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Chronic Liver Disease and Cirrhosis are Associated with Worse Outcomes Following SARS-CoV-2 Infection

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Background and aims: **Studies evaluating the impact of SARS-CoV-2 on chronic liver disease (CLD) are limited and have focused mostly on hospitalized patients or those with cirrhosis. We aim to evaluate the impact of underlying CLD on patient outcomes following COVID-19 using a one of the largest COVID-19+CLD cohorts to date.** ***Methods:*** **Data from the COVID-19 Research Database (https://covid19researchdatabase.org) were evaluated from April 1, 2020, to August 31, 2021, to determine whether concurrent CLD was associated with worse outcomes within 30 day of COVID-19 diagnosis, including need for hospitalization, pneumonia, severe pneumonia, respiratory failure, and multiorgan failure. Among patients with COVID-19+CLD, risks of liver decompensation and acute on chronic liver failure (ACLF) were evaluated, stratified by presence of cirrhosis. Adjusted multivariate logistic regression models evaluated the impact of CLD on COVID-19 outcomes.** ***Results:*** **In total, 1,208,905 unique patients with COVID-19 were identified; 44,008 (3.6%) had concurrent CLD, among which 6515 (14.8%) had cirrhosis. Compared to patients without CLD, COVID-19+CLD patients were significantly more likely to require hospitalization (aOR 1.65, 95% CI 1.61–1.69), develop pneumonia (aOR 1.11, 95% CI 1.08–1.14), severe pneumonia (aOR 1.74, 95% CI 1.62–1.86), respiratory failure (aOR 1.14, 95% CI 1.10–1.17), and multiorgan failure (aOR 1.84, 95% CI 1.72–1.97), $P < 0.0001$ for all. Among COVID-19+CLD patients, underlying cirrhosis was associated with even higher risk of these poor outcomes, and higher risk of acute liver decompensation or ACLF.** ***Conclusions:*** **Among one of the largest studies to date evaluating patients with COVID-19 and CLD, underlying CLD is associated with significantly greater risk of poor outcomes following SARS-CoV-2 infection, particularly among cirrhotic patients. (J Clin Exp Hepatol xxxx;xxx:xxx)**

The novel coronavirus, SARS-CoV-2, and the resulting COVID-19 pandemic has affected over 400 million individuals worldwide, with over 6 million deaths reported to date.[1] Existing data have observed significantly greater COVID-19 morbidity and mortality in patients with underlying medical comorbidities such as metabolic diseases, cardiovascular disease, and chronic respiratory disorders.[2–5] Patients with underlying chronic liver disease (CLD), particularly those with advanced liver disease (e.g., cirrhosis, decompensated liver disease) have underlying immune dysfunction, and these immunocompromised patients are especially vulnerable to severe COVID-19.[6–12] For example, Marjot *et al.* evaluated 745 patients with CLD and COVID-19 (51% with cirrhosis) identified across two international registries.[7] Compared to patients without cirrhosis, presence of cirrhosis, as well as increasing severity of cirrhosis (as measured by Childs–Pugh score) was associated with significantly higher risk of mortality. Data from the multicenter Asia Pacific Association for the Study of the Liver COVID-19 Liver Injury Spectrum (APCOLIS) Study evaluated 228 patients with CLD and COVID-19 (19% with cirrhosis) across 13 countries in Asia.[8] The investigators observed that among CLD patients without cirrhosis, 40% presented with acute liver injury, and among CLD patients with cirrhosis, 12% presented with acute on chronic liver failure (ACLF) and 9% presented with acute hepatic decompensation at time of COVID-19 diagnosis. Smaller cohort studies focusing predominantly on hospitalized patients have reported similar outcomes, observing that patients with underlying CLD and cirrhosis in particular have higher risk of respiratory failure, ACLF, and overall mortality.[6,9,10,13]

The majority of studies to date evaluating COVID-19 outcomes among patients with underlying CLD have

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Abbreviations: ACLF: acute on chronic liver failure; APASL: Asian Pacific Association for the Study of the Liver; APCOLIS: Asia Pacific Association for the Study of the Liver (APASL) COVID-19 Liver Injury Spectrum; CLD: chronic liver disease; OR: odds ratio
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included relatively limited sample sizes or are focused predominantly on patients with cirrhosis or those who are hospitalized.[6–11,13,14] While understanding the impact of COVID-19 outcomes among this sicker population with more advanced liver disease is important, the vast majority of CLD patients who are infected with SARS-CoV-2 do not have advanced liver disease or cirrhosis and are evaluated and managed in the outpatient setting. Thus, understanding COVID-19 outcomes among a broader population of CLD patients, inclusive of those without cirrhosis as well as those not in the hospitalized setting, is important to identify which CLD patients are at greatest risk of severe COVID-19, and which patients are at increased risk of liver decompensation following acute SARS-CoV-2 infection. Our study is one of the largest cohorts to date evaluating clinical outcomes in patients with CLD and concurrent SARS-CoV-2 infection.

