DOI:10.14753/SE.2024.2979

SEMMELWEIS EGYETEM

DOKTORI ISKOLA

Ph.D. értekezések

2979.

DRÁCZ BÁLINT

Gasztroenterológia
című program

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DOI:10.14753/SE.2024.2979

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

Ph.D thesis

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Budapest
2024

DOI:10.14753/SE.2024.2979

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2. LIST OF ABBREVIATIONS

ACE-2: angiotensin-converting enzyme 2
ACLF: Acute-on chronic liver failure
AIH: Autoimmune Hepatitis
ALP: alkaline phosphatase
ALT: alanine aminotransferase
ANOVA: analysis of variance
anti-HBc: antibody to Hepatitis B core
AST: aspartate aminotransferase
AUC: area under the curve
CA: California
Ca: calcium
CAID: Cirrhosis-associated immune dysfunction
CCP: convalescent COVID-19 plasma
CI: confidence intervals
CLIF: Chronic Liver Failure
COPD: chronic obstructive pulmonary disease
COVID-19: coronavirus disease 2019
CRC: colorectal cancer
CRP: C-reactive protein
CTP: Child-Turcette-Pugh
DILI: drug-induced liver injury
EASL: European Association for the Study of the Liver
eGFR: estimated glomerular filtration rate
ER: endoplasmic reticulum
FiO_2: Fraction of inspired oxygen
GGT: gamma-glutamyl transferase
GI: gastrointestinal
HBsAg: Hepatitis B surface antigen
HBV: Hepatitis B Virus
HCC: hepatocellular carcinoma

HCV: Hepatitis C Virus

HE: Hematoxylin/eosin

HRCT: High Resolution Computer Tomography

IBM: International Business Machines

ICU: Intensive Care Unit

IL-2: interleukin-2

IL-6: interleukin-6

IL-10: interleukin-10

INR: international normalized ratio

IQR: interquartile range

iv: intravenous

K: potassium

L/min: liter/min

LDH: lactate dehydrogenase

MELD-Na: Model for End-Stage Liver Disease sodium

Mg: magnesium

mRNA: messenger RNA

Na: sodium

NACSELD: North American Consortium for the Study of End-Stage Liver Disease

NAFLD: non-alcoholic fatty liver disease

NASH: nonalcoholic steatohepatitis

OR: odds ratios

OS: overall survival

PBC: Primary Biliary Cholangitis

PCR: polymerase chain reaction

PCT: procalcitonin

PSC: Primary Sclerosing Cholangitis

PTH: parathyroid hormone

RATs: Rapid antigen tests

RBC: red blood cell

ROC: Receiver Operating Characteristic

RT-PCR: Reverse Transcriptase Polymerase Chain Reaction

SARS-CoV-2: Severe acute respiratory syndrome

$SpO_{2:}$ peripheral oxygen saturation

TMPRSS2: transmembrane protease serine 2

U/L: unit/liter

US: United States

USA: United States of America

WBC: white blood cell

WHO: World Health Organization

3. INTRODUCTION

Severe acute respiratory syndrome (SARS-CoV-2) causing COVID-19 infection has spread over the world, emerging as a global health crisis. SARS-CoV-2 was first isolated in December 2019 and the World Health Organization (WHO) declared the COVID-19 outbreak a pandemic on 11 March 2020 (1). As of April 2023, there have been approximately 763 million confirmed cases, including 7 million deaths around the globe (2). In Hungary, there have been more than 2,1 million confirmed cases of COVID-19 with 49,000 deaths reported to the WHO (3).

SARS-CoV-2 virus is an enveloped, single-stranded RNA virus, that belongs to the family of Coronaviridae (4). The structure and cell entry mechanisms of SARS-CoV-2 are illustrated in Figure 1 (5). The virus particles consist of four primary structural proteins: spike (S), membrane (M), envelope (E) and nucleocapsid (N) (6). The angiotensin-converting enzyme 2 (ACE-2) has been revealed as the main receptor for SARS-CoV-2. The viral attachment to host cells might be mediated by S protein that binds to ACE-2. Proteases like transmembrane protease serine 2 (TMPRSS2), cathepsin and furin could cleave the spike (S) protein domain, allowing the cellular entry of SARS-CoV-2 (7, 8). In the case of insufficient TMPRSS2 or transmembrane protease activity, SARS-CoV-2-ACE-2 complex can be internalized via clathrin-mediated endocytosis (8). After the host cell entry, the viral genome is released from the endosome. In the cytosol, the genomic RNA is translated, the viral RNA is synthesized and the replicase complex could assemble. Newly synthesized viral and structual proteins make viral nucleocapsid and envelope. then mature virions are released by exocytosis.

There are several ways of SARS-CoV-2 transmission. Several studies reported that the virus is primarily transmitted through respiratory droplets expelled by the infected individuals (9, 10). However, it is also possible for COVID-19 to be spread by people not yet showing symptoms (11). These droplets can be inhaled by other people who are nearby, leading to infection. The virus might also spread through aerosols remaining in the air for longer periods of time. Furthermore, SARS-CoV-2 transmission can also develop as a result of contact with contaminated surfaces (12). Therefore, wearing masks, using hand sanitizers and social distancing are important preventive measures.

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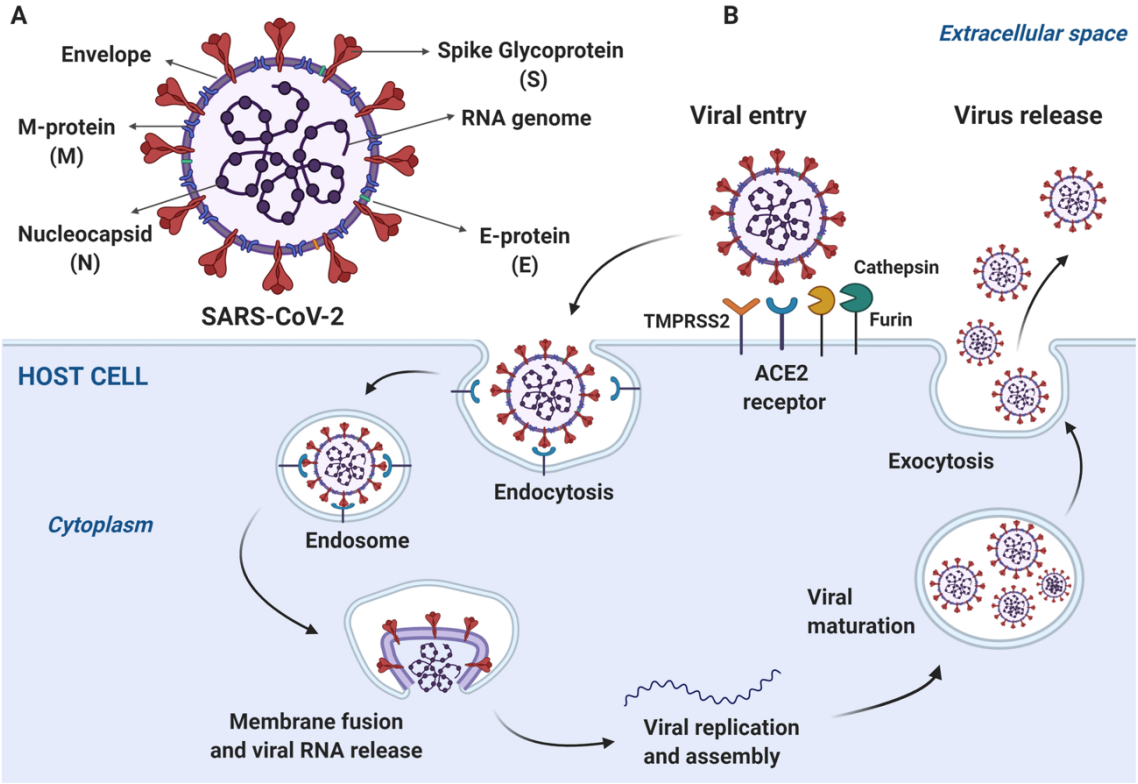


Figure 1. Structure and cell entry mechanism of SARS-CoV-2. Based on Riedel et al: Stem Cell Res Ther, 2021.

COVID-19 can be detected through various methods, including Reverse Transcriptase Polymerase Chain Reaction (RT-PCR), Rapid antigen tests (RATs) and antibody tests. RT-PCR is regarded as the gold standard for detecting COVID-19 (13, 14). It involves taking a nasopharyngeal or throat swab and analyzing the genetic material (RNA) of the virus through a laboratory test. RATs detect specific proteins on the surface of the virus and provide results within minutes. However, these tests are less accurate compared to RT-PCR tests (15). Furthermore, serologic laboratory tests are employed for detecting anti-SARS-CoV-2 antibodies in blood and tissue specimens (16). Additionally, High Resolution Computer Tomography (HRCT) is a non-invasive diagnostic method used for detecting radiological features of COVID-19 (17), which can help physicians to classify COVID-19 patients into different severity groups.

Based on the clinical classification and diagnostic criteria of COVID-19 established by World Health Organization, patients are divided into four types as follows: mild, moderate, severe and critical (Table 1) (18).

COVID-19 predominantly affects the respiratory tract. The most common respiratory

symptoms are as follows: dry cough, dyspnea, chest pain and loss of smell or taste (19).

Table 1. Clinical classification and diagnostic criteria of COVID-19. Based on Xu et al: Glob Health Med, 2020.

Mild type	Moderate type	Severe type	Critical type
The clinical symptoms are mild. There are no pneumonia manifestations found in imaging.	Patients have symptoms, including fever and respiratory symptoms. Pneumonia manifestations can be seen in imaging.	Fraction of inspired oxygen (FiO_2) $\leq$ 300 mmHg. Patient with > 50% lesions progression within 24 to 48 hours in lung imaging should be treated as severe case	Monitoring and treatment in the Intensive Care Unit (ICU)

However, respiratory illness is highly prevalent in COVID-19, gastrointestinal (GI) symptoms may occur in up to 25% of all cases. Most typical GI symptoms are diarrhea, nausea, vomiting, abdominal pain and loss of appetite (20, 21). The pathophysiology of gastrointestinal manifestations in COVID-19 is multifactorial. The ACE-2 receptors, which could regulate the innate immunity and gut microbiome, are highly expressed in the esophagus, stomach, small intestine and colon (22). The virus gains entry into host cells by attaching to the ACE-2 receptor, which leads to viral replication and transmission (23). Therefore, higher ACE-2 expression in the GI tract can cause GI symptoms and gut dysbiosis, leading to translocation of bacteria into the blood and bacteremia during COVID-19 (24). Previous studies reported that SARS-CoV-2 detection in fecal sample proved to be as accurate as nasopharyngeal swabs (25, 26). Laboratory data demonstrated that viral RNA remained detectable even if respiratory sample is negative, which can indicate that fecal-oral transmission is associated with prolonged fecal shedding of viral RNA (27).

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 (28).

Liver cirrhosis is a late-stage condition in which liver is scarred and permanently damaged. Various factors could induce long-term liver damage including excessive alcohol consumption, hepatitis B, hepatitis C, non-alcoholic fatty liver disease (NAFLD) or autoimmune diseases. Patients with cirrhosis report fatigue, weakness, nausea, vomiting, abdominal pain, jaundice, itching and peripherial edema. As acute deterioration in liver function occurs, patients with decompensated cirrhosis are characterised by ascites, hepatic encephalopathy, hepatorenal syndrome or variceal haemorrhage (29). Patients without previous major complications are defined as compensated cirrhosis. Acute-on chronic liver failure (ACLF) is a syndrome described by acute hepatic decompensation associated with organ failures and high short-term mortality (30).
Although comorbidities and diseases such as diabetes, hypertension, chronic obstructive pulmonary disease (COPD) or chronic kidney disease proved to be major risk factors for poor outcome in COVID-19 infection, the prognostic value of liver cirrhosis is still unknown (31, 32).

3.1 SARS-CoV-2 infection in patients with cirrhosis

In the first wave of COVID-19 pandemic, liver cirrhosis cases were not found to be highly prevalent in large COVID-19 population studies, demonstrating that liver cirrhosis was unexpected to increase vulnerability to infection (33, 34). However, it has become clear that these interpretations were limited by retrospective study design and the absence of confounding factors such as socioeconomic status (35). During the pandemic patients with cirrhosis following COVID-19 infection proved to be at higher risk of adverse outcomes. Large registry data reported that in-hospital mortality in COVID-19 patients with cirrhosis was approximately 16-42% and fatal outcome was associated with the severity of cirrhosis (36, 37). Moreover, higher occurence of Intensive Care Unit (ICU) admission, renal replacement therapy and mechanical ventilation were witnessed in

COVID-19 patients with decompensated cirrhosis related to those without cirrhosis (38).

3.1.1 Patophysiological mechanism of liver injury

Liver damage is a common clinical feature of COVID-19. As depicted in Figure 2, there are comprehensive molecular patomechanisms of liver injury, including direct damage, drug-induced liver injury (DILI), cytokine storm, hypoxia, vascular endothelitis and coagulopathy (39).

Chai et al. revealed that ACE-2 receptor was predominantly expressed in cholangiocytes, suggesting that liver damage may be caused by direct viral invasion (40). Higher ACE-2 expression in hepatocytes upon liver cirrhotic conditions gave evidence that underlying liver injury could aggravate SARS-CoV-2 hepatic tropism (41). Moreover, hypoxia and inflammatory conditions in the liver can also upregulate ACE-2 expression (42).

Liver cirrhosis is usually associated with immune dysfunction characterised by systemic inflammation and immune deficiency. Cirrhosis-associated immune dysfunction (CAID) refers to the spectrum of immunological abnormalities, which could cause aberrant inflammatory response via upregulation of macrophages, complement system, impaired lymphocytes and neutrophils (43, 44). CAID can cause deterioration in cirrhosis stage, leading to hepatic decompensation events, organ failure and high in-hospital mortality.

