Chronic Liver Disease and COVID-19: A Perspective From Singapore

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Research article

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Abstract

Background: Chronic liver diseases including non-alcoholic fatty liver disease (NAFLD) are associated with COVID-19 progression. With no signs of the pandemic abating, thousands worldwide are at risk of a severe disease course.

Objective: We aimed to describe the epidemiological features, clinical course, treatment and outcomes of our patients with COVID-19 and chronic liver disease.

Methods: A retrospective descriptive study of COVID-19 patients with chronic liver disease admitted to the National Centre for Infectious Diseases in Singapore between 29th February and 2nd May 2020 was performed.

Results: 16 patients had chronic liver disease – 9 had NAFLD. In the NAFLD group, peak ALT was higher (median: 84 U/L vs 38 U/L; P = 0.042) and more patients had hyperlipidaemia (88.9% vs 28.6%; p=0.035), but median Body Mass Index (BMI) was not significantly higher (24.3 kg/m^2 vs 24.2 kg/m^2). NAFLD patients had a poorer clinical course: more required anti-viral medications (66.7% vs 0%; p=0.011), and time to negative swab was longer (24 days vs 13 days; p=0.008). 3 patients had liver cirrhosis (all non-NAFLD). 1 decompensated but none required intensive care unit admission or died.

Conclusion: Our results show that in COVID-19 patients with chronic liver disease, those with NAFLD experience a more severe clinical course. In Asians, NAFLD can have poorer prognostic implications, despite them having only mildly raised BMI. We advocate that patients with NAFLD and liver cirrhosis should be closely monitored for COVID-19 disease progression.

Introduction

Millions of people around the world have been infected by the Coronavirus disease (COVID-19)[1]. Many countries are facing new waves of infection with no signs of the pandemic abating. While initial studies suggested that the impact of COVID-19 on the liver was mild, there are now findings that COVID-19 may be more severe in patients with non-alcoholic fatty liver disease (NAFLD) and other underlying chronic liver diseases (CLD).

Between 1% and 11% of patients with COVID-19 may have underlying CLD[2]. While the SECURE-Cirrhosis Registry and the COVID-HEP registry are collecting data on pre-existing liver disease and COVID-19, our current knowledge of these patients with CLD continues to evolve. NAFLD has an increasing global prevalence of about 25%[3] and was found to be associated with COVID-19 disease progression[4–6]. The subset of cirrhotic patients was reported to have potentially increased risk for COVID-19, higher risk for severe disease, and increased risk for hepatic decompensation and death[7]. However, no studies in South-East Asia have directly compared NAFLD patients against CLD patients of other aetiologies (non-NAFLD).

We aimed to describe the epidemiological features, clinical course, treatment and outcomes of our patients with COVID-19 and CLD in Singapore.

Materials And Methods

All patients confirmed to have COVID-19 by a positive SARS-CoV-2 real-time reverse transcriptase–polymerase chain reaction (RT-PCR), who were admitted to the National Centre for Infectious Diseases in Singapore between 29th February and 2nd May 2020, were considered for data source. Only patients with an existing diagnosis of CLD or the presence of steatosis on ultrasound liver imaging were included in the final analysis[8–10]. We identified a total of 16 patients with CLD and aimed to retrospectively analyse them according to two groups – NAFLD versus non-NAFLD. Waiver of informed consent for collection of clinical data from infected individuals was granted by the Singapore Ministry of Health, under the Infectious Diseases Act as part of the COVID-19 outbreak investigations.

Patient demographics, co-morbid conditions, presenting symptoms, serial laboratory data and hospitalization outcomes (including need for oxygen, intensive care unit [ICU] admission, time to negative COVID-19 swab and in-hospital mortality) were obtained using a standardized data collection form. The negative swab was either taken as the first out of two consecutive negative swabs (available investigations in hospital) or from the discharge date from community isolation facilities (where actual dates of negative swab results are unavailable). The R ratio was used to describe the pattern of liver injury and was calculated as (Alanine aminotransferase [ALT] ÷ ALT upper limit normal) ÷ (Alkaline phosphatase [ALP] ÷ ALP upper limit normal)[11]. The peak (highest value obtained during the admission) ALT and ALP values were used, and the upper limit of normal for ALT and ALP was 40 U/L and 120 U/L respectively. Child-Turcotte-Pugh (CTP) status and Model for End-Stage Liver Disease (MELD) were calculated for the known cirrhotic patients at and during admission.

