
# Implication of non-alcoholic fatty liver diseases (NAFLD) in patients with COVID-19: a preliminary analysis

Dong Ji, Enqiang Qin, Jing Xu, Dawei Zhang, Gregory Cheng, Yudong Wang, George Lau

PII: S0168-8278(20)30206-3

DOI: https://doi.org/10.1016/j.jhep.2020.03.044

Reference: JHEPAT 7692

To appear in: *Journal of Hepatology*

Received Date: 27 March 2020

Accepted Date: 27 March 2020

Please cite this article as: Ji D, Qin E, Xu J, Zhang D, Cheng G, Wang Y, Lau G, Implication of non-alcoholic fatty liver diseases (NAFLD) in patients with COVID-19: a preliminary analysis, *Journal of Hepatology* (2020), doi: https://doi.org/10.1016/j.jhep.2020.03.044.

# Implication of non-alcoholic fatty liver diseases (NAFLD) in patients with COVID-19: a preliminary analysis

Dong Ji[1,†], Enqiang Qin[1, †], Jing Xu[2], Dawei Zhang[1], Gregory Cheng[3], Yudong Wang[3], George Lau[1,3,*]

[1] The Fifth Medical Center of Chinese PLA General Hospital, Beijing 100039, China; [2] Fuyang Second People's Hospital, Fuyang, Anhui 23600, China; [3] Humanity and Health Clinical Trial Center, Humanity & Health Medical Group, Hong Kong SAR, China

[†]The 2 authors collaborated equally.

*Corresponding author

Prof George Lau, Humanity & Health Medical Group, Hong Kong SAR, China or The Fifth Medical Center of Chinese PLA General Hospital, Beijing 100039, China

Email: gkklau@hnhmgl.com/gkklau@netvigator.com

## Contributors

DJ, DZ, JX, and EQ treated the patients.DJ, GC, YW and GL processed statistical data and drafted the manuscript. DJ and GL had the idea for and designed the study.

## Declaration of interests

We declare no competing interests.

## Acknowledgments

This work is funded by the Capital characteristic clinic project of Beijing Municipal Science and Technology Commission (Z181100001718034). We acknowledge all health-care workers involved in the diagnosis and treatment of patients with COVID-19 in our hospital.

**To the Editor:**

Liver injury had been observed in COVID-19 patients with incidence ranging from 14–53%.[1-3] We examined the liver injury patterns and implication of non-alcoholic fatty liver diseases (NAFLD) on clinical outcomes in Chinese with COVID-19.

**Methods**

From January 20 through February 18, 2020, consecutive patients admitted to two designated COVID-19 Hospitals in China with confirmed COVID-19 and NAFLD status information were studied. The diagnosis and clinical management of COVID-19 patients were in accord to the practice guidelines issued by The Chinese National Health Commission, China.[4] COVID-19 was confirmed with the detection of SAS-CoV-2 sequences in the throat swab by RT-PCR. Liver injury was defined as hepatocellular if the alanine aminotransferase (ALT) level was > 30 IU/L for male and 19 IU/L for female;[5] ductular if alkaline phosphatase( ALP) was > upper limit of normal(ULN) accompanied by glutamyl transferase (GGT) above ULN; mixed if both hepatocellular and ductular enzymes were raised above ULN. NAFLD was identified as hepatic steatosis index [HSI = 8 × (ALT/AST) + BMI (+ 2 if type 2 diabetes yes, + 2 if female)] more than 36 points and/or by abdominal ultrasound examination.[6] The patients were followed till discharged with recovery, death or 23 Mar 2020. The study was approved by the Ethics Committees of FYSPH (20200303006) and the Fifth Medical Center of PLAGH (2020005D).

The significance of clinical characteristics on admission were assessed by univariate and multivariate logistic regression analysis for investigating the independent risk factors of illness progression, *p*-value < 0.05 was considered as significant.

## Results

202 consecutive patients with confirmed COVID-19 and information relating NAFLD status were studied. Liver injury was observed in 101 (50%) and 152 (75.2%) patients on admission and during hospitalization respectively. Almost all liver injury was mild with hepatocellular pattern, only 2.6% (4/152) had ductular or mixed pattern. Sixty-seven (33.2%) patients had persistent abnormal liver function from admission to discharge Thirty-nine (19.3%) and 163(80.7%) had progressive and stable disease respectively. Progressive diseases patients were older, had higher BMI, percentage of comorbidity and NAFLD (Table). Univariate and multivariate logistic regression analysis showed that male sex (OR 3.1, 95% CI 1.1 - 9.4), age > 60 years (OR 4.8, 95% CI 1.5 - 16.2), higher BMI (OR 1.3, 95% CI 1.0 - 1.8), underlying comorbidity (OR 6.3, 95% CI 2.3 - 18.8) and NAFLD (OR 6.4, 95% CI 1.5 - 31.2), were associated with COVID-19 progression.

