Acute Liver Injury and COVID-19

Subjects: Gastroenterology & Hepatology
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COVID-19 patients with severe illness are likely to present with atypical liver biochemistry tests. A number of systematic and meta-analysis studies have examined pooled odds ratios of hepatocellular and hepatobiliary enzymes to differentiate between severe and non-severe COVID-19 illness. In a meta-analysis of 8 studies involving 7467 COVID-19 patients by Xin et al. individuals had pooled odds ratio of 3.21, 2.35 and 1.87 for elevated AST, ALT and total bilirubin levels respectively in severe illness.

Keywords: liver ; coronavirus ; disease ; injury ; acute ; infection ; severity

1. SARS-CoV-2 and Novel Coronavirus Disease 2019 (COVID-19)

The novel coronavirus disease 2019 (COVID-19) is caused by the new strain of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. There is evidence that SARS-CoV-2 infection presents with an asymptomatic stage where there may be little or no detectable virus followed by a non-severe symptomatic period with measurable virus load, and in the last stage severe respiratory symptoms with significantly high viral load [2]. In the last stage there is a biphasic pattern with the viral load present concomitant with the presenting symptoms in the first phase. The second phase with higher viral load is referred to as an ‘inflammatory phase’ characterized by extreme host inflammatory response or cytokine storm with elevated levels of cytokines particularly interleukin-6 (IL-6), interleukin-10 (IL-10) and tumor necrosis factor-α (TNF-α) [3]. This latter phase is also associated with lymphopenia, decreased interferon-γ (IFN-γ) expression and elevated inflammatory indicators including procalcitonin and D-dimer [4]. Cytokine storm is life-threatening and as the disease progress may be responsible for lung damage and severe cardiopulmonary manifestations occasionally resulting in acute respiratory distress syndrome, shock, and death [5].

SARS-CoV-2 mainly attacks the lungs, but it also causes damage to other organs including the liver, kidneys, intestines, heart as well as the central nervous system [6]. The damage to these multiple organs results in acute hepatic failure, acute lung failure, cardiovascular disease, acute kidney injury as well as neurological disorders (acute flaccid paralysis, epilepsy and acute cerebrovascular disease) and hematological abnormalities (lymphopenia and leukopenia) [7].

There is increasing evidence in the literature that some individuals presenting with COVID-19 have hepatic injury and atypical liver function test results with increase in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels due to hepatocellular damage [8]. Studies conducted in Wuhan, China reported mild elevations of AST and ALT levels in 14–53% of cases while higher rates of both enzymes were observed in those patients with severe infection, mainly those needing intensive care unit admission [9][10]. SARS-CoV-2 may damage the biliary tract with subsequent increase in direct and total bilirubin, gamma-glutamyl transferase (GGT) and alkaline phosphatase (ALP) levels [11]. Likewise, in COVID-19 cases where there is significant liver damage and severe clinical symptomatology, variable levels of GGT and ALP (above the upper limit of normal for the reference range) along with elevated levels of total bilirubin and ALT have been observed in 58–78% of patients [12][13].

Given the widespread and harmful nature of SARS-CoV-2 and its impacts on human health and clinical systems, there has been an exponential increased in the number of articles published since December 2019. We have conducted a comprehensive systematic review to summarize numerous articles published regarding abnormal liver biochemistry tests in COVID-19 patients and the possible pathogenesis involved. Furthermore, we highlighted significant findings regarding the disease severity, hepatocellular and cholestatic pattern, incidence and ongoing changes in liver function biochemistry tests as well as related clinical outcomes in COVID-19 patients. This will assist healthcare providers to identify liver complications in COVID-19 patients and closely monitor the liver biochemistry tests in the management of acute hepatic injury in COVID-19 patients.

