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# Thirteen-Year Follow-Up of a Patient with Liver Cirrhosis Resulting from the Overlap Syndrome of Autoimmune Hepatitis and Primary Biliary Cholangitis: Severe COVID-19 and Liver Transplantation

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**Aim:** to present the difficulties of long-term management of a patient with liver cirrhosis in the outcome of overlap syndrome (autoimmune hepatitis and primary biliary cholangitis) who suffered from severe COVID-19 infection.
**Key points.** The diagnosis of liver cirrhosis as an outcome of overlap syndrome (autoimmune hepatitis and primary biliary cholangitis) was established at the patient's age of 33 years. At the age of 40, the patient became pregnant for the first time, the pregnancy proceeded well, and a cesarean section was performed at 36 weeks. At the age of 45, the patient suffered a severe new coronavirus infection, followed by decompensation of liver cirrhosis, which required liver transplantation 4 months after COVID-19, followed by a favorable postoperative course.
**Conclusion.** This clinical case demonstrates the successful onset and outcome of pregnancy in a patient with liver cirrhosis in the outcome of overlap syndrome (autoimmune hepatitis and primary biliary cholangitis). The pronounced activity of the disease after severe new coronavirus infection required liver transplantation with successful outcome.
**Keywords:** autoimmune liver diseases, overlap syndrome, autoimmune hepatitis, primary biliary cholangitis, pregnancy in autoimmune liver diseases, liver transplantation, COVID-19
**Conflict of interest:** the authors declare that there is no conflict of interest.

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## Тринадцатилетнее наблюдение за пациенткой с циррозом печени в исходе синдрома перекреста аутоиммунного гепатита и первичного билиарного холангита: тяжелый COVID-19 и трансплантация печени

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**Цель:** представить сложности длительного ведения пациентки с циррозом печени в исходе синдрома перекреста аутоиммунного гепатита (АИГ) и первичного билиарного холангита (ПБХ), перенесшей тяжелую инфекцию COVID-19.

**Основные положения.** Диагноз цирроза печени в исходе перекреста АИГ и ПБХ был установлен в возрасте 33 лет. В возрасте 40 лет пациентка впервые забеременела, беременность протекала благополучно, на 36-й неделе выполнено кесарево сечение. В возрасте 45 лет пациентка перенесла новую коронавирусную инфекцию тяжелого течения с последующей декомпенсацией цирроза печени, что через 4 месяца после COVID-19 потребовало трансплантации печени с последующим благоприятным постоперационным течением.
**Заключение.** Клинический случай демонстрирует успешное наступление и исход беременности у пациентки с циррозом печени в исходе синдрома перекреста ПБХ и АИГ. Выраженная активность заболевания после перенесенной новой коронавирусной инфекции привела к трансплантации печени, которая прошла успешно.
**Ключевые слова:** аутоиммунные заболевания печени, синдром перекреста, аутоиммунный гепатит, первичный билиарный холангит, беременность при аутоиммунных заболеваниях печени, трансплантация печени, COVID-19
**Конфликт интересов:** авторы заявляют об отсутствии конфликта интересов.

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Autoimmune liver diseases are chronic diffuse liver diseases characterized by progressive liver disease and the possible development of serious complications. Autoimmune liver diseases include autoimmune hepatitis (AIH), cholestatic diseases: primary biliary cholangitis (PBC) and primary sclerosing cholangitis. In gastroenterology, the combination of AIH and cholestatic liver disease is commonly referred to as overlap syndrome [1–4].