METHODS

Data source

This study utilized data from the COVID-19 Research Database (https://covid19researchdatabase.org), a large healthcare claims dataset that captures a network of 1 million distinct providers across professional and institutional claims and over 100 million patients with both inpatient and outpatient data representing >3000 different payers including private, Medicare, Medicare advantage, and Medicaid. Data were extracted by SQL using Snowflake (Snowflake Inc., San Mateo, CA, USA).

Study population

Adults (age ≥18 years) with SARS-CoV-2 from April 1, 2020, to August 31, 2021, were identified using International Statistical Classification of Diseases and Related Health Problems, Tenth Revision; ICD-10: U07.1. Assessment of CLD focused on the four leading etiologies of liver disease among U.S. adults and included nonalcoholic fatty liver disease/nonalcoholic steatohepatitis (NAFLD/NASH), alcohol-associated liver disease (ALD), hepatitis B virus (HBV), and hepatitis C virus (HCV). Identification of CLD utilized methods similar to previously published studies evaluating CLD outcomes among large healthcare datasets and incorporated a comprehensive algorithm of ICD-9/10-based disease diagnosis coding (Supplementary Table 1).[15–17] Similarly, presence of cirrhosis was identified using ICD-10 diagnosis codes and utilized methods similar to previous studies evaluating cirrhosis epidemiology and outcomes based on claims datasets.[15,16]

Study outcomes

The index date was defined as the initial date of COVID- 19 diagnosis. The baseline period to define underlying CLD was defined as 12 months prior to the index date. All study outcomes were evaluated within 30 days of COVID-19 diagnosis. COVID-19 outcomes assessed included need for hospitalization, pneumonia, severe pneumonia (pneumonia + severe sepsis or septic shock), respiratory failure, and multiorgan failure (2 or more organ failures: cardiovascular failure, respiratory failure, renal failure, neurological failure, and liver failure), which were identified using a comprehensive list of ICD-9/10 diagnosis codes (Supplementary Table 2). COVID-19 outcomes were compared between patients with COVID-19 with CLD (COVID-19+CLD) or without CLD.

Liver-related outcomes within 30 days of COVID-19 diagnosis were evaluated among patients with COVID-19+CLD and included incident liver decompensation and ACLF. Liver decompensation was defined as development of at least one of the following liver-related complications: ascites, hepatic encephalopathy, variceal bleeding, hepatorenal syndrome, or liver failure (Supplementary Table 2). ACLF was defined using similar methodology to previously published studies and was based on the North American Consortium for the Study of End-Stage Liver Disease criteria with the presence of 2 or more extrahepatic organ failures (cardiovascular failure, respiratory failure, renal failure, or neurological failure) in patients with cirrhosis (Supplementary Table 2).[18–20] Similar to previously published studies,[21] hospitalization was defined as an inpatient or emergency room overnight visit with an initial COVID-19 diagnosis made during hospitalization and within 7 days of admission or an inpatient or emergency room overnight visit within 30 days of the initial COVID-19 diagnosis, where the hospitalization had a record of this diagnosis.

Statistical analyses

Baseline demographics and clinical characteristics of COVID-19 patients are presented as frequencies and proportions and stratified by patients with or without CLD. We additionally evaluated characteristics of patients with COVID-19+CLD stratified by presence of cirrhosis at time of SARS-CoV-2 infection. Development of outcomes (hospitalization, pneumonia, severe pneumonia, respiratory failure, or multiorgan failure) within 30 days of SARS-CoV-2 diagnosis were evaluated in patients with and without CLD, and stratified by age, sex, and presence of important comorbidities (hypertension, chronic kidney disease, diabetes mellitus, heart failure, chronic respiratory disease). Comparisons of outcomes between groups utilized chi-square testing. Adjusted multivariate logistic regression models were used to evaluate predictors of these outcomes. Variables selected for inclusion in the multivariate model were determined *a priori* based on what was hypothesized to be clinically relevant variables affecting the development of outcomes. The final multivariate model evaluating COVID-19 outcomes include adjustments by

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age, sex, hypertension, diabetes mellitus, heart failure, chronic kidney disease, and chronic respiratory disease (Supplementary Table 3).

Among the subset of COVID-19+CLD patients, we evaluated for aforementioned COVID-19 outcomes as well as for the development of liver decompensation or ACLF within 30 days of SARS-CoV-2 diagnosis. The assessment of these outcomes was evaluated in patients with cirrhosis versus without cirrhosis at time of SARS-CoV-2 diagnosis, and additional stratification was performed by age, sex, and presence of important comorbidities (hypertension, chronic kidney disease, diabetes mellitus, heart failure, chronic respiratory disease). Comparisons of liver decompensation and ACLF outcomes between groups utilized chi-square testing. Adjusted multivariate logistic regression models evaluated for predictors of liver decompensation and ACLF among patients with COVID-19+CLD. For all analyses, statistical significance was met with a two-tailed *P*-value <0.05. All statistical analyses were performed using SAS, version 9.4 software (SAS Institute, Cary, NC, USA). This study was approved by the Stanford University Institutional Review Board.

