



# Acute liver injury in the course of COVID-19

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## Abstract

Although coronavirus disease 19 (COVID-19) most often affects the respiratory system, in the course of this disease, dysfunction of many other organs may also develop. The case is presented of a female patient, treated for a long time due to chronic obstructive pulmonary disease, complicated by chronic complete respiratory failure, and who was undergoing non-invasive mechanical ventilation at home. She was admitted to the Pneumology Department due to exacerbation of the symptoms of her underlying disease. Several tests for SARS-CoV2 infection gave a negative result. During the patient's stay in the clinic, a rapid increase was observed in symptoms of respiratory failure, heart failure, and laboratory signs of acute liver damage. The next PCR test result proved to be positive. In addition to the case report, the possible impact of SARS-CoV2 infection on liver damage is also discussed, along with a literature review on this topic.

## Key words

liver, COPD, transaminases, COVID-19

## INTRODUCTION

COVID-19 is an infectious disease most often affecting the respiratory system, but can also affect many other systems and organs. One of the manifestations of this disease is acute liver damage, which may have a multifactorial aetiology in the course of this disease [1]. Firstly, the infection may overlap pre-existing liver disease. Moreover, drug-induced damage, as well as congestion caused by right ventricular heart failure or complications of COVID-19, such as pulmonary embolism, may also be of importance. The liver damage complicating the COVID-19 infection can increase the severity of the disease, leading to prolonged hospitalization and worsens the prognosis of survival [1, 2, 3, 4].

The case report presents a patient with acute liver injury in the course of COVID-19, with the exacerbation of chronic obstructive pulmonary disease, and includes a review of the latest literature on this topic.

## CASE REPORT

The case is presented of a 75-year-old female patient with a history of chronic obstructive pulmonary disease (COPD) and chronic complete respiratory failure, undergoing a home oxygen treatment programme with non-invasive ventilation (NIV) in a bi-level positive airway pressure mode (bi-PAP). She was admitted to the Department of Pneumology because of dyspnoea, increasing for 3 weeks (at 3 points on the modified Medical Research Council –

mMRC – scale), cough with expectoration of a small amount of yellowish discharge, and pain in the left shoulder. She was treated for arterial hypertension and chronic heart failure. A year earlier, she had been diagnosed with a peripheral pulmonary embolism (PE) and was taking rivaroxaban for anticoagulant treatment for 6 months. On admission, her blood saturation was 73% and raised to 87% with passive oxygen therapy. Respiratory rate – 15/min, temperature – 37°C, blood pressure – 130/75mmHg, and heart rate – 110/min. On auscultation, no additional auscultation phenomena were audible. The electrocardiogram showed regular sinus tachycardia of 150 beats per minute with no evident signs of acute myocardial ischemia. Laboratory test results: C-reactive protein (CRP) – 7 mg/l, ALT – 50 U/l, troponin I 106 ng/l, with a slight upward trend in subsequent determinations, D-dimers – 3,500 µg/l. All other results were normal. The measurement of arterial blood gases showed compensated respiratory acidosis. According to the radiologist, the changes found in the radiograph could partially meet the COVID-19 criteria, but the antigen test and two PCR tests for this disease were negative.

On admission, a diagnosis of non-infectious exacerbation of COPD was made, overlapping the chronic heart failure symptoms. The initial treatment (apart from her everyday treatment) included enoxaparin at a therapeutic dose, furosemide and nebulization with fenoterol and ipratropium bromide. NIV was used in bi-PAP mode with expiratory positive airway pressures (EPAP) of 4 cmH<sub>2</sub>O and inspiratory positive airway pressures (IPAP) of 12 cmH<sub>2</sub>O.

Despite numerous health burdens and advanced lung disease, the patient was in a reasonably good condition, moved independently within the bed, was adapted to dyspnoea and tolerated NIV treatment well.

Due to significantly elevated levels of D-dimers and her previous history of PE, chest angio-computed tomography

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(angio-CT) was performed, which did not confirm PE, but showed features of right ventricular failure, e.g. throwing a contrast into the inferior vena cava and hepatic veins. The cardiologist consulted the patient, on echocardiography III° tricuspid regurgitation, I/II° mitral valve insufficiency, normal left ventricular systolic function and features of pulmonary hypertension with pulmonary systolic pressure (PASP) of 135 mmHg were found. Due to a slight increase in inflammatory parameters, empirical antibiotic therapy with levofloxacin was commenced. On the fifth day of hospitalization, the activity of hepatic transaminases increased significantly with normal bilirubin levels (Tab. 1). Hepatoprotective treatment with timonacic and phospholipids was initiated immediately. On the seventh day of hospitalization, the activity of transaminases increased even more, but a day later it began to decline.

