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Clinical manifestations of SARS-CoV-2 Omicron infection is associated with the stage of liver cirrhosis

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Abstract

Background & aim The impact of Omicron variants on cirrhosis was largely unknown. Herein, we aimed to evaluate the impact of SARS-CoV-2 omicron variants infection on the clinical course and mortality of patients with liver cirrhosis.

Methods Between 26 December 2022, and 27 January 2023, eighty-two hospitalized patients with cirrhosis and confirmed SARS-CoV-2 infection were enrolled. The clinical and pulmonary CT imaging features were retrospectively collected. A gender and age-matched cohort of 51 non-cirrhotic patients with COVID-19 were also included.

Results Our results indicated the symptom heterogeneity in patients with cirrhosis infected with omicron variants. Patients with more severe liver disease tended to have less severe respiratory symptoms and less pulmonary lesions. SARS-CoV-2 omicron did not cause obvious perturbation of liver function or cirrhosis decompensation. In comparison with hospitalized COVID-19 patients without liver cirrhosis, cirrhotic patients showed more severe pulmonary lesions and higher levels of inflammatory cytokine IL-6, but no significant increase in mortality. Multivariate analysis identified lung lesions proportion, MELD ≥ 15 score, and APTT as independent predictors for 28-day-mortality in these patients.

Conclusion SARS-CoV-2 omicron variants caused a more severe inflammatory response in cirrhotic patients than in non-cirrhotic patients, but no further deterioration of liver function. Instead, patients with advanced stage of liver cirrhosis showed milder respiratory symptoms and pulmonary lesions. These results underscore the intricate relationship between Omicron infection and cirrhosis, highlighting the necessity for personalized clinical approaches in managing this specific patient group.

Keywords Omicron variant, Liver cirrhosis, COVID-19

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Introduction

Since its initial emergence in December 2019, SARS-CoV-2 has exerted profound global health impacts while posing unprecedented challenges to clinical management [1–4]. Demonstrating accelerated evolutionary progression, the virus reached a critical inflection point with the Omicron variant establishing global predominance by September 2022 [5–8]. Although Omicron demonstrates attenuated pathogenicity compared to ancestral strains, its heightened transmissibility and immune evasion capacity continue to endanger individuals with chronic comorbidities [9–15]. Patients with chronic liver disease (CLD), particularly cirrhosis, represent a vulnerable population in this context. China bears the world's highest CLD burden, with cirrhosis predominantly caused by viral hepatitis, alcoholic liver disease, and metabolic dysfunction-associated steatotic liver disease [16]. Early-phase studies delineates a distinct risk profile in COVID-19 patients with chronic liver disease, demonstrating robust correlations between hepatic functional reserve and clinical outcomes. A meta-analysis integrating 74 studies revealed that CLD significantly elevates COVID-19 mortality risk [17]. Marjot et al. demonstrated significantly elevated COVID-19 mortality in cirrhotic patients compared to non-cirrhotic controls, with further stratification revealing mortality increments of 20.0% for Child-Pugh B and 38.1%for Child-Pugh C cirrhosis relative to non-CLD patients [18]. Notably, 20% of compensated cirrhosis patients progress to acute-on-chronic liver failure (ACLF) post-infection, while nearly half of decompensated cases develop severe hepatic complications [19, 20].

However, whether Omicron maintains this risk profile remains controversial, as recent studies report comparable mortality between cirrhotic and non-cirrhotic cohorts but lack longitudinal hepatic function assessment and quantitative pulmonary imaging characterization [21]. Previous retrospective studies on cirrhotic patients with COVID-19 predominantly relied on conventional severity stratification, lacking phenotype-driven subgroup characterization [18, 22]. To address critical evidence gaps, this study conducted comparative analyses of cirrhotic patients hospitalized for COVID-19-related respiratory symptoms versus those admitted for cirrhosis, all with confirmed Omicron variant infection. Through Artificial intelligence (AI)-assisted quantification of CT imaging coupled with longitudinal hepatic function evaluation, we systematically delineated symptom heterogeneity and characterized pre-/post-infection liver injury patterns in this vulnerable population. Furthermore, we conducted a comparative analysis of COVID-19 clinical manifestations between cirrhotic patients and non-cirrhotic controls infected with the Omicron variant. This study illuminates novel pathways for addressing critical clinical decision-making challenges in balancing COVID-19 containment and cirrhosis-related complications during the Omicron-dominant phase.

Method

Study design and population

After reviewing overall non-elective in-patients from the First Affiliated Hospital of Zhejiang University School of Medicine between 26 December 2022, and 27 January 2023, we conducted an observational cohort study on 82 consecutive patients. Inclusion criteria for patients diagnosed with SARS-CoV-2 infection via reverse-transcriptase polymerase chain reaction (RT-PCR) of nasopharyngeal swab specimens were included in the study, while those with active malignancies, or prior solid-organ transplantation history were systematically excluded to minimize confounding clinical variables. Patients were divided into two groups: Group CR (47 patients hospitalized for respiratory symptoms related to SARS-CoV-2 infection) and Group CC (35 patients hospitalized for complications of cirrhosis). To assess the impact of pre-exited cirrhosis on in-patients with COVID-19, the control patients were selected from non-cirrhosis patients infected with COVID-19 to match at CR cohort for age and gender, hypertension and diabetes mellitus. For those cases involved in the control group, we excluded those who had hepatic dysfunction, other respiratory diseases, malignant tumors, organ transplants and other systemic diseases except hypertension and diabetes mellitus.

