

Article

Trends and Outcomes of Acute Liver Failure in Patients with COVID-19 Infection: Insights from United States National Inpatient Sample Analysis 2020–2022

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Abstract

Introduction: COVID-19, in addition to its direct detrimental respiratory infection, is associated with multiple systemic complications involving different organs, including the liver. COVID-19 has been associated with liver injury through multiple mechanisms, including direct viral effects on liver cells, immune-mediated injury, cytokine-driven inflammation, ischemic hepatitis, microvascular thrombosis, and sepsis-related multiorgan dysfunction. Acute liver failure (ALF) is the acute form of liver damage, which has a high mortality, and recovery is dependent on various factors. We studied the effect of COVID-19 on clinical outcomes such as mortality, length of stay, and need for non-invasive and invasive ventilation in patients with acute liver failure. **Methods:** We performed a retrospective cohort analysis using the Nationwide Inpatient Sample (NIS) database from 2020 to 2022. Adult patients admitted to the hospital with acute liver failure were divided into 2 groups based on their COVID-19 infection status. We analyzed differences in mortality, length of stay, need for non-invasive and invasive ventilation, acute kidney injury, need for renal replacement therapy, and total charges to evaluate the effects on outcomes, and the results were then adjusted for demographic and hospital factors. **Results:** Of 633,155 patients with acute liver failure, 66,785 had concurrent COVID-19 infection, while 566,370 did not. Patients with concurrent COVID-19 infection had significantly higher in-hospital mortality (63.9% vs. 36.0%) and greater utilization of noninvasive ventilation (14.9% vs. 6.4%), invasive mechanical ventilation (68.9% vs. 41.7%), higher incidence of acute kidney injury (81.4% vs. 70.3%) and higher need for renal replacement therapy (26.8% vs. 16.9%). They also experienced longer hospital stays (17.1 vs. 10.7 days) and higher total charges (\$345,072 vs. \$221,268). The findings were statistically significant after adjusting for demographics and clinical factors. **Conclusions:** Patients hospitalized with acute liver failure and concurrent COVID-19 infection experienced worse clinical outcomes, including higher in-hospital mortality, greater need for ventilatory support and renal replacement therapy, and higher hospital resource utilization. Notably, COVID-19 was independently



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associated with worse outcomes even among patients with fewer baseline comorbidities. These findings underscore the importance of early recognition of COVID-19 in patients presenting with acute liver failure, as well as prompt, multidisciplinary management to optimize clinical outcomes.

Keywords: acute liver failure; COVID-19 infection; coagulopathy; mortality; ventilatory support; length of stay

1. Introduction

Since its emergence in late 2019, COVID-19 infection, caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), has become a major global health concern, with significant morbidity and mortality affecting 770 million people and resulting in 6.9 million deaths [1]. Although COVID-19 primarily affects the respiratory system, increasing evidence indicates multisystem involvement, including cardiovascular, renal, neurological, hematological, and gastrointestinal complications. Existing studies have largely focused on abnormal liver function tests which have been reported in 10.5–69.2% of hospitalized patients with COVID-19 [2]. However, whether concurrent SARS-CoV-2 infection independently influences mortality, renal complications, and healthcare resource utilization in this high-risk population remains unknown.

Acute liver failure (ALF) is defined as a rapid onset of hepatocellular damage resulting in abnormal liver biochemical tests, particularly Aspartate Aminotransferase and Alanine Aminotransferase (AST and ALT), occurring over days to weeks in patients with or without previously known liver disease. ALF may occur secondary to viral infections, drug-induced hepatotoxicity, ischemia, autoimmune disease, toxins, or systemic inflammatory conditions such as COVID-19 [3,4].

ALI (Acute Liver Injury) is generally distinguished from acute liver failure (ALF) by the absence of hepatic encephalopathy and severe synthetic dysfunction. Progression to ALF occurs when acute liver injury is accompanied by coagulopathy ($\text{INR} \geq 1.5$) and hepatic encephalopathy in a patient without preexisting cirrhosis [5].

The pathogenesis of hepatic injury in COVID-19 is multifactorial. Proposed mechanisms include direct viral cytopathic effects via angiotensin-converting enzyme 2 (ACE-2) receptor expression in cholangiocytes and hepatocytes, immune-mediated inflammation, cytokine storm, ischemic hepatitis due to hypoxia and shock, microvascular thrombosis, drug-induced liver injury, and sepsis-associated multiorgan dysfunction [6,7].

Acute liver failure (ALF) is a life-threatening syndrome characterized by rapid hepatic dysfunction, coagulopathy, and encephalopathy in patients without preexisting cirrhosis [8]. Viral infections are recognized causes of acute liver failure, and emerging reports have described SARS-CoV-2 infection precipitating severe acute hepatitis and acute liver failure, even in patients without significant respiratory symptoms [2,9].