2. Interconnection between SARS-CoV-2 Infection and Preexisting Liver Co-Morbidity

Deranged liver function tests due to hepatic injury could arise from underlying chronic liver diseases. Reported prevalence rates of underlying liver diseases present in COVID-19 patients from large observational studies ranged from 3–11% [14][15]. Oyelade et al. carried out a meta-analysis involving 22 observational studies with 5595 COVID-19 patients and found there was a case fatality rate of 16%. They posited that 57.33% COVID-19 patients with underlying chronic liver disease had increased risk of severe illness and 17.65% higher odds of death [16]. The severity of the COVID-19 illness and higher mortality could be associated with abnormal hematological parameters such as low platelets and total lymphocyte counts [17]. Moreover, another recent study involving 123 COVID-19 patients of which 12.2% had chronic hepatitis B infection found that individuals with liver disorder were more susceptible to COVID-19 and greater incidence of liver cirrhosis [18].

The mechanism by which non-alcoholic fatty liver disease could cause severe COVID-19 might be due to the presence of mild chronic systemic inflammation, dysregulated and suppressed immune response, involvement of pro-inflammatory markers and stimulation of macrophages in inflammatory reaction and metabolic pathways [19][20]. Additionally, a recent analysis of 22 studies showed that underlying diabetes mellitus with non-alcoholic fatty liver disease was concomitant with about two-fold higher risk of severe or critical COVID-19 [21], and patients with the liver disease were associated with a higher risk of COVID-19 (OR = 6.4; 95% CI: 1.5–31.2) [20].

The management and wellbeing of patients who are liver transplant recipients are important and can be daunting during the COVID-19 pandemic as these persons receive immunosuppressive drugs that make them more susceptible to SARS-CoV-2 and likely protracted vital shedding [22]. Quin and colleagues described the first case of COVID-19 (and liver transplant), which was that of a 37-year old-man diagnosed with hepatocellular carcinoma who subsequently underwent an orthotopic liver transplant. The procedure was successful as the recipient recovered with no evidence of multi-system organ damage and was discharged after approximately three months [23].

The data pertaining to the management of liver transplant recipients with COVID-19, risk and severity of the respiratory illness is sparse and is an area that warrants urgent investigation. The literature reports a retrospective single-center study comprising 37 liver transplant recipients who were diagnosed with COVID-19. The mortality was 18% while 71% were hospitalized, and the study also found that of the hospitalized patients 46% had severe COVID-19 disease, 79% decreased immunosuppression and 54% presented with acute kidney injury [24]. Similar findings were stated in a study by Pereira et al. where 24% of liver transplant recipients with COVID-19 were hospitalized and 18% died [25]. On the contrary, there are reports of mild COVID-19 and associated 3% mortality in longstanding liver transplant recipients [26].

3. Deranged LFTs in COVID Patients with Severe Illness

COVID-19 patients with severe illness are likely to present with atypical liver biochemistry tests. A number of systematic and meta-analysis studies have examined pooled odds ratios of hepatocellular and hepatobiliary enzymes to differentiate between severe and non-severe COVID-19 illness. In a meta-analysis of 8 studies involving 7467 COVID-19 patients by Xin et al. individuals had pooled odds ratio of 3.21, 2.35 and 1.87 for elevated AST, ALT and total bilirubin levels respectively in severe illness [27]. Kaushik et al. reported a prevalence of 59.04% for abnormal liver function tests in COVID-19 patients. Patients with severe illness presented at admissions with significant higher incidence of elevated AST levels (RR = 2.91), but non-significantly higher incidence of elevated ALT levels (RR = 2.32) and total bilirubin levels (RR = 1.95) [28]. Moreover, in a meta-analysis of 128 studies, the relative risk of elevated liver function tests in severe compared with non-severe COVID-19 patients were 1.76 (ALT), 2.30 (AST), 2.31 (GGT), and for decreased albumin levels a value of 2.65 [29]. In addition, severe COVID-19 had a significantly higher pooled incidence for elevated ALT, AST, GGT, ALP and total bilirubin at admission compared with non-severe cases (**Table 1**) [30]. Of note is a single-center retrospective study of 115 cases where most of the COVID-19 patients with severe illness demonstrated significantly decreased albumin levels, which was even lower during the progression of the disease [31].

Table 1. Abnormal liver biochemistry tests in COVID-19 patients with severe illness.