Data recorded were clinical, biochemical, radiologic findings, reasons for hospitalization, and survival outcome till day 28. Laboratory testing included a serum C-reactive protein, liver function test, coagulation testing and cytokine. We also assessed the Child-Pugh, model for end-stage liver disease (MELD) scores for cirrhosis patients. To simplify the analysis, COVID-19 positive cases were briefly categorized into two levels of severity based on the oxygen supplementation: severe COVID-19 was identified as need of mask oxygen therapy or higher flow oxygen therapy, the other needed lower oxygen supplementation or not needed oxygen supplementation were milder cases. The liver function perturbations of cirrhotic patients before and after COVID-19 were evaluated by biochemical data and the 2 compared to the last outpatient visit or the end of the last hospitalization before this infection. Due to the retrospective nature of this study, pre-infection medical records could be located for only 40 patients.

Artificial Intelligence (AI)-aided analysis of chest CT

AI-assisted detection system has been increasingly utilized in research settings [23–26]. Our AI analytical model performs quantitative analysis of thoracic CT scans, identifying inflammatory lesions through multi-region anatomical assessment. The hallmark radiological

features of COVID-19 pneumonia– ground-glass opacities (GGO), consolidations, and reticular patterns– are reliably identifiable through AI-assisted analysis. However, differentiating mixed patterns remains technically challenging, particularly given the system' limited accuracy in distinguishing between GGO and consolidation areas. We therefore pragmatically merged GGO and consolidation metrics into a unified "lesion" classification quantified by lesion proportion, while maintaining separate quantification of reticular patterns. Additionally, parenchymal bands data were provided and, similar to reticular patterns, were quantified based on the number of discrete lesions.

Statistical analysis

Statistics were performed using SPSS Statistics program (version 25.0) and Graphpad Prism (version 9.0.0). Continuous variables are reported as mean ± standard deviation for normally distributed data or median and interquartile range (IQR) for non-normally distributed data. Categorical variables are presented as percentages (%). The Chi-square test (or Fisher's exact test) was utilized for categorical variables, while continuous variables were compared using the Student's t-test, the Mann-Whitney U test, or the Kruskall-Wallis test, as appropriate. Univariate and multivariate Cox regression analyses were employed to identify factors associated with mortality. Kaplan-Meier survival analysis and the Log-Rank test were conducted to assess survival. No imputation was performed on the missing data. For all comparisons, results were considered statistically significant at $P < 0.05$.

Result

Baseline clinical characteristics of patients with cirrhosis and SARS-CoV-2 infection

From December 26, 2022, to January 27, 2023, 82 hospitalized cirrhosis patients with documented SARS-CoV-2 infection were enrolled. These patients were stratified into two cohorts: 47 patients (57.32%) admitted primarily for SARS-CoV-2-related respiratory symptoms (e.g., fever, chest tightness, dyspnea), and 35 patients (42.68%) hospitalized for cirrhosis complications with minimal or no SARS-CoV-2-related symptoms (Fig. 1). Subsequent analyses compared clinical, biochemical, and pulmonary CT imaging features between groups.

As delineated in Table 1, the respiratory symptom cohort (Group CR) demonstrated higher rates of fever (74.47% vs. 40.00%, $p = 0.002$), elevated peak body temperatures (38.60 ± 1.18 °C vs. 37.77 ± 0.86 °C, $p = 0.001$), and greater incidence of severe COVID-19 (36.17% vs. 14.29%, $p = 0.027$) compared to the cirrhosis complication cohort (Group CC). CT imaging revealed significantly larger total pulmonary inflammatory lesions in the Group CR (16.1 [5.85–43.2]% vs. 3.1 [0.8–13.08]%, $p = 0.002$), with similar trends across individual lung lobes ($p < 0.05$). Conversely, the Group CC exhibited elevated markers of