Upregulation of the innate immune system may also increase the levels of IL-2, IL-6, IL-10 and C-reactive protein (CRP) in severe COVID-19, which could alarm the onset of life-threatening cytokine storm. Cytokine storm is associated with rapid progression of the patient's condition characterized by systemic inflammation and multiple organ failure, which may cause liver injury (45).

COVID-19 associated hypoxia from respiratory failure could induce hepatic cell death and centrilobular necrosis, which might result in hypoxic hepatitis (46).

At the beginning of the pandemic, evidence-based pharmacotherapy was not feasible. Over the different waves of COVID-19, international studies revealed that drugs for COVID-19 such as remdesivir, macrolids, corticosteroids, tocilizumab and acetaminophen may cause hepatic toxicity in some patients (47-49). Therefore, it is highly recommended to monitor the liver function parameters in association with the timing of medication in COVID-19 patients during hospitalization.

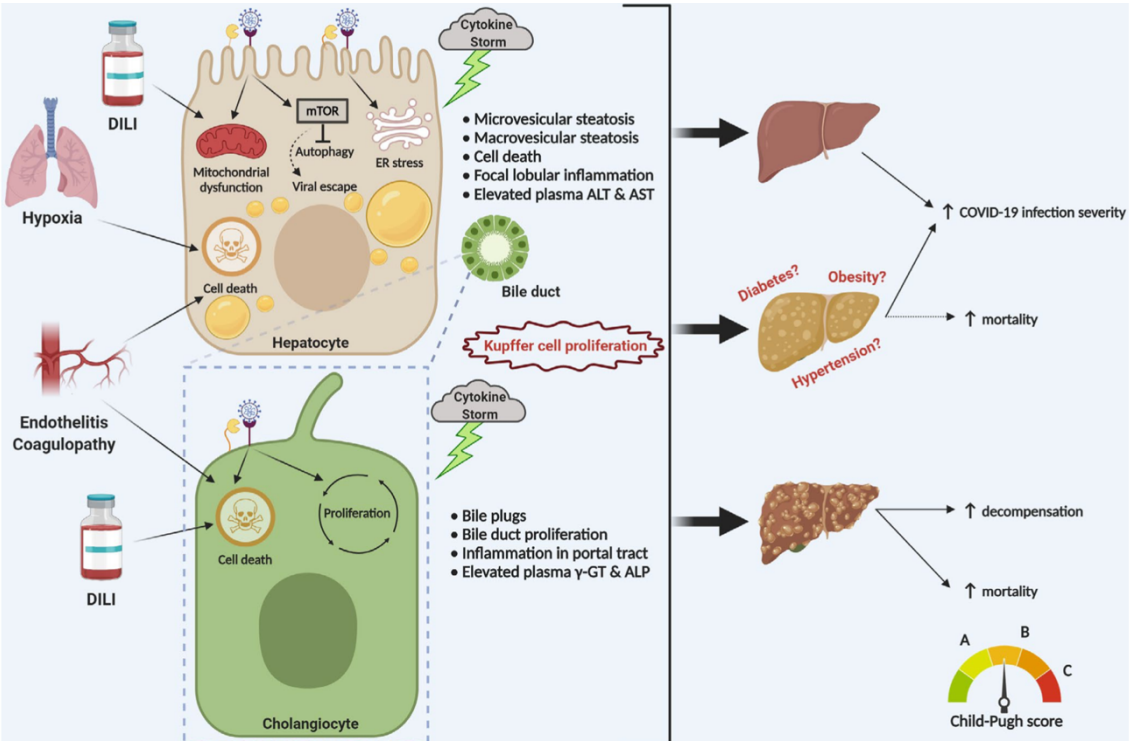


Figure 2. Patophysiological mechanisms of liver injury in COVID-19. Based on Nardo et al: Liver Int, 2021**.** COVID-19 induced liver damage is associated with direct damage via ACE-2 receptor, hypoxia, drug induced liver injury (DILI), cytokine storm vascular endothelitis and coagulopathy. COVID-19 could provoke mitochondrial dysfunction and endoplasmic reticulum (ER) stress in the hepatocytes, leading to moderate steatosis, focal lobular inflammation and elevated liver transaminases. Regarding cholangiocytes, cholangiocellular injury is primarily described by bile duct proliferation, bile plugs higher levels of GGT and ALP. GGT, gamma-glutamyl transferase; ALP, alkaline phosphatase

3.1.2 Liver histopathological changes in SARS-CoV-2 infection

Although the histopathology features of the lung have been highlighted in SARS-CoV-2 infection, liver is found to be a particularly affected organ. Previous studies investigating hepatic pathology in COVID-19 autopsies revealed that macro-, and microvesicular steatosis, portal and periportal inflammation, acute hepatitis, vascular findings including sinusoidal microthrombi and cholestasis are the most common findings (50, 51).

Macrovesicular steatosis and inflammatory infiltration are highly prevalent in histological evaluation (up to 51%) (Figure 3a) (51, 52). Aggravation of macrophages and

lymphocytes are primarily seen in the hepatic lobe. However, chronic infiltration of inflammatory cells are observed next to the portal regions (52).

Regarding biliary findings, canalicular cholestasis is frequently detected (Figure 3b) (53).

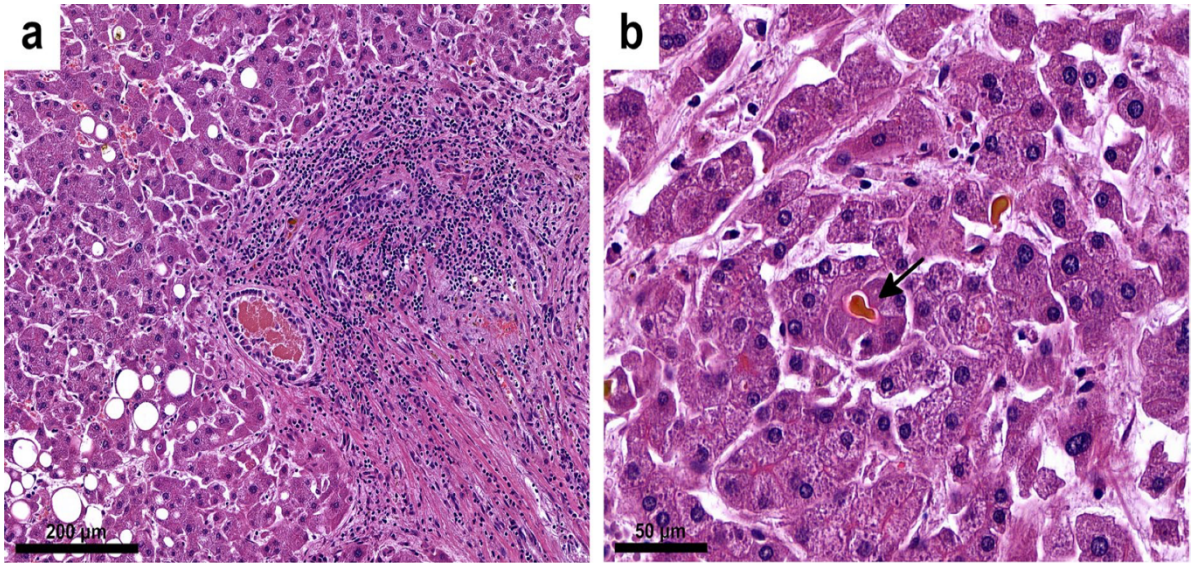


Figure 3. Liver autopsies of COVID-19 deceased patients Macrovesicular steatosis, inflammatory infiltration (a), and canalicular cholestasis (b, arrow). Hematoxylin/eosin (HE). Based on Pesti et al: Geroscience, 2023.

International data reported that thrombosis in the portal system occurred in 45.3-70.7% in COVID-19 patients (52, 54). COVID-19 could cause endothelial damage and trigger the coagulation cascade, leading to excessive generation of thrombin and fibrinogen-fibrin conversion (55). Consequently, endothelial disruption is usually detected in COVID-19 autopsies (Figure 4). Moreover, sinusoidal microtrombi are commonly associated with COVID-19 induced vascular injury.

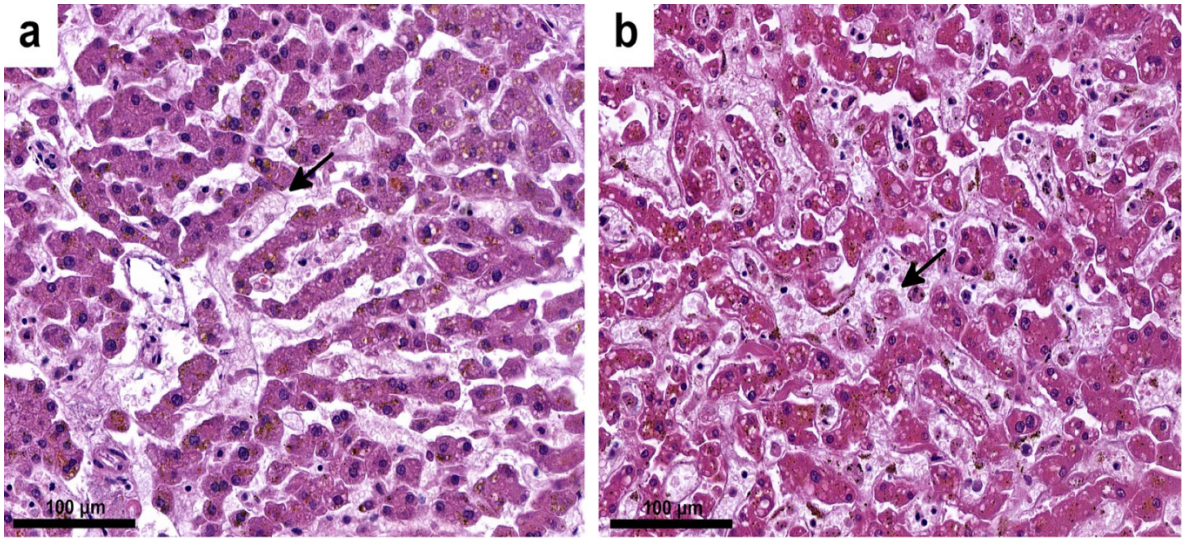


Figure 4. Vascular injury and sinusoidal damage in COVID-19 liver autopsy Endothelial damage including the extension of Disse space (a, arrow) and fibrin deposits in the ectatic sinusoids (b, arrow) are depicted. Based on Pesti et al: Geroscience, 2023.

3.1.3 Laboratory findings

Several studies showed that hospitalized COVID-19 patients have elevated liver enzymes on admission. (56, 57). Moreover, abnormal liver function was associated with severe clinical course. Wang et al. reported that aspartate aminotransferase (AST), alanine aminotransferase (ALT) and total bilirubin levels were significantly higher in severe cases compared to mild ones (58). The calculated AST/ALT ratio, known as the De Ritis ratio on admission proved to be a highly sensitive predictor for in-hospital mortality in COVID-19 patients (59, 60). Regarding other liver parameters, higher levels of GGT, ALP, the international normalized ratio (INR), and hypalbuminaemia were commonly associated with disease severity (61-64). Relevant to inflammatory markers, elevated CRP, IL-6 and procalcitonin (PCT) levels were commonly presented in severe cases of COVID-19 (65). Mineral deficiencies are common features in patients with cirrhosis. Several studies showed that hypocalcaemia on admission was a predictor for disease severity and mortality in COVID-19 patients (66, 67). Additionally, cirrhosis patients with hypocalcaemia were prone to acute hepatic decompensation events and poor prognosis in COVID-19 (68, 69).

3.1.4 Prognostic factors and clinical outcome

There is a worldwide consensus that older age, gender, hypertension, diabetes, obesity, cardiovascular and lung diseases, immune dysfunction, elevated inflammatory markers and prolonged hospitalization are both risk factors for COVID-19 related mortality. An international registry study of 745 patients with chronic liver disease showed that the etiology of liver cirrhosis could affect the prognosis for COVID-19 patients. Alcoholic cirrhosis was significantly associated with poor prognosis. However, NAFLD and Hepatitis B virus (HBV) showed negative correlations for mortality (32).

Cirrhosis severity could also determine the mortality rates. Recently, there are two highly sensitive scoring systems used for evaluating the severity of cirrhosis: Child-Turcette-Pugh (CTP) and Model for End-Stage Liver Disease sodium (MELD-Na) scores. The modified CTP score comprises five clinical and laboratory parameters as follows: ascites, hepatic encephalopathy, the serum levels of total bilirubin and albumin as well as INR. A CTP score of 5-6 points is considered as CTP-A (well-compensated cirrhosis), of 7-9 points as CTP-B (significant functional compromise), and of 10-15 points as CTP-C (decompensated cirrhosis) (70). The MELD-Na is applied using serum values of sodium, bilirubin and creatinine, INR as well as hemodialysis at least twice in the past week (71). A multicenter United States (US) cohort study across 21 institutions reported that increasing CTP scores are followed by higher fatality rates and patients with decompensated cirrhosis are at higher risk of poor prognosis in COVID-19 (38).

Relevant to major hospital outcomes, mechanical ventilation and admission to ICU proved to be significant risk factors for in-hospital mortality in COVID-19 patients with cirrhosis, suggesting that respiratory failure is still the predominant cause of death (72).

3.1.5 Management and therapy

As a vulnerable patient population to SARS-CoV-2 infection, protective measures such as wearing a mask, keeping a safe distance from others or regularly hand sanitizing are essential for cirrhosis patients to reduce the risk of transmission (72). Regular follow-up care needs to be complied for patients with cirrhosis. Patients requiring inpatient follow-

up, there could be many alternatives, including telemedicine or video consultation to avoid in-person visits (73).

Diagnosis of viral hepatitis and the preservation of antiviral therapy are strongly encouraged (35). Decompensation events such as spontaneous bacterial peritonitis, hepatic encephalopathy and variceal bleeding should be avoided following the prophylaxis guidelines (74).

