ARDS in sepsis; however, our study may have been underpowered for small differences in this outcome. Additionally, patients with cirrhosis had a peripheral plasma profile characterized by higher markers of endothelial dysfunction and coagulopathy, lower levels of pro-inflammatory IL-1β and anti-inflammatory IL-10 and IL- 1Ra, and no detected difference between IL-6 levels.

It may be unsurprising that severity of illness scoring was higher in critically ill patients with cirrhosis as the APACHE-III score awards 4 points to cirrhosis as a chronic health condition. Despite this however, we observed that our sepsis participants with cirrhosis had a median APACHE-III score that was 13 points higher than participants without cirrhosis. Notably, cirrhosis patients enrolled in our cohort mounted a higher neutrophil response to sepsis and exhibited more abnormal vital signs. Prior studies have established that patients with cirrhosis experience increased pro-inflammatory cytokine production and systemic inflammation, resulting in an increased neutrophil level and lower lymphocyte level [32]. There is also evidence of impaired function of neutrophil phagocytic ability and neutrophil delivery in cirrhosis, possibly resulting in exaggerated physiologic abnormalities [33]. There were no significant differences in albumin levels between groups, which was surprising given the prevalence of hypoalbuminemia in patients with advanced cirrhosis [34]. This may be explained by generally high incidence (~ 70–80%) of hypoalbuminemia in a general population of critically ill sepsis patients [35]. As expected, cirrhosis patients exhibited worse coagulation abnormalities, which aligns with prior findings that cirrhosis patients in sepsis have decreased synthesis of coagulation factors [36].

While it is well known that inflammatory and endothelial biomarkers are higher in patients with cirrhosis compared to those without at baseline [37–39], the evoked state of early sepsis is characterized by large increases in these biomarkers from their baseline. We observed differences in biomarker profiles between cirrhosis and non-cirrhosis patients in the setting of the evoked state of sepsis, differences that are generally larger than seen at baseline [40]. Specifically, Ang-2, vWF, and STM levels, plasma biomarkers that are also significantly associated with ARDS and AKI risk [15, 16, 18, 21, 42], were all significantly higher amongst patients with cirrhosis compared to those without. Given that we did not identify an association between cirrhosis and ARDS, the impact of endothelial dysfunction on ARDS appears independent of cirrhosis. Additionally, adjusting for the endothelial biomarkers Ang-2 and STM attenuated the association of cirrhosis with AKI and mortality, supporting the conclusion that the impact of cirrhosis on AKI risk is partially explained by endothelial dysfunction. Ang-2 and vWF are stored in Weibel-Palade bodies of endothelial cells and are implicated in exacerbated vascular instability and permeability during sepsis. VWF is known to be higher in patients with cirrhosis at baseline and may predict clinical deterioration suggesting the baseline endothelial and platelet activation in cirrhosis may impact sepsis physiology and outcomes [41]. Ang-2 is an established biomarker of endothelial permeability and has previously been demonstrated to predict mortality and AKI in decompensated cirrhosis [42]. Similarly, high levels of STM are a marker of endothelial damage and dysfunction. Increased STM levels in patients with cirrhosis may result from impaired clearance, underlying hepatic

endothelial dysfunction, or baseline endothelial injury due to cirrhosis [43]. Portal hypertension also leads to additional stress of the vascular endothelium, promoting release of vWF and potentially STM, further explaining higher levels of vWF and STM in cirrhosis patients [44]. Thus, cirrhosis patients may benefit from therapeutics specifically targeting endothelial dysfunction that may be uniquely effective in this population, such as recombinant thrombomodulin and angiopoietin-1 [17, 18].

Our findings regarding cytokine biomarkers are intriguing and are contrary to our initial hypothesis: cirrhosis patients exhibited significantly lower plasma concentrations of IL-10, IL-1β, and IL-1Ra compared to septic patients without cirrhosis. This is opposite of the relation seen in non-septic patients whereby patients with cirrhosis have higher levels of inflammatory cytokines. While cirrhosis is categorized by systemic inflammation, it is now thought that over time this prolonged inflammatory response may suppress the immune system, resulting in cirrhosis-associated immune dysfunction (CAID) [11, 45]. Our findings might suggest that cirrhosis patients in sepsis exhibit an exhaustion of immune cell activation and recruitment, resulting in a dampened evoked inflammatory response. While both patient groups exhibited highly elevated IL-1Ra levels, cirrhosis patients had lower levels of IL-1Ra compared to their non-cirrhosis counterparts. This could similarly reflect immune exhaustion and dysfunction of inflammatory pathways. Prior studies have found that IL-6 levels are higher in cirrhosis patients during early stages of bacterial infection compared to non-cirrhosis patients, and while we found that cirrhosis patients tended to have more elevated levels, the difference was not significant [46]. Notably, IL-6 levels are elevated in both groups, suggesting that while pro-inflammatory cytokine production remains high, cirrhosis patients struggle to mount an adequate anti-inflammatory response, exacerbating immune dysregulation and contributing to worse outcomes.