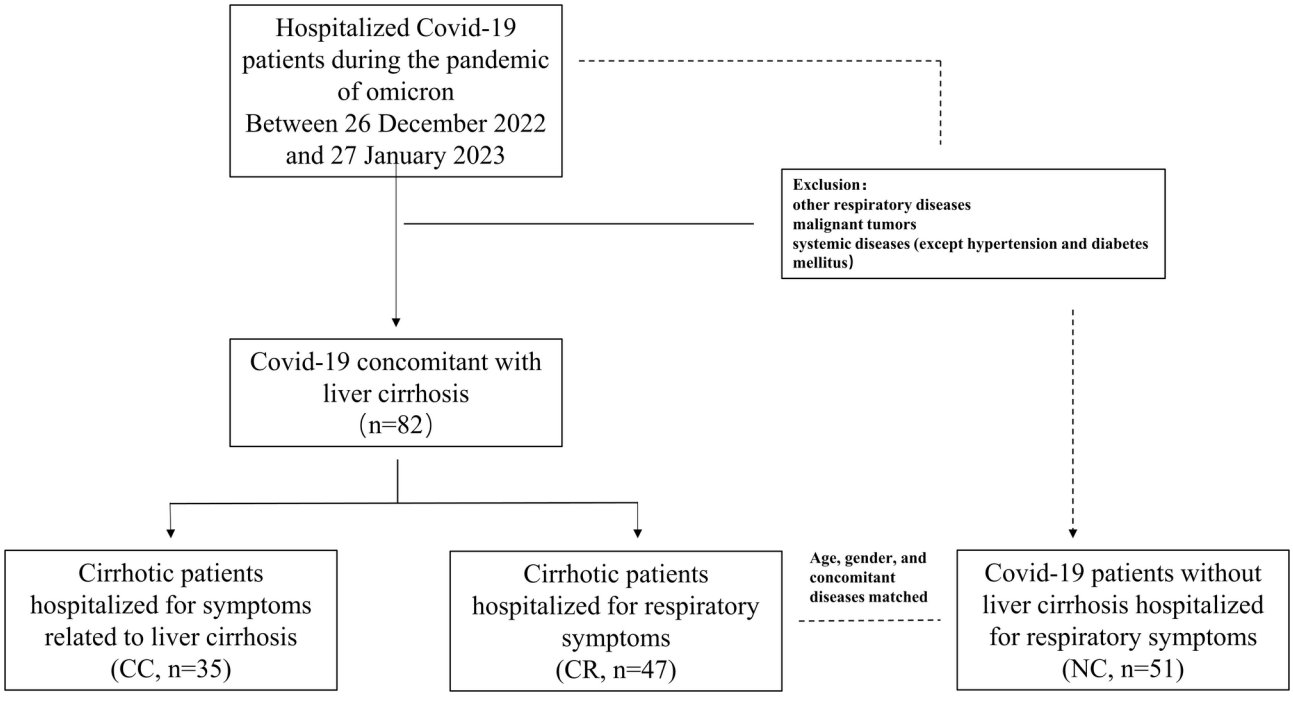

Fig. 1 Patient Recruitment and Matching Flowchart. This study enrolled 82 cirrhotic patients who were stratified into groups based on their primary admission diagnoses: Group CC (patients hospitalized for complications of cirrhosis) and Group CR (patients hospitalized for respiratory symptoms related to SARS-CoV-2 infection) groups. Concurrently, the Group CR was matched with a control Group(NC) according to the same inclusion and exclusion criteria

Table 1 Baseline clinical characteristics of patients with cirrhosis and SARS-Cov-2 infection

Variables	Group CR(*n* = 47)	Group CC(*n* = 35)	*P* value	Total (*n* = 82)
Age	69.43 ± 12.52	65.83 ± 11.89	0.192	67.89 ± 12.31
Males	31(65.96%)	27(77.14%)	0.271	58(70.73%)
Hypertension	20(42.55%)	9(25.71%)	0.115	29(35.37%)
Diabetes mellitus	17(36.17%)	8(22.86%)	0.195	25(30.49%)
Severity of COVID-19				
Severe	17(36.17%)	5(14.29%)	0.027	22(26.83%)
Higher flow oxygen therapy	5(10.64%)	1(2.86%)	0.363	6(7.32%)
Invasive mechanical ventilation	2(4.26%)	1(2.86%)	1.00	3(3.66%)
Admitted to ICU	3(6.38%)	0	0.353	3(3.67%)
Fever	35(74.47%)	14(40.00%)	0.002	49(59.76%)
T max/℃	38.60 ± 1.18	37.77 ± 0.86	0.001	38.23 ± 1.13
Cause of cirrhosis				
HBV	18(38.30%)	16(45.71%)	0.50	34(41.46%)
Alcohol	5(10.64%)	5(14.29%)	0.874	10(12.20%)
AIH	3(6.38%)	2(5.71%)	1.00	5(6.10%)
Schistosomiasis	4(8.51%)	1(2.86%)	0.55	5(6.10%)
Encephalopathy	3(6.38%)	11(31.43%)	0.003	14(17.07%)
Liver failure	3(6.38%)	11(31.43%)	0.003	14(17.07%)
Hepatocellular carcinoma	14(29.79%)	12(34.29%)	0.665	26(31.71%)
Decompensated	31(65.96)	33(96.29%)	0.002	64(78.05%)
Prior COVID-19 vaccination	23(48.93%)	17(48.57%)	0.974	40(48.78%)
Doses of vaccination*			0.358	
1	2(4.26%)	2(5.71%)		
2	8(17.02%)	4(11.42%)		
3	11(23.4%)	11(31.43%)		
4	2(4.26%)	0		
ALB, g/L	31.15(28.13, 35.55)	27.8(25.65, 31.5)	0.028	30.75 ± 7.22
ALT, U/L	25.5(15.75, 40)	27(12, 130.5)	0.537	26(14, 47)
AST, U/L	36(25.75, 57.5)	45(28.5, 129)	0.035	37(26, 74)
ALP, U/L	86.5(65.25, 116.5)	107(78, 189)	0.006	92(69, 149)
GGT, U/L	42(28.75, 80.5)	56(15.5, 172.5)	0.701	44(21, 105)
TB, umol/L	11.75(8.28, 22.03)	49.4(17.85, 217)	<0.001	17.6(10.6, 54.4)
DB, umol/L	7.1(4.35, 14.8)	25.3(11.05, 184.4)	<0.001	10.7(5.5, 41.1)
INR	1.21(1.09, 1.33)	1.4(1.31, 1.77)	<0.001	1.29(1.13, 1.5)
PT, /s	13.95(12.8, 15.28)	16.2(14.95, 20.15)	<0.001	14.8(13.2, 17.1)
APTT, /s	31.05(28, 35.93)	35.9(32.95, 47.45)	<0.001	33.4(28.9, 39.8)
WBC, 10E9/L	5.78(3.66, 8.36)	4.91(3.14, 7.71)	0.351	5.62(3.56, 8)
HGB, 10E9/L	116.5(91.75, 130)	104(76, 122.5)	0.321	107.15 ± 30.68
PLT, 10E9/L	104.5(50.25, 168)	73(38, 113)	0.022	86(48, 152)
CRP, mg/L	34.05(9.44, 55.17)	18.2(6.11, 38.76)	0.139	23.2(8.2, 51.03)
D-dimer, ug/L	2227.5(566, 4525.25)	2678(1538, 4385.5)	0.112	2350(956, 4411)
Serum creatinine, umol/L	64(52.75, 84)	74(61, 100.5)	0.142	67(55.5, 89.5)
Child-Pugh score:			0.001	
A (5–6)	26(55.32%)	6(17.14%)		32(39.02%)
B (7–9)	17(36.17%)	16(45.71%)		33(40.24%)
C (10–15)	4(8.51%)	13(37.14%)		17(19.51%)
MELD score	9.00(7.0, 13.0)	14.0(10.0, 18.0)	<0.001	10.5(8, 15)
MELD score ≥ 15	8(17.02%)	15(42.86%)	0.01	23(28.05%)
Lesion proportion, %				
Whole lung	16.1(5.85, 43.2)	3.1(0.8, 13.08)	0.002	9.3(2.6, 33.1)
Left lung	15.4(2.65, 45)	1.25(0.1, 8.05)	0.002	7.3(0.7, 32.8)
Right lung	21.1(5.35, 39.45)	3.15(1.05, 20.55)	0.008	12.6(2.5, 34)
Superior lobe of left lung	4.8(0.55, 32.55)	0.7(0, 4.33)	0.015	2.7(0.4, 28.6)

