Acute liver failure (ALF) and acute-on-chronic liver failure (ACLF), respectively, occur in patients with normal liver and patients with chronic liver diseases, including cirrhosis [1]. In general, both syndromes possess poor prognosis. The etiology of liver failure, such as hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis D virus (HDV) or hepatitis E virus (HEV), drugs, autoimmune hepatitis (AIH) and others, varies in various countries [1–4]. Although liver failure is currently a common medical disease, its incidence is increasing with the use of alcohol and with the growing epidemic of obesity and diabetes, leading to increases in the incidence of ACLF [4–6]. In this editorial, we discuss the recent progress regarding research on ALF and ACLF in the coronavirus disease 2019 (COVID-19) era (Figure 1).

**Figure 1.** Acute liver failure (ALF) and acute-on-chronic liver failure (ACLF) in the coronavirus disease 2019 (COVID-19) era. CPE, cytopathic effect; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ACE2R, angiotensin-converting enzyme 2 receptor; MAFLD, metabolic associated fatty liver diseases; NASH, non-alcoholic steatohepatitis; HAV, hepatitis A virus; HBV, hepatitis B virus; HDV, hepatitis D virus; HEV, hepatitis E virus; AIH, autoimmune hepatitis.

In the COVID-19 era, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is also an important acute insult in ACLF patients [7]. To some extent, hepatocytes and biliary epithelial cells express the angiotensin-converting enzyme 2 (ACE2) receptor, which is one of the receptor candidates for SARS-CoV-2 [8]. COVID-19 infections may contribute to both primary and secondary liver injuries in patients with or without pre-existing liver diseases, respectively, leading to ALF or exacerbation of underlying liver
diseases and ACLF [8]. In younger women, female sex hormones are protective in this regard [8]. A Fibrosis-4 (FIB-4) score above the threshold of 3.25 suggests the presence of liver fibrosis and is associated with higher mortality in people hospitalized with COVID-19 infections [9]. These patients may be associated with previously undocumented liver diseases, fibrosis and/or quiescent metabolic associated fatty liver diseases (MAFLD), and undiagnosed non-alcoholic steatohepatitis (NASH) (Figure 1) [9,10].

In patients with COVID-19, drug-induced liver injury (DILI) has often been observed (Figure 1). In total, 10.9% patients with COVID-19 were found to have DILI [11]. The frequency of DILI in patients who recovered from COVID-19-induced hepatitis was 36.2% [11]. The most commonly associated drugs were hydroxychloroquine, azithromycin, tocilizumab and ceftriaxone [11]. Delgado et al. reported that remdesivir had the highest incidence of DILI per administration [11].

Although a recent study [12] reported that liver injury in patients infected with COVID-19 did not seem to be associated with a higher risk of mortality, these results may be associated the distribution of COVID-19 vaccination or the SARS-CoV-2 Omicron variant. Further studies will be needed. Patients with chronic liver diseases should be vaccinated against COVID-19, and special attention for COVID-19 should be paid to patients with liver diseases [9,13].

AIH was occasionally observed after COVID-19 vaccination (i.e., vaccine-induced AIH) (Figure 1) [14,15]. A recent study indicated fast uptake of the COVID-19 mRNA vaccine BNT162b2 into human liver cell line Huh7, leading to changes in the expression and distribution of long interspersed nuclear element-1 (LINE-1), which is an endogenous reverse transcriptase, and that BNT162b2 mRNA is reverse transcribed intracellularly into DNA in as fast as 6 h upon BNT162b2 exposure. Thus, the COVID-19 mRNA vaccine is able to enter the human liver cell line Huh7 in vitro [16]. The use of immunosuppressants has been correlated to an increase in autoimmune liver disease severity and to lower levels of anti-SARS-CoV-2 antibodies upon vaccination [15]. All of the cases with AIH and post-COVID-19 vaccination have been successfully treated with steroids [15]. The assessment of low-density granulocytes (LDGs) may turn out to be a useful marker in the diagnosis of AIH [17].