RESULTS

Overall, the study cohort included 1,208,905 unique patients with COVID-19, among which 44,008 (3.6%) had concurrent CLD and 1,164,897 (96.4%) did not have CLD. Among patients with concurrent CLD, 47.5% had ALD, 37.3% had NAFLD/NASH, 8.6% had chronic HCV, 4.1% had chronic HBV, and 2.5% had other etiologies. Compared to patients with COVID-19 without CLD, COVID-19+CLD patients were more likely to be male (51.4% vs. 44.4%, $P < 0.0001$) and were older (age >45: 72.7% vs. 61.5%, $P < 0.0001$) (Table 1). COVID-19+CLD patients had significantly greater prevalence of comorbidities compared to COVID-19 patients without CLD, including diabetes, hypertension, chronic kidney disease, heart failure, and chronic and respiratory disease.

Among COVID-19+CLD patients, 6515 (14.8%) had cirrhosis and 37,493 (85.2%) did not have cirrhosis (Table 2). Compared to COVID-19+CLD without cirrhosis, patients with COVID-19+CLD with cirrhosis were more likely to be male (56.2% vs. 50.6%, $P < 0.0001$) and older (age > 45: 90.3% vs. 69.6%, $P < 0.0001$). COVID-19+CLD patients with cirrhosis had significantly greater prevalence of comorbidities compared to COVID-19+CLD patients without cirrhosis (Table 2).

Compared to patients with COVID-19 without CLD, COVID-19+CLD patients were significantly more likely to require hospitalization (26.1% vs. 13.0%, $P < 0.0001$), develop pneumonia (23.4% vs. 18.1%, $P < 0.0001$), severe pneumonia (2.3% vs. 0.9%, $P < 0.0001$), respiratory failure (14.7% vs. 10.6%, $P < 0.0001$), and multiorgan failure (2.4% vs. 0.9%, $P < 0.0001$) (Figure 1). On adjusted multivariate logistic regression, patients with concurrent CLD at time of SARS-CoV-2 infection were associated with significantly greater risk of hospitalization (OR 1.65, 95% CI 1.61–1.69, $P < 0.0001$), pneumonia (OR 1.11, 95% CI 1.08–1.14, $P < 0.0001$), severe pneumonia (OR 1.74, 95%

Table 1 Baseline Characteristics of the COVID-19 Cohort in Patients With and Without Underlying CLD.

	COVID-19 without CLD		COVID-19 + CLD		*P* value
	Percent (%)	N	Percent (%)	N	
Total	100%	1,164,897	100%	44,008	
Sex					<0.0001
Male	44.4%	517,216	51.4%	22,626	
Female	55.6%	647,681	48.6%	21,382	
Age groups					<0.0001
18–45 years	38.5%	448,793	27.3%	12,034	
46–64 years	32.0%	372,851	42.3%	18,598	
65 years and over	29.5%	343,253	30.4%	13,376	
Comorbidities					
Diabetes mellitus	11.8%	137,833	29.9%	13,163	<0.0001
Hypertension	20.5%	238,725	47.3%	20,802	<0.0001
Chronic kidney disease	4.9%	57,381	15.1%	6648	<0.0001
Heart failure	3.6%	42,390	11.1%	4891	<0.0001
Chronic respiratory disease	7.2%	84,295	17.4%	7667	<0.0001
Tobacco smoker	2.2%	26,053	11.3%	4973	<0.0001

CLD, chronic liver disease

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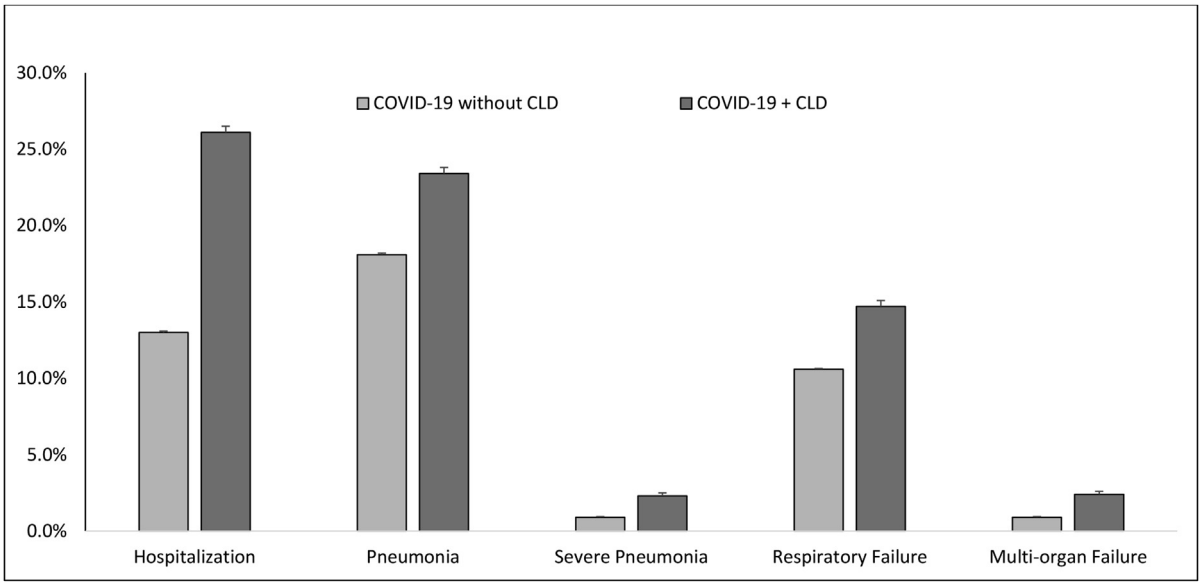
Table 2 Baseline Characteristics of COVID-19+CLD Patients With and Without Underlying Cirrhosis.