Although several studies have evaluated liver enzyme abnormalities in COVID-19, there is limited large-scale national data examining the impact of concurrent COVID-19 infection on clinical outcomes in patients hospitalized with acute liver failure from the initial pandemic phase to 2022. Understanding this association is important for early recognition, risk stratification, and management of this high-risk population. Therefore, we conducted a retrospective cohort study using the National Inpatient Sample (NIS) database from 2020 to 2022 to evaluate the effect of COVID-19 infection on clinical outcomes, including in-hospital mortality, need for invasive and noninvasive ventilatory support, complication of acute kidney injury (AKI), need for renal replacement therapy (RRT), length of hospital stay and

total charges among patients admitted with acute liver failure and to determine the impact on hospital resource utilization.

2. Methods

We conducted a retrospective cohort study using the Healthcare Cost and Utilization Project (HCUP) National Inpatient Sample Database (NIS) from January 2020 to December 2022. The NIS is the largest inpatient database, with a survey design that collects discharge information from non-federal, non-rehabilitation, acute care, and short-term hospitals. Its database is derived from billing data submitted by hospitals to statewide data organizations across the USA, covering more than 97% of the US population. Institutional Review Board (IRB) approval was not required because the HCUP NIS is a publicly available deidentified database and the analysis complied with the HCUP data use agreement, which contains no identifiable patient information.

We included all patients admitted from January 2020 to December 2022 with a diagnosis of acute liver failure and COVID-19 infection, as defined by International Classification of Diseases, 10th revision (ICD-10) codes. Acute liver failure was identified using ICD-10 codes K72.00 and K72.01, and COVID-19 infection was identified using the ICD-10 code U07.1. Stratification of patients with acute liver failure was based on the presence or absence of concurrent COVID-19 infection.

The primary outcome of interest in this study was to investigate the impact of COVID-19 infection on in-hospital mortality among hospitalized patients with acute liver failure. Secondary outcomes included the need for Invasive Mechanical Ventilation, Non-invasive Ventilation (NIV), the complication of acute kidney injury, the need for renal replacement therapy, Length of Stay (LOS) in days, and total charges in United States Dollars (USD). Covariates used in this study included age, sex, race, median household income quartile, insurance, Charlson Comorbidity Index (derived from diagnosis fields and categorized as 0, 1, 2, ≥ 3), hospital region, hospital location/teaching status, and hospital bed size.

The patient information and data were analyzed using Stata/BE version 17.0 (StataCorp LLC, College Station, TX, USA). The NIS uses a complex sampling design that includes stratification, clustering, and weighting of patient- and hospital-level data to facilitate analyses and produce nationally representative results, variance estimates, and *p*-values. Continuous variables were reported as weighted means and compared using survey-weighted linear regression with adjusted Wald tests. Categorical/Dichotomous variables were presented as weighted percentages and compared using the Rao–Scott corrected chi-square test. The *p*-values reported in Table 1 represent overall comparisons of each variable between study groups rather than comparisons of individual category levels. Survey-weighted univariable regression analyses were initially performed to estimate crude associations between concurrent COVID-19 infection and each study outcome. Survey-weighted multivariable logistic regression analyses estimated adjusted odds ratios for outcomes of mortality, invasive ventilation, NIV, AKI, and RRT. Survey-weighted multivariable linear regression analysis assessed associations with LOS and total charges. Variables included in all multivariable models were prespecified based on established clinical relevance and evidence from previous literature and comprised age, sex, race, median household income quartile, insurance status, Charlson Comorbidity Index, hospital region, hospital location/teaching status, and hospital bed size. These variables were included irrespective of their univariable statistical significance, and automated forward or backward stepwise variable selection procedures were not used. The primary objective of the multivariable models was to estimate adjusted associations while controlling for potential confounding rather than to develop predictive models; therefore, formal measures of model

discrimination or calibration were not assessed. Statistical significance was defined as a p -value < 0.05 .

Table 1. Demographic and clinical characteristics of hospitalized patients with acute liver failure, stratified by COVID-19 infection status.

Variable	Without COVID-19 (N = 566,370)	With COVID-19 (N = 66,785)	p -Value
Age, mean (years)	61.6	62.3	<0.001
Sex			<0.001
Male	55.7%	58.8%	
Female	44.3%	41.2%	
Race			<0.001
Caucasian	66.4%	52.8%	
African American	14.7%	18.3%	
Hispanic	12.3%	19.5%	
Asian/Pacific Islander	3.1%	3.7%	
Native American	1.1%	1.2%	
Other	3.3%	4.4%	
National Income Quartile			<0.001
1–\$38,999	32.0%	33.6%	
39,000–47,999	26.5%	26.5%	
48,000–62,999	23.1%	23.2%	
$> \$63,000$	18.4%	16.6%	
Insurance			<0.001
Medicare	52.3%	50.9%	
Medicaid	20.2%	18.7%	
Private	22.3%	26.1%	
Uninsured	5.2%	4.4%	
Charlson Comorbidity Index			<0.001
0	7.7%	13.2%	
1	14.7%	20.6%	
2	14.9%	18.7%	
≥ 3	62.6%	47.5%	
Hospital Region			<0.001
Northeast	16.3%	17.6%	
Mid-West	20.0%	18.6%	
South	42.1%	42.5%	
West	21.6%	21.2%	
Hospital Location & Teaching Status			0.26
Rural	5.8%	5.5%	
Urban, Non-Teaching	15.4%	15.9%	
Urban, Teaching	78.8%	78.6%	
Hospital Bed Size			<0.001
Small	18.3%	19.5%	
Medium	27.3%	28.4%	
Large	54.4%	52.1%	