Reference	Liver Biochemistry Test	Type of Study/Number of Articles	Study Design	Sample Size	Main Findings/Incidence
Xin et al., 2020 [27]	**AST, ALT and total bilirubin**	**Review (8 articles)**	**Systematic review and meta-analysis**	**7467**	**The ORs for severe COVID-19 patients were 2.35 (ALT), 3.21 (AST) and 1.87 (total bilirubin).**

Reference	Liver Biochemistry Test	Type of Study/Number of Articles	Study Design	Sample Size	Main Findings/Incidence
Kaushik et al., 2020 [28]	AST, ALT and total bilirubin	Original	Cross-sectional	105	Prevalence of abnormal LFTs is 59.04%. The RR for AST is 2.91, 2.32 for ALT and 1.95 for total bilirubin in severe COVID-19.
Wu et al., 2020 [30]	ALT, AST, GGT, ALP and total bilirubin	Review (45 articles)	Systematic review and meta-analysis	-	Pooled incidence of abnormal LFTs at admission was 27.2%. Severe patients had a significantly higher pooled incidence of abnormal LFTs (ALT, AST, GGT, ALP and total bilirubin).
Kumar-M [29]	ALT, AST, GGT and albumin	Review (128 articles)	Systematic review and meta-analysis	-	The RRs for severe COVID-19 patients were 1.76 (ALT), 2.30 (AST), 2.31 (GGT), and for albumin, 2.65.
Sultan et al., 2020 [32]	ALT and AST	Review (47 articles)	Systematic review and meta-analysis	10,890	The pooled prevalence estimates of 15.0% for AST and 15.0% for ALT in hospitalized COVID-19 patients.
Cholankeril et al., 2020 [33]	ALT, AST, GGT and total bilirubin	Original	Retrospective	116	40% of patients had abnormal liver function tests (ALT, AST, GGT and total bilirubin).
Hajifathalian et al., 2020 [34]	ALT, AST, GGT and total bilirubin	Original	Retrospective	1059	62% presented with at least one elevated liver enzyme.
Schattenberg et al., 2020 [35]	ALT and AST	Original	Case series	44	70% of COVID-19 patients had elevated AST and 15.8% increased ALT on admission.
Hundt et al., 2020 [36]	ALT, AST, GGT and total bilirubin	Original	Retrospective	1827	41.6% ALT, 66.9% AST, 4.3% total bilirubin and 13.5% ALP were elevated at admission.

At the time of admission liver function test of COVID-19 patients are usually determined and the prevalence are reported in a number of observational cohort and retrospective studies. The reported prevalence of deranged liver function tests for COVID-19 patients in China was approximately 14.9% on analysis of 14 recent studies comprising of 2595 individuals [32], compared with the United Stare of America with stated 40.0–67.5% in prospective cohort studies with populations up to 1059 persons [33][34][37]. In a case series of 44 consecutive hospitalized COVID-19 patients, 70% had elevated AST and 15.8% ALT levels on admission [35]. Moreover, in a retrospective cohort study comprising 1827 patients, 41.6% ALT, 66.9% AST, 4.3% total bilirubin and 13.5% ALP levels were elevated at admission [38].

Abnormal liver biochemistry tests in COVID-19 patients with severe illness.

4. Deranged LFTs in COVID Patients and Mortality

A number of studies have examined the relationship between liver function tests on admission and prognostic outcome in COVID-19 patients. AST and ALT, biomarkers of hepatocellular damage were significantly increased in a retrospective study including 675 COVID-19 patients, and individuals with AST > 3 times the upper limit of normal had the greatest risk of death [36]. In a meta-analysis and systematic review, AST (OR = 5.39) and ALT (OR = 2.49) levels were associated with a high rate of mortality [39]. Moreover, in another retrospective study comprising 544 COVID-19 patients where there were elevated AST and ALT levels, the AST/ALT ratio > 1 was concomitant with increased mortality (**Table 2**) [40]. AST along with LDH levels were significantly elevated in a non-survival group of COVID-19 patients with an area under the ROC curve of 0.854 in predicting disease prognosis [41]. Decreased levels of albumin and higher levels of AST were also associated with the mortality of COVID-19 patients [42]. However, abnormal liver function tests were not associated with survival in hospitalized COVID-19 patients [43] but with increased risk of ICU admission [44].