Numbers and proportions were presented for categorical variables, with median values and range for continuous variables. Fisher's exact or Chi-square test was used to compare categorical variables, and Mann-Whitney U test to compare continuous variables between NAFLD and non-NAFLD patients. All statistical tests were two-sided, and statistical significance was taken as $p < 0.05$. Statistical analyses were performed using IBM SPSS Statistics for Windows, V.24.0.

Results

Out of a total of 16 patients with CLD – 9 had NAFLD, 6 had Hepatitis B and 1 had alcoholic liver disease. Table 1 shows the patient demographics and baseline characteristics. The majority were Chinese ethnicity (75%), one was Indian, two were Filipino and one was Bangladeshi. The median age was 61 years (range 28–80 years) and nine (56.3%) were female. More patients in the NAFLD group as compared to the non-NAFLD group had hyperlipidaemia (8 [88.9%] vs 2 [28.6%]; $p = 0.035$). The median Body Mass Index (BMI) was 24.3 kg/m^2 (range 18.5 kg/m^2 – 33.1 kg/m^2), with no significant difference between the two groups.

Serial laboratory data from each patient obtained during their hospitalization stay was analysed. 62.5% of patients had abnormal liver function tests (LFT) during the admission. The median peak ALT was 61 U/L (range 19 U/L – 518 U/L) and the median peak ALP was 86 U/L (range 45 U/L – 332 U/L). The median day of illness corresponding to the peak ALT was day 5 (range day 1–23), and this was similar for both the NAFLD and non-NAFLD groups. The difference in median peak ALT values between the two groups was statistically significant (84 U/L vs 38 U/L; p = 0.042). Derangement in LFT was transient with an improving trend as the illness resolved. The temporal patterns of selected laboratory investigations over a 30-day period between the two groups were mostly similar (Fig. 1). The median peak R ratio for all patients in our study was 2.1, corresponding to a mixed picture of liver injury (defined as R ratio 2 to 5)[11]. Our analysis showed that patients in the non-NAFLD group had a cholestatic pattern of liver injury (defined as R ratio < 2)[11] with a median peak R ratio of 1.3 versus a mixed picture (2.4) in the NAFLD group (p = 0.055).

Overall, our study found that patients in the NAFLD group developed a more severe clinical course, as compared to those in the non-NAFLD group. 6 patients in the NAFLD group (66.7%) required one or more anti-viral medications versus none in the non-NAFLD group (p = 0.011). Patients were started on anti-viral medications based on the attending physician's clinical discretion. Kaletra was the most common anti-viral used (4 patients) followed by Remdesivir (2 patients). Other drugs administered included Hydroxychloroquine and Interferon beta 1b. 43.8% of all patients required supplemental oxygen therapy with similar numbers in both groups. Only two patients required intubation and ICU admission; both of them belonged to the NAFLD group. There were no deaths. In terms of biochemical markers of disease severity, patients in the NAFLD group had higher levels of Lactate Dehydrogenase (LDH) and C-Reactive Protein (CRP) levels as compared to patients in the non-NAFLD group, though this was not statistically significant. Those in the NAFLD group also took a longer time to achieve a negative swab (median 24 days vs 13 days; p = 0.008) and had a longer hospitalization stay (median 21 days vs 12 days; p = 0.210) as compared to patients in the non-NAFLD group.