Regarding antiviral therapies, the 3-day course of remdesivir within 7 days of onset is associated with higher survival rates (75). However, patients requiring mechanical ventilation are not recommended using remdesivir owing to the lack of efficient therapeutic effect (76).

Corticosteroids especially dexamethasone have been identified as potent therapeutic agent in severe COVID-19 (77). Therefore, the administration of dexamethasone is approved in patients requiring oxygen therapy or noninvasive ventilation (78).

Relevant to monoclonal antibody therapy, tocilizumab as an intravenous recombinant anti-IL-6 monoclonal antibody is considered to be used additional to corticosteroids in critically ill patients (79). Tocilizumab should be administered within 24 hours with high-flow oxygen supply and mechanical ventilation (35). However, patients receiving tocilizumab may develop ALT elevations and HBV reactivation could hardly occur during hospitalization (80, 81). Accordingly, testing of HBsAg and anti-HBc should be maintained preliminary the onset of tocilizumab therapy.

According to European Association for the Study of the Liver (EASL) position paper, convalescent COVID-19 plasma (CCP) was found to be ineffective against COVID-19 in patient with cirrhosis. Therefore, CCP treatment is not recommended for COVID-19 patients with cirrhosis (35).

Antibiotic primarily azithromycin was not associated with efficacy in randomized clinical trials (82, 83).

COVID-19 could commonly induce microtrombosis and endothelial damage, contributing to multiorgan failure and consequently higher mortality rates. Accordingly, therapeutic-dose anticoagulation with heparin as an initial strategy is reported to increase the survival probabilities (84). As patients with cirrhosis are at higher risk of venous thromboembolism, anticoagulation therapy should not be suspended.

3.2 Primary vaccination against COVID-19 in patients with cirrhosis

Since the outbreak of the pandemic, there has been an enormous battle to develop efficient vaccines against SARS-CoV-2 infection. Actually, there are four different types of vaccine available: mRNA-based vaccines, viral vector vaccines, inactivated or protein subunit vaccines and traditional adjuvanted vaccines (35).

In Hungary, the primary vaccination campaign employing mRNA-based vaccines (Pfizer-BioNTech, Moderna) started on 15 January 2021. Since March 2021, six different vaccines have been used in Hungarians, including patients with cirrhosis: BNT162b2-Pfizer-BioNTech and mRNA-1273-Moderna (mRNA-based vaccines); AZD1222-Astra Zeneca, Johnson&Johnson/Janssen and GAM-COVID-Vac-Sputnik V (vector vaccines); HB02-Sinopharm (inactivated vaccine) (85). Patients receiving primary vaccination were defined as follows: 14 days subsequently the two doses of BNT162b2 or mRNA-1273, or one dose of BNT162b2 and one-dose of mRNA-1273, or only two doses of GAM-COVID-Vac or HB02 (86).

COVID-19 vaccination is highly preferred for patients with cirrhosis. A large US cohort study of 762 patients with cirrhosis demonstrated that patients receiving at least one mRNA-based vaccine had better survival rates compared to unvaccinated patients (87). Among different COVID-19 vaccines, mRNA-based vaccines could prevent most effectively the severe clinical course of COVID-19 (88).

Booster vaccination could decrease hospital mortality of COVID-19. Accordingly, patients with cirrhosis are recommended receiving mRNA-based vaccine following non-mRNA vaccines (89).

4. 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.

5. METHODS

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 physical assessment and a detailed medical history with special emphasis on cirrhosis severity and acute hepatic decompensation events.

Diagnostic criteria for COVID-19 severity grades and risk stratification were based on our national protocol correspondingly the 7th version of the guidelines established by the Chinese National Health Commission (18).

Our study protocol was approved by the Scientific and Research Ethics Committee of the Medical Research Council of Hungary (IV/7946-1/2021/EKU, Budapest, 14.10.2021). It conforms to the ethical norms and standards in the Declaration of Helsinki (86).

5.1 Patient population

Between March 2020 and May 2022, we recruited 6394 COVID-19 patients being hospitalized in several institutes 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 RT-PCR test (SEQONCE qPCR Multi Kit, IVD, SeqOnce Biosciences, Carlsbad, CA 92008, USA) based on a nasopharyngeal swab using the protocol of the WHO (14). 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.

Inclusion and exclusion criteria are summarized in Table 2. 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. According to our national protocol, arterial partial pressure of oxygen (PaO_2) < 60 mm Hg or peripheral oxygen saturation (SpO_2) $\leq$ 90% on room air were indicated for oxygen administration (90). A low-flow system up to 2 L/min via nasal cannulae was employed as initial strategy and was stepped-up over 6 to 15 L/min with reservoir facemask. Patients requiring low-flow oxygen were recommended for the administration of 5-day-long remdesivir regimen and dexamethasone 8-16 mg oral / 8-16 mg iv (90). Mechanical ventilation was used for patients requiring consistently high-flow oxygen therapy (> 60 L/min) or presenting symptoms such as rapid progression over hours, hemodynamic instability or multiorgan failure (86).

DOI:10.14753/SE.2024.2979

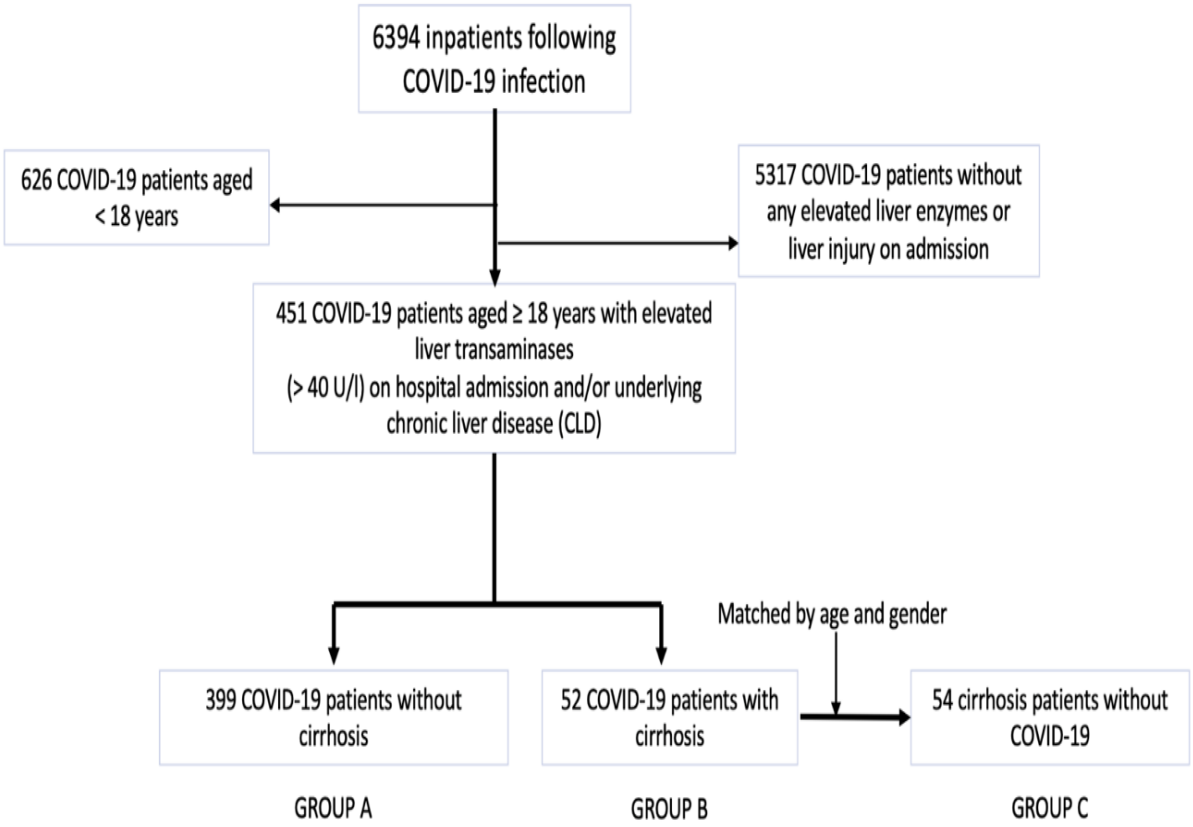


Figure 5. Study design and flow chart of cohort selection

Figure was adapted without modifications from: Drácz B. et al: Vaccines, 2023.

Table 2. Inclusion and exclusion criteria

Table was adapted without modifications from: Drácz B. et al: Vaccines, 2023.

Patient group	Inclusion criteria	Exclusion criteria
GROUP A and GROUP B	• Laboratory-confirmed SARS-CoV-2 infection • Age ≥ 18 years • Elevated liver transaminases (> 40 U/l) on hospital admission and/or underlying liver cirrhosis in the medical history	• Rapid Antigen Test-confirmed SARS-CoV-2 infection without PCR-positivity • Age <18 years
GROUP A	Absence of liver cirrhosis diagnosis	• Patients receiving one dose of COVID-19 vaccine including single-dose Janssen vaccine
GROUP B	Clinicopathologically confirmed liver cirrhosis	
GROUP C	• Clinicopathologically confirmed liver cirrhosis; at least 2 days of hospitalisation in hepatology units; matched with GROUP B for equivalent severity grades and clinical course • Laboratory-confirmed SARS-CoV-2 negativity • Age ≥18 years	• SARS-CoV-2 positivity on admission • Age <18 years

5.2 Data collection

Laboratory tests were regularly performed from admission time to discharge or death. Criteria of hospital discharge for COVID-19 inpatients were as follows: (1) resolution of

fever for > 48 hours without antipyretics, (2) without supplementary oxygen therapy, (3) no signs of increased work of breathing or respiratory distress, (4) improvement in the signs and symptoms of illness (cough, shortness of breath, and oxygen requirement), and (5) two negative RT-PCR tests on nasopharyngeal swabs in a row, at least 24 hours apart. 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 (91). Hence, corrected calcium for albumin was calculated using the correction formula as follows: corrected calcium = (0.8x[normal albumin - patient's albumin]) + serum calcium (92). Hypocalcaemia was defined as a corrected serum calcium level < 2.2 mmol/L (8.9 mg/dl) (93, 94).

5.3 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) (70). MELD-Na score was based on serum bilirubin, serum creatinine, INR, serum sodium and hemodialysis treatments at least twice in the past week (71). Patients with cirrhosis were classified into three severity groups: compensated, decompensated and ACLF. Decompensated cirrhosis was described by ascites, variceal haemorrhage or hepatic encephalopathy (86). 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 (95). We used the West Haven Criteria for grading the severity of hepatic encephalopathy (96). 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 (97). The diagnosis of ACLF was characterised by EASL-CLIF-C and the North American Consortium for the Study of End-Stage Liver Disease (NACSELD) (98, 99).

5.4 COVID-19 vaccine regimens

In Hungary, the primary vaccination campaign started on 15 January 2021 using mRNA vaccines (Pfizer-BioNTech and Moderna). In 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. From August 2021, booster vaccination with mRNA vaccines were available and highly recommended for patients with cirrhosis who had not yet received any mRNA vaccines (89). 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.

5.5 Statistical analysis

Statistical analysis was performed using the IBM® SPSS® 28.0 software version (IBM Corporation, Armonk, NY, USA). The Kolmogorov–Smirnov test was applied for

checking the normality of the data. All the variables were found to be non-normally distributed. Categorical variables were presented as frequencies and percentages. Pearson's chi-square test and the two-tailed Fisher's exact test were used for a comparison of the categorical variables between GROUP A and GROUP B; and GROUP B with GROUP C. Continuous variables were characterized using descriptive statistics, including the number of samples (*n*) and median with the interquartile range. The Kruskal–Wallis ANOVA with Bonferroni correction and the Mann–Whitney U test were used to determine significance between pairs of groups. The laboratory findings were analysed using univariate and multivariate logistic regression and odds ratios (OR) with 95% confidence intervals (CI) were calculated. A Receiver Operating Characteristic (ROC) curve analysis was performed to investigate the capacity of abnormal laboratory markers such as sodium (Na), serum calcium corrected for albumin, albumin, INR, white blood cell (WBC) and CTP levels to predict mortality. The cut-off values were calculated using the Youden index. Spearman's rank correlation coefficient (Spearman's r) was calculated for comparing novel risk factors and disease progression in GROUP B. Moreover, survival rates of the three groups receiving different COVID-19 vaccines were displayed on a Kaplan–Meier plot and compared with a log-rank test. The analysis was two-sided with a significance level of $\alpha = 0.05$.

DOI:10.14753/SE.2024.2979

6. RESULTS

6.1 Evaluation of clinical outcomes and vaccine effectiveness in cirrhosis patients

6.1.1 Baseline characteristics

Overall 505 patients were divided into three groups in our analysis. Baseline characteristics are listed in Table 3. Patient comorbidities including gender, diabetes, hypertension, cardiovascular and renal diseases were not significantly different between the three groups. Nevertheless, patients with cirrhosis were significantly associated with higher prevalence of cancer compared to those without cirrhosis. Among cancer cases, hepatocellular carcinoma (HCC) was the most prevalent. 227 COVID-19 patients smoked, and smoking was significantly different between the three groups. Primary vaccination was administered in ninety percent of all patients (453/505). As depicted in Figure 6, the administration of mRNA-based COVID-19 vaccines was the most frequent in all three groups. especially in in GROUP B and GROUP C. However, vaccination rate of viral vector vaccines was higher in GROUP B related to GROUP C (11.5% vs. 7.4%).

Table 3. Comparison of patient characteristics across the three groups

Categorical variables are presented as frequency (percentage). Statistically significant values are highlighted using bold texts.

GROUP A: 399 COVID-19 patients without cirrhosis.

GROUP B: 52 COVID-19 patients with cirrhosis

GROUP C: 54 patients with cirrhosis without COVID-19 infection

P*: Kruskal-Wallis, chi-square and Analysis of Variance (ANOVA) as appropriate.

P^{-} <.05 statistically significant between GROUP A and GROUP B.