COVID-19 = Coronavirus Disease 2019.

3. Results

A total of 5,934,565 weighted adult COVID-19 hospitalizations and a total of 633,155 weighted adult hospitalizations with acute liver failure were identified from the 2020–2022

National Inpatient Sample database. The patients with diagnoses of acute liver failure were stratified based on the presence of COVID-19 infection. 66,785 had concomitant COVID-19 infection, whereas 566,370 did not have concomitant COVID-19 infection (Figure 1).

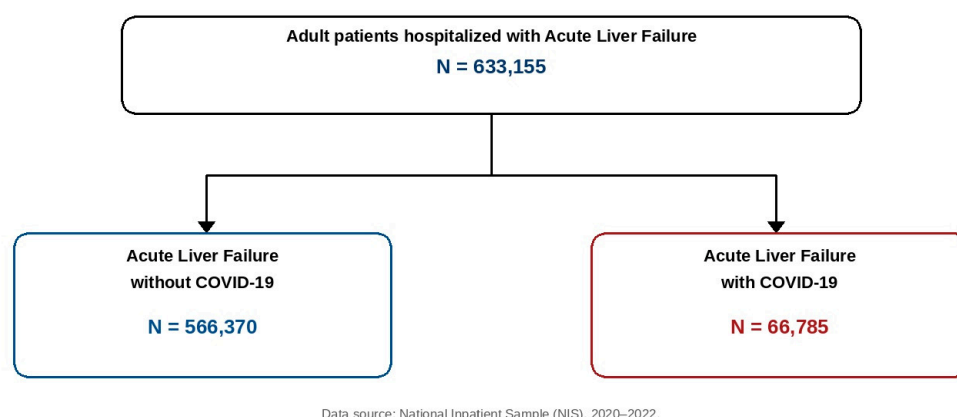


Figure 1. Flowchart of patient distribution in this study.

Baseline demographic and hospital characteristics were compared using overall survey-weighted tests for each variable, with *p*-values representing differences in the overall distribution of each variable between the two study groups and are summarized in Table 1. Patients with acute liver failure and concomitant COVID-19 infection were slightly older than those without COVID-19 infection (62.3 vs. 61.6 years, $p < 0.001$), while the sex distribution was similar, with males accounting for the majority of hospitalizations in both groups (58.8% vs. 55.7%, $p < 0.001$). Caucasians constituted the largest racial group in both cohorts (52.8% vs. 66.4%), among patients with concomitant COVID-19 infection, Hispanics represented the second-largest racial group (19.5%), whereas African Americans were the second-largest group (14.7%) among patients without COVID-19 infection ($p < 0.001$). The largest proportion of patients belonged to the lowest household income quartile (33.6% vs. 32.0%), followed by the second lowest income quartile (26.5%) in both cohorts ($p < 0.001$). Medicare was the most common primary payer in both groups (50.9% vs. 52.3%), followed by private insurance (26.1% vs. 22.3%) ($p < 0.001$). Most patients had a Charlson Comorbidity Index of ≥ 3 (47.5% vs. 62.6%), followed by a Charlson Comorbidity Index of 1 (20.6% vs. 14.7%) ($p < 0.001$). Most hospitalizations occurred in the Southern region (42.5% vs. 42.1%), followed by the West (21.2% vs. 21.6%) ($p < 0.001$). Similarly, most patients were admitted to urban teaching hospitals (78.6% vs. 78.8%), followed by urban non-teaching hospitals (15.9% vs. 15.4%) ($p = 0.26$), and to large hospitals (52.1% vs. 54.4%), followed by medium-sized hospitals (28.4% vs. 27.3%) ($p < 0.001$). Compared with patients with acute liver failure without COVID-19 infection, those with concomitant COVID-19 infection had significantly higher in-hospital mortality (63.9% vs. 36.0%; aOR 3.18, 95% CI 3.04–3.32), non-invasive ventilation (14.9% vs. 6.4%; aOR 2.64, 95% CI 2.49–2.81), invasive ventilation (68.9% vs. 41.7%; aOR 2.94, 95% CI 2.81–3.07), acute kidney injury (81.4% vs. 70.3%; aOR 1.89, 95% CI 1.79–1.98), renal replacement therapy (26.8% vs. 16.9%; aOR 1.96, 95% CI 1.87–2.06) ($p < 0.001$) (Figure 2).

