The impact of COVID-19 on the clinical course of patients with cirrhosis

Ph.D thesis

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Budapest, 2024

1. Introduction

Severe acute respiratory syndrome (SARS-CoV-2) causing COVID-19 infection has spread over the world, emerging as a global health crisis. However, respiratory illness is highly prevalent in COVID-19, gastrointestinal (GI) symptoms may occur in up to 25% of all cases. Liver damage is a common clinical feature of COVID-19. There are comprehensive molecular patomechanisms of liver injury, including direct damage, drug-induced liver injury (DILI), cytokine storm, hypoxia and endothelitis coagulopathy. Although the histopathology features of the lung have been highlighted in SARS-CoV-2 infection, liver is found to be a particularly affected organ. Macro-and microvesicular steatosis, portal and periportal inflammation, acute hepatitis, vascular findings including sinusoidal microtrombi and cholestasis are the most common findings. Abnormal liver function parameters and elevated inflammatory markers were associated with severe clinical course. Relevant to risk factors and clinical outcome, cirrhosis severity and etiological agents such as non-alcoholic fatty liver disease (NAFLD), hepatitis B virus and alcoholic cirrhosis are both risk factors for COVID-19 related mortality. As acute deterioration in liver function occurs, patients with decompensated cirrhosis are characterised by ascites, hepatic encephalopathy, hepatorenal syndrome or variceal haemorrhage. Consequently,

higher occurence of Intensive Care Unit (ICU) admission, renal replacement therapy and mechanical ventilation were witnessed in COVID-19 patients with decompensated cirrhosis, leading to higher mortality rates. As COVID-19 is a new challenge for the humanity, there is no specific treatment for COVID-19. However, there are several safe and efficient therapeutic options available such as steroids, remdesivir, tocilizumab, eculizumab, immunoglobulins, neutralizing IgG1 monoclonal antibodies and convalescent plasma.

COVID-19 vaccination is highly preferred for patients with cirrhosis. There are four different types of vaccine available: mRNA-based vaccines, viral vector vaccines, inactivated or protein subunit vaccines and traditional adjuvanted vaccines. Among different COVID-19 vaccines, mRNA-based vaccines could prevent most effectively the severe clinical course of COVID-19. Patients with cirrhosis receiving at least one mRNA-based vaccine are reported to have better survival rates compared to unvaccinated patients. Moreover, booster vaccination could decrease hospital mortality of COVID-19.

2. Objectives

In the research fields of my doctoral thesis, we aimed to evaluate the impact of COVID-19 on clinical characteristics and laboratory findings in patients

with cirrhosis revealing the prognostic and preventive factors associated with in-hospital mortality. The principal aims of my study are outlined as follows:

- Recently, there are limited data available about the impact of COVID-19 on the clinical outcomes of patients with cirrhosis. We hypothesized that patients with cirrhosis following COVID-19 are more susceptible to disease progression and severe clinical course.

- Apart from alcohol use disorder, older age, male gender, higher CTP scores and hypalbuminaemia, novel prognostic factors are still unknown. Therefore, we aimed to investigate novel prognostic and predictive factors for mortality in COVID-19 patients with cirrhosis.

- Moreover, our goal was to evaluate the cirrhosis severity and hepatic decompensation events in COVID-19 patients with cirrhosis compared to cirrhosis patients without COVID-19.

- To date, multiple types of COVID-19 vaccines have been employed in the entire population including patients with cirrhosis. There are limited data available about the

effectiveness of different COVID-19 vaccines in liver cirrhosis. Therefore, our goal was to evaluate the efficacy of several vaccines against SARS-CoV-2 infection in patients with cirrhosis and identify the most effective COVID-19 vaccine to prevent COVID-19 related complications and deaths.

3. Methods

3.1 Patient population

A retrospective multicentre study was performed using data from electronic medical records. All data including epidemiological features, clinical characteristics and laboratory data were recorded and reviewed. On hospital admission, a complete health assessment was done including a comprehensive head-to-toe physical assessment and a detailed medical history with special emphasis on cirrhosis severity and acute hepatic decompensation events.