Table 2. Abnormal liver biochemistry tests and clinical outcome (mortality) in COVID-19 patients.

Reference	Liver Biochemistry Test	Type of Study	Study Design	Sample Size	Main Findings/Incidence
Vancsa et al. 2020 [39]	AST and ALT	Review (50 articles)	Systematic review and meta-analysis	-	AST (OR = 5.39) and ALT (OR = 2.49) levels were associated with a high rate of mortality.
Medetalibeyoglu et al., 2021 [40]	AST and ALT	Original	Retrospective	614	AST/ALT ratio > 1 was associated with mortality risk (AUC = 0.713, *p* = 0.001).
Li et al., 2020 [30]	AST and albumin	Original	Retrospective	80	Decreased levels of albumin and higher levels of AST were also associated with mortality of COVID-19 patients (*p* = 0.002 and *p* = 0.009 respectively).
Bernal-Monterde et al., 2020 [32]	AST and GGT	Original	Retrospective	540	Increased AST (40.9%) and GGT (47.3%) were not associated with survival.
Lei et al., 2020 [45]	AST, ALT, ALP and total bilirubin	Original	Retrospective	5771	Significantly elevated AST and ALT, mild total bilirubin and modest ALP; elevated AST was associated with highest mortality risks.
Ding et al., 2020 [46]	AST and total bilirubin	Original	Retrospective	2071	Significantly elevated AST and direct bilirubin and their levels at admission were independent risk factors of mortality.
Chu et al., 2020 [47]	AST, ALT, ALP, GGT and total bilirubin	Original	Retrospective	838	Mortality of the cholestatic pattern was the highest with 28.2% of individuals followed by hepatocellular injury pattern with 25.0% and mixed pattern with 22.3%.
Wang et al., 2020 [48]	Total bilirubin	Original	Retrospective	657	More COVID-19 patients who died (17%) had significantly elevated serum total bilirubin than discharged patients (4.7%).
Xu et al., 2021 [49]	AST, ALT and total bilirubin	Original	Retrospective	1003	AST > 2 ULN (HR = 34.7), ALT > 2 ULN (HR = 7.0) and total bilirubin > 2 ULN were significantly related to higher mortality.
Ponziani et al., 2020 [44]	ALP	Original	Prospective	515	Peak values of ALP were associated with risk of death (OR 1.007, *p* = 0.005).

Studies have also investigated the relationship between cholangiocyte-related enzymes and hepatobiliary biomarkers such as ALP, GGT, direct and total bilirubin, and the hepatocellular biochemical markers ALT and AST, and clinical outcomes. In a multi-center retrospective cohort study comprising 5771 adult COVID-19 patients that examine temporal patterns of liver function biomarkers in a longitudinal manner, significant increase in AST than ALT levels were observed followed by mildly elevated total bilirubin and modest increase in ALP levels in hospitalized patients. The study reported that elevated AST levels were related to the highest mortality risks in hospitalized patients [45] (**Table 2**). Likewise, in a large retrospective cohort study comprising 2071 COVID-19 patients in China, 14.3% had liver injury and the prevalence of abnormal liver biochemistry results was 61.8%. The study also found that early after the onset of symptoms AST and direct bilirubin were significantly increased and their levels at admission were independent risk factors of mortality [AST (adjusted HR = 1.39) and direct bilirubin (adjusted HR = 1.66)] [46]. In addition, in a study that examined the various hepatic injury pattern in COVID-19 patients and associated prognosis, 51.2% presented with hepatic injury and the mortality of the cholestatic pattern was the highest with 28.2% of individuals followed by hepatocellular injury pattern with 25.0% and mixed pattern with 22.3% [50].