Patients with concomitant COVID-19 infection also had significantly longer hospital stays (17.1 vs. 10.7 days; adjusted mean difference 6.34 days, 95% CI 5.98–6.70) and higher hospitalization charges (\$345,072 vs. \$221,268; adjusted mean difference \$112,754, 95% CI \$101,829–\$123,679) (both $p < 0.001$) (Figures 3 and 4).

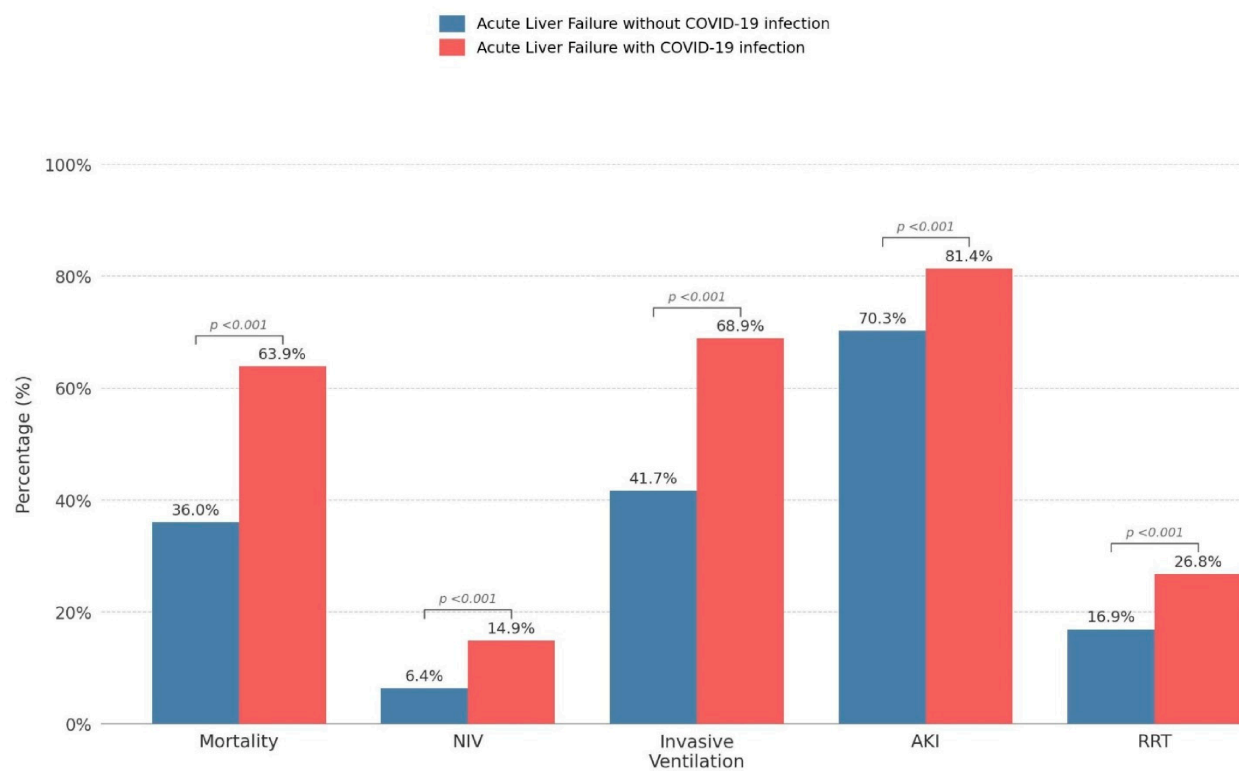


Figure 2. Clinical outcomes comparing mortality, non-invasive ventilation, invasive ventilation, Acute kidney injury and Renal replacement therapy in patients with acute liver failure, with and without concomitant COVID-19 infection.