Between March 2020 and May 2022, we recruited 6394 COVID-19 patients being hospitalized in several centers of Semmelweis University. As illustrated in Figure 5, 451 COVID-19 adult patients with elevated liver transaminases (>40 U/L) on admission and/or underlying liver cirrhosis were included in our study. Of the 451 COVID-19 patients, we selected 399 COVID-19

patients without cirrhosis (GROUP A) and 52 COVID-19 patients with cirrhosis (GROUP B) to investigate and compare the patient characteristics, including comorbid conditions, COVID-19 medications and major hospital outcomes between the two groups. The diagnosis of COVID-19 required a positive reverse transcription polymerase chain reaction (RT-PCR, SEQONCE qPCR Multi Kit, IVD, SeqOnce Biosciences, Carlsbad, CA 92008, USA) test based on a nasopharyngeal swab using the protocol of the World Health Organization. All the included COVID-19 patients underwent a high-resolution computer tomography (HRCT, Philips Incisive 128, Philips, Amsterdam, the Netherlands) for detecting the pulmonary findings in COVID-19. The diagnosis of liver cirrhosis was formerly determined by liver biopsy, liver elastography, clinical presentations of portal hypertension (e.g., gastrointestinal varices on endoscopy) and morphological hepatic alterations (e.g., liver surface nodularity, ascites). Moreover, we matched 52 GROUP B patients with 54 cirrhosis patients without COVID-19 (GROUP C) respecting age and gender in approximately 1:1 ratio. In both groups the representation of cirrhosis patients was proportional. The GROUP C controls aged $\geq$ 18 years were laboratory-confirmed COVID-19 negative cirrhosis patients, who were previously hospitalised in the collaborating centres between

March 2020 and May 2022, owing to acute hepatic decompensation events.

Patients with the absence of liver cirrhosis diagnosis or laboratory not confirmed COVID-19 positive cases were excluded from our study. In addition, we excluded 5317 COVID-19 inpatients without liver disease in the medical history or elevated liver enzymes on admission.

3.2 Data collection

Laboratory tests were regularly performed from admission time to discharge or death. During hospitalization, laboratory parameters such as liver transaminases (AST, ALT), cholestatic parameters (GGT, total bilirubin, direct bilirubin, ALP), liver function tests (albumin, INR, total protein), inflammatory biomarker (CRP), complete blood count and basic metabolic panel (sodium, potassium, total serum calcium, glucose, creatinine, glomerular filtration rate) were frequently measured in COVID-19 patients with cirrhosis.

The total serum calcium concentration in patients with cirrhosis could not precisely indicate the physiologically active calcium concentration due to hypalbuminaemia. Hence, corrected calcium for albumin was calculated using the correction formula as follows: corrected calcium = (0.8x[normal albumin - patient's albumin]) + serum calcium. Hypocalcaemia was defined as a corrected serum calcium level < 2.2 mmol/L (8.9 mg/dl).

3.3 Liver cirrhosis severity

The classification systems used for grading the severity of liver cirrhosis were the modified Child-Turcette-Pugh (CTP) score and Model for End-Stage Liver Disease sodium (MELD-Na) score. The CTP score was calculated using five clinical measures as follows: serum concentrations of total bilirubin and albumin, INR, ascites grades, and stages of hepatic encephalopathy. Regarding different CTP scores, patients are classified as follows: 5 to 6 points considered as class A (well-compensated cirrhosis), 7 to 9 points as class B (significant functional compromise), and 10 to 15 points as class C (decompensated cirrhosis). MELD-Na score was based on serum bilirubin, serum creatinine, INR, serum sodium and hemodialysis treatments at least twice in the past week. Patients with cirrhosis were classified into three severity groups: compensated, decompensated and ACLF. Decompensated cirrhosis was described by ascites, variceal haemorrhage or hepatic encephalopathy. The interpretation of ascites was characterised by the volume of abdominal fluid: grade 1 ascites detected by ultrasound; grade 2 ascites described by proportional abdominal distension; grade 3 ascites with marked abdominal extension. We used the West Haven Criteria for grading the severity of hepatic encephalopathy. Patients with acute hepatic decompensation were assessed for prognosis according to the European Association for the Study

of the Liver Chronic Liver Failure (CLIF) consortium definition. The diagnosis of ACLF was characterised by EASL-CLIF-C and the North American Consortium for the Study of End-Stage Liver Disease (NACSELD).