$P^{;}$ <.05 statistically significant between GROUP B and GROUP C.

Abbreviations: ACLF, acute-on-chronic liver failure; PBC, Primary Biliary Cholangitis; PSC, Primary Sclerosing Cholangitis; AIH, Autoimmune Hepatitis; HBV, Hepatitis B Virus; HCV, Hepatitis C Virus; NASH, nonalcoholic steatohepatitis; HCC, hepatocellular cancer; CRC, colorectal cancer; COVID-19, Coronavirus disease 2019; mRNA,

messenger RNA

Table was adapted without modifications from: Drácz B. et al: Vaccines, 2023.

Variables	GROUP A (n=399)	GROUP B (n=52)	GROUP C (n=54)	p*	p-	p;
Gender (male/female)	219/180	36/16	33/21	.121	.054	.420
Fatal outcome	47 (11.8)	5 (9.6)	7 (13.0)	.880	.819	.761
Liver disease	46 (11.5)	52 (100)	54 (100)	**<.001**	**<.001**	-
Stage of cirrhosis				**<.001**	**<.001**	.130
Compensated	-	4 (7.7)	14 (25.9)			
Decompensated		42 (80.8)	32 (59.3)			
ACLF		6 (11.5)	8 (14.8)			
Cirrhosis etiology						
Alcohol	3 (0.8)	27 (51.9)	22 (40.7)	**<.001**	**<.001**	.330
PBC	1 (0.3)	2 (3.8)	0 (0)	**<.05**	**<.05**	.238
PSC	5 (1.3)	6 (11.5)	5 (9.3)	**<.001**	**<.001**	.759
AIH	0 (0)	5 (9.6)	3 (5.6)	**<.001**	**<.001**	.484
HBV	1 (0.3)	2 (3.8)	4 (7.4)	**<.001**	**<.05**	.679
HCV	2 (0.6)	8 (15.4)	10 (18.6)	**<.001**	**<.001**	.797
Cryptogen	0 (0)	3 (5.8)	8 (14.8)	**<.001**	**<.05**	.202
NASH	0 (0)	0 (0)	1 (1.9)	**<.05**	.692	.509
Budd-Chiari	0 (0)	1 (1.9)	0 (0)	**.**103	.115	.491
Wilson’s disease	1 (0.3)	0 (0)	1 (1.9)	**<.05**	.885	.509
Haemochromatosis	1 (0.3)	0 (0)	1 (1.9)	**<.05**	.885	.509
Cystic fibrosis	0 (0)	0 (0)	1 (1.9)	**<.05**	-	.509
Ascites grades				**<.001**	**<.001**	.143
Mild	0 (0)	2 (3.8)	13 (24)			
Moderate	0 (0)	15 (28.8)	9 (16.7)			
Severe	0 (0)	35 (67.4)	32 (59.3)			
Encephalopathy stages				**<.001**	**<.001**	**<.05**
1-2	398 (99.7)	25 (48.0)	36 (66.7)			
3	1 (0.3)	18 (34.5)	9 (16.7)			

4	0 (0)	9 (17.3)	9 (16.7)			
Erosive esophagitis	93 (23.3)	31 (59.6)	41 (75.9)	**<.001**	**<.001**	.096
Esophageal varices				**<.001**	**<.001**	.131
Grade 1	2 (0.6)	5 (9.6)	7 (13.0)			
Grade 2	1 (0.3)	29 (55.8)	19 (35.2)			
Grade 3	0 (0)	9 (17.3)	10 (18.5)			
Hypertension	239 (59.9)	29 (55.8)	32 (59.3)	.882	.653	.844
Cardiovascular disease	172 (43.1)	22 (42.3)	29 (53.7)	.337	.518	.251
Diabetes mellitus	133 (33.3)	20 (38.5)	20 (37.0)	.700	.534	.519
Renal disease	60 (15.0)	6 (11.5)	8 (14.8)	.810	.544	.776
Cancer	29 (7.3)	9 (17.3)	9 (16.7)	**<.05**	**<.05**	.795
HCC	18 (4.5)	6 (11.5)	9 (16.7)			
CRC	5 (1.3)	2 (3.8)	0 (0)			
Pancreas	3 (0.8)	0 (0)	0 (0)			
Klatskin	1 (0.3)	1 (1.9)	0 (0)			
Smoking	202 (50.6)	25 (48.0)	17 (31.5)	**<.05**	.769	.112
COVID-19 Treatment						
Remdesivir	44 (11)	3 (5.8)	0 (0)	**<.05**	.336	.115
Steroid use	287 (71.9)	37 (71.2)	0 (0)	**<.001**	.511	**<.001**
Convalescent Plasma	68 (17.0)	14 (26.9)	0 (0)	**<.001**	.088	**<.001**
Oxygen supply	147 (36.8)	21 (40.4)	3 (5.6)	**<.001**	.649	**<.001**
Mechanical ventilation	159 (39.8)	24 (46.2)	6 (11.1)	**<.001**	.453	**<.001**
COVID-19 vaccination	357 (89.5)	47 (90.4)	49 (90.7)	.966	.535	.605
COVID-19 vaccines				.545	.818	.171
mRNA	272 (68.2)	39 (75.0)	41 (75.9)			
viral vector	55 (13.8)	6 (11.5)	4 (7.4)			
inactivated	30 (7.5)	2 (3.8)	4 (7.4)			

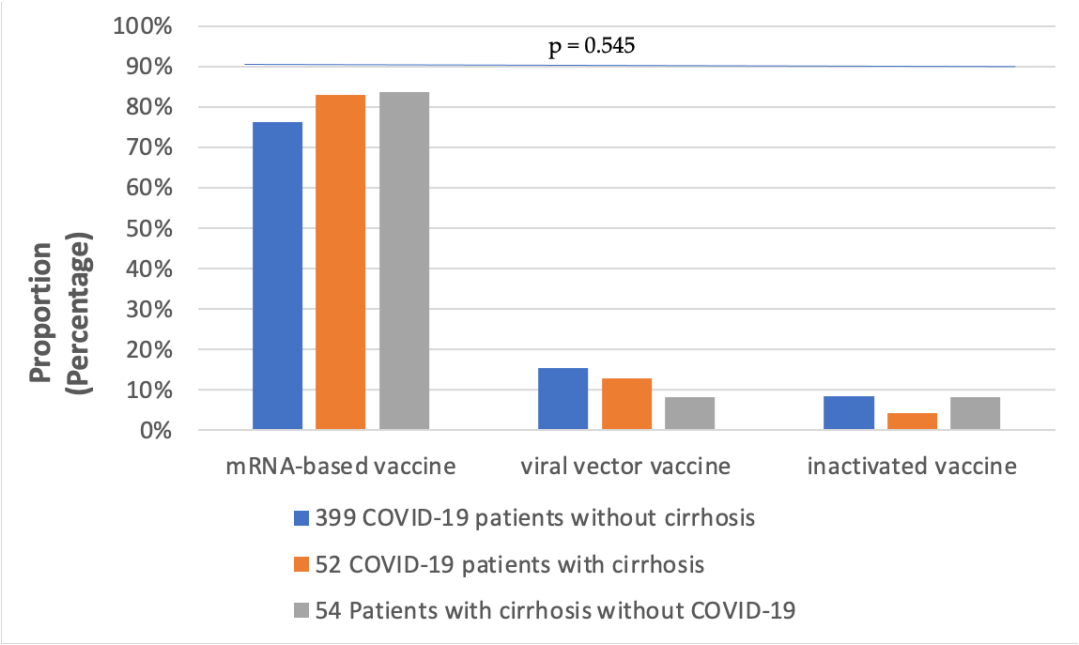


Figure 6. The vaccination rates of patients with different COVID-19 vaccines in the three groups

Figure was adapted without modifications from: Drácz B. et al: Vaccines, 2023.

6.1.2 Clinical characteristics of patients with cirrhosis

As demonstrated in Figure 7, 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 (Figure 7). Regarding the causes of cirrhosis, alcohol abuse was the most frequent etiological factor, followed by HCV (Figure 8). 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.

DOI:10.14753/SE.2024.2979

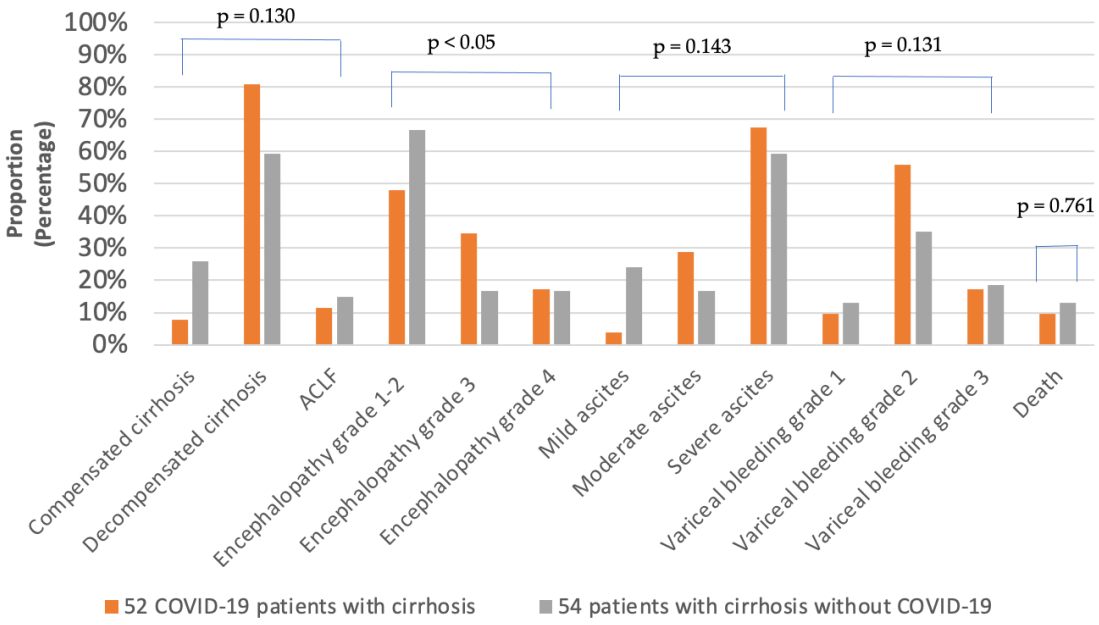


Figure 7. Acute hepatic decompensation events and mortality in patients with cirrhosis

Figure was adapted without modifications from: Drácz B. et al: Vaccines, 2023.

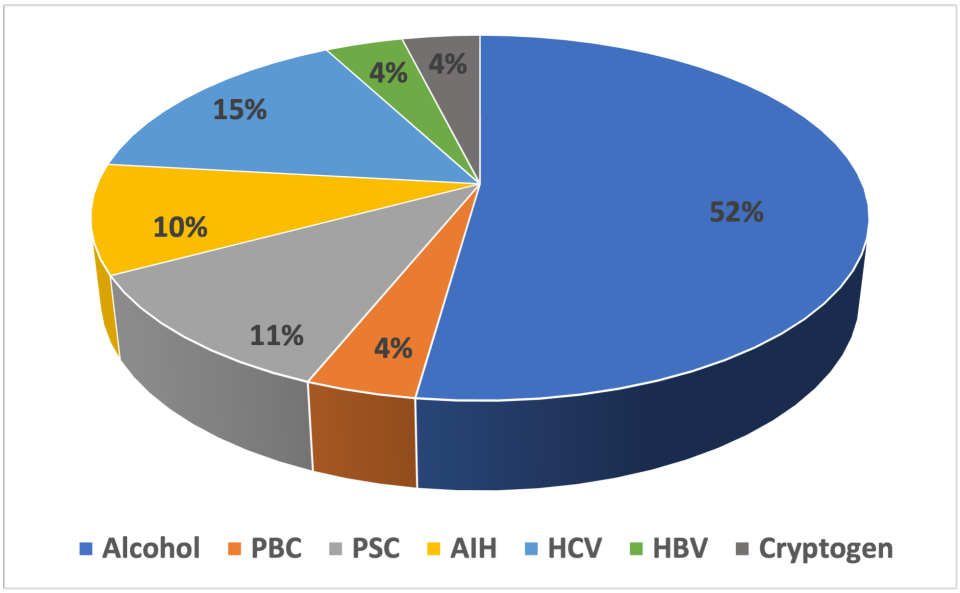


Figure 8. Etiological agents of cirrhosis in COVID-19 patients with cirrhosis

PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; AIH, autoimmune hepatitis; HCV, hepatitis C virus; HBV, hepatitis B virus.

Figure was adapted without modifications from: Drácz B. et al: Biomedicines, 2023.

Regarding total cases, there was an incremental developing cirrhosis severity in GROUP B grouped by different CTP stages (Figure 9). 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 (Figure 9).