	COVID-19 + CLD with Cirrhosis		COVID-19 + CLD without Cirrhosis		*P* value
	Percent (%)	N	Percent (%)	N	
Total	100%	6515	100%	37,493	
Sex					<0.0001
Male	56.2%	3661	50.6%	18,965	
Female	43.8%	2854	49.4%	18,528	
Age groups					<0.0001
18–45 years	9.7%	634	30.4%	11,400	
46–64 years	46.0%	2995	41.6%	15,603	
65 years and over	44.3%	2886	28.0%	10,490	
Comorbidities					
Diabetes	43.0%	2802	27.6%	10,361	<0.0001
Hypertension	60.3%	3930	45.0%	16,872	<0.0001
Chronic kidney disease	25.6%	1668	13.3%	4980	<0.0001
Heart failure	22.6%	1470	9.1%	3421	<0.0001
Chronic respiratory disease	21.3%	1388	16.7%	6279	<0.0001
Tobacco smoker	10.6%	693	11.4%	4280	<0.0001

CLD, chronic liver disease

CI 1.62–1.86, $P < 0.0001$), respiratory failure (OR 1.14, 95% CI 1.10–1.17, $P < 0.0001$), and multiorgan failure (OR 1.84, 95% CI 1.72–1.97, $P < 0.0001$) (Table 3). Male sex, older age, and presence of medical comorbidities were also associated with higher odds of these outcomes.

Among the cohort of patients with COVID-19+CLD, those with cirrhosis at time of SARS-CoV-2 infection were more likely to require hospitalization (38.9% vs. 23.8%, $P < 0.0001$), develop pneumonia (31.1% vs. 22.2%, $P < 0.0001$), severe pneumonia (4.6% vs. 2.0%, $P < 0.0001$), respiratory



Note: Error bars represent the upper limit of the 95% confidence intervals. P<0.0001 for all comparisons

Figure 1 Proportion of patients with COVID-19 who developed pneumonia, severe pneumonia, respiratory failure, need for hospitalization, and multi-organ failure stratified by whether patients had concurrent CLD. Abbreviation: CLD, chronic liver disease.

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Table 3 Adjusted Multivariate Logistic Regression Models Evaluating Predictors of COVID-19 Outcomes.

Total Cohort	Hospitalization			Pneumonia			Severe Pneumonia		
	Odds ratio	95% CI	*P* value	Odds ratio	95% CI	*P* value	Odds ratio	95% CI	*P* value
COVID-19 + CLD (vs. without CLD)	**1.65**	**1.61–1.69**	**<0.0001**	**1.11**	**1.08–1.14**	**<0.0001**	**1.74**	**1.62–1.86**	**<0.0001**
Female	1.00	Reference		1.00	Reference		1.00	Reference	
Male	1.53	1.51–1.54	<0.0001	1.52	1.51–1.54	<0.0001	1.79	1.72–1.86	<0.0001
18–45 years	1.00	Reference		1.00	Reference		1.00	Reference	
46–64 years	2.35	2.31–2.39	<0.0001	2.50	2.46–2.53	<0.0001	3.54	3.30–3.81	<0.0001
65 years and over	4.37	4.30–4.44	<0.0001	4.17	4.11–4.22	<0.0001	6.78	6.32–7.28	<0.0001
Diabetes	1.52	1.49–1.54	<0.0001	1.33	1.31–1.35	<0.0001	1.49	1.43–1.56	<0.0001
Hypertension	1.40	1.38–1.41	<0.0001	1.05	1.03–1.06	<0.0001	1.23	1.18–1.29	<0.0001
Chronic kidney disease	1.81	1.77–1.84	<0.0001	1.39	1.36–1.41	<0.0001	1.71	1.62–1.81	<0.0001
Heart failure	1.74	1.70–1.78	<0.0001	1.34	1.31–1.37	<0.0001	1.53	1.45–1.63	<0.0001
Chronic respiratory disease	1.32	1.30–1.34	<0.0001	1.29	1.27–1.31	<0.0001	1.27	1.20–1.34	<0.0001