Patients with NAFLD had higher risk of disease progression [6.6% (5/126) vs 44.7% (34/76) p<0.0001], higher likelihood of abnormal liver function from admission to discharge[70% (53/76) vs 11.1% (14/126) p<0.0001] and longer viral shedding time(17.5±5.2 days vs 12.1±4.4 days p<0.0001) when compared with non-NAFLD subjects.

## Discussion

Similar to other reports our study showed that liver injury in COVID-19 patients was frequent but mild in nature.[1-3] The pattern of liver injury was mostly hepatocellular rather than cholestatic. This is of interest as it had been shown that biliary cells have high expression of angiotensin-converting enzyme (ACE2) receptor with a high affinity to the spike protein of SARS-CoV-2.[7] In other respiratory viral infection,

hepatitis has been related to the collateral damage mediated by virus-specific effector cells generated in response to the pulmonary infection.[8] The postmortem liver biopsy in one of our patients showed only microvesicular steatosis, accompanied by overactivation of T cells suggesting that liver injury in COVID-19 is likely immune mediated rather than direct cytopathic damage as described in other viral respiratory disease.[9] Majority of patients in our series with persistent liver injury had NAFLD and high BMI. Patients with NAFLD also had a higher risk of progression to severe COVID-19 and longer viral shedding time. With NAFLD increasing global prevalence, this may suggest a large proportion of our population could be at risk of severe COVID-19.

There are abundant ACE2 receptors in the small intestine and the liver with its rich blood supply from the small bowel, is expected to encounter the SARS-CoV-2. The liver contains the largest number of macrophages (Kupffer cells) in the body and is a potent cytokine producer. Impaired hepatic innate immune status might play a critical role in COVID-19 outcome. In NAFLD patients, the polarization status of macrophage might be skewed, thus affecting host inflammatory or tolerant response to SARS-CoV-2 signals generated from the gut-liver axis. Obesity and NAFLD have been associated with increased production of pro-inflammatory cytokines like TNF-α by adipose cells and Kupffer cells.[10] It remains speculative that the impaired innate immunity, manifested by derailed functional diversity of macrophages, imbalance between inflammation-promoting M1 macrophages and inflammation-suppressing M2 macrophages will lead to progression of COVID-19.[10] A better understanding of the role of NAFLD in COVID-19 may enable one to elucidate the pathogenesis and have therapeutic implications.

**References:**


1. Xu L, Liu J, Lu M, Yang D, Zheng X. Liver injury during highly pathogenic human coronavirus infections. Liver Int. 2020 Mar 14. doi: 10.1111/liv.14435. [Epub ahead of print]
2. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA. 2020 Feb 7. doi: 10.1001/jama.2020.1585. [Epub ahead of print]
3. Xu XW, Wu XX, Jiang XG, Xu KJ, Ying LJ, Ma CL, 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 Feb 19;368: m606. doi: 10.1136/bmj.m606.
4. http://kjfy.meetingchina.org/msite/news/show/cn/3337.html
5. Park JH, Choi J, Jun DW, Han SW, Yeo YH, Nguyen MH. Low Alanine Aminotransferase Cut-Off for Predicting Liver Outcomes; A Nationwide Population-Based Longitudinal Cohort Study. J Clin Med. 2019 Sep 11;8(9). pii: E1445. doi: 10.3390/jcm8091445.
6. Lee JH, Kim D, Kim HJ, Lee CH, Yang JI, Kim W, Kim YJ, Yoon JH, Cho SH, Sung MW, Lee HS.Hepatic steatosis index: a simple screening tool reflecting nonalcoholic fatty liver disease. Dig Liver Dis. 2010;42(7):503-8.
7. Zou X, Chen K, Zou J, Han P, Hao J, Han Z. Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection. Front Med. 2020 Mar 12. doi: 10.1007/s11684-020-0754-0. [Epub ahead of print]