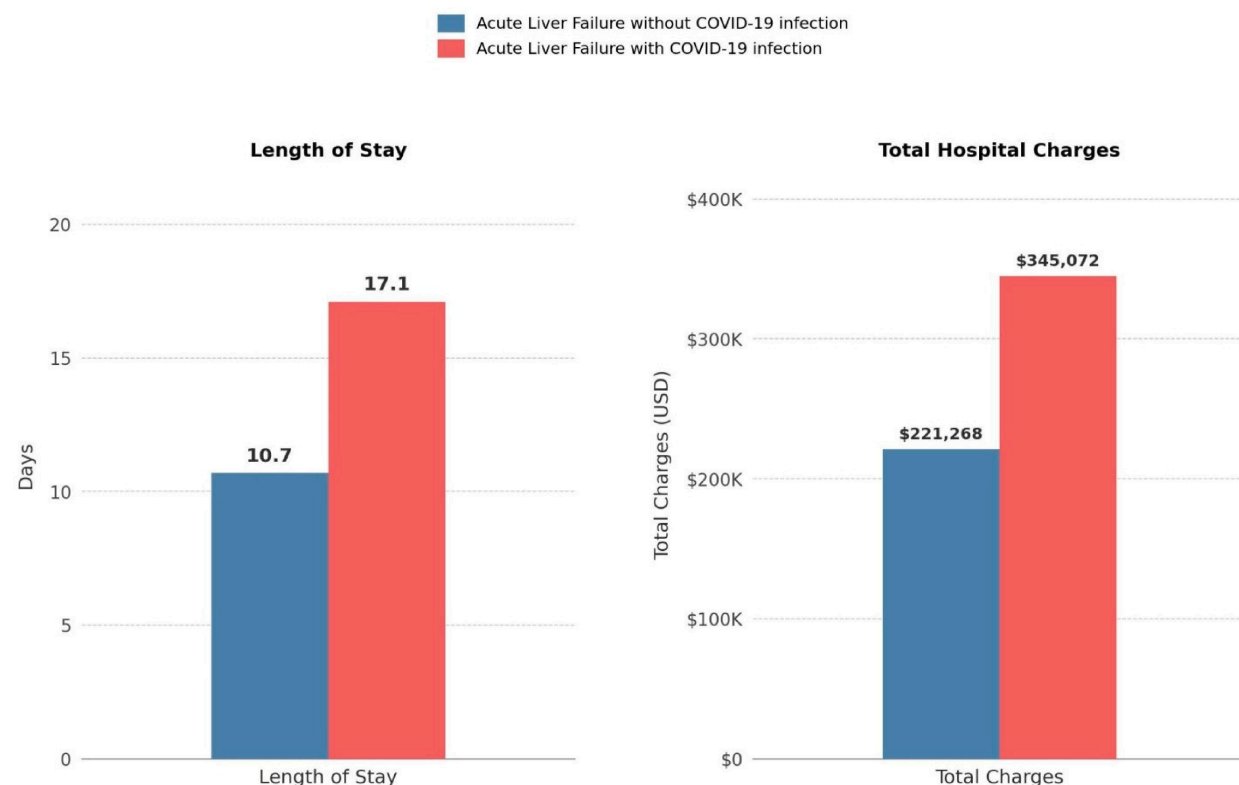


Figure 3. Length of hospital stay and total hospital charges for patients hospitalized with acute liver failure, with and without COVID-19 infection.