	Respiratory Failure			Multiorgan Failure		
	Odds Ratio	95% CI	*P* value	Odds Ratio	95% CI	*P* value
COVID-19 + CLD (vs. without CLD)	**1.14**	**1.10–1.17**	**<0.0001**	**1.84**	**1.72–1.97**	**<0.0001**
Female	1.00	Reference		1.00	Reference	
Male	1.68	1.66–1.70	<0.0001	1.8	1.74–1.87	<0.0001
18–45 years	1.00	Reference		1.00	Reference	
46–64 years	3.25	3.18–3.31	<0.0001	3.58	3.33–3.86	<0.0001
65 years and over	6.05	5.94–6.17	<0.0001	6.86	6.39–7.37	<0.0001
Diabetes	1.39	1.37–1.41	<0.0001	1.49	1.42–1.56	<0.0001
Hypertension	1.05	1.03–1.07	<0.0001	1.24	1.19–1.30	<0.0001
Chronic kidney disease	1.38	1.35–1.41	<0.0001	1.69	1.60–1.78	<0.0001
Heart failure	1.54	1.50–1.58	<0.0001	1.56	1.47–1.65	<0.0001
Chronic respiratory disease	1.28	1.23–1.33	<0.0001	1.26	1.19–1.33	<0.0001

CLD, chronic liver disease

failure (21.6% vs. 13.6%, $P < 0.0001$), liver decompensation (6.7% vs. 3.4%, $P < 0.0001$), and ACLF (4.4% vs. 0.3%, $P < 0.0001$) (Figure 2). Among patients who developed ACLF, the major drivers of ACLF were the development of cardiovascular or respiratory failure. In addition, the major drivers of decompensation were the development of ascites and hepatic encephalopathy, which was observed in 66.5% and 33.8% of patients who developed liver decompensation, respectively. On adjusted multivariate logistic regression, COVID-19+CLD patients with underlying cirrhosis at time of SARS-CoV-2 infection were observed to have significantly greater odds of requiring hospitalization (OR 1.46, 95% CI 1.38–1.55, $P < 0.0001$), developing pneumonia (OR 1.16, 95% CI 1.09–1.24, $P < 0.0001$), severe pneumonia (OR 1.66, 95% CI 1.44–1.91, $P < 0.0001$), respiratory failure (OR 1.20, 95% CI 1.12–1.30, $P < 0.0001$), liver decompensation (OR 1.69, 95% CI 1.45–1.96, $P < 0.0001$), and ACLF (OR 12.71, 95% CI 10.0–16.0, $P < 0.0001$) (Table 4). Male sex, older age, and presence of medical comorbidities were also generally associated with higher odds of these outcomes. We also performed additional analyses to determine whether underlying etiology of liver disease was associated with differences in these outcomes. Compared to patients with NAFLD/NASH, patients with ALD had lower odds of developing pneumonia (OR 0.72, 95% CI 0.64–0.81, $P < 0.01$), but no differences in odds of severe pneumonia or respiratory failure by etiology was observed. Compared to patients with NAFLD/NASH, higher odds of hospitalization were observed in patients with ALD (OR 1.42, 95% CI 1.27–1.59, $P < 0.01$) and patients with HCV (OR 1.28, 95% CI 1.06–1.55, $P < 0.01$). Compared to patients with NAFLD/NASH, lower odds of liver decompensation were observed in patients with HBV (OR 0.14, 95% CI 0.02–0.99, $P < 0.01$) and patients with HCV (OR 0.17, 95% CI 0.07–0.42, $P < 0.01$), but no etiology-specific differences in odds of developing ACLF were observed.