3.4 COVID-19 vaccine regimens

IIn the third wave between March and April 2021, five different vaccines such as two mRNA-based vaccines (BNT162b2-Pfizer-BioNTech, mRNA-1273-Moderna), two vector vaccines (AZD1222-Astra Zeneca, Gam-COVID-Vac-Sputnik V) and one inactivated vaccine (HB02-Sinopharm) were extensively administered in patient with cirrhosis. Patients receiving primary immunization (were 14 days after receiving two doses of Pfizer-BioNTech or Moderna, or one dose of Pfizer-BioNTech and one dose of Moderna, or two doses of Sputnik or Sinopharm), or having already booster vaccination following the primary vaccination series or not receiving any vaccines, were included in our study. Regarding inadequate primary vaccination, patients with only one dose of COVID-19 vaccination such as the single-dose Janssen vaccine were excluded from our study.

4. Results

4.1. Clinical characteristics of patients with cirrhosis

The stages of cirrhosis were not significantly different between GROUP B and GROUP C. Related to the cirrhosis stages, decompensated cirrhosis was the most common in both groups, with rates of 80.8% (GROUP B) and 59.3% (GROUP C), respectively. However, the life-threatening ACLF was found to be more prevalent in GROUP C (14.8%) compared to GROUP B (11.5%), which may have led to higher mortality rates in GROUP C. Regarding the causes of cirrhosis, alcohol abuse was the most frequent etiological factor, followed by HCV. Furthermore, the prevalence of autoimmune liver diseases such as PBC, PSC and AIH was higher GROUP B (13/52) in comparison with GROUP C (8/54). Regarding the acute hepatic decompensation events, stage 3-4 encephalopathy was significantly more common in GROUP B (27/52) related to GROUP C (18/54). GROUP B patients (38/52) were more commonly associated with higher occurrence of grade 2-3 esophageal varices on endoscopy, indicating vascular decompensation and higher risk of bleeding. Regarding total cases, there was an incremental developing cirrhosis severity in GROUP B grouped by different CTP stages. In contrast, GROUP C with worsening cirrhosis was associated with higher mortality rates related to GROUP B. Nevertheless, we found no significant differences between GROUP B and GROUP C in the proportions of total and deceased cases.

4.2 Major hospital outcomes

Oxygen support was more frequently needed in GROUP B (40.1%) compared to GROUP A (36.8%). Moreover, 46% of GROUP B patients required mechanical ventilation, indicating the onset of respiratory failure consequently severing COVID-19 pneumonia. Regarding the medications for COVID-19, the administration of 5-day remdesivir was lower in GROUP B compared to GROUP A. Corticosteroids were the most frequently administered pharmacological treatments in GROUP A and GROUP B, with rates of 71.9% and 71.2%, respectively. In addition, there was a slight majority of patients in GROUP B who received convalescent plasma therapy. The in-hospital mortality rates in COVID-19 patients were as follows: 11.8% (GROUP A) and 9.6% (GROUP C).

4.3 Effectiveness of mRNA-based vaccines in patients with cirrhosis

Patients receiving mRNA vaccines had better survival rates compared to those vaccinated with viral vector or inactivated vaccines. Patients in GROUP A who were vaccinated with Moderna had a significantly better survival outcome (log-rank test: $p=0.039$) contrasted to those receiving Sputnik V. With regard to mRNA vaccines, primary vaccination with Pfizer-BioNTech was found to be significantly more efficient (log-rank test: $p = 0.017$)

in comparison with Moderna. Furthermore, unvaccinated patients were associated with worse survival rates in all groups compared to those receiving any vaccine. Additionally, patients in GROUP C without any COVID-19 vaccine administered were significantly susceptible to increased fatal outcome (log-rank test: p =0.003). Major hospital outcomes such as encephalopathy and ascites grades, esophageal varices on endoscopy, oxygen support and mechanical ventilation were found to be significantly different between the three groups classified by mRNA vaccines. Despite the proportional COVID-19 vaccination rate in GROUP B and GROUP C, higher occurence of stage 3-4 encephalopathy, severing ascites and grade 2-3 esophageal varices were found in GROUP B patients, which may indicate the onset of acute hepatic decompensation and worsening cirrhosis stage. Moreover, the administration of oxygen support and mechanical ventilation were significantly more prevalent in GROUP B due to the development of COVID-19-induced respiratory failure. Related to Pfizer-BioNTech vaccine, vaccination rates in GROUP B and GROUP C were as follows: 51.9% and 66.7%, respectively. More patients were vaccinated with Moderna in GROUP B compared to GROUP C (23% vs. 9.3%). patients in GROUP C receiving Pfizer-BioNTech were significantly associated with lower rates of worsening encephalopathy leading to poor prognosis

compared to those in GROUP B ($p<0.05$). In addition, patients vaccinated with Moderna had significantly higher in-hospital mortality rates in GROUP C compared to GROUP B (3.7% vs. 0%; $p<0.05$).