Table 1 (continued)

Variables	Group CR($n=47$)	Group CC($n=35$)	*P* value	Total ($n=82$)
Inferior lobe of left lung	26.2(5.15, 69.65)	0.9(0.2, 11.78)	0.001	9.8(0.8, 52.5)
Superior lobe of right lung	14(1.75, 42.9)	0.75(0, 16.05)	0.019	7.9(0, 35.3)
Middle lobe of right lung	7.9(0.55, 36.35)	0.95(0, 9.1)	0.017	3.4(0.2, 23.6)
Inferior lobe of right lung	21.7(7.15, 66.55)	5.85(0.65, 21.25)	0.012	16.6(3.1, 46.9)
Parenchymal band	1(0, 3)	2(1, 4.25)	0.045	1(0, 3)
Reticular pattern	1(0, 2)	0(0, 2)	0.146	1(0, 2)
Mortality	6(12.77%)	9(25.71%)	0.134	15(18.29%)

* The vaccines administered in this study were inactivated COVID-19 vaccines

#CR: patients hospitalized for respiratory symptoms related to SARS-CoV-2 infection; CC, patients hospitalized for complications of cirrhosis

Table 2 Comparison of biochemical and clinical characteristics of cirrhotic patients before SARS-Cov2 infection and at SARS-CoV-2 diagnosis

Variables	Before SARS-Cov2 infection*($n=40$)	After SARS-Cov2 infection($n=40$)	*P* value
ALB, g/L	33.1(31.1, 35.1)	28.6(26.8, 34.9)	0.001
ALT, U/L	20(11, 39)	25(14, 38)	0.204
AST, U/L	31(24, 56)	36(26, 74)	0.108
ALP, U/L	91(77, 187)	92(69, 174)	0.578
TB, umol/L	25.4(12.1, 41.9)	21.3(10.9, 52.1)	0.918
DB, umol/L	18.8(6.3, 24.4)	15.4(6.4, 33.8)	0.383
GGT, U/L	44(22, 85)	47(28, 95)	0.71
INR	1.28(1.13, 1.39)	1.31(1.2, 1.5)	0.935
APTT, /s	31(30.1, 33.9)	33.9(30.1, 37.5)	0.097
PT, /s	14.7(12.9, 15.8)	15(13.8, 17.1)	0.691
D-dimer, ug/L	1760(980, 3659)	2522(1025, 4411)	0.147
WBC, 10E9/L	4.29(2.83, 6.34)	5.68(2.75, 8)	0.27
HGB, 10E9/L	103.97 ± 28.41	99.25 ± 32.08	0.501
PLT, 10E9/L	57(38, 115)	73(38, 156)	0.655
Serum creatinine, umol/L	59(53, 93)	70(53, 120)	0.878
Ascites	20(50%)	26(62%)	0.175

hepatic dysfunction (TB, DB, INR, PT, APTT, D-dimer, AST, ALP; $p<0.05$), reduced ALB and PLT levels ($p<0.05$), higher Child-Pugh score variability ($p=0.01$), increased MELD ≥ 15 prevalence (42.86% vs. 17.02%, $p=0.01$), and higher rates of decompensation (96.29% vs. 31.43%) and liver failure (31.43% vs. not reported) compared to the Group CR ($p<0.05$). These findings indicate distinct clinical profiles: the Group CR manifested more severe respiratory involvement, while the Group CC demonstrated exacerbated hepatic impairment.