Our cohort included three patients with liver cirrhosis, all of whom were in the non-NAFLD group. The first patient had hepatitis B and primary biliary cholangitis with CTP-A(5) class, MELD 6 score at baseline. This patient remained well and had normal LFT. The second patient had hepatitis B with underlying chronic kidney disease, and was CTP-A(6) class MELD 12 score at baseline. Despite having a slight increase in the CTP class to B(7) on day 7 of illness due to a drop in Albumin levels, this patient did not decompensate and remained well. The third patient was CTP-C(11) class MELD 17 score at baseline and decompensated on day 7 of illness with an increase in international normalised ratio (INR) that peaked at 2.5, ascites, variceal bleed requiring endoscopic ligation and a newly diagnosed hepatocellular carcinoma. However, this patient did not require anti-viral medications or ICU admission and was discharged on day 14 of illness.

Discussion

Our study showed that patients in the NAFLD group had a worse clinical course as compared to those in the non-NAFLD group. A higher proportion of NAFLD patients required the administration of anti-viral

medications, had higher levels of LDH and CRP, required ICU admission, and had prolonged hospitalization. This supports the current evidence that patients with NAFLD do worse with COVID-19 as compared to non-NAFLD patients[4,12]. SARS-CoV-2 enters host cells via angiotensin I converting enzyme 2 (ACE2) receptors present in abundance in adipose tissues which can serve as a viral reservoir[13]. In addition, NAFLD patients may be more vulnerable to increased cytokine production associated with COVID-19[14]. We note that despite a poorer clinical course, patients in the NAFLD group had mild transaminitis with no persistent deterioration in liver function. Studies looking at LFT in COVID-19 patients have also found that the majority had mild LFT abnormalities that were self-limiting[15–17]. Thus, other factors such as associated metabolic co-morbidities may contribute to the increased risk of severe COVID-19 infection in NAFLD patients[18]. We found that more patients in the NAFLD group had hyperlipidaemia as compared to those in the non-NAFLD group.

Ji et al[4]. reported that COVID-19 patients who had illness progression had significantly higher BMI levels (26.6 ± 2.2 kg/m^2), with 87% of these patients having NAFLD. However, we found that the median BMI in our NAFLD group who had a more severe clinical course, was lower than expected (24.3 kg/m^2). Thus, it is unclear if weight or the underlying aetiology of fatty liver disease plays a bigger role in determining a patient's clinical course in COVID-19. NAFLD is traditionally associated with central obesity but can also occur in lean subjects, especially in the Asian population. Body fat distribution is more important than total body fat content in the development of non-obese NAFLD[19–23]. Though Asians with NAFLD may have a lower BMI, they are still at an increased risk for adverse cardiometabolic outcomes. This has been attributed primarily to alterations in body fat distribution, in particular visceral adiposity which can be measured by waist circumference or waist-to-hip ratio[24]. Recently, sagittal abdominal diameter (SAD) - measured by the anteroposterior diameter of the abdomen in the supine position, has emerged as the preferred anthropometric indicator for visceral adiposity. SAD is clinically feasible and is an independent measurement with high reproducibility and correlation to adverse metabolic outcomes[25–26]. Genetic susceptibility of Asians to non-obese NAFLD has been postulated to be via predisposition to Type 2 diabetes mellitus, patatin-like phospholipase domain-containing-3 (PNPLA3) gene / Sterol regulatory element-binding factor 2 (SREBF) single nucleotide polymorphisms (SNP) and polymorphisms in apolipoprotein[25,27–29]. More studies will be needed to identify the factors that causally drive COVID-19 progression in individuals with obese and non-obese NAFLD.

One out of three of our cirrhotic patients had worsening LFT and decompensation, though none required ICU admission or died. Multiple mechanisms involved in liver injury in COVID-19 have been described. These include immune-mediated damage, direct cytotoxicity, anoxia due to respiratory failure, drug-induced liver injury, and reactivation of pre-existing liver disease[30]. In addition, the presence of cirrhosis associated immune dysfunction syndrome (CAIDS) can predispose cirrhotic patients to severe infection[31] and result in more severe liver injury[32]. A recent study looking at cirrhotic patients with COVID-19 infection showed that mortality correlated strongly with baseline CTP class and MELD score, with a greater proportion of patients with CTP-C liver cirrhosis dying[7]. Other authors have found that patients with

advanced liver cirrhosis did poorer with COVID-19 infection[33–34]. We postulate that our 3 cirrhotic patients ran a milder COVID-19 clinical course possibly from the absence of NAFLD and that 2 of 3 were CTP-A at baseline. This may explain why they had better outcomes in terms of not requiring ICU admission and not dying.