There are studies that assert that in severe hospitalized COVID-19 patients there is significant elevation of GGT, direct and total bilirubin and moderate elevations of ALP. The alterations in the liver biochemistry tests could possibly be due to the dysfunction of cholangiocytes as they possess a significant amount of ACE2 receptors, which can become infected by SARS-CoV-2 [13]. Elevated GGT levels observed in some studies could be related to bile duct injury [47]. Wang et al. reported significantly elevated serum ALT, total bilirubin and GGT levels in severe and critically ill COVID-19 patients than in those who were moderately ill, and there were more deceased patients with total bilirubin two times above the upper limit of normal than survivors (**Table 2**) [48]. In a similar manner, Bernal-Monterde reported that elevated GGT levels were observed in 47.0% and 60.5% of COVID-19 patients at admission and during hospitalization respectively [43]. Supporting

findings also comes from two Chinese cohorts of COVID-19 patients where GGT levels were elevated in more than one-half of the individuals [11][31]. Bernal-Monterde and colleagues also find a strong relationship between longitudinal changes in GGT levels and to a minor extent total bilirubin levels and suggests that elevated biomarkers indicate cholestatic liver injury and may have a negative impact on survival [43]. However, in the meta-analysis by Vancsa et al. ALP was not a significant prognostic biomarker of mortality in patients with acute liver injury related to COVID-19 [39].

Abnormal liver biochemistry tests and clinical outcome (mortality) in COVID-19 patients.

References

1. Pal, M.; Berhanu, G.; Desalegn, C.; Kandi, V. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2): An update. Cureus 2020, 12, e7423.
2. Shi, Y.; Wang, Y.; Shao, C.; Huang, J.; Gan, J.; Huang, X.; Bucci, E.; Piacentini, M.; Ippolito, G.; Melino, G. COVID-19 infection: The perspectives on immune responses. Cell Death Differ. 2020, 27, 1451–1454.
3. Pedersen, S.F.; Ho, Y.-C. SARS-CoV-2: A storm is raging. J. Clin. Investig. 2020, 130, 2202–2205.
4. Giamarellos-Bourboulis, E.J.; Netea, M.G.; Rovina, N.; Akinosoglou, K.; Antoniadou, A.; Antonakos, N.; Damoraki, G.; Gkavogianni, T.; Adami, M.-E.; Katsaounou, P.; et al. Complex immune dysregulation in COVID-19 patients with severe respiratory failure. Cell Host Microbe 2020, 27, 992–1000.e3.
5. Cappanera, S.; Palumbo, M.; Kwan, S.H.; Priante, G.; Martella, L.A.; Saraca, L.M.; Sicari, F.; Vernelli, C.; Di Giuli, C.; Andreani, P.; et al. When does the cytokine storm begin in COVID-19 patients? A quick score to recognize it. J. Clin. Med. 2021, 10, 297.
6. Zhang, Y.; Geng, X.; Tan, Y.; Li, Q.; Xu, C.; Xu, J.; Hao, L.; Zeng, Z.; Luo, X.; Liu, F.; et al. New understanding of the damage of SARS-CoV-2 infection outside the respiratory system. Biomed. Pharmacother. 2020, 127, 110195.
7. Mokhtari, T.; Hassani, F.; Ghaffari, N.; Ebrahimi, B.; Yarahmadi, A.; Hassanzadeh, G. COVID-19 and multi-organ failure: A narrative review on potential mechanisms. J. Mol. Histol. 2020, 51, 613–628.
8. Kukla, M.; Skonieczna-Żydecka, K.; Kotfis, K. COVID-19, MERS and SARS with concomitant liver injury-systematic review of the existing literature. J. Clin. Med. 2020, 9, 1420.
9. Chen, N.; Zhou, M.; Dong, X.; Qu, J.; Gong, F.; Han, Y.; Qiu, Y.; Wang, J.; Liu, Y.; Wei, Y.; et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: A descriptive study. Lancet 2020, 395, 507–513.
10. Huang, C.; Wang, Y.; Li, X.; Ren, L.; Zhao, J.; Hu, Y.; Zhang, L.; Fan, G.; Xu, J.; Gu, X.; et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020, 395, 497–506.
11. Cai, Q.; Huang, D.; Yu, H.; Zhu, Z.; Xia, Z.; Su, Y.; Li, Z.; Zhou, G.; Gou, J.; Qu, J.; et al. COVID-19: Abnormal liver function tests. J. Hepatol. 2020, 73, 566–574.
12. Xu, L.; Liu, J.; Lu, M.; Yang, D.; Zheng, X. Liver injury during highly pathogenic human coronavirus infections. Liver Int. 2020, 40, 998–1004.
13. Chai, X.; Hu, L.; Zhang, Y.; Han, W.; Lu, Z.; Ke, A.; Zhou, J.; Shi, G.; Fang, N.; Fan, J.; et al. Specific ACE2 expression in cholangiocytes may cause liver damage after 2019-nCoV infection. BioRxiv. 2020.
14. Fan, Z.; Chen, L.; Li, J.; Cheng, X.; Yang, J.; Tian, C.; Zhang, Y.; Huang, S.; Liu, Z.; Cheng, J. Clinical features of COVID-19-related liver functional abnormality. Clin. Gastroenterol. Hepatol. 2020, 18, 1561–1566.
15. Mantovani, A.; Beatrice, G.; Dalbeni, A. Coronavirus disease 2019 and prevalence of chronic liver disease: A meta-analysis. Liver Int. 2020, 40, 1316–1320.
16. Oyelade, T.; Alqahtani, J.; Canciani, G. Prognosis of COVID-19 in patients with liver and kidney diseases: An early systematic review and meta-analysis. Trop. Med. Infect. Dis. 2020, 5, 80.
17. Qi, X.; Liu, Y.; Wang, J.; Fallowfield, J.A.; Wang, J.; Li, X.; Shi, J.; Pan, H.; Zou, S.; Zhang, H.; et al. Clinical course and risk factors for mortality of COVID-19 patients with pre-existing cirrhosis: A multi-centre cohort study. Gut 2021, 70, 433–436.
18. Chen, X.; Jiang, Q.; Ma, Z.; Ling, J.; Hu, W.; Cao, Q.; Mo, P.; Yao, L.; Yang, R.; Gao, S.; et al. Clinical characteristics of hospitalized patients with SARS-CoV-2 and hepatitis B virus co-infection. Virol. Sin. 2020, 35, 842–845.
19. Michalakis, K.; Ilias, I. SARS-CoV-2 infection and obesity: Common inflammatory and metabolic aspects. Diabetes Metab. Syndr. Clin. Res. Rev. 2020, 14, 469–471.