The outbreak of acute severe hepatitis of unknown origin in children has recently been reported [18]. Some cases have tested positive for human adenoviruses and/or SARS-CoV-2 infection. Pediatric ALF differs from adult ALF, according to the type, the diversity of causes and the late appearance of hepatic encephalopathy [19]. In pediatric ALF, 20% of those who never developed hepatic encephalopathy died or underwent liver transplantation. Currently, 10–15% of liver transplantation indications in children are in ALF patients [19]. Finding the best-predicting score in pediatric ALF and early referral of the children to a specialized center are the most important issues (Figure 1) [19].

In certain cases, bacterial infection is also related to the development of ACLF. Takaya et al. reported that endotoxin level was a predictive factor independently associated with ACLF development [20]. They also showed that rifaximin decreased the endotoxin level and the risk of ACLF development in Child–Pugh class B, Japanese cirrhotic patients [20]. Endotoxin concentration was determined in whole blood by luminol chemiluminescence using a commercially available semiquantitative endotoxin activity assay [20]. Endotoxin, a lipopolysaccharide, is derived from the outer membrane of Gram-negative bacteria, and lipopolysaccharide (LPS) was recognized by Toll-like receptors (TLRs) of the liver, resulting in the activation of innate immune responses and the development of liver failure to some extent [20,21]. Endotoxin levels as well as Child–Pugh scores reflect the functional liver capacity and are independently associated with the development of ACLF in cirrhotic patients.

A meta-analysis of published studies on patients following liver resection for hepatocellular carcinoma (HCC) demonstrated that albumin-bilirubin (ALBI) grades 2 and 3 showed increased rates of post-hepatectomy liver failure compared with patients with grade 1 ALBI [22]. ALBI grade is a useful liver-function assessment method in the sys-
temic treatment for HCC patients [23]. ALBI grade is a non-invasive, blood-test-based simple score that is able to reduce post-operative complications in patients with HCC.

Novel strategies to treat patients with ACLF have also been under development [24,25]. We are currently developing new strategies against HAV infections as acute insults [26,27]. In summary, the articles mentioned above offer a critical overview of ALF, ACLF and the related areas, and these medical conditions also play important roles in the COVID-19 era.

**Author Contributions:** Conceptualization, T.K. and R.S.-T.; writing—original draft preparation, T.K., R.S.-T. and H.E.; writing—review and editing, T.K., R.S.-T., T.I., H.A., M.O. and H.E.; funding acquisition, T.K. and R.S.-T. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research was partly funded by the Japan Agency for Medical Research and Development (AMED), grant number JP22fk0210075h0003.

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Not applicable.