Our study had some limitations during the process of data acquisition due to missing clinical information, resulting in a smaller sample size of identifiable CLD patients. The majority of patients who were admitted and found to be overweight or have abnormal LFT, did not undergo liver imaging which could have picked up more patients with fatty liver. We also did not have baseline laboratory values of most patients prior to their admission. These values could have been used to calculate fibrosis scores as elevated Fibrosis-4 (FIB-4) scores have been shown to increase the likelihood of severe COVID-19 illness[5,35].

Conclusion

Our results demonstrate that in COVID-19 patients with underlying CLD, those with NAFLD have modest ALT elevations and a benign liver outcome. However, these patients with NAFLD have an overall poorer clinical course – requiring anti-viral medications and ICU admission, compared to those of other aetiologies. In Asians, NAFLD can have poor prognostic implications, even when BMI is only mildly raised. Our group of NAFLD patients had a lower than expected BMI, which suggests that non-obese NAFLD patients with COVID-19 can also run a more severe clinical course regardless of weight. Clinically feasible and non-invasive measurements such as waist circumference / sagittal abdominal diameter, may have prognostic value in these patients. In addition, although one out of three of our cirrhotic patients decompensated when infected by COVID-19, none of them required ICU admission or died.

Clinicians should be cognisant of NAFLD as a poor prognostic indicator in COVID-19 and duly prioritize their management. However, the role of pro-active surveillance for NAFLD amongst those infected with COVID-19 has yet to be determined and further studies are needed to better understand the interplay between these two diseases.

Declarations

Ethics approval and consent to participate

Waiver of ethics approval and informed consent for collection of clinical data from infected individuals was granted by the Singapore Ministry of Health, under the Infectious Diseases Act as part of the COVID-19 outbreak investigations.

Consent for publication

Not applicable. No individual data was presented in this article

Availability of data and materials

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

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

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References

1. World Health Organization, Coronavirus disease (COVID-19) – Situation Report 164, 02 July 2020, www.who.int/docs/default-source/coronaviruse/situation-reports/20200702-covid-19-sitrep-164.pdf?sfvrsn=ac074f58_2 (2020, accessed 03 July 2020).

2. Zhang C, Shi L and Wang FS. Liver injury in COVID-19: Management and challenges. *Lancet Gastroenterol Hepatol* 2020; 5: 428-430.

3. Younossi ZM, Koenig AB, Abdelatif D, et al. Global epidemiology of non-alcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology* 2016; 64(1): 73-84.

4. Ji D, Qin E, Xu J, et al. Non-alcoholic fatty liver diseases in patients with COVID-19: a retrospective study. *J Hepatol* 2020; 73(2): 451-453.

5. Targher G, Mantovani A, Byrne CD, et al. Risk of severe illness from COVID-19 in patients with metabolic dysfunction-associated fatty liver disease and increased fibrosis scores. *Gut* 2020; 69(8):

1545-1547.

6. Portincasa P, Krawczyk M, Smyk W, et al. COVID-19 and non-alcoholic fatty liver disease: two intersecting pandemics. *Eur J Clin Invest* 2020. Epub ahead of print 26 June 2020. DOI: 10.1111/eci.13338.

7. Moon AM, Webb GJ, Aloman C, et al. High mortality rates for SARS-CoV-2 infection in patients with pre-existing chronic liver disease and cirrhosis: Preliminary results from an international registry. *J Hepatol* 2020. Epub ahead of print 21 May 2020. DOI: 10.1016/j.jhep.2020.05.013.

8. Siddiqui MS, Harrison SA, Abdelmalek MF, et al. Case definitions for inclusion and analysis of endpoints in clinical trials for non-alcoholic steatohepatitis through the lens of regulatory science. *Hepatology* 2018; 67: 2001–2012.