**Table 1.** Results of laboratory tests

Lab test (normal ranges)	Day of hospitalization						
	1	3	5	7	8	9	10
ALT (< 34 U/L)		50	659	1397	1108	933	1338
AST (< 31 U/L)		28	1120	1831	1077	909	1905
AST/ALT		0.56	1.7	1.3	0.97	0.97	1.4
Bilirubin(0.3–1.2 mg/dl)		0.7	0.8	0.8	0.8	1.2	1.9
GGTP (<38 U/L)					24	28	
ALP (46–116 U/L)					74	82	
CRP (0–5 mg/L)	7	2	25	29	32	33	24
BNP (0–100 pg/mL)					608		4966
Il-6 (< 7 pg/mL)						50.9	
Albumins (3.2–4.8 g/dL)			3.65				

On the eighth day of hospitalization, the patient's general condition suddenly deteriorated. She was drowsy and confused, with dyspnoea and central cyanosis and crackles heard above the lungs. Tachypnoea and tachycardia were observed, SpO<sub>2</sub> decreased to 70% despite optimization of NIV parameters, mask fitting and increasing oxygen flow, pH was 7.25, pCO<sub>2</sub> 83 mmHg, pO<sub>2</sub> 50 mmHg and HCO<sub>3</sub><sup>-</sup> – 36 mmol/l. The immediate administration of furosemide and dexamethasone was ineffective and her condition continued to deteriorate. She was intubated while sedated with propofol. Due to a drop in blood pressure, the fluid supply was increased, and norepinephrine infusion was started through the central line. An antigen test for COVID-19 was performed, again with a positive result. The patient was placed in an isolation room with a sanitary regime. Meropenem and dexamethasone were added to the treatment. Efforts were initiated to transfer the patient to a department that provides specialist treatment for COVID-19 patients.

The next day, sudden cardiac arrest in the pulseless electrical activity mechanism (PEA) occurred. Circulation was restored immediately after resuscitation. Supraventricular tachycardia with hypotension was observed – dobutamine and amiodarone were added to the treatment. In the morning, two days after the exacerbation, circulation stopped for the third time, resuscitation was unsuccessful. At the request of the patient's family and due to the known cause of death, an autopsy was not carried out.

## DISCUSSION AND LITERATURE REVIEW

In the presented case, the patient had numerous and severe internal diseases despite her initially stable general condition. We are convinced that the development of COVID-19 symptoms contributed to the rapid deterioration of the patient's clinical condition and to the development of multi-organ failure, including acute liver injury. Liver dysfunction in the patient did not meet the criteria of acute liver failure because neither jaundice, plasma coagulation disorders nor hepatic encephalopathy were observed.

Acute liver injury, although rare, can turn into a life-threatening situation. Therefore, it requires a multidisciplinary approach and a quick search for causes in order to apply treatment, preferably a causal one [5,6]. In developing countries, hepatotropic viruses are the dominant cause of liver injury, while in the USA and Western Europe, the main cause is drugs [7]. We excluded numerous causes of acute liver damage in the presented patient. Being aware that viral hepatitis may, in this situation, aggravate the features of liver damage [2, 8], tests for hepatotropic virus infections were performed, but they were all negative. Other causes of acute liver injury were also considered, but no apparent cause was confirmed.

Drug effects accounted for 50% of the causes of acute liver damage in the United States, although the response to many drugs other than acetaminophen is unpredictable and may not be dose-related (idiosyncrasy) [9]. Risk factors include old age and baseline hypertransaminasemia [10]. Commonly used drugs that can cause the idiosyncratic acute liver failure mentioned in numerous studies are statins and amoxicillin-clavulanate [11, 12, 13]. In the presented patient, drug-induced injury seemed unlikely because she did not take medications that typically damage the liver: paracetamol, statins, or antibiotics, with the exception of levofloxacin. Liver damage after the use of levofloxacin is very rare – the percentage of patients showing elevation in alanine transaminase (ALT) and aspartate transaminase (AST) activity due to levofloxacin administration accounted for 2% – 5%. The latency to onset usually lasts 1 – 3 weeks [14]. In the presented patient, starting levofloxacin and the onset of symptoms occurred on the same day, which renders any relationship between them very doubtful. In a Canadian study, the administration of levofloxacin and moxifloxacin was associated with a two-fold risk of hospital admission for acute liver injury. However, this risk was only examined in relation to the use of clarithromycin [15]. The mechanism of damage associated with fluoroquinolone intake can be hepatocellular, cholestatic, or a combination of the two [16]. It is worth mentioning that some of the drugs used in treatment of COVID-19 have been found to be toxic to the liver. These include, apart from the already mentioned antipyretic drugs and antibiotics (e.g. azitromycin), antiviral drugs like remdesivir and lopinavir/ritonavir, immunomodulators (tocilizumab, glucocorticoids) and antimalarics (hydroxychloroquine) [17, 18, 19, 20].

In a study by Goldman et al., the use of remdesivir resulted in an increase in transaminase activity in 6% of patients [21]. Hydroxychloroquine treatment is considered as a rare cause for the elevation of liver enzymes [22]. Azitromycin can cause liver injury in hepatocellular [23] or cholestatic mechanism [24]. The use of tocilizumab can result in the elevation of liver enzymes [24] and suppression of liver regeneration [25]. It is worth noting that pre-existing, non-alcoholic fatty liver

disease (NAFLD) can be responsible for higher susceptibility to liver damage caused by acetaminophen, compared to the healthy population [18]. In addition, patients with COVID-19 who require treatment and hospitalization are treated with numerous drugs, the hepatotoxic effects of which may overlap and intensify [20].