Limited hepatic impact of SARS-CoV-2 Omicron variant in cirrhosis

Longitudinal analysis of 40 patients (23 CR, 17 CC) comparing pre- and post-infection parameters revealed minimal hepatic functional changes post-Omicron infection (Table 2). Only ALB levels significantly declined (33.1 [31.1–35.1] g/L vs. 28.6 [26.8–34.9] g/L, $p=0.001$), with no significant alterations in other biochemical markers or ascites prevalence. These results suggest Omicron infection does not substantially exacerbate pre-existing liver dysfunction in cirrhotic patients.

Exacerbated inflammatory responses in cirrhotic COVID-19 patients

Comparative analysis with non-cirrhotic COVID-19 patients revealed heightened inflammatory burden in cirrhotic individuals (Table 3). The Group CR demonstrated more extensive pulmonary lesions (16.1 [5.58–43.2]% vs. 5.7 [2–17]%, $p=0.02$), elevated proinflammatory cytokines (IL-6: 11.96 [4.16–52.31] vs. 5.13 [3.18–7.7] pg/mL, $p=0.026$; IL-8: 12.47 [5.58–43] vs. 5.11 [1.88–9.68] pg/mL, $p<0.001$), and marked hepatic parameter abnormalities (AST, ALP, GGT, TB, DB, INR, PT, D-dimer; $p<0.05$) compared to non-cirrhotic controls. This underscores the dual burden of enhanced systemic inflammation and baseline hepatic compromise in cirrhotic COVID-19 patients.

Predictors of 28-Day mortality in cirrhotic COVID-19 patients

The overall 28-day mortality rate was 18.29% ($n=15$), with median survival of 7 (4–12) days. Mortality rates differed non-significantly between CR (12.8%, 95% CI 2.9–22.7) and CC groups (25.7%, 95% CI 10.5–40.9; $p=0.134$) (Figs. 2A-B). Multivariate analysis identified MELD ≥ 15 (HR 42.406; 95% CI 1.320–1362.248), prolonged APTT (HR 1.282; 95% CI 1.060–1.550), and pulmonary lesion extent (HR 1.072; 95% CI 0.014–1.134) as independent mortality predictors (Table 4). Survival curves (Figs. 3A-C) confirmed significantly higher mortality with MELD ≥ 15, elevated APTT (> median), and extensive lung involvement (> median). Etiology of cirrhosis, comorbidities, and other biochemical markers showed no mortality association in univariate analysis.

Discussion

This study characterizes the clinical, biochemical, and pulmonary CT imaging features of cirrhotic patients infected with the SARS-CoV-2 Omicron variant. Our findings reveal heterogeneity in COVID-19 manifestations among cirrhotic patients: those hospitalized for

Table 3 Comparison of clinical and biochemical characteristics of cirrhotic patients and no-cirrhosis patients