Our study builds and expands on existing literature regarding diagnosis and management of cirrhosis patients with sepsis. AKI is common in patients with cirrhosis but the specific risk of AKI in patients with cirrhosis who develop sepsis is incompletely understood [47]. Our findings support a significantly higher AKI risk in patients with cirrhosis and corroborate a similar study by Chebl et al., which identified an increased risk of AKI, greater sepsis severity, and higher mortality rates in patients with cirrhosis who develop sepsis [48]. Notably, etiology of cirrhosis in this patient population in Saudi Arabia was driven by viral hepatitis or cryptogenic sources, whereas etiology of cirrhosis in the United States is driven to a higher degree by alcohol use, resulting in different demographic characteristics of cirrhosis patients. Prior studies have also highlighted challenges in managing fluid resuscitation and vasopressor use in cirrhosis patients due to their hemodynamic instability and cardiac dysfunction associated with cirrhosis, possibly explaining the altered hemodynamic responses and increased risk of AKI and mortality [49, 50]. However, unlike previous studies which focus primarily on systemic inflammation, our data suggest endothelial injury also plays a critical role, highlighting the clinical need for biomarkers that track endothelial health in sepsis [51]. This unique biomarker profile of cirrhosis patients identified in our study suggests potential benefits from therapies directly targeting endothelial injury. Regarding ARDS, prior studies have reported an association between pre-existing cirrhosis and mortality among patients with ARDS [52, 53]. However, our study suggests that cirrhosis is not a risk factor for ARDS, in sepsis compared to septic patients without cirrhosis, despite the association of pre-existing cirrhosis and endothelial dysfunction and endothelial dysfunction and ARDS.

Given that sepsis is a heterogeneous syndrome, a rapidly emerging area of sepsis research is the identification of subclasses, which enables precision treatment [54–56]. One approach includes stratifying patients based on existing comorbidities to identify distinct pathobiologies, while other approaches include the integration of molecular and -omic data, or prognosis-based approaches. Our findings suggest a unique pathobiology of sepsis experienced by cirrhosis, categorized by excessive endothelial activation and injury and worse outcomes in AKI and mortality. Cirrhosis is thus a relevant, significant comorbidity that should be considered in the creation of standardized subclasses.

Our study has several strengths. To the best of our knowledge, this is among the largest American studies on the epidemiology of cirrhosis in sepsis. This study includes novel plasma biomarker analysis of cirrhosis patients in sepsis measured early in the "golden hours" of sepsis resusitation. We have also included organ dysfunction outcomes for both ARDS and AKI. Our study also has important limitations. First, our analysis was a retrospective analysis of a prospectively enrolled cohort recruited from a single quaternary referral center and may not be generalizable to the entire population. However, our center is a large quaternary referral center with an active liver transplant and cirrhosis program. Second, due to limitations in data, we could not identify the underlying cause of cirrhosis for each patient (for example, related to alcohol use, viral hepatitis, autoimmune disorder, or cryptogenic sources). Third, our biomarker subset included a small panel of pre-specified plasma proteins, measured at a single time-point, and may be

underpowered to identify smaller differences in inflammatory markers. Fourth, limiting our cohort to patients admitted to the ICU has the potential to introduce selection bias if the likelihood of ICU admission is influenced by the diagnosis of cirrhosis. Additionally, our study was not designed to determine if cirrhosis is a risk factor for particular infections, but rather to describe the characteristics of septic patients with pre-existing cirrhosis relative to septic patients without cirrhosis.

Conclusions

In conclusion, these findings highlight the importance of consideration for unique clinical characteristics and biology for patients with cirrhosis when diagnosing and treating sepsis. Patients with cirrhosis are at high risk for poor sepsis outcomes and may benefit from targeted therapies to prevent or treat organ failure. Further research is needed to understand the molecular mechanisms of immune response in cirrhosis patients during sepsis. Particularly, this study highlights the need to better understand the impact of cirrhosis-associated immune dysfunction on the molecular mechanisms of endothelial dysfunction in critical illness.

Abbreviations

APACHE-III	Acute Physiology and Chronic Health Evaluation III
AKI	Acute kidney injury
Ang-2	Angiopoietin-2
ARDS	Acute Respiratory Distress Syndrome
CAID	Cirrhosis Associated Immune Dysfunction
ESKD	End stage kidney disease
ICU	Intensive Care Unit
IL	Interleukin
IL-1RA	Interleukin-1 receptor antagonist
KDIGO	Kidney Disease Improving Global Outcomes
MELD	Model for end stage liver disease
MESSI	Molecular Epidemiology of Sepsis in the Intesive Care Unit
MSD	MesoScale Descovery
SOFA	Sequential Organ Failure Assessment
STM	Soluble thrombomodulin
vWF	Von Willebrand Factor

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13054-025-05423-6.

Supplementary Material 1.

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Author contributions

AD, NJM, and JPR conceptualized and designed the current study. TKJ, HG, RB, GE, TM, BJA, MGSS, NJM, and JPR designed and conducted the parent cohort study. KH, CAGI, AT, and ME performed data collection and data management. AG, KH, and JPR performed data analyses. AD and JPR wrote the first draft of the manuscript, and all authors contributed to the critical revision of the manuscript. All authors have read and approved the final version of the manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Patients were initially enrolled with a waiver of timely informed consent allowing for the prompt collection of biospecimens, as approved by the Institutional Review Board of the University of Pennsylvania (Protocol #808542). Patients or their surrogates were later approached for consent and had the opportunity to withdraw consent at any time.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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