9. Marchesini G, Day C, Dufour JF, et al. European Association for the Study of the Liver, European Association for the Study of Diabetes, European Association for the Study of Obesity. EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. *J Hepatol* 2016; 64: 1388–1402.

10. Wong VW, Chan WK, Chitturi S, et al. Asia pacific working party on non-alcoholic fatty liver disease guidelines 2017-Part 1: definition, risk factors and assessment. *J Gastroenterol Hepatol* 2018; 33: 70–85.
11. Kwo P, Cohen S and Lim, J. ACG Clinical Guideline: Evaluation of Abnormal Liver Chemistries. Am J Gastroenterol 2017; 112: 18–35.

12. Sharma P and Kumar A. Metabolic dysfunction associated fatty liver disease increases risk of severe Covid-19. Diabetes & Metabolic Syndrome. *Clinical Research & Reviews* 2020; 14: 825-827.

13. Kassir R. Risk of COVID-19 for patients with obesity. *Obes Rev* 2020; 21(6): e13034.

14. Prins G and Olinga P. Potential implications of COVID-19 in non-alcoholic fatty liver disease. *Liver International* 2020. Epub ahead of print 25 May 2020. DOI: 10.1111/liv.14484.

15. Xu L, Liu J, Lu M, et al. Liver injury during highly pathogenic human coronavirus infections. *Liver Int* 2020. Epub ahead of print 30 March 2020. DOI: 10.1111/liv.14435.

16. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA* 2020; 323(11): 1061-1069.

17. Xu XW, Wu XX, Jiang XG, et al. Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: retrospective case series. *BMJ* 2020; 368: m606.

18. Wong G, Wong V, Thompson A, et al. Management of patients with liver derangement during the COVID-19 pandemic: an Asia-Pacific position statement. *Lancet Gastroenterol Hepatol* 2020; 5(8):

776-787.

19. Park BJ, Kim YJ, Kim DH, et al. Visceral adipose tissue area is an independent risk factor for hepatic steatosis. *J Gastroenterol Hepatol* 2008; 23: 900–907.

20. Hamaguchi M, Kojima T, Itoh Y, et al. The severity of ultrasonographic findings in non-alcoholic fatty liver disease reflects the metabolic syndrome and visceral fat accumulation. *Am J Gastroenterol* 2007; 102: 2708–2715.

21. Kim D, Park BJ, Kim W, et al. Visceral fat as a strong and independent risk factor of non-alcoholic fatty liver disease. *Gastroenterology* 2008; 134: 782–783.

22. Eguchi Y, Eguchi T, Mizuta T, et al. Visceral fat accumulation and insulin resistance are important factors in non-alcoholic fatty liver disease. *J Gastroenterol* 2006; 41: 462–469.

23. Farrell GC and Larter CZ. Non-alcoholic fatty liver disease: from steatosis to cirrhosis. *Hepatology* 2006; 43(1): 99–112.

24. Vanwagner L and Armstrong M. Lean NAFLD: A Not So Benign Condition? Hepatol Commun 2018; 2(1): 5-8.

25. Kim D and Kim W. Nonobese Fatty Liver Disease. *Clin Gastroenterol and Hepatol* 2017; 15: 474–485.

26. World Health Organization. Waist Circumference and Waist–Hip Ratio: Report of a WHO Expert Consultation, Geneva, 8–11 December 2008, www.who.int/nutrition/publications/obesity/WHO_report_waistcircumference_and_waisthip_ratio/en/ (2011, accessed 3 July 2020).

27. Wong VW, Chan WK, Chitturi S, et al. Asia–Pacific Working Party on Non-alcoholic Fatty Liver Disease guidelines 2017—part 1: definition, risk factors and assessment. *J Gastroenterol Hepatol* 2018; 33: 70–85.