8. Polakos NK, Cornejo JC, Murray DA, Wright KO, Treanor JJ, Crispe IN, et al. Kupffer Cell-Dependent Hepatitis Occurs during Influenza Infection. Am J Pathol. 2006 Apr; 168(4): 1169–1178.
9. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med. 2020 Feb 18. pii: S2213-2600(20)30076-X. doi: 10.1016/S2213-2600(20)30076-X. [Epub ahead of print]
10. Lefere S, Tacke F. Macrophages in obesity and non-alcoholic fatty liver disease: Crosstalk with metabolism. JHEP Rep. 2019 23;1(1):30-43

**Table. Baseline characteristics of COVID-19 patients on admission.**

| Clinical characteristics on admission | overall n = 202 | Stable n = 163 | Progressive [a] n = 39 | *p* values |
|---|---|---|---|---|
| Male sex (n, %) | 113 (55.9) | 86 (52.8) | 27 (69.2) | 0.093 |
| Age (years) | 44.5 (34.8 - 54.1) | 42.9 (32.6 - 51.8) | 55.1 (43.7 -71.8) | <0.001 |
| Age > 60 years (n, %) | 31 (15.3) | 14 (8.6) | 17 (43.6) | <0.001 |
| BMI (kg/m$^2$) | 24.0 ± 2.8 | 23.4 ± 2.5 | 26.6 ± 2.2 | <0.001 |
| Smoke (n, %) | 19 (9.4) | 15 (9.2) | 4 (10.3) | 1.000 |
| Drink (n, %) | 6 (3.0) | 5 (3.1) | 1 (2.6) | 1.000 |
| Comorbidity (n, %) [†] | 47 (23.3) | 23 (14.1) | 24 (61.5) | <0.001 |
| NAFLD (n, %) | 76 (37.6) | 42 (25.8) | 34 (87.2) | <0.001 |
| HBsAg positive (n, %) | 7 (3.5) | 5 (3.1) | 2 (5.1) | 0.885 |
| Epidemiology (n, %) | | | | 0.866 |
| No contact history | 46 (22.8) | 36 (22.1) | 10 (25.6) | |
| Travel to Wuhan | 100 (49.5) | 82 (50.3) | 18 (46.2) | |
| Close contact | 56 (27.7) | 45 (27.6) | 11 (28.2) | |
| Severity (n, %) | | | | <0.001 |
| Mild | 5 (2.5) | 4 (2.5) | 1 (2.6) | |
| Moderate | 168 (83.2) | 146 (89.6) | 22 (56.4) | |
| Severe | 28 (13.9) | 12 (7.4) | 16 (41.0) | |
| Critical | 1 (0.5) | 1 (0.6) | 0 (0.0) | |
| Elevated ALT (n, %) | 101 (50.0) | 82 (50.3) | 19 (48.7) | 0.859 |
| Elevated ALP (n, %) | 5 (2.5) | 5 (3.1) | 0 (0) | 0.585 |
| Elevated AST (n, %) | 34 (16.8) | 24 (14.7) | 10 (25.6) | 0.102 |
| Elevated GGT (n, %) | 46 (22.8) | 31 (19.0) | 15 (38.5) | 0.009 |
| Elevated TBIL (n, %) | 17 (8.4) | 13 (8.0) | 4 (10.3) | 0.747 |
| Elevated GGT plus ALP* (n, %) | 1 (0.5) | 1 (0.6) | 0 (0) | 1.000 |
| Viral shedding days [b] | 13.0 (10.0 - 17.0) | 12.0 (10.0 - 16.0) | 17.0 (16.0 - 19.5) | <0.001 |
| Hospitalization days [c] | 16.0 (12.0 - 22.0) | 15.0 (12.0 - 20.0) | 21.0 (16.5 - 27.0) | 0.001 |

The continuous variables were expressed in median (interquartile range, IQR), and compared using the Mann-Whitney test, categorical variables were presented as numbers (percentage) and compared by the chi-square test or Fisher's exact test.

[†] Comorbidity included hypertension, diabetes, cardiovascular disease, chronic lung disease and HIV infections.

* One patient had elevated ALP and GGT on admission. Another three developed during hospitalization.

a. Progression of illness was defined as development of at least one of the followings: respiratory rate ≥ 30 breaths/min, resting oxygen saturation ≤ 93% and PaO2/FiO2 ≤ 300 mmHg or worsening of lung CT findings, during the hospitalization period.

b. Viral shedding period was defined as the time to undetectable SARS-CoV-2 from admission.

c. The criteria of discharge include all the following conditions: body temperatures remain normal over 3 days, significant improvement of respiratory symptoms, resolution of pulmonary imaging of inflammation, and repeated tests at least 24 hours apart confirms SARS-CoV-2 clearance.