

Research Article

Comparison of Liver Disease in Patients Before and During the COVID-19 Pandemic Who were Admitted to the General Hospital of the University of Muhammadiyah Malang

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COVID-19-associated liver injury is defined as any liver damage that occurred during the course of infection and treatment of COVID-19 patients, with or without pre-existing liver disease. This includes a broad spectrum of potential pathomechanisms, including direct cytotoxicity from active viral replication of SARS-CoV-2 in the liver and immune-mediated liver damage due to the severe inflammatory response/ systemic inflammatory response syndrome (SIRS) in COVID-19. Data was taken from 206 patients with COVID-19 who were admitted to our hospital and were examined physically. Laboratory and ultrasound results showed abnormal rates associated with liver disease. The four-year study was conducted from January 2018 to December 2021. 116 pts were collected in the period 2018 to 2019 (2 years precov) and 90 pts 2 years (2020-2021) in the era of the COVID-19 pandemic. Women's precov was 60 pts and dcov was 30 pts, while men showed 56 pts and 60 pts precov during COVID-19 infection. Liver cirrhosis was 28 pts precov and 41 pts dcov, followed by NSRH 25 pts precov and 12 pts dcov, NASH 24 pts precov and 6 pts dcov, Hep. B 20 precov and 10 dcov, acute viral hepatitis 12 precov and 16 dcov points. In total liver cirrhosis placed the first rank 69 pts (33, 5%). Followed by NSRH 17, 96 %; NASH 14, 56%, B. Hep. 14, 56 % and Ac.viral Hep. 13, 59%.

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1. INTRODUCTION

COVID-19 associated liver injury is defined as any liver damage occurring during disease course and treatment of COVID-19 patients, with or without pre-existing liver disease (1). This includes a broad spectrum of potential patho-mechanisms including direct cytotoxicity from active viral replication of SARS-CoV-2 in the liver, immune-mediated liver damage due to the severe inflammatory response/ systemic inflammatory response syndrome (SIRS) in COVID-19 (2)(3). Liver disease is a deterioration of liver functions. That can be acute or chronic progression, which includes synthesis of clotting factors, other

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proteins, detoxification of harmful products of metabolism, excretion of bile, process of inflammation, destruction, and regeneration of liver parenchyma which leads to fibrosis and cirrhosis (4). Toxins, alcohol abuse for a prolonged time, infection, autoimmune diseases, genetic and metabolic-hereditary, pregnancy-related, ischemic and vascular are the spectrum of broad etiologies for chronic liver disease (4).

Nonalcoholic hepatic steatosis (NASH) is present in 33% of the adult population in the United States (5) and is characterized by the accumulation of triacylglycerol (TAG)-rich macrovesicular and/or microvesicular lipid droplets within the hepatocytes, in the absence of inflammation or liver injury. Increased caloric intake and reduced physical activity in recent years have undoubtedly contributed to increased obesity and a parallel increase in the prevalence of nonalcoholic fatty liver disease (NAFLD) (5). Physical examination findings are due to the underlying diseases and laboratory result (SGOT/ SGPT) are therefore very variable. Survey abdominal radiographs and ultrasonography are usually unremarkable but could be useful. The poor outcomes are more frequent in patients in whom biopsies show ballooning degeneration and Mallory hyaline or fibrosis (6). NSRH is a wide variety of inflammatory / febrile conditions, that characterized by an inflammatory infiltrate in portal areas and the hepatic parenchyma without hepatocellular necrosis/ apoptosis (7).

Chronic liver disease is an extremely common clinical condition, and the focus is done on the common etiologies (such as Toxins, alcohol abuse for a prolonged time, infection, autoimmune diseases, genetic and metabolic-hereditary, pregnancy-related, ischemic and vascular), clinical manifestations, and management. The underlying mechanism of fibrosis and cirrhosis at a cellular level is the recruitment of stellate cells and fibroblasts, resulting in fibrosis, while parenchymal regeneration relies on hepatic stem cells. Cirrhosis is a final stage of chronic liver disease that results in disruption of liver architecture, the formation of widespread nodules, vascular reorganization, neo-angiogenesis, and deposition of an extracellular matrix (4).

2. MATERIALS AND METHODS

The study was undertaken in the General Hospital of the University of Muhammadiyah Malang in periods January 2018 until December 2021. We obtained the medical records and compiled data for hospitalized patients. The datas devided into two groups, before covid-19 pandemic (January 2018 until December 2019) and during pandemic (January 2020 until December 2021) with laboratory-confirmed Covid-19. Including criteria were patients diagnosed as liver disease based on laboratory (increasing of SGOT/SGPT

level, HbSAg, HbAntiHcV) and Ultrasonographic (USG) examination that showed fatty liver, fibrosis and malignancy. All the observational and retrospective secondary data were analyzed and interpreted by the authors.