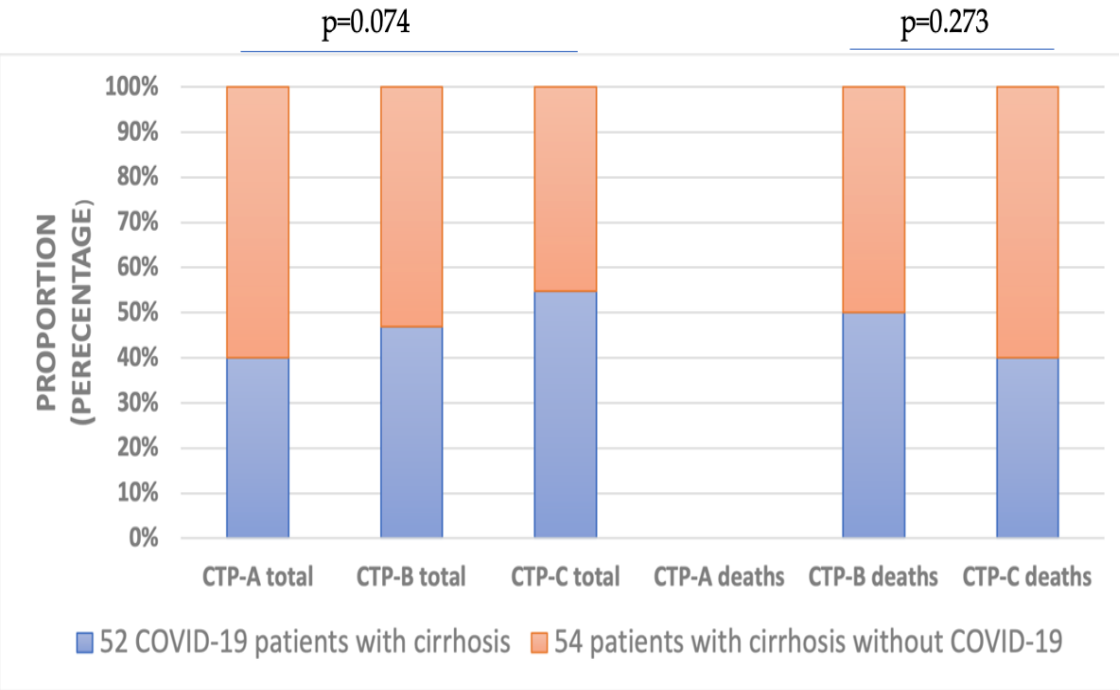


Figure 9. Percentage of various CTP stages in total and deceased cirrhosis patients

There was an absence of CTP-A deceased patients in both groups. The CTP score was used for grading the severity of cirrhosis.

Figure was adapted without modifications from: Drácz B. et al: Vaccines, 2023.

6.1.3 Major hospital outcomes

As depicted in Figure 10, 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 needed less frequently 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 (Figure 10). The in-hospital mortality rates in COVID-19 patients were as follows: 11.8% (GROUP A) and 9.6% (GROUP C).

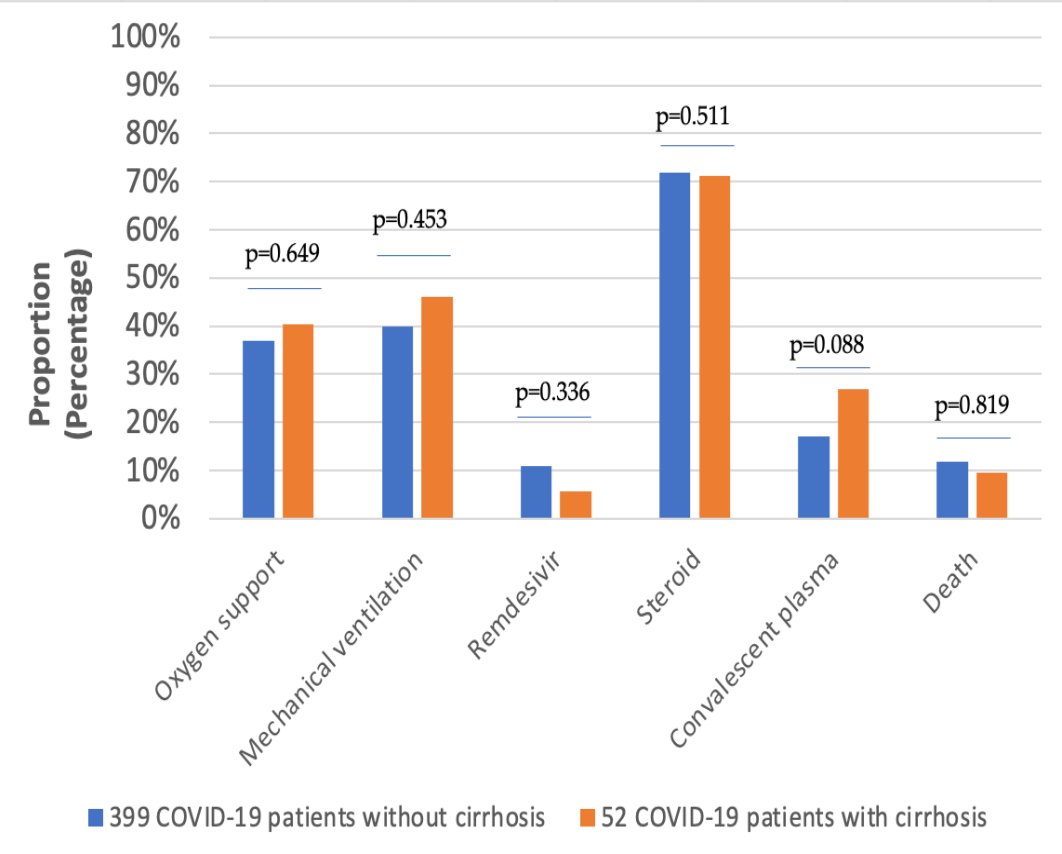


Figure 10. Major hospital outcomes and medications received in COVID-19 patients

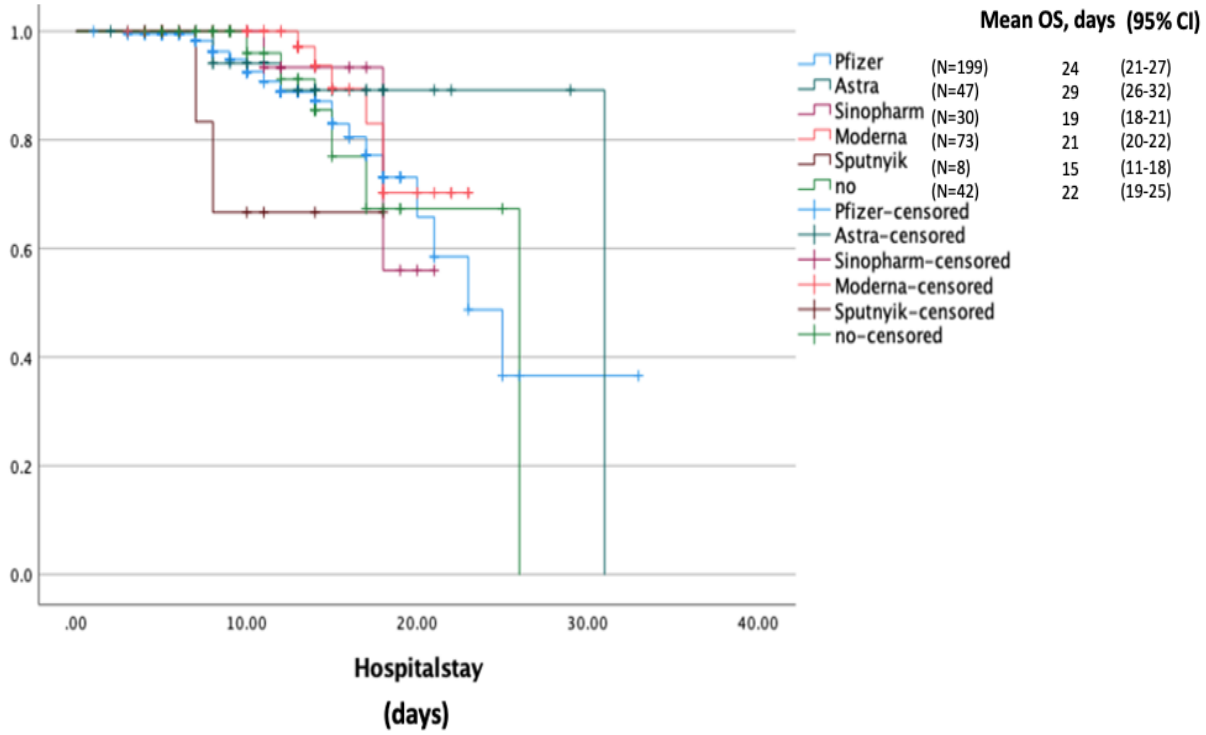
Figure was adapted without modifications from: Drácz B. et al: Vaccines, 2023.

6.1.4 Effectiveness of mRNA-based vaccines in patients with cirrhosis

The in-hospital survivals of patients who received primary immunization with different COVID-19 vaccines are demonstrated in Figure 11. As depicted in Figure 11 A-C, 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

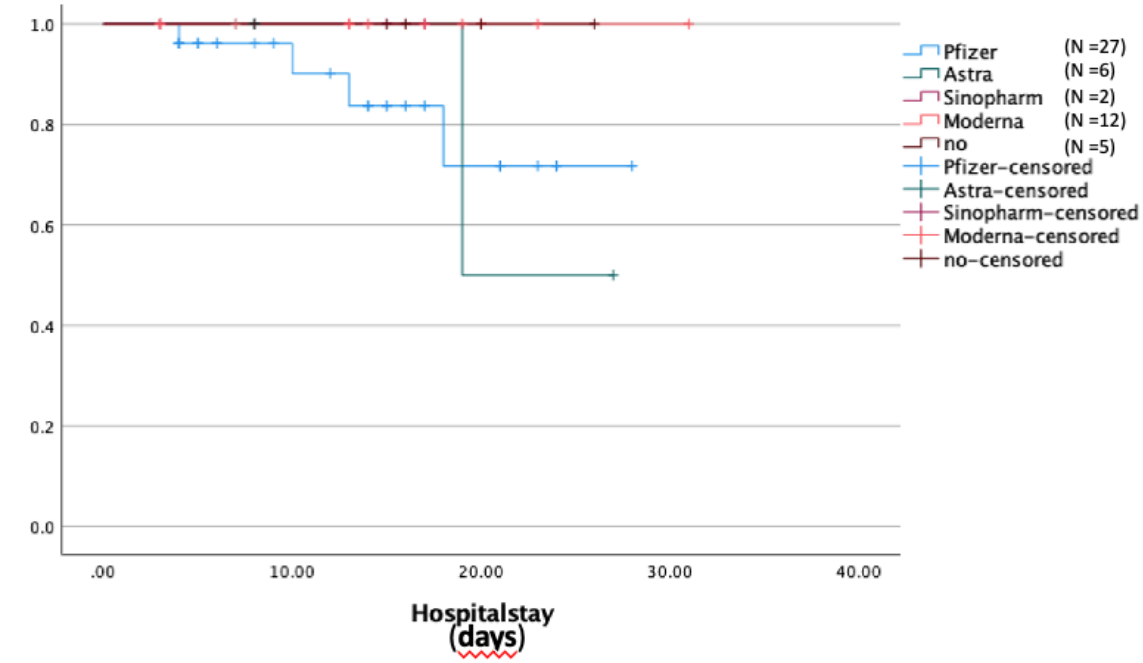
to those receiving Sputnik V (Figure 11 A). With regard to mRNA vaccines, primary vaccination with Pfizer-BioNTech was found to be significantly more efficient (log-rank test: p = 0.017) in comparison with Moderna (Figure 11 C). Furthermore, unvaccinated patients were associated with worse survival rates in all groups compared to those receiving any vaccine (Figure 1 A-C). Additionally, patients in GROUP C without any COVID-19 vaccine administered were significantly susceptible to increased fatal outcome (log-rank test: p =0.003).

A COVID-19 patients without cirrhosis



DOI:10.14753/SE.2024.2979

B COVID-19 patients with cirrhosis



C Cirrhosis patients without COVID-19

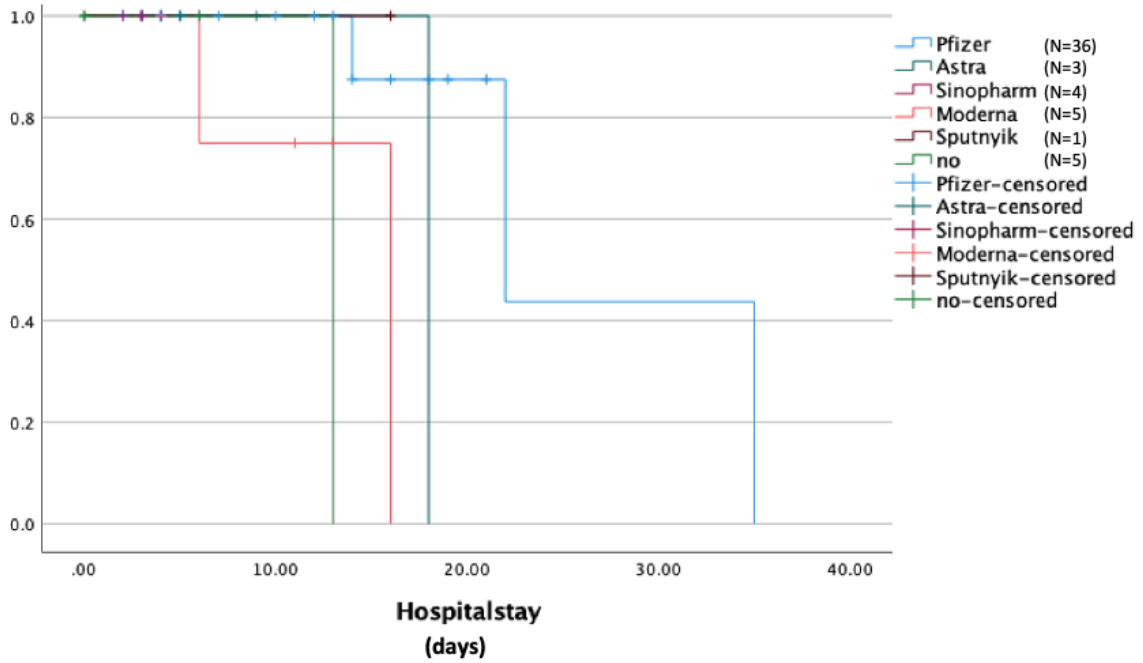


Figure 11. Hospital survivals are displayed in the three patient groups classified by different COVID-19 vaccines using Kaplan-Meier plot

Mean overall survival (OS) and 95% confidence intervals (95% CI) are counted, where appropriate. (A) The administration of Sputnik-V in COVID-19 patients without cirrhosis

was significantly associated with worse hospital outcome compared to Moderna (log-rank test: p = 0.039). (B) AstraZeneca used in COVID-19 patients with cirrhosis was less efficient to prevent COVID-19-related in-hospital mortality in contrast to Moderna (log-rank test: p = 0.157). (C) Cirrhosis patients vaccinated with Pfizer-BioNTech had significantly better survival outcome related to those receiving Moderna (log-rank test: p = 0.017).