Another cause of drug-induced liver damage is the use of herbal drugs [26], but the presented patient did not take any herbal medications of uncertain composition, such as consumption of poisonous forest mushrooms [27]; therefore, the effect of alpha-amanitin was not confirmed. The patient had also not been exposed to carbon tetrachloride, one of the substances responsible for direct liver injury [28]. Alcoholic liver disease was excluded because the patient was completely abstinent. Other causes, such as hepatic insufficiency, Wilson's disease, auto-immune hepatitis, Rey's syndrome, sepsis, Budd-Chiari syndrome, or HELLP syndrome, also seemed very unlikely.

One of the causes of acute liver injury in the presented patient could be the exacerbation of right ventricular heart failure. The occurrence of liver injury caused by cardiac disorders in the absence of other known causes is called cardiac hepatopathy, which is usually the effect of passive venous congestion [29]. Acute cardiogenic liver injury (ACLI), also called 'ischemic/hypoxic hepatitis', is most commonly associated with acute cardiocirculatory failure resulting from acute cardiac conditions. There are different possible mechanisms responsible for hypoxic hepatitis, e.g. cellular damage caused by hypoxia induced by hypoperfusion, or hepatic congestion due to heart failure [30, 31]. However, it should be borne in mind that this cause-and-effect relationship is not very obvious or commonplace. A large study confirmed the relationship between acute liver failure and ischemic hepatitis in only 4.4% of cases [32]. It is worth noting, however, that in isolated liver injury, the activity of alanine transaminase would probably increase more than that of aspartate transaminase, which is more typical for liver cells. AST is also produced by cardiomyocytes and skeletal muscles.

All this led to the suspicion that such acute deterioration in liver function was related to the developing COVID-19. On the day of admission to the Clinic, the patient had several tests for COVID-19, which turned out to be negative. Only the test taken on the day of rapid clinical deterioration was positive.

Although respiratory symptoms are the most common in the course of COVID-19 infection, the complicated course of this disease may also lead to impairment of the functions of other organs. Among gastrointestinal symptoms, nausea, vomiting and diarrhoea were the most common during COVID-19 infection [33]; however, many reports also discuss the impact of SARS-CoV2 on many different types of liver dysfunction [34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46].

The abnormality found most often among liver function tests was hypoalbuminemia, followed by the increasing activity of aminotransferases [47]. Fan et al. reported that nearly 40% of patients admitted to hospital due to COVID-19 had abnormal liver function laboratory test results, with the following the percentages: lactate dehydrogenase (LDH) – 35.1%, AST – 21.6%, ALT – 18.2%, gamma glutamyl transpeptidase (GGTP) – 17.6%, total bilirubin (TB) – 6.1%, and alkaline phosphatase (ALP) – 4.1% [48]. Together with the albumin level, the results of the above-mentioned laboratory tests can be used as the biochemical indicators of liver injury in the course of COVID-19, and on the other

hand, abnormalities in liver function tests can be used as predictors of the severity of COVID-19 [4].

The SARS-CoV2 virus enters liver cells through angiotensin-converting enzyme-2 receptors (ACE2) [49, 50, 51, 52] located in many tissues and liver cells—hepatocytes and cholangiocytes [52]. Chai et al. proved that the expression of ACE2 receptors, compared to hepatocytes, is much higher in cholangiocytes, which play an important role not only in bile production, but also in the immune response and liver regeneration [53]. Liver damage in the course of COVID-19 is classified into 3 main sub-types: hepatocellular, cholestatic and mixed [54]. Potential mechanisms of action of SARS-CoV-2 leading to liver damage include direct cytotoxicity [55, 56, 57], activation of the immune system in the course of viral infection, systemic inflammatory response syndrome (SIRS) and cytokine storm [55, 56], damage associated with hypoxia in the course of respiratory failure [56], congestion caused by right ventricular failure, and exacerbation of coexisting liver disease [57, 58, 59]. Biopsies of liver in patients with COVID-19 revealed the presence of microthrombi and haemophagocytes [60], which may suggest that ischemia and hypoxia developing in critically ill patients can be one of the main mechanisms leading to liver damage [34].

In laboratory tests of serum taken from the presented patient, an increased concentration of interleukin-6 (IL-6) was noted. It is now known that the increased concentration of this cytokine correlates with higher liver enzyme activity [61]. It is very likely that in this patient, acute liver damage in the course of coronavirus infection coincided with injury to this organ in the course of heart failure. We do not believe that the patient died of acute liver injury, or at least that was not the only cause of her death. It is most likely that the direct cause of death was increasing respiratory failure due to COVID-19. The example of the patient in this case report confirms previous observations that COVID-19 is a disease that can damage many organs or entire systems.

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