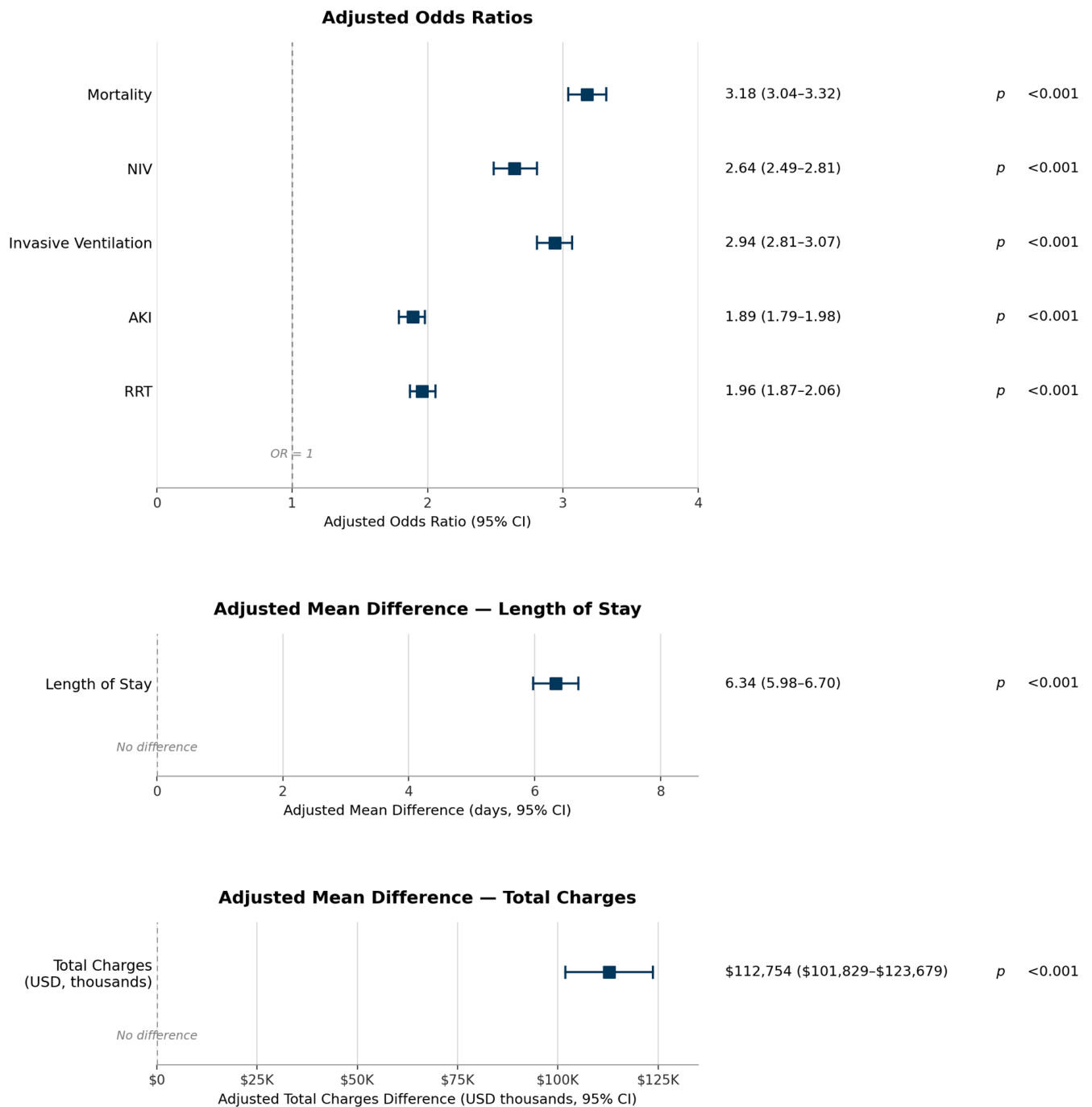


Figure 4. Forest Plot depicting Adjusted Odds Ratios and Adjusted Mean Differences for patients with Acute Liver Failure with COVID-19 infection.

Temporal analysis demonstrated that in-hospital mortality among patients with acute liver failure with concomitant COVID-19 infection increased from 69.2% in 2020 to 69.6% in 2021 before declining to 52.0% in 2022 ($p < 0.001$) (Figure 5).

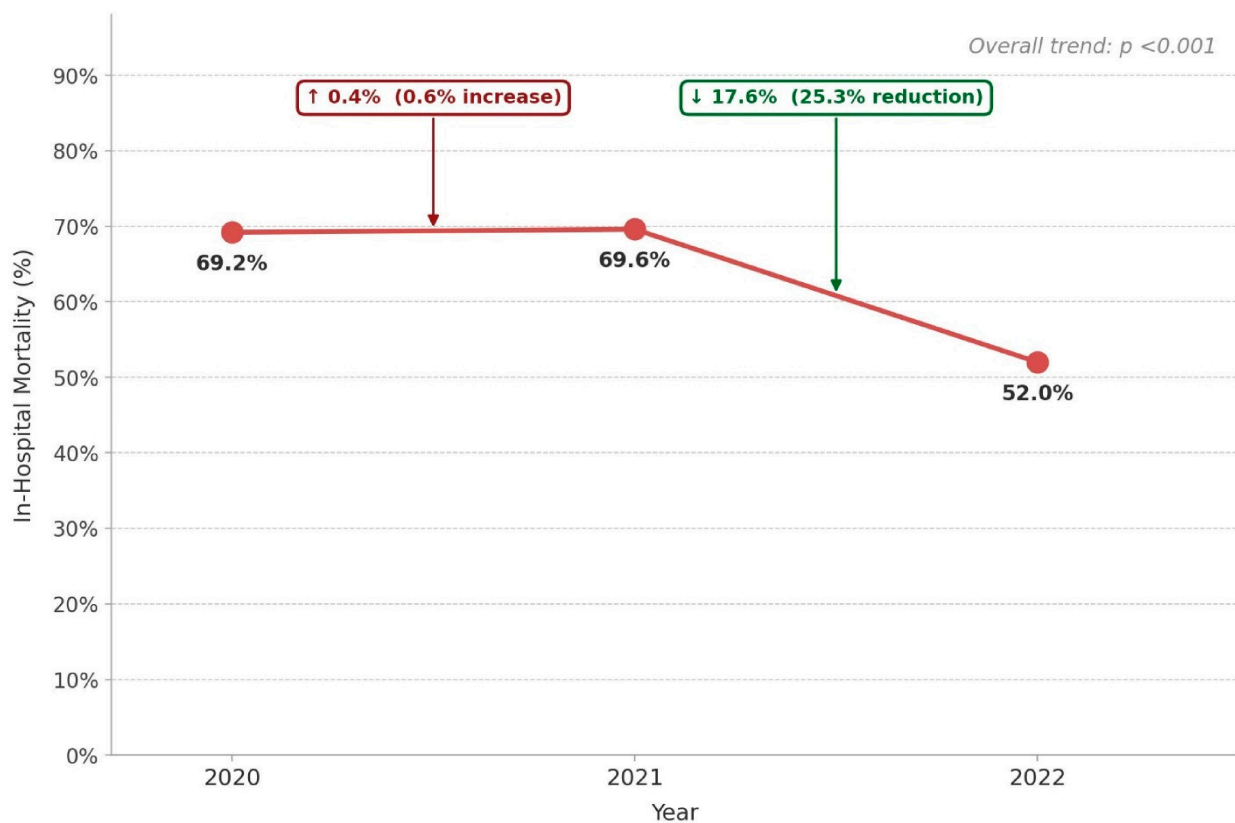


Figure 5. Mortality trends in patients with acute liver failure with concomitant COVID-19 from the years 2020–2022.