Variables	Group CR (*n* = 47)	No-cirrhosis patients(*n* = 51)	*P* value
Age	69.43 ± 12.52	71.71 ± 12.98	0.611
Males	31(65.96%)	41(80.39%)	0.106
Hypertension	20(42.55%)	12(23.53%)	0.045
Diabetes mellitus	17(36.17%)	12(23.53%)	0.171
Severity of COVID-19			
Severe	17(36.17%)	10(19.61%)	0.067
Higher flow oxygen therapy	5(10.64%)	2(3.92%)	0.370
Invasive mechanical ventilation	2(4.26%)	0	
Admitted to ICU	3(6.38%)	0	
Prior COVID-19 vaccination	23(48.93%)	33(64.7%)	0.115
Doses of vaccination			0.899
1	2(4.26%)	2(3.92%)	
2	8(17.02%)	10(19.61%)	
3	11(23.4%)	19(37.25%)	
4	2(4.26%)	2(3.92%)	
ALB, g/L	31.15(28.13, 35.55)	36.1(32.1, 40.1)	<0.001
ALT, U/L	25.5(15.75, 40)	22(15, 33)	0.269
AST, U/L	36(25.75, 57.5)	25(20, 34)	0.001
ALP, U/L	86.5(65.25, 116.5)	64(53, 84)	0.003
GGT, U/L	42(28.75, 80.5)	27(17, 42)	0.019
TB, umol/L	11.75(8.28, 22.03)	7.8(6.3, 10.6)	<0.001
DB, umol/L	7.1(4.35, 14.8)	3.8(3.1, 6)	<0.001
INR	1.21(1.09, 1.33)	1.05(0.99, 1.14)	<0.001
PT, /s	13.95(12.8, 15.28)	12.2(11.5, 13.2)	<0.001
APTT, /s	31.05(28, 35.93)	30(27.4, 32.3)	0.143
WBC, 10E9/L	5.78(3.66, 8.36)	5.96(4.41, 7.9)	0.670
HGB, 10E9/L	116.5(91.75, 130)	127.74 ± 17.67	0.001
PLT, 10E9/L	104.5(50.25, 168)	207(147, 300)	<0.001
CRP, mg/L	34.05(9.44, 55.17)	33.1(13, 76.52)	0.728
D-dimer, ug/L	2227.5(566, 4525.25)	641(270, 1620)	<0.001
IL-1β, pg/mL	0.1(0.1, 0.48)	0.1(0.1, 0.67)	0.886
IL-2, pg/mL	2.06(0.18, 2.98)	1.08(0.59, 3.04)	0.791
IL-4, pg/mL	0.71(0.01, 2.81)	0.99(0.01, 3.15)	0.529
IL-5, pg/mL	0.94(0.06, 2.38)	0.73(0.08, 1.98)	0.398
IL-6, pg/mL	11.96(4.16, 52.31)	5.13(3.18, 7.7)	0.026
IL-8, pg/mL	12.47(5.58, 43)	5.11(1.88, 9.68)	<0.001
IL-10, pg/mL	3.99(2.42, 7.52)	3.07(1.83, 4.51)	0.080
IL-17 A, pg/mL	1.02(0.01, 37.66)	0.1(0.01, 2.63)	0.327
IL-12P70, pg/mL	2.19(0.11, 4.64)	1.8(0.56, 3.8)	0.690
IFN-α, pg/mL	1.51(0.41, 2.67)	1.39(0.66, 2.39)	0.936
IFN-γ, pg/mL	2.11(0.16, 3.68)	1.62(0.7, 3.18)	0.548
TNF-α, pg/mL	3.42(1.01, 5.01)	1.4(0.97, 4.87)	0.272
Lesion proportion, %			
Whole lung	16.1(5.85, 43.2)	5.7(2, 17)	0.020
Left lung	15.4(2.65, 45)	3.7(1.3, 21.9)	0.025
Right lung	21.1(5.35, 39.45)	7.7(2.5, 18.7)	0.026
Superior lobe of left lung	4.8(0.55, 32.55)	1.5(0, 13.6)	0.021
Inferior lobe of left lung	26.2(5.15, 69.65)	8.7(1.3, 28.8)	0.033
Superior lobe of right lung	14(1.75, 42.9)	2.3(0, 14.5)	0.011
Middle lobe of right lung	7.9(0.55, 36.35)	1.9(0, 8.7)	0.063
Inferior lobe of right lung	21.7(7.15, 66.55)	13(1.5, 35.9)	0.082
Parenchymal band	1(0, 3)	2(1, 3)	0.040

Table 3 (continued)

Variables	Group CR (*n* = 47)	No-cirrhosis patients(*n* = 51)	*P* value
Reticular pattern	1(0, 2)	0(0, 1)	0.017
Mortality	6(12.77%)	3(5.88%)	0.407

* CR: patients hospitalized for respiratory symptoms related to SARS-CoV-2 infection

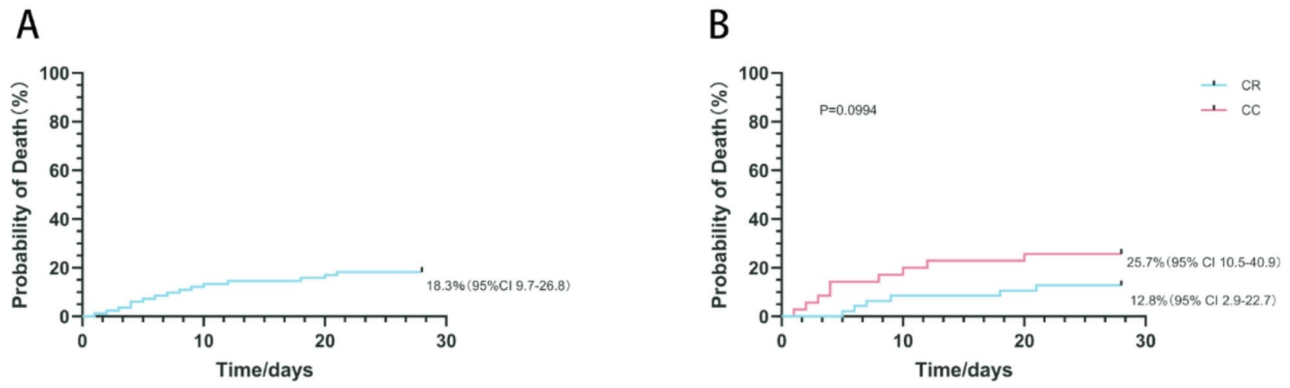

Fig. 2 28-day probability of overall mortality and mortality related to causes of hospitalization (**A**): The 28-day probability of overall mortality. (**B**): The 28-day probability of overall mortality according to the causes of hospitalization

Table 4 Risk factors of 28-day mortality in cirrhotic patients at COVID-19 diagnosis