28. Nishioji K, Mochizuki N, Kobayashi M, et al. The impact of PNPLA3 rs738409 genetic polymorphism and weight gain ≥ 10 kg after age 20 on non-alcoholic fatty liver disease in non-obese Japanese individuals. *PLoS ONE* 2015; 10: e0140427.

29. Sookoian S and Pirola CJ. Systematic review with meta-analysis: risk factors for non-alcoholic fatty liver disease suggest a shared altered metabolic and cardiovascular profile between lean and obese patients. *Aliment Pharmacol Ther* 2017; 46: 85-95.

30. Sun J, Aghemo A, Forner A, et al. COVID-19 and liver disease. *Liver Int* 2020; 40(6): 1278-1281.

31. Albillos A, Lario M and Álvarez-Mon M. Cirrhosis-associated immune dysfunction: distinctive features and clinical relevance. *J Hepatol* 2014; 61(6): 1385–1396.

32. Sarin S, Choudhury A, Lau G, et al. Pre-existing liver disease is associated with poor outcome in patients with SARS CoV2 infection; The APCOLIS Study (APASL COVID-19 Liver Injury Spectrum Study). *Hepatol Int* 2020. Epub ahead of print 4 July 2020. DOI:10.1007/s12072-020-10072-8.

33. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020; 395: 1054–1062.

34. Iavarone M, D'Ambrosio R, Soria A, et al. High rates of 30-day mortality in patients with cirrhosis and COVID-19. *J Hepatol* 2020. Epub ahead of print 9 June 2020. DOI: 10.1016/j.jhep.2020.06.001

35. Ibáñez-Samaniego L, Bighelli F, Usón C, et al. Elevation of Liver Fibrosis Index FIB-4 Is Associated With Poor Clinical Outcomes in Patients With COVID-19. *J Infect Dis* 2020; 222(5): 726-733.

Tables

Table 1. Demographics, co-morbidities, laboratory investigations and clinical outcomes of COVID-19 patients with chronic liver disease

Characteristics	All (n=16)	NAFLD (n=9)	Non-NAFLD (n=7)	*P* value
Age in years, median (range)	61 (28–80)	62 (47–69)	43 (28–80)	0.299
Gender, n (%)				0.358
Male	7 (43.8)	5 (55.6)	2 (28.6)	
Female	9 (56.3)	4 (44.4)	5 (71.4)	
Ethnic group, n (%)				0.487
Chinese	12 (75.0)	7 (77.8)	5 (71.4)	
Malay	0 (0.0)	0 (0.0)	0 (0.0)	
Indian	1 (6.3)	1 (11.1)	0 (0.0)	
Others	3 (18.8)	1 (11.1)	2 (28.6)	
Comorbidities, n (%)				
Diabetes mellitus	3 (18.8)	3 (33.3)	0 (0.0)	0.213
Hypertension	6 (37.5)	3 (33.3)	3 (42.9)	1.000
Hyperlipidaemia	10 (62.5)	8 (88.9)	2 (28.6)	**0.035**
Ischemic heart disease	2 (12.5)	2 (22.2)	0 (0.0)	0.475
Liver Cirrhosis	3 (18.8)	0 (0.0)	3 (42.9)	0.063
BMI, kg/m^2, median (range), n=14	24.3 (18.5–33.1)	24.3 (22.7–33.1)	24.2 (18.5–29.0)	0.491

Sample size, n=16, except where indicated.

Laboratory investigations refer to peak values except where indicated.

P values comparing NAFLD and non-NAFLD patients are from Fisher's exact test or Chi-square test for categorical variables and Mann-Whitney U test for continuous variables. *P* values< 0.05 are in bold.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; BIL, bilirubin; BMI, body mass index; CRP, c-reactive protein; GGT, gamma-glutamyl transferase; ICU, intensive care unit; LDH, lactate dehydrogenase; NAFLD, non-alcoholic fatty liver disease; PLT, platelet; WBC, white blood cell.