Figure was adapted without modifications from: Drácz B. et al: Vaccines, 2023.

As summarized in Table 4, 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%). As described in Table 4, 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%; $p <0.05$).

Table 4. The significance of mRNA vaccines on the major clinical outcomes in relation to COVID-19 severity and cirrhosis

Categorical variables are presented as frequency (percentage). The statistically significant values are highlighted using bold text. GROUP A: 399 COVID-19 patients without cirrhosis. GROUP B: 52 COVID-19 patients with cirrhosis. GROUP C: 54 patients with cirrhosis without

COVID-19 infection. P*: Kruskal–Wallis, chi-square and analysis of variance as appropriate among the 3 groups. $P^{-} < 0.05$ statistically significant between GROUP A and GROUP B receiving different mRNA vaccines. $P^{;} < 0.05$ statistically significant between GROUP B and GROUP C receiving different mRNA vaccines.

Table was adapted without modifications from: Drácz B. et al: Vaccines, 2023.

Variable	GROUP B (*n* = 52)		GROUP A (*n* = 399)		GROUP C (*n* = 54)		*p**		*p*-		*p*;	
	Pfizer-BioNTech (*n* = 27)	Moderna (*n* = 12)	Pfizer-BioNTech (*n* = 199)	Moderna (*n* = 73)	Pfizer-BioNTech (*n* = 36)	Moderna (*n* = 5)	Pfizer-BioNTech	Moderna	Pfizer-BioNTech	Moderna	Pfizer-BioNTech	Moderna
Encephalopathy stage							**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.05**	0.082
Stage 1-2	11 (21.2	6 (11.5)	199 (49.9)	72 (18)	25 (46.3)	1 (1.9)						
Stage 3	8 (15.4)	6 (11.5)	0 (0)	1 (0.3)	7 (13)	2 (3.7)						
Stage 4	8 (15.4)	0 (0)	0 (0)	0 (0)	4 (7.4)	2 (3.7)						
Ascites grade							**<0.001**	**<0.001**	**<0.001**	**<0.001**	0.094	0.503
Mild	0 (0)	0 (0)	199 (49.9)	72 (18)	10 (18.5)	0 (0)						
Moderate	6 (11.5)	5 (9.6)	0 (0)	1 (0.3)	3 (5.6)	3 (5.6)						
Severe	21 (40.4)	7 (13.5)	0 (0)	0 (0)	23 (42.6)	2 (3.7)						
Esophageal varices							**<0.001**	**<0.001**	**<0.001**	**<0.001**	0.162	0.412
Grade 1	3 (5.8)	0 (0)	1 (0.3)	1 (0.3)	4 (7.4)	0 (0)						
Grade 2	15 (28.8)	8 (15.4)	1 (0.3)	0 (0)	14 (25.9)	1 (1.9)						
Grade 3	6 (11.5)	1 (1.9)	0 (0)	0 (0)	7 (13)	1 (1.9)						
Oxygen support	9 (17.3)	6 (11.5)	65 (16.3)	29 (7.3)	1 (1.9)	1 (1.9)	**<0.05**	0.517	0.945	0.505	**<0.05**	0.267
Mechanical ventilation	16 (30.8)	4 (7.7)	89 (22.3)	22 (5.5)	5 (9.3)	1 (1.9)	**<0.001**	0.861	0.156	0.825	**<0.001**	0.594
Fatal outcome	4 (7.7)	0 (0)	25 (6.3)	6 (1.5)	3 (5.6)	2 (3.7)	0.706	**<0.05**	0.743	0.306	0.422	**<0.05**

DOI:10.14753/SE.2024.2979

DOI:10.14753/SE.2024.2979

6.2 Evaluation of novel prognostic factors for mortality in COVID-19 patients with cirrhosis

6.2.1 Clinical data and laboratory findings in COVID-19 patients with cirrhosis

Patient characteristics of COVID-19 patients with cirrhosis (n = 52) were analysed and compared to COVID-19 patients without cirrhosis (n = 399) in Table 5. COVID-19 patients with cirrhosis were younger related to those without cirrhosis (62 years vs. 65 years, $p<0.05$) and had prelonged hospitalization (14 days vs. 11 days, $p = 0.082$). With regard to minerals, the median levels of potassium, magnesium and albumin-corrected total serum calcium were significantly decreased in the cirrhosis cases ($p <0.05$). Kidney function laboratory parameters, such as estimated glomerular filtration rate (eGFR) and serum creatinine, were found to be significantly different between the two groups ($p <0.05$). Related to complete blood count and inflammatory biomarkers, we found significantly lower median values of red blood count, platelets and CRP in COVID-19 patients with cirrhosis vs. COVID-19 patients without cirrhosis ($p<0.05$). In contrast, cirrhosis patients were associated with higher levels of WBC count.

Table 5. Comparison of clinical and laboratory data on hospital admission between COVID-19 patients with cirrhosis and COVID-19 patients without cirrhosis

Statistically significant values are highlighted in bold. The data are presented as frequencies (%) or medians with IQRs. Na, sodium; K, potassium; Ca, calcium, Mg, magnesium; AST, aspartate aminotransferase; ALT, alanine aminotransferase; INR, international normalized ratio; GGT, gamma-glutamyl transferase; ALP, alkaline

phosphatase; LDH, lactate dehydrogenase; CRP, C-reactive protein; RBC, red blood cell; WBC, white blood cell; eGFR, estimated glomerular filtration rate, CTP, Child–Turcette–Pugh; MELD-Na, Model for End-Stage Liver Disease sodium; IQR, interquartile range. * Corrected serum calcium is defined as the total serum calcium level corrected for the serum albumin concentration.

Table was adapted without modifications from: Drácz B. et al: Biomedicines, 2023.

Variables	**COVID-19 Patients without Cirrhosis (*n* = 399)**	**COVID-19 Patients with Cirrhosis (*n* = 52)**	***p***
Age, years	65 (53–75)	62 (53–67)	**<0.05**
In-hospital mortality (%)	47 (11.8)	5 (9.6)	0.819
Hospital stay, days	11 (7–14)	14 (7–19)	0.082
Oxygen therapy (%)	147 (41)	21 (40.4)	0.649
Mechanical ventilation (%)	159 (39.8)	24 (46.2)	0.453
Cancer (%)	29 (7.3)	9 (17.3)	**<0.05**
Na, mmol/L	136 (132–138)	135 (130–138)	0.184
K, mmol/L	4.5 (4.12–4.9)	4.2 (3.7–4.6)	**<0.05**
Total serum calcium, mmol/L	2.08 (1.94–2.32)	1.44 (1.38–1.56)	**<0.05**
* Corrected serum Ca, mmol/L	2.32 (2.18–2.46)	2.16 (2.05–2.25)	**<0.05**
Mg, mmol/L	0.86 (0.79–0.94)	0.8 (0.74–0.86)	**<0.05**
AST, U/L	41 (29–62)	48 (31–102)	**<0.05**
ALT, U/L	31 (19–51)	35 (24–68)	0.109
Albumin, g/L	37 (32–43)	30.7 (26.8–35.2)	**<0.05**
INR	1.01 (0.87–1.17)	1.33 (1.11–1.53)	**<0.05**
Total Bilirubin, μmol/L	14.6 (8.5–21.4)	28.7 (13.1–73.8)	**<0.05**
Direct Bilirubin, μmol/L	6.87 (3.67–12.3)	9.6 (5.4–25.3)	**<0.05**
Total protein, g/L	65.4 (56.87–72.5)	63.9 (51.4–71)	0.051

GGT, U/L	51 (30–82)	86.5 (47–289)	**<0.05**
ALP, U/L	99 (78–170)	103 (78.5–205.8)	0.634
LDH, U/L	231 (167–312)	251 (213–304)	0.376
CRP, mg/L	114 (34.2–412)	62.2 (12.3–152.8)	**<0.05**
Hemoglobin, g/L	124 (102–130)	111.5 (102.3–131)	0.693
RBC, T/L	4.13 (3.78–4.65)	3.7 (3.35–4.06)	**<0.05**
WBC, G/L	8.03 (6.78–11.35)	10.0 (6–14.5)	0.111
Platelets, G/L	189 (123–312)	146 (95–221.8)	**<0.05**
Creatinine, μmol/L	92 (75–121)	115 (78.5–159.3)	**<0.05**
eGFR, ml/min	84 (67.8–90)	64.6 (42.8–90)	**<0.05**
Glucose, mmol/L	6.4 (5.76–7.46)	6.3 (5.6–6.8)	0.13
CTP score	-	9 (7–11)	**<0.05**
MELD-Na	-	20 (14–25)	**<0.05**

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

As summarized in Table 6, 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).

Table 6. Univariate and multivariate regression analysis for identification of risk factors associated with COVID-19 related mortality

Statistically significant values are highlighted in bold. Na, sodium; K, potassium; Ca, calcium, Mg, magnesium; AST, aspartate aminotransferase; ALT, alanine aminotransferase; INR, international normalized ratio; GGT, gamma-glutamyl transferase; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; CRP, C-reactive protein; RBC, red blood cell; WBC, white blood cell; CTP, Child–Turcette–Pugh; MELD-Na, Model for End-Stage Liver Disease sodium; OR odds ratio; CI confidence interval. * Total serum calcium is defined as corrected calcium level for serum albumin concentration.

Table was adapted without modifications from: Drácz B. et al: Biomedicines, 2023.

Variable	Univariate Analysis				Multivariate Analysis			
	β	*p*	OR	95% CI	β	*p*	OR	95% CI
Age	0.080	**<0.05**	1.083	1.053–1.115	−0.090	**<0.05**	0.914	0.885–0.944
Hospital stay	0.152	**<0.05**	1.164	1.097–1.236	−0.138	**<0.05**	0.871	0.818–0.928
Na	−0.100	**<0.05**	0.905	0.847–0.966	0.096	**<0.05**	1.100	1.037–1.167
K	−0.020	0.938	0.980	0.588–1.634	0.224	0.352	1.251	0.781–2.007
Ca*	−0.574	0.418	0.563	0.141–2.257	1.583	**<0.05**	4.871	1.566–15.146
Mg	−1.594	0.276	0.203	0.012–3.572	2.424	0.084	11.292	0.724–176.050
AST	0.004	0.211	1.004	0.998–1.011	−0.005	0.216	0.995	0.987–1.003
ALT	−0.006	0.131	0.994	0.987–1.002	0.003	0.580	1.003	0.992–1.015
Albumin	−0.132	**<0.05**	0.876	0.827–0.929	0.143	**<0.05**	1.154	1.089–1.224
INR	1.259	**<0.05**	3.523	1.414–8.780	−1.356	**<0.05**	0.258	0.102–0.647
Total bilirubin	0.003	**<0.05**	1.003	1.000–1.006	−0.003	0.051	0.997	0.994–1.000

Direct bilirubin	−0.018	**<0.05**	0.982	0.968–0.997	0.014	**<0.05**	1.014	1.000–1.027
Total protein	−0.004	0.755	0.996	0.970–1.022	0.009	0.513	1.009	0.982–1.036
GGT	−0.001	0.395	0.999	0.997–1.001	0.000	0.698	1.000	0.998–1.002
ALP	0.001	0.329	1.001	0.999–1.002	0.000	0.592	1.000	0.998–1.001
LDH	−0.002	0.269	0.998	0.994–1.002	0.002	0.162	1.002	0.999–1.005
CRP	0.001	0.244	1.001	1.000–1.002	−0.001	0.069	0.999	0.998–1.000
Hemoglobin	−0.017	0.132	0.983	0.962–1.005	0.019	0.108	1.019	0.996–1.043
RBC	−0.591	0.068	0.554	0.293–1.045	0.622	0.065	1.863	0.963–3.604
WBC	0.273	**<0.05**	1.314	1.226–1.409	−0.300	**<0.05**	0.741	0.686–0.799
Platelets	−0.005	**<0.05**	0.995	0.990–1.000	0.005	0.057	1.005	1.000–1.010
Creatinine	0.002	0.331	1.002	0.998–1.006	−0.002	0.298	0.998	0.994–1.002
CTP	1.211	**<0.05**	3.358	1.545–7.300	−1.209	**<0.05**	0.299	0.115–0.775
MELD-Na	−0.128	0.635	0.880	0.519–1.493	0.264	0.490	1.301	0.616–2.750

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

The ROC curves of sodium, total serum calcium, albumin, INR, WBC and CTP are compared in Figure 12. 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. As demonstrated in Table 7, 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.