Variables	B	SE	*P* value	HR(95%CI)
Meld ≥ 15	3.747	1.770	0.034	42.406(1.320—1362.248)
APTT	0.249	0.097	0.010	1.282 (1.060—1.550)
WBC	-0.271	0.249	0.276	0.763 (0.468—1.241)
PLT	-0.012	0.011	0.304	0.989 (0.967—1.011)
Lesions proportion#	0.070	0.028	0.014	1.072 (0.014—1.134)
Reason for hospitalization	0.411	1.031	0.690	1.509 (0.328—11.387)

*Other indicators included in the univariate analysis were cirrhosis etiology, liver failure, decompensation, hepatocellular carcinoma, diabetes mellitus, gender, CRP, D-2 polymers, ALB, HGB, and cytokines, and none of the above indicators were correlated with 28-day mortality

Lesions proportion indicated the proportion of lung volume involved in whole lung

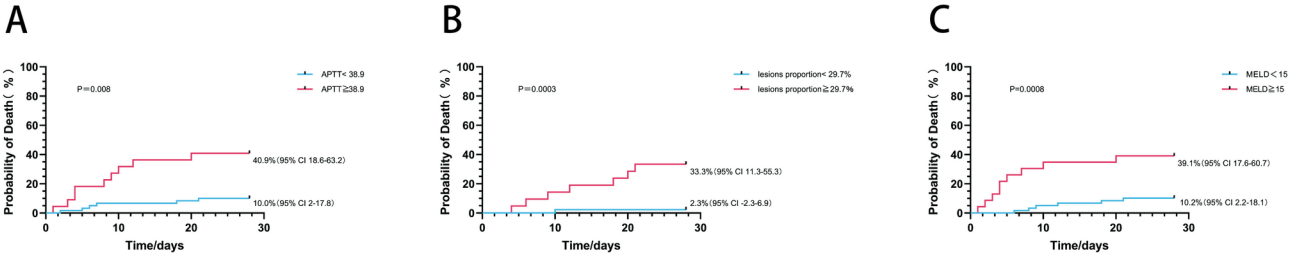

Fig. 3 28-day probability of overall mortality according to APTT, MELD and lesions proportion. (**A**): The 28-day probability of overall mortality according to APTT ≥ 38.9. (**B**): The 28-day probability of overall mortality according to lesions proportion ≥ 29.7%. (**C**): The 28-day probability of overall mortality according to MELD ≥ 15. CR: patients hospitalized for respiratory symptoms related to SARS-CoV-2 infection; CC, patients hospitalized for complications of cirrhosis

respiratory symptoms related to SARS-CoV-2 infection exhibited more extensive pulmonary lesions and higher inflammatory markers but no significant increase in 28-day mortality compared to non-cirrhotic controls. Conversely, patients admitted primarily for hepatic decompensation demonstrated milder respiratory symptoms and less severe pulmonary involvement. Notably, our findings indicate that Omicron infection in cirrhotic patients did not induce significant perturbations in liver function parameters, with the exception of a marked reduction in serum albumin levels.

Current evidence regarding pulmonary CT features in cirrhotic patients following SARS-CoV-2 infection remains limited. This study is the first to employ AI-based CT quantification for assessing pulmonary infiltration extent, integrating multidimensional clinical data

to delineate the clinical phenotypic heterogeneity of cirrhotic patients infected with the SARS-CoV-2 Omicron variant. While prior studies reported similar qualitative chest imaging features between cirrhotic and non-cirrhotic individuals [27], our quantitative analysis provides critical insights. This study demonstrated that cirrhotic patients hospitalized with COVID-19-related respiratory syndrome exhibited more severe pulmonary lesions and significantly elevated IL-6/IL-8 levels compared to non-cirrhotic COVID-19 patients. These findings corroborate the established association between pre-existing liver disease and poorer prognostic outcomes in SARS-CoV-2 infection [28, 29]. We propose that compensatory cirrhosis with low-grade systemic inflammation predisposes to immune hyperactivation upon SARS-CoV-2 infection ("second-hit" mechanism) [30]. Paradoxically, patients admitted primarily for hepatic decompensation exhibited higher COVID-19-related fever incidence and more severe pulmonary involvement. These findings may be linked to divergent immune profiles across cirrhosis stages [30]. Previous studies of HIV-infected cases with COVID-19 have indicated that immunosuppression due to HIV infection may be protective against COVID [31–34]. A recent study observed that HIV-infected individuals have a lower risk of Omicron variant infection than HIV-negative people [35]. It was assumed that lower CD4 count in HIV-infected individuals could reduce the excessive immune response to COVID-19, resulting in milder symptoms in these individuals [36]. Immune dysfunction associated with cirrhosis includes a distinct spectrum of immune alterations, which varied at different stages [37]. Patients with advanced cirrhosis usually showed high-grade systemic inflammatory phenotype with intense immune paralysis, in contrast to the low-grade systemic inflammatory phenotype in compensated cirrhosis [30]. One of the hallmarks in the immunopathology mechanisms of severe cases in COVID-19 is a hyperinflammatory innate immune response along with an inadequate adaptive response may elicit extensive local and systemic tissue injury [38]. The immune paralysis in advanced cirrhosis might partly explain the milder respiratory symptoms of COVID-19 and less pulmonary CT lesions as immunosuppression may tamper the cytokine storm of COVID-19.