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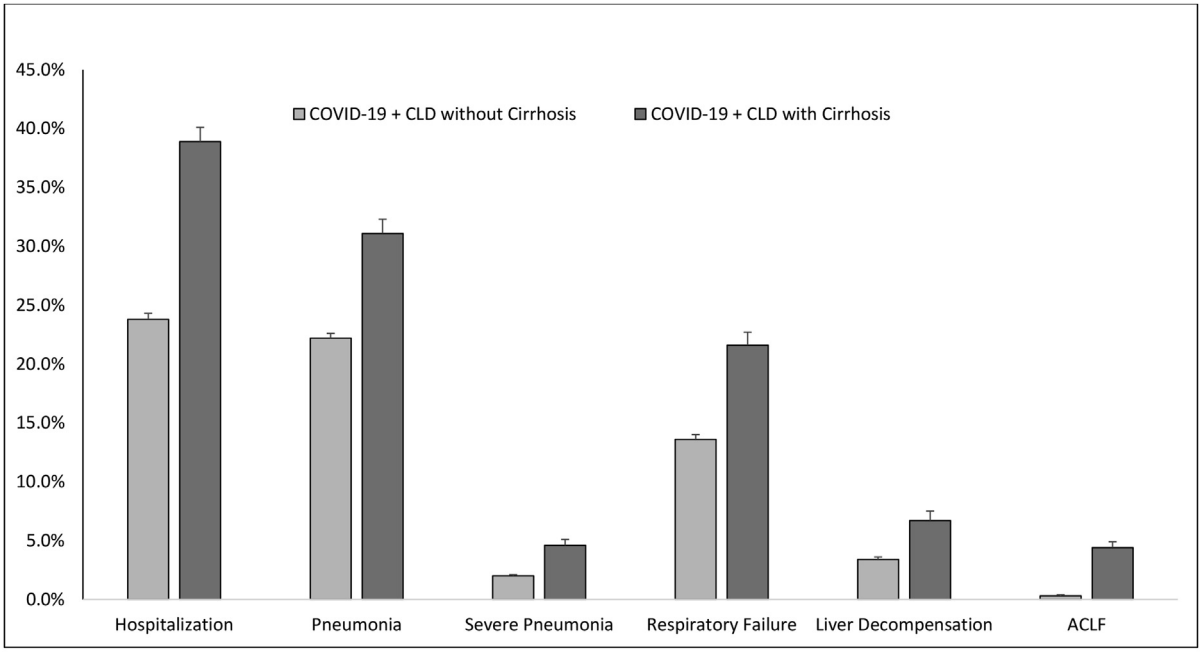

Note: Error bars represent the upper limit of the 95% confidence intervals. P<0.0001 for all comparisons

Figure 2 Proportion of patients with COVID + CLD who developed pneumonia, severe pneumonia, respiratory failure, need for hospitalization, liver decompensation, and ACLF, stratified by whether patients had cirrhosis at time of SARS-CoV-2 infection. Abbreviations: CLD, chronic liver disease; ACLF, acute on chronic liver failure.

DISCUSSION

The current study of over 1.2 million U.S. adults with COVID-19, inclusive of over 44,000 COVID-19 patients with concurrent CLD, is one of the largest cohorts evaluating the impact of underlying CLD on patient outcomes following SARS-CoV-2 infection. We observed that patients with underlying CLD are at significantly greater risk of developing poor outcomes following SARS-CoV-2 infection, including greater risk requiring hospitalization, developing pneumonia, severe pneumonia, respiratory failure, and multiorgan failure. In particular, patients with underlying cirrhosis were at especially higher risk of these poor outcomes following SARS-CoV-2 infection. Our study also demonstrated that risk of liver decompensation and development of ACLF following SARS-CoV-2 infection in patients with underlying CLD is not inconsequential, and presence of cirrhosis significantly increased the risk of these liver-related complications.

Existing studies evaluating COVID-19 outcomes in patients with underlying CLD have been limited by relatively smaller sample sizes, focused on single center cohorts, or including only hospitalized patients.[6–11,13,14] Hashemi *et al.* conduced a multicenter analysis of 363 hospitalized patients with laboratory confirmed COVID-19, among which 69 (19%) had underlying CLD.[6] After controlling for relevant comorbidities, including obesity, hypertension, diabetes, cardiac and respiratory diseases, the investigators observed that among hospitalized patients, underlying CLD was associated with greater odds of ICU admission (aOR 1.77, 95% CI 1.03–3.04) and need for mechanical ventilation (aOR 2.08, 95% CI 1.20–3.60). Another multicenter study in China that focused specifically on hospitalized patients with cirrhosis observed that 23.8% required ICU admission, 14.3% required invasive mechanical ventilation, and 28.6% developed acute respiratory distress syndrome.[10] Marjot *et al.* evaluated 745 patients with CLD and COVID-19 (including 359 with underlying cirrhosis) across two international registries.[7] Overall, 668 (90%) of the COVID-19+CLD cohort required hospitalization, 24% were admitted to the ICU, 18% received mechanical ventilation, 4% required renal replacement therapy, and 20% died. Increasing severity of liver disease was associated with higher odds of requiring ICU admission and overall mortality. When compared to a matched cohort of COVID-19 patients with CLD, significantly greater risk of mortality was only observed among patients with Childs–Pugh B or higher cirrhosis. Ge *et al.* utilized data from the National COVID Cohort Collaborative (N3C), which included 8941 patients with COVID-19 and cirrhosis, and 29,446 COVID-19 patients with noncirrhotic CLD.[14] Compared to COVID-19 patients with noncirrhotic CLD, those with COVID-19 and cirrhosis had significantly higher rates of 30-day hospitalization (47.2% vs. 20.4%), 30-day mechanical ventilation (8.8% vs. 1.8%), and 30-day mortality (8.9% vs. 1.7%). Our current study is unique in our comprehensive approach that evaluates

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Table 4 Adjusted Multivariate Logistic Regression Models Evaluating Predictors of COVID-19 Outcomes and Liver Complications in COVID-19+CLD Patients.