3. RESULTS

116 patients were collected in the pre-pandemic periode and 90 patients during the pandemic that fulfilled the liver disease criteria (lab and USG). In total there were 90 women pts (43,69%), where precov was 60 pts (66,67%) and during covid 30 pts (33,33%), while men showed 116 pts (56,31%), where 56 precovid (48,28%) and 60 pts during covid (66,67%). Liver Cirrhosis with 69 pts (33,50%) consist from 28 pts precovid (24,14%) and 41 pts dcov (45,56%), NSRH with 37 pts (17,96%) consist from 25 pts precovid (67,57%) and 12 pts dcov (32,43%), NASH with 30 pts (14,56%) consist from 24 pts precovid (80%) and 6 pts dcov (20%), Hep. B with 30 pts (14,56%) consist from 20 pts precovid (66,67%) and 10 pts dcov (33,33%), Acute Viral Hepatitis with 28 pts (13,59%) consist from 12 pts precovid (42,86%) and 16 pts dcov (57,14%), Hep. A with 10 pts (4,85%) consist from 6 pts precovid (60%) and 4 pts dcov (40%), Hep. C with 2 pts (0,97%) consist from 1 pts precovid (50%) and 1 pts dcov (50%).

TABLE 1: Liver Diseases Rank among patients admitted during Jan. 2018 - Dec. 2021.

| No | Diseases | 2018-2019 | % | 2020-2021 | % | Σ | Σ % |
|----|---|-----------|-------|-----------|-------|-----|--------|
| 1 | Sirosis | 28 | 40,58 | 41 | 59,42 | 69 | 33,50 |
| 2 | NSRH | 25 | 67,57 | 12 | 32,43 | 37 | 17,96 |
| 3 | NASH/ NAFLD | 24 | 80,00 | 6 | 20,00 | 30 | 14,56 |
| 4 | Hepatitis B | 20 | 66,67 | 10 | 33,33 | 30 | 14,56 |
| 5 | Acute viral Hepatitis (non A, non B, non C) | 12 | 42,86 | 16 | 57,14 | 28 | 13,59 |
| 6 | Hepatitis A | 6 | 60,00 | 4 | 40,00 | 10 | 4,85 |
| 7 | Hepatitis C | 1 | 50,00 | 1 | 50,00 | 2 | 0,97 |
| | Total | 116 | | 90 | | 206 | 100,00 |

Elevated liver enzymes reflecting, hepatitis viral marker (IgM-AntiHAV, HBSAg, Anti-HCV), ultrasonographic (USG) examination reflecting hepatic injury (Non Spesific Reactiv Hepatic/ NSRH), Fatty liver (Non-Alcoholic Steatotic Hepatis/ NASH/ Non-Alcoholic Fatty Liver Disease/ NAFLD), A Hepatitis, B Hepatitis, C Hepatitis, Fibrosis of the Liver and Liver Cirrhosis with/ without sign of portal hypertension / Hepatic failure (Encephalopathic Liver Cirrhosis). 116 patients fulfill the liver disease criteria precov compare with 206 patients during Covid, It means that during Covid pandemic era, patients with comorbid liver disease more vulnerable suffers from the disease (Tabel 1).

Among 28 pts precovid there were 3 death cases (10,71%) while during COVID there were 41 pts during COVID and 2 death cases (4,887%). It meant that was no correlation between SARS-COV-2 infections as fatal complication between cases.

4. DISCUSSION

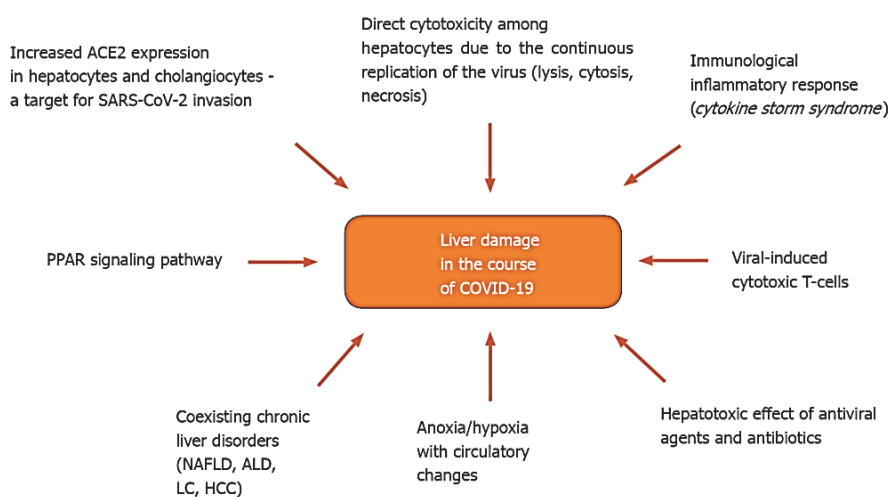


Figure 1: Mechanisms of liver injury in Covid-19.

(ACE2: Angiotensin converting enzyme 2; SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2; PPAR: Peroxisome proliferator-activated receptors; NAFLD: Non-alcoholic fatty liver disease; ALD: Alcohol-related liver disease; LC: Liver cirrhosis; HCC: Hepatocellular carcinoma) (8).