4. Discussion

In our analysis of adult hospitalizations for acute liver failure, concurrent COVID-19 was associated with a worse in-hospital course. Compared with patients without COVID-19, those with COVID-19 had higher in-hospital mortality (63.9% vs. 36.0%), greater use of noninvasive ventilation (14.9% vs. 6.4%) and invasive mechanical ventilation (68.9% vs. 41.7%), and a longer hospital stay (17.1 vs. 10.7 days). These differences persisted after adjustment for demographic and clinical factors. COVID-19 remained independently associated with higher odds of death, invasive mechanical ventilation, and noninvasive ventilation, as well as increased length of stay. Notably, patients in the COVID-19 group had a lower proportion of Charlson Comorbidity Index scores ≥ 3 , suggesting that the worse outcomes were not simply explained by a greater baseline burden of comorbidity. Taken together, our findings suggest that concurrent SARS-CoV-2 infection substantially worsens the hospital course of patients admitted with acute liver failure.

Most prior studies have described liver involvement in COVID-19 as common but usually mild. The updated EASL (European Association for the Study of the Liver) position paper reported acute liver injury in approximately 10% to 65% of infected patients, most often with mild aminotransferase elevations, whereas severe liver injury with hyperbilirubinemia and hepatic synthetic dysfunction was considered uncommon [10]. Similarly, the earlier EASL-ESCMID (European Association for the Study of the Liver–the European Society of Clinical Microbiology and Infectious Diseases) position paper reported abnormal liver biochemistry in 19% to 76% of patients, usually in a hepatocellular pattern [6]. Other reviews have estimated that liver dysfunction occurs in about one-third of patients with COVID-19 and is more often seen in men and older adults [11–15]. Additional studies have shown that abnormal liver tests are more frequent in patients with severe disease and may correlate with worse outcomes, longer hospitalization, organ failure, ICU (intensive care

unit) admission, and mortality [13,16–24]. Against that background, progression to acute liver failure appears to be rare [10–12].

Even so, severe hepatic presentations have been reported. Melquist et al. described acute hepatic failure as the presenting manifestation of COVID-19 in a young woman without significant respiratory symptoms [25]. Matsuki et al. later reported COVID-19-triggered acute liver failure with rhabdomyolysis and reviewed additional cases of SARS-CoV-2-associated acute liver failure in the literature [26]. Our findings build on those reports by showing that, at the national level, patients with both COVID-19 and acute liver failure had markedly worse in-hospital outcomes [25,26].

The mechanism behind this association is likely multifactorial. Current literature suggests that liver injury in COVID-19 may result from direct viral effects on hepatocytes or cholangiocytes, immune-mediated injury, cytokine-driven inflammation, ischemic or hypoxic hepatitis in severe illness, microvascular thrombosis, drug-induced liver injury, and sepsis-related multiorgan dysfunction [9–12,14,15,21–24]. Direct hepatic involvement has also been supported by reports demonstrating SARS-CoV-2 infection in liver tissue [9]. In addition, several studies have shown that the presence and severity of liver injury correlate with overall disease severity and clinical outcomes in COVID-19 [10,13,16–20]. In patients with acute liver failure, who already have limited physiologic reserve, these overlapping insults may further destabilize an already critical condition. This is consistent with the greater need for ventilatory support and the excess mortality observed in our cohort.

We also found differences in the demographic profile of affected patients. Those with concurrent COVID-19 were slightly older, more often male, and more frequently Hispanic or African American. The male predominance in our cohort is in line with prior reports showing that liver dysfunction during COVID-19 is more common in men and older adults [11–13,16,17,20]. The racial and ethnic differences we observed may reflect disparities in exposure risk, severity at presentation, access to care, and broader social determinants of health, although those factors cannot be directly measured in the NIS database.

From a clinical standpoint, these findings support close monitoring for hepatic decompensation in hospitalized patients with COVID-19, especially when mental status changes, coagulopathy, or rapidly worsening liver tests are present. The EASL position paper recommends regular assessment of AST, ALT, GGT, ALP, and bilirubin during hospitalization with COVID-19 [10]. For patients with both acute liver failure and COVID-19, early intensive care involvement, aggressive supportive management, timely respiratory support, and hemodynamic optimization may be particularly important. Prior studies showing that abnormal liver biochemistry in COVID-19 is associated with more severe disease, longer hospitalization, ICU admission, and mortality further support the importance of recognizing hepatic involvement early [6,15–24,27].