COVID-19 with CLD Cohort	Hospitalization			Pneumonia			Severe Pneumonia		
	Odds ratio	95% CI	*P* value	Odds ratio	95% CI	*P* value	Odds ratio	95% CI	*P* value
Cirrhosis vs. no Cirrhosis	**1.46**	**1.38–1.55**	**<0.0001**	**1.16**	**1.09–1.24**	**<0.0001**	**1.66**	**1.44–1.91**	**<0.0001**
Female	1.00	Reference		1.00	Reference		1.00	Reference	
Male	1.45	1.38–1.52	<0.0001	1.31	1.25–1.38	<0.0001	1.51	1.32–1.72	<0.0001
18–45 years	1.00	Reference		1.00	Reference		1.00	Reference	
46–64 years	1.31	1.23–1.40	<0.0001	1.58	1.48–1.69	<0.0001	1.96	1.57–2.45	<0.0001
65 years and over	1.63	1.53–1.75	<0.0001	2.32	2.16–2.49	<0.0001	2.74	2.18–3.43	<0.0001
Diabetes	1.24	1.18–1.31	<0.0001	1.29	1.22–1.36	<0.0001	1.20	1.04–1.38	<0.0001
Hypertension	1.29	1.22–1.35	<0.0001	1.11	1.05–1.17	<0.0001	1.14	0.98–1.32	0.085
Chronic kidney disease	2.06	1.94–2.19	<0.0001	1.40	1.31–1.50	<0.0001	1.73	1.48–2.01	<0.0001
Heart failure	2.14	2.00–2.29	<0.0001	1.63	1.50–1.76	<0.0001	1.68	1.43–1.98	<0.0001
Chronic respiratory disease	1.21	1.14–1.29	<0.0001	1.23	1.15–1.31	<0.0001	1.16	1.00–1.36	0.058
	Respiratory Failure			**Liver Decompensation**			**ACLF**		
	Odds Ratio	**95% CI**	**P-Value**	**Odds Ratio**	**95% CI**	**P-Value**	**Odds Ratio**	**95% CI**	**P-Value**
Cirrhosis vs. no Cirrhosis	**1.20**	**1.12–1.30**	**< 0.0001**	**1.69**	**1.45–1.96**	**< 0.0001**	**12.71**	**10.0–16.01**	**< 0.0001**
Female	1.00	Reference		1.00	Reference		1.00	Reference	
Male	1.42	1.35–1.51	<0.0001	1.25	1.13–1.40	<0.0001	1.44	1.16–1.79	<0.0001
18–45 years	1.00	Reference		1.00	Reference		1.00	Reference	
46–64 years	1.97	1.80–2.14	<0.0001	1.81	1.56–2.11	<0.0001	1.17	0.82–1.66	0.917
65 years and over	2.94	2.68–3.22	<0.0001	2.37	2.02–2.79	<0.0001	1.40	0.97–2.01	0.04
Diabetes	1.33	1.25–1.42	<0.0001	0.79	0.70–0.90	<0.0001	1.28	1.02–1.61	0.034
Hypertension	1.15	1.08–1.22	<0.0001	0.49	0.43–0.55	<0.0001	0.85	0.67–1.08	0.175
Chronic kidney disease	1.56	1.45–1.68	<0.0001	1.64	1.41–1.90	<0.0001	1.41	1.10–1.81	0.006
Heart failure	1.80	1.65–1.95	<0.0001	2.7	2.31–3.16	<0.0001	1.97	1.53–2.53	<0.0001
Chronic respiratory disease	1.21	1.12–1.30	<0.0001	0.62	0.52–0.73	<0.0001	0.87	0.66–1.15	0.325

ACLF, acute on chronic liver failure; CLD, chronic liver disease

outcomes among all CLD patients with and without cirrhosis. Furthermore, we included patients across both outpatient and inpatient settings and demonstrated that presence of cirrhosis was associated with significantly greater risk of poor outcomes following SARS-CoV-2 infection. Unique to our study, we also demonstrated that among a large U.S. cohort, presence of underlying CLD alone, even without cirrhosis, is associated with significantly greater risk of requiring hospitalization and poor respiratory outcomes following SARS-CoV-2 infection when compared to patients without underlying CLD. Our more comprehensively cohort provides data that are more generalizable to the overall CLD population.