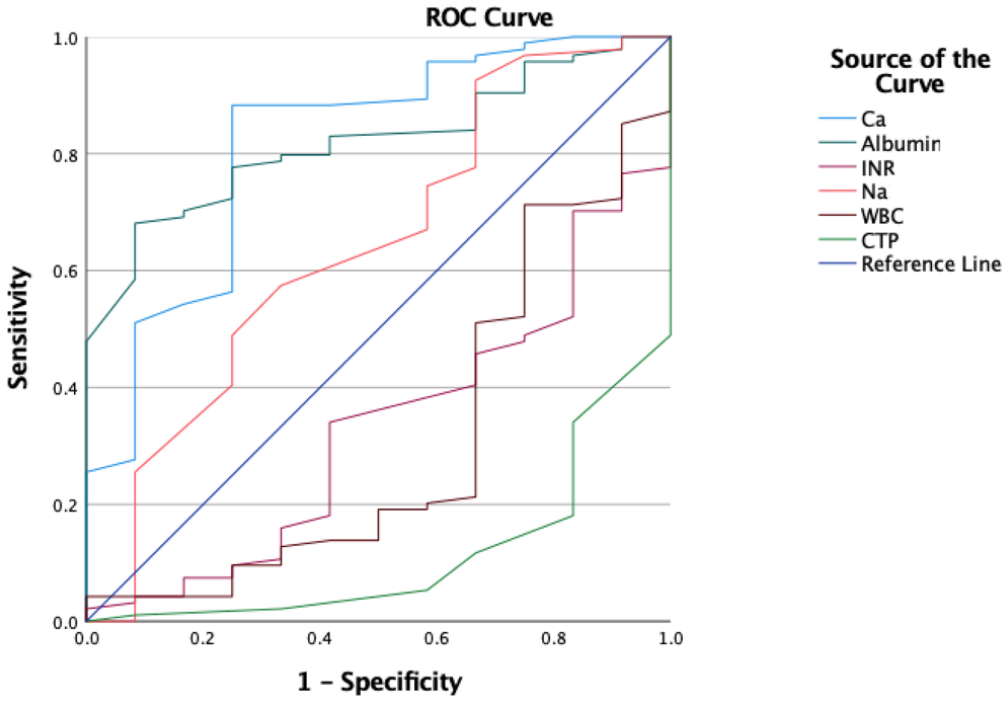


Figure 12. ROC curves of the six investigated prognostic factors

Na, sodium; INR, international normalized ratio; WBC, white blood cell; CTP, Child–Turcette-Pugh.

Figure was adapted without modifications from: Drácz B. et al: Biomedicines, 2023.

Table 7. Diagnostic efficacy of sodium, total serum calcium, albumin, INR, WBC and CTP

Statistically significant values are highlighted in bold. INR, international normalized ratio; WBC, white blood cell; CTP, Child–Turcette–Pugh; AUC area under the curve; CI confidence interval. * Corrected serum calcium is defined as the calcium level corrected for the serum albumin concentration.

Table was adapted without modifications from: Drácz B. et al: Biomedicines 2023.

Prognostic Marker	AUC (95% CI)	Cut-off	Sensitivity	Specificity	*p*
Na	0.643 (0.465–0.821)	133.5	0.745	0.417	0.108
Ca*	0.818 (0.683–0.953)	2.02	0.883	0.750	**<0.05**
Albumin	0.821 (0.729–0.914)	27.9	0.777	0.750	**<0.05**
INR	0.332 (0.181–0.482)	1.345	0.340	0.583	0.058
WBC	0.309 (0.136–0.481)	6.905	0.511	0.333	**<0.05**

CTP	0.115 (0.025–0.205)	9.5	0.340	0.167	**<0.05**

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

The clinical characteristics and laboratory findings of COVID-19 patients with cirrhosis stratified by different total serum calcium levels are compared in Table 8. Among cirrhosis cases, patients with hypocalcemia on admission were associated with higher mortality rates compared to normocalcemic patients (16% vs. 3.7%). As demonstrated in Table 8, decompensated cirrhosis was the most common in both groups. 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 ($p < 0.05$).

Table 8. Clinical characteristics and laboratory data of COVID-19 patients with cirrhosis classified by different total serum calcium levels

Categorical variables are defined as frequencies (percentages). Continuous variables are defined as medians (interquartile ranges). Bold text is used for highlighting the statistically significant values. ACLF, acute-on-chronic liver failure; INR, international normalized ratio; GGT, gamma-glutamyl transferase; WBC, white blood cell; CRP, C-reactive protein; CTP, Child–Turcette–Pugh; MELD-Na, Model for End-Stage Liver Disease sodium.

Hypocalcaemia was considered as an albumin-corrected total serum calcium level below 2.2 mmol/L (8.9 mg/dL). Normocalcaemia was defined as an albumin-corrected total serum calcium level between 2.2 mmol/L and 2.6 mmol/L.

Table was adapted without modifications from: Drácz B. et al: Biomedicines, 2023.

Variable	COVID-19 Patients with Cirrhosis (*n* = 52)		*p*
	Hypocalcemia (*n* = 25)	Normocalcemia (*n* = 27)	
Fatal outcome	4 (16)	1 (3.7)	0.183
Type of cirrhosis			0.430
compensated	1 (4)	3 (11.1)	
decompensated	20 (80)	22 (81.5)	
ACLF	4 (16)	2 (7.4)	
Age	65 (53–68)	60 (52–65)	0.359
Oxygen therapy	6 (24)	15 (55.6)	**<0.05**
Mechanical ventilation	16 (64)	8 (29.6)	**<0.05**
Ascites grades			**<0.05**
mild	0 (0)	2 (7.4)	
moderate	4 (16)	11 (40.7)	
severe	21 (84)	14 (51.9)	
Hospital stay	14 (5–20)	13 (8–17)	0.776
Albumin	28 (22.5–31.2)	32 (29–38)	**<0.05**
INR	1.36 (1.12–1.66)	1.2 (1.1–1.4)	0.148
Total bilirubin	32.1 (21–130)	24.1 (11.8–38.7)	0.200
Direct bilirubin	19.6 (8–26.1)	6.4 (4.1–14.1)	**<0.05**
Total protein	52 (45.8–65.4)	69 (61–73)	**<0.05**
GGT	149 (80–326)	64 (39–128)	**<0.05**
WBC	11.4 (6–16.9)	8.5 (5.9–14.5)	0.272
CRP	79.3 (15.2–122.8)	26.5 (3.9–176)	0.280
CTP	10 (9–12)	8 (7–10)	**<0.05**
MELD-Na	22 (15–25)	17 (14–23)	0.110

According to the results of Spearman's correlation analysis, albumin-corrected total serum calcium was significantly negatively correlated with direct bilirubin, GGT and CRP: r = −0.275, r = −0.350 and r = −0.341, respectively (Table 9). As depicted in Figure 13, a significant negative correlation was found between he total serum calcium level and CTP (r = −0.400, $p < 0.05$).

Table 9. Spearman's correlation coefficients between the total serum calcium, age and the abnormal laboratory parameters.

A significant correlation is defined at the 0.05 level ($p < 0.05$). Bold text is used for highlighting the statistically significant values. R: Spearman's correlation coefficient; INR, international normalized ratio; GGT, gamma-glutamyl transferase; WBC, white blood cell; CRP, C-reactive protein; CTP, Child–Turcette–Pugh. * Total serum calcium is defined as the calcium level corrected for the serum albumin concentration.

Table was adapted without modifications from: Drácz B. et al: Biomedicines, 2023.

Variables between	Spearman's Correlation Coefficient	*p*
Ca* and Age	−0.139	0.325
Ca* and INR	−0.247	0.077
Ca* and Total bilirubin	−0.173	0.219
Ca* and Direct bilirubin	−0.275	**<0.05**
Ca* and GGT	−0.350	**<0.05**
Ca* and CRP	−0.341	**<0.05**
Ca* and WBC	−0.242	0.084
Ca* and CTP	−0.400	**<0.05**

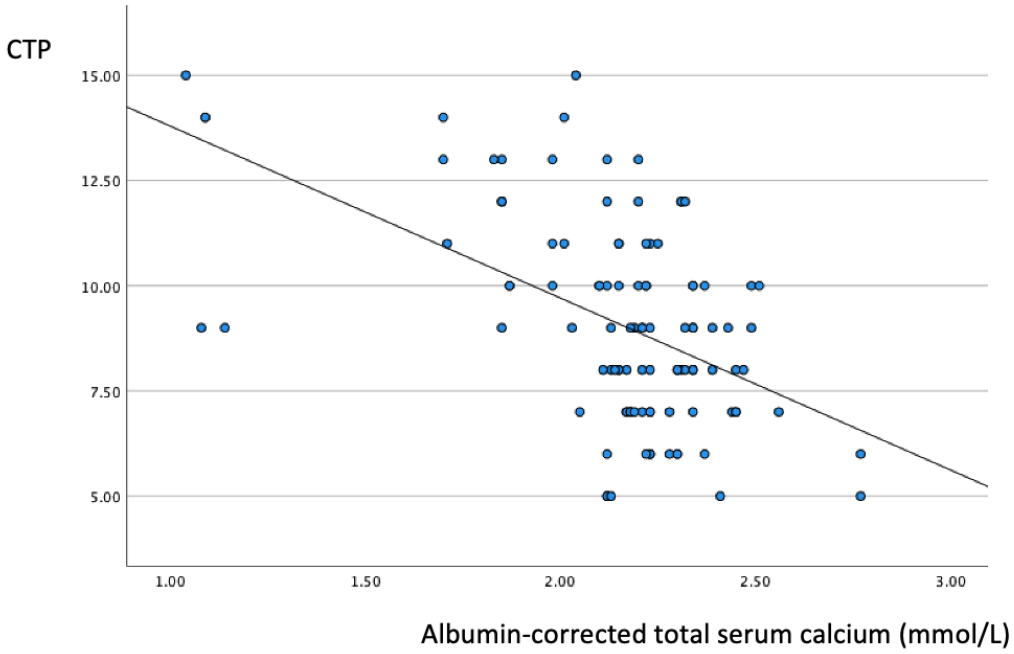


Figure 13. A significant negative correlation (r = −0.400; *p* < 0.05) between the total serum calcium levels and CTP portrayed by a Scatter plot. CTP, Child–Turcette–Pugh.

Figure was adapted without modifications from: Drácz B. et al: Biomedicines, 2023.

DOI:10.14753/SE.2024.2979

7. DISCUSSION

Patients with cirrhosis are reported to be prone to acute deterioration in cirrhosis stage and worse hospital outcomes. Our hypothesis was that COVID-19 could trigger the onset of acute hepatic decompensations and might lead to worse prognosis in patients with cirrhosis. However, there are several clinical conditions and laboratory parameters associated with increased risk for in-hospital mortality, novel and highly sensitive prognostic factors in liver cirrhosis are still unknown. To date, several types of COVID-19 vaccines have been used in vulnerable patient populations including cirrhosis patients to prevent severe clinical course of COVID-19. Nevertheless, the impact of different COVID-19 vaccines on the clinical outcomes of patients with cirrhosis is yet unrevealed. Therefore, we conducted a multicentre matched cohort study to investigate novel prognostic factors for mortality and the efficacy of different COVID-19 vaccines in patients with cirrhosis following COVID-19 (GROUP B) compared to those without COVID-19 (GROUP C) and COVID-19 patients without cirrhosis (GROUP A).

Paizis et al. reported that the ACE-2 receptor is sufficiently overexpressed in cirrhotic livers compared to healthy ones, indicating that patients with cirrhosis are at increased risk of severe clinical course in COVID-19 (100). Our study also demonstrated that patients in GROUP B were more commonly associated with adverse hospital outcomes such as oxygen support or mechanical ventilation in comparison with patients in GROUP A (Figure 10). According to previous studies, remdesivir was associated with liver injury in COVID-19 patients (101-103). Furthermore, Gao et al. revealed that COVID-19 patients receiving corticosteroids were at increased risk of drug-induced liver injury (DILI) contrary to those without any steroids (26). Accordingly, the administrations of remdesivir or steroids were mostly occured in GROUP A (Figure 10). In contrast, the administration of convalescent COVID-19 plasma (CCP) is more frequently occurred in GROUP B compared to GROUP A, suggesting contraindications to start remdesivir in patients with five times the upper limit of transaminases. Improved outcomes in GROUP B might be explained by higher administration rates of CCP, particularly when the protein supplementation effect of this therapeutic approach is also considered (104).

A large COVID-19 cohort study of 220,727 US patients showed that in-hospital mortality rates of patients with cirrhosis following COVID-19 vs. those without cirrhosis were 8.9% vs. 3.9%, respectively (105). Relevant to cirrhotic patients, the mortality rates in our analysis were not significantly different in the two groups: 9.6% (GROUP B) and 11.8% (GROUP C), respectively. The poor outcome was similar in patients with cirrhosis, regardless of COVID-19 status, which was in line with a North American multicentre matched cohort study (106).

Regarding the etiology of liver cirrhosis, alcohol use disorder was the most frequent cause (Figure 8). Patients with excessive alcohol consumption are susceptible to infections notably due to their immune dysfunction and poor general health. During the COVID-19 pandemic, the general condition of these patients may have worsened owing to alcohol relapse and postponed medical checkups. According to recently published studies, patients with alcohol-use disorder are more prone to hepatic decompensations following COVID-19 (60, 107).

The significance of regular clinical screening to detect and treat the complications of cirrhosis is emphasized by the Clinical Practice Guidelines of the European Association for the Study of the Liver (EASL) (108). In the pandemic, surveillance procedures were presumably delayed, which might lead to disease progression and higher prevalence of decompensation events. The development of severe complications is usually occured in COVID-19 patients with cirrhosis. Acute hepatic decompensation events such as worsening ascites or hepatic encephalopathy are common, existing in up to 46% of patients (32). Our study also showed that COVID-19 could trigger acute hepatic decompensation events, especially severe ascites and hepatic encephalopathy stages as well as higher rates of acute variceal haemorrhage (Figure 7).
Although viral infections might provoke ACLF, lower rates were found in GROUP B compared to GROUP C, suggesting that ACLF was largely associated with bacterial infections and higher in-hospital mortality rates.

In accordance with a large registry cohort of 745 COVID-19 patients with chronic liver

disease, the severity of liver cirrhosis classified by Child–Turcette-Pugh score is a reliable predictor of poor prognosis (32). We also found that COVID-19 precipitated disease progression in liver cirrhosis and increasing CTP score could indicate worse hospital outcomes (Figure 9). Although there was a stepwise development in cirrhosis stage following COVID-19, GROUP B was not associated with higher death rates classified by different CTP cirrhosis stages, contrary to GROUP C (Figure 9). In line with international findings, our current data give evidence that patients with cirrhosis, regardless of COVID-19 status, remained at higher risk of fatal outcome (109).