20. Chiappetta, S.; Sharma, A.M.; Bottino, V.; Stier, C. COVID-19 and the role of chronic inflammation in patients with obesity. Int. J. Obes. (Lond.) 2020, 44, 1790–1792.

21. Mantovani, A.; Byrne, C.D.; Zheng, M.H.; Targher, G. Diabetes as a risk factor for greater COVID-19 severity and in-hospital death: A meta-analysis of observational studies. Nutr. Metab. Cardiovasc. Dis. 2020, 30, 1236–1248.

22. Forns, X.; Navasa, M. Liver transplant immunosuppression during the COVID-19 pandemic . Gastroenterol. Hepatol. (Engl. Ed.) 2020, 43, 457–463.

23. Qin, J.; Wang, H.; Qin, X.; Zhang, P.; Zhu, L.; Cai, J.; Yuan, Y.; Li, H. Perioperative presentation of COVID-19 disease in a liver transplant recipient. Hepatology 2020, 72, 1491–1493.

24. Lee, B.T.; Perumalswami, P.V.; Im, G.Y.; Florman, S.; Schiano, T.D. COVID-19 in liver transplant recipients: An initial experience from the U.S. Gastroenterology 2020, 146, 1489–1499.

25. Pereira, M.R.; Mohan, S.; Cohen, D.J.; Husain, S.A.; Dube, G.K.; Ratner, L.E.; Arcasoy, S.; Aversa, M.M.; Benvenuto, L.J.; Dadhania, D.M.; et al. COVID-19 in solid organ transplant recipients: Initial report from the US epicenter. Am. J. Transplant. 2020, 20, 1800–1808.