The current study also specifically evaluated liver-related complications among the subset of patients with COVID-19+CLD. Compared to CLD patients without cirrhosis, those with cirrhosis at the time of SARS-CoV-2 infection had significantly greater risk of liver decompensation (6.7% vs. 3.4%, aOR 1.69, 95% CI 1.45–1.96, $P < 0.0001$) and development of ACLF (4.4% vs. 0.3%, aOR 12.7, 95% CI 10.0–16.0, $P < 0.0001$). However, even among patients without cirrhosis, a 3.4% rate of acute liver decompensation is not inconsequential and raises the importance of close monitoring of CLD patients infected with SARS-CoV-2. In a retrospective study of 50 hospitalized patients with COVID-19 and cirrhosis in Italy, the investigators observed that 28% developed ACLF following SARS-CoV-2 infection, and 46% of patients with MELD ≥ 15 at time of infection developed liver decompensation.[13] In the previously mentioned study by Marjot *et al.*, among 386 patients with cirrhosis, acute hepatic decompensation following SARS-CoV-2 infection occurred in 46% of patients, and among those with evidence of acute decompensation, 50% met criteria for ACLF.[7] Similarly, in a multicenter study in China of 21 hospitalized cirrhosis patients with COVID-19, 23.8% developed ascites, 19.0% had

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acute upper gastrointestinal bleeding, and 4.8% developed ACLF.[10] In the multicenter APCOLIS Study from the Asia Pacific world region, 228 patients with COVID-19+CLD were evaluated, among which 43 had cirrhosis.[8] Overall, 43% of the noncirrhotic patients presented with acute liver injury at time of SARS-CoV-2 infection, and among those with cirrhosis, 11.6% developed ACLF, and 9% developed acute liver decompensation.[8]

Our study of a large U.S. cohort of COVID patients with underlying CLD confirms that presence of underlying CLD, and especially if there is cirrhosis, is associated with significantly worse outcomes following SARS-CoV-2 infection. Our findings and others emphasize the importance of SARS-CoV-2 vaccination among patients with CLD and also highlight the need for close monitoring of CLD patients with low threshold for hospitalization for clinical deterioration, especially those with cirrhosis, following diagnosis of SARS-CoV-2. Despite the strengths of this study including one of the largest cohorts evaluating COVID-19 outcomes in patients with COVID-19+CLD, the comprehensive assessment of patients in both the inpatient and outpatient settings, and including CLD patients with and without cirrhosis, certain limitations should be acknowledged. Due to the nature of the dataset, we did not have data for vaccination status or COVID-19 specific treatment that was available for inclusion in the analyses. During the early onset of the pandemic, disparities in access to diagnostic testing and COVID-19-related care were reported. Thus, it is possible that some patients, including those with CLD, may have been infected with SARS-CoV-2 and either recovered or died without knowing they had COVID-19. Furthermore, throughout the course of the pandemic, there have been different variants of SARS-CoV-2, with varying levels of severity. We did not have data to determine the specific variant of SARS-CoV-2 that was present in each patient. We also did not have laboratory data to assess severity of CLD (e.g., fibrosis-4 score) but were able to incorporate ICD-9/10 diagnosis coding to evaluate for features of liver decompensation and ACLF as described in the methods. Similar to existing studies that utilized ICD-9/10 diagnostic coding, the identification of outcomes may have been subject to misclassification bias. However, we based our definitions on previously published comprehensive algorithms used in similar types of analyses.[15,18–21] In addition, given the primarily claims-based methods for identifications of disease states, we were not able to perform detailed evaluation of different variants of SARS-CoV-2. Despite these limitations, this study provides important data to improve our understanding of the impact of the COVID-19 pandemic on patients with CLD.

In summary, among a large U.S. cohort of COVID-19 patients with and without CLD, we observed that presence of underlying CLD at time of SARS-CoV-2 infection was associated with significantly greater risk of poor outcomes, including respiratory complications as well as liver-related decompensation. Patients with underlying cirrhosis had particularly higher risk of respiratory complications and liver-related decompensation. These data emphasize the importance of close monitoring of CLD patients following SARS-CoV-2 infection for any signs of clinical deterioration and further emphasize the importance of ensuring SARS-CoV-2 vaccination.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Study concept and design: All authors.

Acquisition of data: Zhang, Thamer.

Analysis and interpretation of data: All authors.

Statistical analysis: Zhang, Thamer.

Drafting of the manuscript: All authors.

Critical revision of the manuscript for important intellectual content: All authors.

Study supervision: Wong, Thamer.

All authors approve this version of the manuscript. All authors had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

CONFLICTS OF INTEREST

Robert Wong has received research grants from Gilead Sciences (to his institution) and has served as a consultant and advisor.

Yi Zhang: Nothing to disclose.

Mae Thamer has received research grants from Gilead Sciences (to her institution).

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AUTHORSHIP STATEMENT

Guarantor of the article: Robert Wong.

DATA AVAILABILITY

Data and study materials used for this study are publicly available. Analytic methods will be provided to other researchers by the authors upon request. The data, technology, and services used in the generation of these research findings were generously supplied pro bono by the COVID-19 Research Database partners, who are acknowledged at https://covid19researchdatabase.org. The datasets in this publication were linked using privacy-preserving record linkage provided by Datavant.

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Datavant's solution uses personally identifiable information (PII) to create tokens, which are de-identified, unique, irreversible patient keys. Tokens are then used to match individual records across different data sets without ever exposing the PII of the patient to whom each record belongs.

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APPENDIX A

SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jceh.2023.01.014.

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