**Data Availability Statement:** The data might be available from the authors of the cited papers.

**Conflicts of Interest:** The authors declare no conflict of interest.

**References**

1. Jindal, A.; Sarin, S.K. Epidemiology of liver failure in Asia-Pacific region. Liver Int. 2022. [CrossRef] [PubMed]
2. Kanda, T.; Yokosuka, O.; Imazeki, F.; Saisho, H. Acute hepatitis C virus infection, 1986–2001: A rare cause of fulminant hepatitis in Chiba, Japan. Hepatogastroenterology 2004, 51, 556–558. [PubMed]
3. Kanda, T.; Yokosuka, O.; Hirasa, Y.; Imazeki, F.; Nagao, K.; Suzuki, Y.; Saisho, H. Acute-onset autoimmune hepatitis resembling acute hepatitis: A case report and review of reported cases. Hepatogastroenterology 2005, 52, 1233–1235. [PubMed]
4. Sarin, S.K.; Choudhury, A.; Sharma, M.K.; Maiwall, R.; Al Mahtab, M.; Rahman, S.; Saigal, S.; Saraf, N.; Soin, A.S.; Devarbhavi, H.; et al. APASL ACLF Research Consortium (AARC) for APASL ACLF working Party. Acute-on-chronic liver failure: Consensus recommendations of the Asian Pacific association for the study of the liver (APASL): An update. Hepatol. Int. 2019, 13, 353–390. [CrossRef]
5. Mochida, S.; Nakayama, N.; Terai, S.; Yoshiji, H.; Shimizu, M.; Ido, A.; Inoue, K.; Genda, T.; Takikawa, Y.; Takami, T.; et al. Diagnostic criteria for acute-on-chronic liver failure and related disease conditions in Japan. Hepatol. Res. 2022, 52, 417–421. [CrossRef]
6. Gambino, C.; Piano, S.; Angeli, P. Acute-on-Chronic Liver Failure in Cirrhosis. J. Clin. Med. 2021, 10, 4406. [CrossRef]
7. Ikegami, C.; Kanda, T.; Ishii, T.; Honda, M.; Yamana, Y.; Tanaka, R.S.; Kumagawa, M.; Kanezawa, S.; Mizutani, T.; Yamagami, H.; et al. COVID-19 After Treatment With Direct-acting Antivirals for HCV Infection and Decompensated Cirrhosis: A Case Report. In Vivo 2022, 36, 1986–1993. [CrossRef]
8. Lykowska-Szuber, L.; Wołodźko, K.; Rychter, A.M.; Szymczak-Tomczak, A.; Krela-Kązmierczak, I.; Dobrowska, A.; Maniscalco, A.; Kamiński, T.; Yamagami, H.; et al. COVID-19 and Autoimmune Liver Diseases. J. Clin. Med. 2022, 11, 417–421. [CrossRef]
9. Crisan, D.; Avram, L.; Dragan, A.; Radulescu, D.; Crisan, S.; Grosu, A.; Militaru, V.; Stoicescu, L.; et al. In vitro and in vivo Characterisation of Drug-Induced Liver Injury in Patients with COVID-19 Detected by a Proactive Pharmacovigilance Program from Laboratory Signals. J. Clin. Med. 2021, 10, 4432. [CrossRef] [PubMed]
10. Pazgan-Simon, M.; Serafinska, S.; Kukla, M.; Kucharska, M.; Zuwała-Jagiełło, J.; Buczyńska, I.; Zielinska, K.; Simon, K. Letter to the editor: Autoimmune hepatitis after COVID-19 vaccination: Need for population-based epidemiological study. Hepatology 2022, 75, 759–760. [CrossRef]
11. Delgado, A.; Steward, S.; Urroz, M.; Rodriguez, A.; Borobia, A.M.; Akatbach-Bousaid, I.; Gonzalez-Muñoz, R.; Ramírez, E.ervoirs of Drug-Induced Liver Injury in Patients with COVID-19 Detected by a Proactive Pharmacovigilance Program from Laboratory Signals. J. Clin. Med. 2021, 10, 4432. [CrossRef] [PubMed]
12. Cerbu, B.; Grigoras, M.L.; Bratosin, F.; Bogdan, I.; Citu, C.; Bota, A.V.; Timircan, M.; Bratu, M.L.; Levai, M.C.; Marincu, I. Laboratory Profile of COVID-19 Patients with Hepatitis C-Related Liver Cirrhosis. J. Clin. Med. 2022, 11, 652. [CrossRef] [PubMed]
13. Suzuki, Y.; Kakisaka, K.; Takikawa, Y. Letter to the editor: Autoimmune hepatitis after COVID-19 vaccination: Need for population-based epidemiological study. Hepatology 2022, 75, 759–760. [CrossRef]
14. Floreani, A.; De Martin, S. COVID-19 and Autoimmune Liver Diseases. J. Clin. Med. 2022, 11, 2681. [CrossRef]
15. Aldén, M.; Olofsson Falla, F.; Yang, D.; Barghouth, M.; Luan, C.; Rasmussen, M.; De Marinis, Y. Intracellular Reverse Transcription of Pfizer BioNTech COVID-19 mRNA Vaccine BNT162b2 In Vitro in Human Liver Cell Line. Curr. Issues Mol. Biol. 2022, 44, 1115–1126. [CrossRef]
17. Domerecka, W.; Homa-Mlak, I.; Mlak, R.; Michalak, A.; Wilińska, A.; Kowalska-Kępczyńska, A.; Dreher, P.; Cichoż-Lach, H.; Małecka-Massalska, T. Indicator of Inflammation and NETosis—Low-Density Granulocytes as a Biomarker of Autoimmune Hepatitis. *J. Clin. Med.* **2022**, 11, 2174. [CrossRef]