Multivariate analysis identified MELD ≥ 15, prolonged APTT, and pulmonary lesion burden as independent predictors of 28-day outcomes. The exceptionally wide confidence interval for MELD ≥ 15 (1.320–1362.248) necessitates validation in expanded cohorts. Previous studies demonstrated that COVID-19 infection significantly increases the proportion of cirrhotic patients progressing to end-stage liver disease (MELD ≥ 15), with MELD scores established as an independent predictor of mortality [39]. Moon et al. further demonstrated a strong correlation between COVID-19 mortality and MELD scores in cirrhotic populations [29]. In our cohort, despite statistical uncertainties, the high event rate (39.1%) in the MELD ≥ 15 subgroup highlights its potential utility for risk stratification. Future prospective studies with larger sample sizes will refine these effect estimates.

Notably, Omicron infection did not significantly elevate liver enzymes in cirrhotic patients, contrasting with earlier variants [40, 41]. This discrepancy may reflect the attenuated virulence of Omicron, as demonstrated by Zhang et al. in their analysis of 1,001 hospitalized patients showing a lower incidence of liver injury compared to Delta-variant infection [42]. Notably, Twohig et al. further observed reduced mortality rates among cirrhotic patients during the Omicron-dominant phase relative to earlier variant waves [43].However, the observed serum albumin decline post-infection aligns with reported risks of ascites exacerbation, suggesting Omicron-dominant may indirect hepatic dysfunction via systemic inflammation rather than direct viral cytopathy [41, 43, 44]. Pulmonary lesion severity remained a key prognostic determinant, consistent with the Moon et al. [27]. Further multicenter studies are needed to elucidate causal relationships between albumin dynamics and delayed hepatic decompensation in this population.

Several limitations of this study should be explicitly acknowledged. Firstly, the inherent constraints of our single-center retrospective design, particularly regarding sample size limitations exacerbated by reduced cirrhotic admissions during the COVID-19 pandemic. Secondly, the current AI-based imaging analysis system exhibits technical constraints in accurately differentiating ground-glass opacities from consolidation areas, necessitating pooled analysis of heterogeneous lesion types when assessing pneumonia severity. This non-specific evaluation approach might hinder precise interpretation of pathophysiological mechanisms. Future multicenter prospective cohort studies incorporating refined AI lesion segmentation algorithms should be conducted to validate these findings and further elucidate the heterogeneous mechanisms underlying Omicron variant infection in cirrhotic populations.

Conclusion

In conclusion, SARS-CoV-2 Omicron variants elicit a more pronounced inflammatory response in cirrhotic patients compared to non-cirrhotic patients, yet they do not exacerbate liver function or lead to cirrhosis decompensation. Cirrhotic patients with advanced liver disease tend to exhibit milder respiratory symptoms and pulmonary lesions. These findings highlight the complex interplay between Omicron infection and cirrhosis, emphasizing the need for tailored clinical management strategies for this patient population.

Abbreviations

COVID-19	Corona Virus Disease 2019
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus-2
ACLF	Acute-on-chronic liver failure
CT	Computerized tomography
PCR	Polymerase chain reaction
CR	Patients hospitalized for respiratory symptoms related to SARS-CoV-2 infection
CC	Patients hospitalized for complications of cirrhosis
MELD	Model for end-stage liver disease
AI	Artificial intelligence
IQR	Interquartile range
HBV	Hepatitis B virus
AIH	Autoimmune hepatitis
ALB	Albumin
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ALP	Alkaline phosphatase
GGT	γ-glutamyltransferase
TB	Total bilirubin
DB	Direct bilirubin
INR	International normalized ratio
PT	Prothrombin time
APTT	Activated partial thromboplastin time
PLT	Platelets
WBC	White blood cell
HGB	Hemoglobin
CRP	C reactive protein
IL-1β	Interleukin- 1β
IL-2	Interleukin- 2
IL-4	Interleukin- 4
IL-6	Interleukin- 6
IL-8	Interleukin- 8
IL-10	Interleukin- 10
IL-17A	Interleukin- 17 A
IL-12P70	Interleukin- 12P70
IFN-α	Interferonα
IFN-γ	Interferonγ
TNF-α	Tumor necrosis factor-α

Author contributions

Z.L. played a role in the acquisition of clinical data from patients with COVID-19 and liver cirhosis, while W.F. is responsible for the procurement, organization, and analysis of clinical data, as well as the composition of articles. All authors read and approved the final manuscript.

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Data availability

All data and materials in this article are included in the manuscript.

Declarations

Ethics approval and consent to participate

Our study received approval from the Institutional Review Boards at the The First Affiliated Hospital, Zhejiang University School of Medicine (IIT20210312B-R1). As a retrospective study using anonymized clinical data, the ethics committee waived the requirement for individual patient consent. We certify that the study was performed in accordance with the 1964 Declaration of Helsinki and later amendments.

Consent for publication

Not applicable.

Clinical trial number

not applicable.

Competing interests

The authors declare no competing interests.

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