Characteristics	All (n=16)	NAFLD (n=9)	Non-NAFLD (n=7)	*P* value
Baseline symptoms, n (%)				
Fever	12 (75.0)	8 (88.9)	4 (57.1)	0.262
Cough	9 (56.3)	7 (77.8)	2 (28.6)	0.126
Sore throat	7 (43.8)	6 (66.7)	1 (14.3)	0.060
Rhinorrhoea	1 (6.3)	1 (11.1)	0 (0.0)	1.000
Shortness of breath	3 (18.8)	3 (33.3)	0 (0.0)	0.213
Headache	2 (12.5)	0 (0.0)	2 (28.6)	0.175
Fatigue/myalgia	5 (31.3)	3 (33.3)	2 (28.6)	1.000
Diarrhoea	4 (25.0)	2 (22.2)	2 (28.6)	1.000
Chest pain	2 (12.5)	2 (22.2)	0 (0.0)	0.475
Days of symptoms before admission, median (range)	2 (0–9)	2 (1–9)	4 (0–8)	0.837
Laboratory investigations, median (range)				
ALT, U/L	61 (19–518)	84 (36–518)	38 (19–149)	**0.042**
AST, U/L	60 (19–367)	75 (31–330)	30 (19–367)	0.174
ALP, U/L	86 (45–332)	96 (45–332)	82 (50–158)	0.681
GGT, U/L	84 (16–1896)	110 (34–1047)	43 (16–1896)	0.181
BIL, μmol/L	15.5 (8–73)	15 (8–61)	16 (10–73)	0.918
Albumin trough, g/L	32 (19–42)	31 (19–42)	33 (20–41)	1.000

Sample size, n=16, except where indicated.

Laboratory investigations refer to peak values except where indicated.

P values comparing NAFLD and non-NAFLD patients are from Fisher's exact test or Chi-square test for categorical variables and Mann-Whitney U test for continuous variables. *P* values< 0.05 are in bold.

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Characteristics	All (n=16)	NAFLD (n=9)	Non-NAFLD (n=7)	*P* value
R ratio	2.1 (0.7–21.3)	2.4 (1.3–21.3)	1.3 (0.7–3.2)	0.055
Creatinine, μmol/L	68.5 (53–223)	69 (53–202)	61 (53–223)	0.299
PLT trough, x 10^9/L	166 (86–257)	161 (86–257)	178 (90–214)	0.837
WBC trough, x10^9/L	3.6 (2.1–5.9)	3.9 (2.5–4.9)	3.4 (2.1–5.9)	0.408
CRP, mg/L	66.7 (0.9–358.9)	106.2(0.9-358.9)	9.2 (4.7–79.9)	0.091
LDH, U/L	530.5 (291–1981)	730 (291–1,981)	446 (339–605)	0.142
Required COVID-19 anti-viral medication, n (%)	6 (37.5)	6 (66.7)	0 (0.0)	**0.011**
Length of stay in days, median (range)	17 (5–44)	21 (5–44)	12 (5–37)	0.210
Days to negative swab, median (range), n=13	21 (1–29)	24 (17–29)	13 (1–22)	**0.008**
Clinical outcomes, n (%)				
Required supplementary oxygen	7 (43.8)	4 (44.4)	3 (42.9)	1.000
ICU	2 (12.5)	2 (22.2)	0 (0.0)	0.475
Death	0 (0.0)	0 (0.0)	0 (0.0)	-

Sample size, n=16, except where indicated.

Laboratory investigations refer to peak values except where indicated.

P values comparing NAFLD and non-NAFLD patients are from Fisher's exact test or Chi-square test for categorical variables and Mann-Whitney U test for continuous variables. *P* values< 0.05 are in bold.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; BIL, bilirubin; BMI, body mass index; CRP, c-reactive protein; GGT, gamma-glutamyl transferase; ICU, intensive care unit; LDH, lactate dehydrogenase; NAFLD, non-alcoholic fatty liver disease; PLT, platelet; WBC, white blood cell.