26. Bhoori, S.; Rossi, R.E.; Citterio, D.; Mazzaferro, V. COVID-19 in long-term liver transplant patients: Preliminary experience from an Italian transplant centre in Lombardy. Lancet Gastroenterol Hepatol. 2020, 5, 532–533.

27. Xin, S.; Xu, J.; Yu, Y. Abnormal liver function tests of patients with coronavirus disease 2019 in Mainland China: A systematic review and meta—Analysis. J. Gastrointest. Liver Dis. 2020, 29, 219–226.

28. Kaushik, A.; Wani, S.N.; Baba, M.A.; Agarwal, A.K. Prevalence of abnormal liver function tests in COVID-19 patients at a tertiary care centre. J. Assoc. Physicians India 2020, 68, 73–75.

29. Kumar, M.P.; Mishra, S.; Jha, D.K.; Shukla, J.; Choudhury, A.; Mohindra, R.; Mandavdhare, H.S.; Dutta, U.; Sharma, V. Coronavirus disease (COVID-19) and the liver: A comprehensive systematic review and meta-analysis. Hepatol. Int. 2020, 14, 711–722.

30. Wu, Y.; Li, H.; Guo, X.; Yoshida, E.M.; Mendez-Sanchez, N.; Levi Sandri, G.B.; Teschke, R.; Romeiro, F.G.; Shukla, A.; Qi, X. Incidence, risk factors, and prognosis of abnormal liver biochemical tests in COVID-19 patients: A systematic review and meta-analysis. Hepatol. Int. 2020, 14, 621–637.

31. Zhang, C.; Shi, L.; Wang, F.S. Liver injury in COVID-19: Management and challenges. Lancet Gastroenterol. Hepatol. 2020, 5, 428–430.

32. Sultan, S.; Altayar, O.; Siddique, S.M.; Davitkov, P.; Feuerstein, J.D.; Lim, J.K.; Falck-Ytter, Y.; El-Serag, H.B.; AGA Institute. AGA Institute rapid review of the GI and liver manifestations of COVID-19, meta-analysis of international data, and recommendations for the consultative management of patients with COVID-19. Gastroenterology 2020, 159, 320–334.e27.

33. Cholankeril, G.; Podboy, A.; Aivaliotis, V.I.; Tarlow, B.; Pham, E.A.; Spencer, S.; Kim, D.; Hsing, A.; Ahmed, A. High prevalence of concurrent gastrointestinal manifestations in patients with SARS-CoV-2: Early experience from California. Gastroenterology 2020, 159, 775–777.

34. Hajifathalian, K.; Krisko, T.; Mehta, A.; Kumar, S.; Schwartz, R.; Fortune, B.; Sharaiha, R.Z.; WCM-GI Research Group. Gastrointestinal and hepatic manifestations of 2019 novel coronavirus disease in a large cohort of infected patients from New York: Clinical implications. Gastroenterology 2020, 159, 1137–1140.e2.

35. Schattenberg, J.M.; Labenz, C.; Wörns, M.A.; Menge, P.; Weinmann, A.; Galle, P.R.; Sprinzl, M.F. Patterns of liver injury in COVID-19—A German case series. United Eur. Gastroenterol. J. 2020, 8, 814–819.

36. Huang, H.; Chen, S.; Li, H.; Zhou, X.L.; Dai, Y.; Wu, J.; Zhang, J.; Shao, L.; Yan, R.; Wang, M.; et al. The association between markers of liver injury and clinical outcomes in patients with COVID-19 in Wuhan. Aliment. Pharmacol. Ther. 2020, 52, 1051–1059.

37. Singh, S.; Khan, A. Clinical characteristics and outcomes of COVID-19 among patients with pre-existing liver disease in the United States: A multi-center research network study. Gastroenterology 2020, 159, 768–771.e3.

38. Hundt, M.A.; Deng, Y.; Ciarleglio, M.M.; Nathanson, M.H.; Lim, J.K. Abnormal liver tests in COVID-19: A retrospective observational cohort study of 1827 patients in a major U.S. hospital network. Hepatology 2020, 72, 1169–1176.