18. Mücke, M.M.; Zeuzem, S. The recent outbreak of acute severe hepatitis in children of unknown origin—what is known so far. *J. Hepatol.* **2022**, 77, 237–242. [CrossRef]

19. Pop, T.L.; Aldea, C.O.; Delean, D.; Bulata, B.; Boghiţoiu, D.; Păcurar, D.; Ulmeanu, C.E.; Grama, A. The Role of Predictive Models in the Assessment of the Poor Outcomes in Pediatric Acute Liver Failure. *J. Clin. Med.* **2022**, 11, 432. [CrossRef]

20. Takaya, H.; Namisaki, T.; Sato, S.; Kaji, K.; Tsuji, Y.; Kaya, D.; Fujinaga, Y.; Sawada, Y.; Shimozato, N.; Kawaratani, H.; et al. Increased Endotoxin Activity Is Associated with the Risk of Developing Acute-on-Chronic Liver Failure. *J. Clin. Med.* **2020**, 9, 1467. [CrossRef]

21. Jiang, X.; Kanda, T.; Tanaka, T.; Wu, S.; Nakamoto, S.; Imazeki, F.; Yokosuka, O. Lipopolysaccharide blocks induction of unfolded protein response in human hepatoma cell lines. *Immunol. Lett.* **2013**, 152, 8–15. [CrossRef] [PubMed]

22. Marasco, G.; Alemanni, L.V.; Colecchia, A.; Festi, D.; Bazzoli, F.; Mazzella, G.; Montagnani, M.; Azzaroli, F. Prognostic Value of the Albumin-Bilirubin Grade for the Prediction of Post-Hepatectomy Liver Failure: A Systematic Review and Meta-Analysis. *J. Clin. Med.* **2021**, 10, 2011. [CrossRef] [PubMed]

23. Ogasawara, S.; Chiba, T.; Ooka, Y.; Suzuki, E.; Kanogawa, N.; Saito, T.; Motoyama, T.; Tawada, A.; Kanai, F.; Yokosuka, O. Liver function assessment according to the Albumin-Bilirubin (ALBI) grade in sorafenib-treated patients with advanced hepatocellular carcinoma. *Investig. New Drugs* **2015**, 33, 1257–1262. [CrossRef]

24. Kaps, L.; Schleicher, E.M.; Medina Montano, C.; Bros, M.; Gairing, S.J.; Ahlbrand, C.J.; Michel, M.; Klimpke, P.; Kremer, W.M.; Holtz, S.; et al. Influence of Advanced Organ Support (ADVOS) on Cytokine Levels in Patients with Acute-on-Chronic Liver Failure (ACLF). *J. Clin. Med.* **2022**, 11, 2782. [CrossRef] [PubMed]

25. Zhang, P.; Li, H.; Zhou, C.; Liu, K.; Peng, B.; She, X.; Cheng, K.; Liu, H.; Ming, Y. Single-Cell RNA Transcriptomics Reveals the State of Hepatic Lymphatic Endothelial Cells in Hepatitis B Virus-Related Acute-on-Chronic Liver Failure. *J. Clin. Med.* **2022**, 11, 2910. [CrossRef]

26. Sasaki-Tanaka, R.; Shibata, T.; Okamoto, H.; Moriyama, M.; Kanda, T. Favipiravir Inhibits Hepatitis A Virus Infection in Human Hepatocytes. *Int. J. Mol. Sci.* **2022**, 23, 2631. [CrossRef]

27. Sasaki-Tanaka, R.; Nagulapalli Venkata, K.C.; Okamoto, H.; Moriyama, M.; Kanda, T. Evaluation of Potential Anti-Hepatitis A Virus 3C Protease Inhibitors Using Molecular Docking. *Int. J. Mol. Sci.* **2022**, 23, 6044. [CrossRef]