Figures

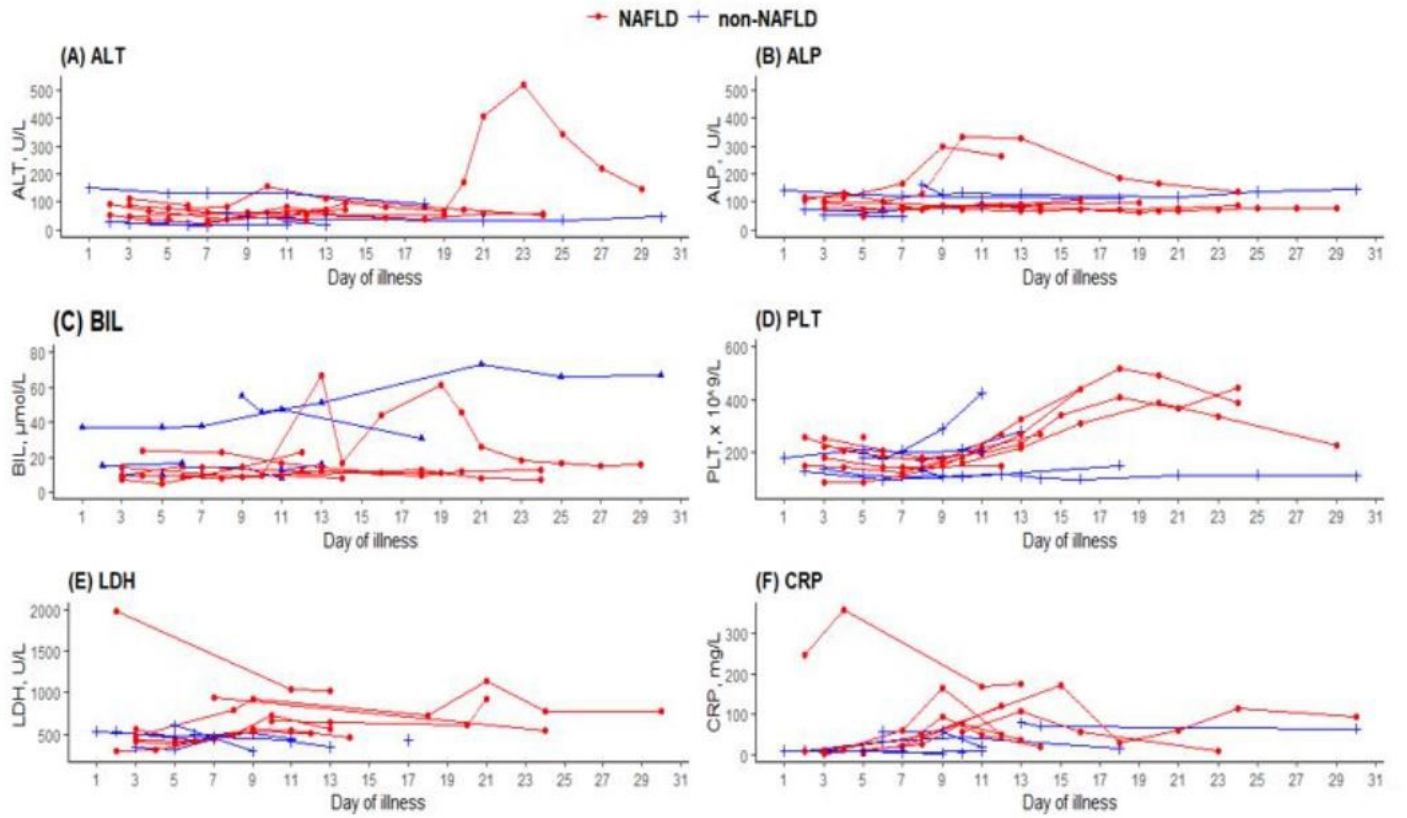

Figure 1

Temporal patterns of laboratory investigations of COVID-19 patients with chronic liver disease. (A) ALT, (B) ALP, (C) BIL, (D) PLT, (E) LDH, (F) CRP ALP, alkaline phosphatatse; ALT, Alanine aminotransferase; BIL, bilirubin; CRP, c-reactive protein; LDH, lactate dehydrogenase; PLT, platelet