A North American matched cohort investigating 762 patients revealed that COVID-19-related mortality rates were decreased in patients with cirrhosis after the administration of one or two mRNA vaccines compared to unvaccinated cirrhosis cases (87). Moreover, the two-dose administration of mRNA vaccines could prevent most effectively a severe clinical course of COVID-19 compared to other vaccines (88). Contrary to international studies, our data showed that vaccines were unable to prevent COVID-19-related hospitalisations (110, 111). However, our survival analysis showed that unvaccinated patients, particularly those with liver cirrhosis, had significantly worse survival outcomes (Figure 11). In spite of COVID-19 status and liver cirrhosis, primary immunization with mRNA vaccines, relevant to viral vector and inactivated vaccines, significantly improved the survival outcomes, in line with previously published studies (112, 113). Comparing the efficacy of the two mRNA vaccines, Pfizer-BioNTech vaccine was more efficient to prevent symptomatic SARS-CoV-2 infection requiring hospitalization, and significantly decreased the requirements for oxygen support and mechanical ventilation in patients with cirrhosis (Table 4). Moreover, primary vaccination with Pfizer-BioNTech in cirrhosis cases significantly protected against acute hepatic decompensations in association with hepatic encephalopathy. Nevertheless, primary immunization with Moderna was significantly associated with a fatal outcome in COVID-19 patients with cirrhosis related to those vaccinated with Pfizer-BioNTech (Table 4).

Besides mRNA vaccines, AZD1222-AstraZeneca, Gam-COVID-Vac-Sputnik V and HB02-Sinopharm vaccines were also included in the Hungarian vaccination campaign.

In a nationwide, retrospective study of 3 740 066 Hungarian citizens, the overall estimated survivals of COVID-19 patients previously vaccinated with AstraZeneca, Sputnik-V and Sinopharm were lower in comparison with Pfizer-BioNTech and Moderna (85). Our study also gave evidence that primary immunization with viral vector and inactivated vaccines was less effective to avoid COVID-19-related deaths, regardless of liver cirrhosis.

Altogether, our data gave proof that COVID-19 could trigger the disease progression of liver cirrhosis and the development of acute hepatic decompensation events likely owing to aggravated immune dysfunction. In addition, our findings highlight the effectiveness of primary immunization with mRNA vaccines in vulnerable patient populations such as patients with liver cirrhosis, predominantly in cirrhosis cases receiving the Pfizer-BioNTech vaccine.

Previous studies reported that higher values of total bilirubin, direct bilirubin and INR and lower levels of albumin are risk factors for severe clinical course and in-hospital mortality in COVID-19 (45, 60, 114). We found that cirrhosis patients with higher values of liver transaminases, liver function parameters and lower levels of albumin on admission required prolonged hospitalization (Table 5). According to our results, higher values of total bilirubin, direct bilirubin and INR as well as lower levels of albumin were significant predictors of in-hospital mortality (Table 6). Regarding further alterations in laboratory findings, COVID-19 patients with cirrhosis were found to be more susceptible to significant thrombocytopenia, hypocalcemia and worsening kidney function on admission (115-117)

Hypocalcaemia is a common condition of liver cirrhosis and might be observed in SARS-CoV-2 infection. Therefore, a multicenter retrospective study was conducted to determine the prognostic value of hypocalcemia for disease progression and mortality in COVID-19 patients with cirrhosis and compare its diagnostic efficacy to other abnormal laboratory parameters.
In a systemic review and meta-analysis including 953 COVID-19 patients, hypocalcemia was found to be associated with fatal outcome, with a sensitivity of 76% and specificity

of 53% (118). Relevant to the performance and predictive value of prognostic factors for mortality, the total serum calcium corrected for albumin was revealed as a highly sensitive and specific prognostic marker for mortality. The cut-off value of total serum calcium was 2.02 mmol/L, which was defined as hypocalcemia (Table 7). International data showed that hypocalcemia could be used as a predictive marker for poor hospital outcome, with an AUC value above 0.70 (118, 119). In our analysis, hypocalcemia could predict effectively the poor prognosis, with an AUC of 0.818 (95% CI 0.683–0.953, $p < 0.05$) (Table 7). Our findings provide evidence that total serum calcium corrected for albumin is an accurate and highly sensitive prognostic marker that can be employed to predict fatal outcome in COVID-19 patients with cirrhosis (Figure 12).

A meta-analysis investigating 2032 patients reported that a strong association was found between hypocalcemia and disease progression as well as in-hospital mortality in COVID-19 patients (67). A retrospective study, which compared the disease severity of COVID-19 between patients with hypocalcemia and those with normocalcemia revealed that the hypocalcemic patients were vulnerable to severe clinical course and prolonged hospital stay (66). Our data also showed that hypocalcemia on admission had a significant predictive value for in-hospital mortality in COVID-19 patients with cirrhosis. Although mineral deficiencies, such as hypocalcemia, are frequently occured in liver cirrhosis, hypocalcemic patients were more susceptible to acute hepatic decompensations following COVID-19 (Table 8) (68, 69). Our study also gave evidence that grading ascites was significantly associated with lower levels of corrected serum calcium, which might indicate that hypocalcemia on admission is a clinical warning of disease progression in COVID-19 (Table 8).

Literature data previously reported that SARS-CoV-2 virus could utilize calcium for replication, and consequently excessive immune response might lead to impairment in calcium homeostais (120, 121). In our findings, the level of albumin-corrected total serum calcium was inversely proportional to the CRP level and, as a consequence, the disease severity (Figure 13).

As demonstrated in Table 8, development of respiratory injury was associated with lower levels of calcium. The increased administration of mechanical ventilation in patients with

hypocalcemia might warn health care providers that patients become critically ill due to COVID-19-induced acute hypoxaemic respiratory failure. Our study also revealed that worsening hypocalcemia can indicate the dysregulation of the immune system with excessive immune response, which could lead to disease progression and increased predisposition to acute hepatic decompensation events. Our results are conforming with the findings of Alemzadeh (122).

Altogether, our findings give evidence that hypocalcemia on admission is a reliable predictor of disease progression in patients with cirrhosis following COVID-19. Cirrhosis patients with grading hypocalcemia might develop decompensations in the cirrhosis stage and more excessive immune response following COVID-19. Hence, albumin-corrected total serum calcium is of specific importance, as it can warn as a red flag indicating the exacerbation of COVID-19 and disease progression in patients with cirrhosis. We also propose that hypocalcemia in COVID-19 patients with cirrhosis should be more closely monitored to assist medical providers in risk stratification and proper decision-making process.

The limitations of our study must be acknowledged, including the retrospective study design and relatively small sample size. First, the number of enrolled COVID-19 patients with cirrhosis was limited in our study. Regarding major hospital outcomes, there were restrictions to in-hospital mortality and the length of hospital stay. The hospital discharge criteria, such as two negative RT-PCR tests acquired consecutively at least 24 h apart, might have affected the major outcomes. The higher mortality rates in GROUP C vs. GROUP B endorses the concept that GROUP C patients were hospitalized in a more susceptible condition due to rapid development of disease in cirrhosis. Moreover, the higher mortality rates of GROUP A vs. GROUP B support the concept that cirrhosis patients display higher adherence to regular screening and surveillance programs, which prevent severe clinical course and fatal outcome following COVID-19. Second, the administration of single-dose Ad26.COV2.S-Janssen vaccine was excluded from our analysis owing to inadequate primary vaccination campaign. Potential biases are expected as patient cohorts were recorded over prolonged time periods and were exposed to different contagion circumstances. The study period was covered by different waves with

multiple variants of SARS-CoV-2 virus, which may have affected the efficacy of the divergent COVID-19 vaccines evaluated in our findings. Third, some vaccines were principally targeted for elderly patients or those with comorbidities, consequently confounding clinical characteristics could result in anticipated variations in the effectiveness of COVID-19 vaccines. Therefore, future prospective studies are necessary to evaluate the efficacy of all recognised COVID-19 vaccines employing against the latest upcoming variants in patients with cirrhosis. Fourth, laboratory data such as serum 25-hydroxyvitamin D [25(OH)D], parathyroid hormone (PTH) and the arterial blood gas test were excluded due to the unavailability of laboratory examinations. Hence, further prospective studies should analyze the prognostic significance of hypocalcemia associated with serum 25-hydroxyvitamin D [25(OH)D], parathyroid hormone (PTH) and blood gas levels.

Additionally, the strengths of our study must be acknowledged, including the multicentre matched cohort design and the scope of a vulnerable patient population with a higher risk of COVID-19-related hospital deaths. Although there are limited data available about the impact of primary immunization with different COVID-19 vaccines on the clinical outcome of cirrhosis cases, our methodology could uniquely provide better understanding to evaluate the effectiveness of different COVID-19 vaccines in hospitalized patients regardless of COVID-19 status and liver cirrhosis. Although there are several international studies investigating the impact of hypocalcemia on the clinical outcomes of COVID-19, our study exclusively allows a better interpretation of the prognostic value of hypocalcemia in cirrhosis patients following COVID-19.

DOI:10.14753/SE.2024.2979

8. 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.

DOI:10.14753/SE.2024.2979

9. SUMMARY

Patients with cirrhosis are susceptible to hepatic decompensation events and in-hospital mortality following COVID-19. Therefore, primary immunization with COVID-19 vaccines is essential to decrease the risk of COVID-19 related adverse events, including fatal outcome in cirrhosis cases. However, there are limited data available about the effectiveness of mRNA vaccines compared to other vaccines and novel reliable prognostic markers for in-hospital mortality in COVID-19 patients with cirrhosis. First, this study aimed to investigate the clinical characteristics with special emphasis on liver cirrhosis severity and acute hepatic decompensation events relevant to in-hospital mortality and the effectiveness of different COVID-19 vaccines in patients with cirrhosis. Our goal was also to analyze abnormal laboratory findings and evaluate novel highly sensitive prognostic and predictive markers for mortality in COVID-19 patients with cirrhosis. In this retrospective matched cohort study, we selected 399 COVID-19 patients without cirrhosis (GROUP A) and compared the patient characteristics, vaccine effectiveness and laboratory findings to 52 COVID-19 patients with cirrhosis (GROUP B). Hence, 54 cirrhosis inpatients without COVID-19 (GROUP C) were at random sampled 1:1 and matched by gender and age.

In summary, COVID-19 patients with liver cirrhosis is a highly vulnerable patient group. Although the impact of COVID-19 is significant on the clinical outcome of patients with cirrhosis, the stage of cirrhosis severity is the main determinant of developing severe COVID-19. COVID-19 patients with cirrhosis might present without ordinary respiratory symptoms on admission but respiratory failure is still the predominant cause of in-hospital mortality. Our data primarily gave evidence the beneficial role of primary vaccination with mRNA vaccines in patients with liver cirrhosis, with special attention to the two-dose administration of Pfizer-BioNTech vaccine. We highlighted the first time the clinical benefits of mRNA vaccines, particularly Pfizer-BioNTech, compared to viral vector and inactivated COVID-19 vaccines in liver cirrhosis. Our study uniqually revealed that corrected serum calcium for albumin is a highly sensitive prognotic marker in COVID-19 patients with cirrhosis. Since it is a cheap, rapid and highly accessible laboratory test, total serum calcium should be routenily performed to assess the severity of disease and monitor the clinical course of patients with cirrhosis following COVID-19.

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DOI:10.14753/SE.2024.2979

11. BIBLIOGRAPHY OF THE CANDIDATE'S PUBLICATIONS

Σ IF: 17.8

11.1 Bibliography related to the thesis Σ IF: 17.2

1. **B. Dracz;** D. Czompa; K. Mullner; K. Hagymasi; P. Miheller; H. Szekely; V. Papp; M. Horvath; I. Hritz; A. Szijarto; K. Werling
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   IF: 4.7

2. **B. Dracz;** V. Muller; I. Takacs; K. Hagymasi; E. Dinya; P. Miheller; A. Szijarto; K. Werling
   Effectiveness of COVID-19 Vaccination with mRNA Vaccines for Patients with Cirrhosis in Hungary: Multicentre Matched Cohort Study
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11.2 Bibliography not related to the thesis Σ IF:0.60

4. A. Kata; M. Anna Tajthy; **B. Dracz;** P. Miheller; M. Horvath; H. Szekely; V. Papp; D. Czompa; A. Szijarto; K. Werling
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gastrointestinalis eltérései

Orvosi Hetilap 164 : 31 pp. 1206-1212. , 7 p. (2023)

IF: 0.6

DOI:10.14753/SE.2024.2979

12. ACKNOWLEDGEMENTS

First of all, I would like to express my sincere gratitude to my supervisor, *Klára Werling*, for her continuous support and guidance. It was a privilege to spend two rewarding years under her supervision and I am extremely grateful for her great knowledge and plentiful experience that have shaped my scientific perspective.

I am also highly grateful to the chair of Department of Surgery, Transplantation and Gastroenterology, *Professor Attila Szijártó*, whose leadership and unbroken guidance paved the way to become a researcher. Without his financial and professional support, these achievements would not have been possible.

During the PhD course, I have received enormous support from patologists: *Professor Ilona Kovalszky* from Department of Pathology and Experimental Cancer Research; *Professor Zsuzsa Schaff* and Professor András Kiss from Department of Pathology, Forensic and Insurance Medicine. I deeply appreciate their continued effort and support in the field of pathology. I want to express my appreciation to *Erzsébet Kovács* and *Adrián Pesti* for all the support as well.

I am also thankful for my colleagues and national collaboration partners: *Krisztina Hagymási*, *Pál Miheller*, *István Hritz*, *Miklós Horváth*, *Hajnal Székely*, *Veronika Papp* and *Diána Czompa* from Department of Surgery, Transplantation and Gastroenterology; *Professor Veronika Müller* from Department of Pulmonology; *István Takács* from Department of Internal Medicine and Oncology; Elek Dinya from Digital Health Department.

Finally, I would like to express my deepest gratitude to my family for their tremendous support and giving me love. I am especially thankful for my fiancée, dr. Bianka Rita Práger, who always supported me to overcome this challenging period of my life.