Acute kidney injury is a well-recognized complication of acute liver failure and usually reflects the severity of systemic illness, hemodynamic instability, renal hypoperfusion, systemic inflammation, and multiorgan dysfunction. In patients with concurrent COVID-19, this risk may be further amplified by cytokine-driven injury, sepsis, microvascular thrombosis, hypoxemia and circulatory compromise, all of which may contribute to worsening renal function and a greater need for renal replacement therapy. In our cohort, patients with acute liver failure and concurrent COVID-19 had significantly higher rates of acute kidney injury (81.4% vs. 70.3%) and renal replacement therapy use (26.8% vs. 16.9%). These associations remained significant after adjustment, with concurrent COVID-19 associated with higher odds of acute kidney injury (aOR 1.89, 95% CI 1.79–1.98) and renal replacement therapy (aOR 1.96, 95% CI 1.87–2.06). These findings suggest that renal dysfunction is an important contributor to the greater clinical severity observed in this population [3–5,28,29].

Concurrent COVID-19 infection also had a marked effect on hospital resource utilization in patients admitted with acute liver failure. In addition to higher mortality, these patients had a greater need for noninvasive ventilation (14.9% vs. 6.4%) and invasive mechanical ventilation (68.9% vs. 41.7%), a longer length of stay (17.1 vs. 10.7 days), higher use of renal replacement therapy (26.8% vs. 16.9%) and greater total hospital charges (\$345,072 vs. \$221,268). On adjusted analysis, concurrent COVID-19 remained associated with a 6.34 day increase in length of stay and an additional \$112,754 in total hospital charges. Taken together, these findings indicate that acute liver failure with concurrent COVID-19 is associated not only with worse clinical outcomes but also with substantially greater inpatient resource utilization and a more intensive overall hospital course.

The decline in mortality observed between 2020 and 2022 may reflect improvements in the clinical management of COVID-19, evolving treatment protocols, increasing vaccination coverage and the emergence of the Omicron variant, which was generally associated with lower disease severity than earlier variants such as Delta [30,31].

5. Limitations

As a retrospective analysis of an administrative database, it is subject to residual confounding. The NIS database does not provide timing of COVID-19 relative to hepatic injury, COVID-19 disease severity, medication exposure, ICU-specific interventions, transplant candidacy, vaccination status, SARS-CoV-2 variants, etiology of acute liver failure, or post-discharge outcomes. The database lacks detailed laboratory parameters and physiological data, including liver function tests, coagulation profiles, inflammatory markers, Model for End-Stage Liver Disease (MELD) scores, and hepatic encephalopathy grading, limiting prognostic risk stratification. In addition, the database does not allow us to determine whether COVID-19 directly caused liver injury or whether the observed association was mediated through hypoxia, shock, systemic inflammation, drug-induced liver injury, or sepsis-related multiorgan dysfunction. These mechanisms are biologically plausible based on the current liver-COVID literature, but they cannot be distinguished using this dataset [9–11,14,17,22–27]. Patients with acute on chronic liver failure could not be reliably distinguished using the NIS database. Despite these limitations, the large sample, significant impact on clinical outcomes, mortality trend, and consistency of the adjusted findings suggest that patients with concurrent COVID-19 and acute liver failure represent a particularly high-risk group.

Future Research Directions

Future research should involve prospective multicenter clinical studies to better characterize the temporal relationship between SARS-CoV-2 infection and the development of acute liver failure. The clinical studies should enable integration of laboratory parameters, liver injury biomarkers, imaging findings, disease severity scores, vaccination status, antiviral and immunomodulatory therapies, and liver transplantation data to better elucidate the mechanisms underlying the observed association.

6. Conclusions

Among adults hospitalized with acute liver failure, concurrent COVID-19 was associated with markedly worse in-hospital outcomes, including higher mortality, greater need for ventilatory support, higher rates of acute kidney injury and renal replacement therapy, longer hospitalization and greater hospital charges. These findings identify patients with both acute liver failure and concurrent COVID-19 as a particularly high-risk group who warrant early multidisciplinary management and intensive supportive care.

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Institutional Review Board Statement: All data were obtained through a request to the Online Healthcare Cost and Utilization Project (HCUP) Central Distributor, which administers the database (certificate HCUP-28M71GVP5). We followed all AHRQ guidelines (<https://hcup-us.ahrq.gov/db/publishing.jsp>, accessed on 15 March 2026) and were exempt from IRB review as the National Inpatient Sample is a publicly available, deidentified dataset.

Informed Consent Statement: Patient consent was waived due to the study analyzing secondary data from the NIS database; patients and the public were not involved directly. And all data in the NIS database are de-identified.

Data Availability Statement: The datasets analyzed during the current study are available from the Healthcare Cost and Utilization Project (HCUP) National Inpatient Sample (NIS) database and can be obtained as requested.

Conflicts of Interest: The authors declare no conflicts of interest.

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