39. Vancsa, S.; Hegyi, P.J.; Zádori, N.; Szakó, L.; Vörhendi, N.; Ocskay, K.; Földi, M.; Dembrovszky, F.; Dömötör, Z.R.; Jánosi, K.; et al. Pre-existing liver diseases and on-admission liver-related laboratory ests in COVID-19: A prognostic accuracy meta-analysis with systematic review. Front. Med. 2020, 7, 572115.

40. Medetalibeyoglu, A.; Catma, Y.; Senkal, N.; Ormeci, A.; Cavus, B.; Kose, M.; Bayramlar, O.F.; Yildiz, G.; Akyuz, F.; Kaymakoglu, S.; et al. The effect of liver test abnormalities on the prognosis of COVID-19. Ann. Hepatol. 2020, 19, 614–621.

41. Zhu, Y.; Du, Z.; Zhu, Y.; Li, W.; Miao, H.; Li, Z. Evaluation of organ function in patients with severe COVID-19 infections. Med. Clin. (Barc.) 2020, 155, 191–196.
42. Li, T.; Guo, Y.; Zhuang, X.; Huang, L.; Zhang, X.; Wei, F.; Yang, B. Abnormal liver-related biomarkers in COVID-19 patients and the role of pre-albumin. Saudi J. Gastroenterol. 2020, 26, 272–278.
43. Bernal-Monterde, V.; Casas-Deza, D.; Letona-Giménez, L.; de la Llama-Celis, N.; Calmarza, P.; Sierra-Gabarda, O.; Betoré-Glaria, E.; Martínez-de Lagos, M.; Martínez-Barredo, L.; Espinosa-Pérez, M.M.; et al. SARS-CoV-2 infection induces a dual response in liver function tests: Association with mortality during hospitalization. Biomedicines 2020, 8, 328.
44. Ponziani, F.R.; Del Zompo, F.; Nesci, A.; Santopaolo, F.; Ianiro, G.; Pompili, M.; Gasbarrini, A.; Gemelli against COVID-19 Group. Liver involvement is not associated with mortality: Results from a large cohort of SARS-CoV-2-positive patients. Aliment. Pharmacol. Ther. 2020, 52, 1060–1068.
45. Lei, F.; Liu, Y.M.; Zhou, F.; Qin, J.J.; Zhang, P.; Zhu, L.; Zhang, X.J.; Cai, J.; Lin, L.; Ouyang, S.; et al. Longitudinal association between markers of liver injury and mortality in COVID-19 in China. Hepatology 2020, 72, 389–398.
46. Ding, Z.Y.; Li, G.X.; Chen, L.; Shu, C.; Song, J.; Wang, W.; Wang, Y.W.; Chen, Q.; Jin, G.N.; Liu, T.T.; et al. Association of liver abnormalities with in-hospital mortality in patients with COVID-19. J. Hepatol. 2020, 74, 1295–1302.
47. Lin, L.; Zhong, C.; Rao, S.; Lin, H.; Huang, R.; Chen, F. Clinical characteristics of 78 cases of patients infected with coronavirus disease 2019 in Wuhan, China. Exp. Ther. Med. 2021, 21, 7.
48. Wang, M.; Yan, W.; Qi, W.; Wu, D.; Zhu, L.; Li, W.; Wang, X.; Ma, K.; Ni, M.; Xu, D.; et al. Clinical characteristics and risk factors of liver injury in COVID-19: A retrospective cohort study from Wuhan, China. Hepatol. Int. 2020, 14, 723–732.
49. Mitjà, O.; Clotet, B. Use of antiviral drugs to reduce COVID-19 transmission. Lancet Glob. Health 2020, 8, e639–e640.
50. Chu, H.; Bai, T.; Chen, L.; Hu, L.; Xiao, L.; Yao, L.; Zhu, R.; Niu, X.; Li, Z.; Zhang, L.; et al. Multicenter analysis of liver injury patterns and mortality in COVID-19. Front. Med. (Lausanne) 2020, 7, 584342.