4.4 Hypocalcaemia as a significant prognostic marker for poor prognosis in COVID-19 patients with cirrhosis

Age and the length of hospitalization were independently associated with in-hospital mortality in COVID-19 patients with cirrhosis. The univariate analysis showed that albumin, INR, total bilirubin, direct bilirubin and CTP were significantly associated with fatal outcomes ($p<0.05$). Moreover, Na, WBC and platelets were proved to be significant prognostic factors for poor prognosis, with ORs of 0.905 ($p < 0.05$; 95% CI 0.847–0.966), 1.314 ($p < 0.05$; 95% CI 1.226–1.409) and 0.995 ($p < 0.05$ 95% CI 0.990–1.000), respectively.

The multivariate logistic regression for mortality with respect to gender and cirrhosis severity demonstrated that Na, albumin, INR, direct bilirubin, WBC and CTP remained significant prognostic markers for fatal outcome in COVID-19 patients with cirrhosis. In addition, hypocalcemia on admission was independently associated with poor outcome, with an OR of 4.871 ($p < 0.05$; 95% CI 1.566–15.146).

4.5 Predictive value of corrected total serum calcium for in-hospital mortality in COVID-19 patients with cirrhosis

In the case of total serum calcium, the area under the curve (AUC) value was 0.818 (95% CI 0.683–0.953, $p < 0.05$), which was nearly the highest among those investigated. the optimal cut-off value of total serum calcium was 2.02 mmol/L, with a sensitivity of 88.3% and a specificity of 75%, which were prominent among the factors evaluated.

4.6 Hypocalcaemia on admission is significantly associated with disease progression in COVID-19 patients with cirrhosis

Among cirrhosis cases, patients with hypocalcemia on admission were associated with higher mortality rates compared to normocalcemic patients (16% vs. 3.7%). Regarding hepatic decompensation events, severe ascites was found more commonly in hypocalcemic patients (21/25) compared to normocalcemic patients (14/27). With respect to COVID-19 severity, hypocalcemic patients developed severe respiratory failure requiring mechanical ventilation during the hospital stay. Nevertheless, oxygen therapy was frequent, being administered in 55.6% of patients with normocalcaemia. Patients with hypocalcaemia were older and were associated with prolonged hospital stay relative to normocalcemic patients (65 vs. 60,

14 vs. 13). Moreover, hypocalcemic patients had significantly higher levels of direct bilirubin, GGT and CTP in comparison with normocalcemic patients ($p < 0.05$). However, significantly lower values of albumin and total protein were witnessed in patients with hypocalcaemia ($p < 0.05$).

5. Conclusions

The main conclusions of my study are outlined in the following statements:

- COVID-19 inpatients with cirrhosis were significantly prone to acute hepatic decompensation events. Nevertheless, the severity of liver cirrhosis on admission is a major determinant of poor hospital outcome. Moreover, primary immunization with mRNA vaccines was significantly associated with better survival rates in cirrhosis cases.

- Notably, the administration of the BNT162b2 vaccine was the most efficient to prevent the development of acute hepatic decompensations, COVID-19-related adverse events, and consequently the fatal outcome.

- Hypocalcemia on hospital admission was a significant prognostic marker of disease

progression and deterioration in cirrhosis severity in COVID-19 patients with cirrhosis. Hypocalcemic cirrhosis patients were highly vulnerable to excessive immune response and grading cirrhosis stage. Furthermore, hypocalcemic cirrhosis patients were significantly asssociated with prolonged hospitalization and COVID-19 induced respiratory failure.

- Following the accessible feasibility of corrected total serum calcium for albumin in emergency departments, serum calcium levels should be monitored regularly to assess the disease progression in COVID-19 patients with cirrhosis.

6. Bibliography of the candidate's publications

Σ IF: 17.8

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