Angiotensin converting enzyme 2 (ACE2) appears to be a key agent in liver injury due to COVID-19. This metallopeptidase, which serves as a functional receptor for SARS-CoV-2, is not only localized on the surface of respiratory tract epithelium, but also observed in cholangiocytes (59.7% of cells) and to a lesser extent in hepatocytes (2.6% of cells). SARS-CoV-2 may exert a cytopathic effect, either by lysis and/or by inducing necrosis and apoptosis (9)(10).

This proves that SARS-CoV-2 infection impairs liver function by direct cytotoxicity due to the continuous replication of the virus in the above-mentioned cell populations (11), (12). Additionally, gene expression of ACE2 transmembrane serine protease 2 together with paired basic amino acid cleaving enzyme have also been proved in cholangiocytes and hepatocytes.

Thus, ACE2 plays a fundamental role in host cells as a receptor of Spike-I Glycoprotein of COVID-19 which finally leads to infection. A recent finding revealed that

the renin-angiotensin system and peroxisome proliferator-activated receptor signaling pathway can even enhance the infection at this stage. Therefore, both angiotensin and peroxisome proliferator-activated receptor family proteins may potentially be perceived as possible therapeutic targets (13), (14). Viral-induced cytotoxic T-cells, is pathological pathway responsible for liver dysfunction in COVID-19 (an immunological inflammatory response (C-reactive protein (CRP), ferritin, lactate dehydrogenase (LDH), D-dimers, interleukin-6 (IL-6), IL-2), suggesting a direct link between the presence of the cytokine storm syndrome and disease severity (15), (16). Furthermore, hepatic anoxia that related to respiratory failure and antiviral agents (lopinavir, ritonavir, ramdevpir, umifenovir, or antibiotics used, antipyretics or steroids) might also cause deterioration of liver function (17), (18). In a recently published survey of 2780 persons with COVID-19, 250 patients with known chronic liver disease (CLD) were at a higher risk of prolonged hospitalization and death (19). Unfortunately, according to available data, it is difficult to predict which liver diseases are mostly dangerous, but of note, biologics such as baricitinib and tocilizumab may lead to a reactivation of HBV infection. Thus, these patients require special supervision (20). Figure 1 presents the spectrum of mechanisms involved in liver damage accompanying COVID-19. In our data liver cirrhosis showed higher prevalence during pandemic compare with pre pandemic (41 pts vs 28 pts), similar data also present in Acute viral hepatitis (16 pts vs 12 pts), the rest data (NSRH, NASH/NAFLD, Hep. B, Hep. A, Hep. C) showed a lower prevalence during pandemic COVID-19.

Male predominate (56,31%) during COVID because of socioeconomic responsibility and cause a higher opportunity to suffer from SARS COVID-19 (Table 2). Distancing, over crowded, close space meeting would be the factors enhancing man predominated.

TABLE 2: Patient in Gender admitted during Jan. 2018 - Dec. 2021.

| Periods | Years | F | % | M | % | Σ | Total % |
|--------------|--------------------|----|-------|-----|-------|-----|---------|
| Pre covid | 2018 | 23 | 25,56 | 20 | 17,24 | 43 | 20,87 |
| | 2019 | 37 | 41,11 | 36 | 31,03 | 73 | 35,44 |
| | Total Pra- COVID | 60 | 51,72 | 56 | 48,28 | 116 | |
| During covid | 2020 | 16 | 17,78 | 20 | 17,24 | 36 | 17,48 |
| | 2021 | 14 | 15,56 | 40 | 34,48 | 54 | 26,21 |
| | Total During COVID | 30 | 33,33 | 60 | 66,67 | 90 | |
| | Total | 90 | 43,69 | 116 | 56,31 | 206 | |

It still needs a future research to give the answer the real contribution of direct cytopathic effects, cytokine storm, DILI (Drug Induced Liver Injury) or hypoxia in hepatic dysfunction, By which means could liver injury promote respiratory failure and predispose to a severe course of COVID-19 (7).

The pathogenesis of hepatic steatosis involves multiple pathways, and is often considered a benign condition; however, once the initiation of inflammation occurs, there is an increased risk of progression to fibrosis and cirrhosis. Fatty acid uptake, de novo lipogenesis, mitochondrial fatty acid oxidation, lipoprotein secretion, lifestyle and lipid dietary must be an option strategy that would be beneficial in preventing hepatic steatosis and further forms of NAFLD.

5. CONCLUSION

In total liver cirrhosis placed the first rank 69 pts (33, 5%), and among them 41 pts (59,42%) occur in the pandemic COVID era it means that chronic liver disease showed a higher prevalence, followed by NSRH 17, 96 %; NASH 14, 56%, B. Hep. 14, 56 % and Ac.viral Hep. 13, 59%. However, patients with preexisting liver disease, notably cirrhosis, are at higher risk for hospitalizations and mortality. Although it is not proven in our hospital (10,71% vs 4,88%), precovid shows a higher rate. Early isolation, intensive surveillance, and prompt diagnosis are essential to manage these patients. Further research identifying interventions to reduce poor outcomes in high-risk patients with COVID-19 is needed.

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