It is known that autoimmune liver diseases can severely worsen the course of a new coronavirus infection [5]. The most vulnerable to the SARS-CoV-2 virus (risk groups) are patients with liver cirrhosis (especially decompensated), with decompensated (progressive) chronic diffuse liver diseases, with autoimmune liver diseases (especially those receiving immunosuppressive therapy), after liver transplantation, with hepatocellular carcinoma, with non-alcoholic fatty liver disease [6–8]. Although the primary clinical manifestations are associated with pulmonary involvement, it is now recognized that COVID-19 is a systemic disease associated with an unpredictable immune response of the human body, leading to activation of the blood coagulation system, multiple organ failure and death [9–11]. It is known that in patients with concomitant chronic parenchymal liver disease, in particular decompensated by liver cirrhosis, COVID-19 infection can be associated with a higher risk of death [12–16] — mortality reaches more than 30 % [8].

Here is a clinical example of a 13-year follow-up of a female patient with a verified diagnosis of AIH/PBC, pregnancy and delivery with a favorable outcome, who suffered a severe course of COVID-19 infection and subsequent liver transplantation.

## Clinical observation

Patient L., born in 1976, 46 years old.

The first complaints appeared in 2008 at the age of 32: weakness, rapid fatigue, periodic skin itching. The surrounding people noted the darkening of the skin. A year later (2009) after the first complaints appeared, the woman was hospitalized in the gastroenterological department of the Republican Clinical Hospital of the Ministry of Health of the Republic of Tatarstan (Republican Clinical Hospital), where the diagnosis was first established: liver cirrhosis in the outcome of the overlap syndrome (stage 4 PBC and AIH), Child — Pugh class B, minimal activity. The MELD index — 16. Laboratory tests showed the following: alanine aminotransferase — 185 U/L, aspartate aminotransferase — 156 U/L, alkaline phosphatase — 538 U/L, gamma-glutamyl transpeptidase — 663 U/L, cholesterol — 7.18 mmol/L, total bilirubin — 59 mmol/L, direct bilirubin — 55.8 mmol/L, albumin — 31 %, gamma globulins — 25 %, anti-mitochondrial (AMA) and anti-nuclear (ANA) antibodies are positive. Taking into account the history and laboratory changes, the presence of AIH was indicated by the absence of acute viral infection (negative markers of viral hepatitis), the absence of a history of blood transfusions, use of hepatotoxic drugs and alcohol abuse, the presence of elevated levels of gamma globulins, significantly increased activity of alanine aminotransferase and aspartate aminotransferase, positive autoantibodies (ANA). According to ultrasound of the abdominal organs: the size of the liver is increased. The lower edge of the liver has a rounded shape. The external contours of the organ are uneven. The structure of the liver is heterogeneous due to the presence of regeneration nodes. The echostructure of the liver is

elevated. The echogenicity of the liver is reduced. Splenomegalia. Portal vein — 14 mm, splenic vein — 10 mm. According to the upper endoscopy varicose veins of the esophagus were not detected. Steroids and UDCA therapy were prescribed with positive dynamics. The patient was under constant supervision and treatment.

In 2017, at the age of 40, the patient became pregnant for the first time, pregnancy proceeded satisfactorily. At the 36th week of pregnancy the patient underwent a cesarean section, the child corresponded to the gestational term. After childbirth until 2021, the patient did not go to the gastroenterologist, took steroids and UDCA in a maintenance dose.

In August 2021, the patient admitted to the gastroenterology department of the Republic Clinical Hospital for routine examination and, if necessary, correction of therapy. Laboratory tests the following: alanine aminotransferase — 71 U/L, aspartate aminotransferase — 78 U/L, alkaline phosphatase — 293 U/L, gamma-glutamyl transpeptidase — 216 U/L, cholesterol — 5.6 mmol/L, total bilirubin — 85.9 mmol/L, direct bilirubin — 51.4 mmol/L, total protein — 65 g/L, albumin — 32 %. Endoscopy revealed grade 1 varicose veins of the esophagus (first identified in 2015). Given persistent cytolysis, esophageal varices and a MELD score of 18, the patient was placed on the waiting list for liver transplantation.

In October 2021, the patient developed febrile fever up to 39 °C. She was treated symptomatically on her own. On the 10th day of illness, with suspicion of a new coronavirus infection, the patient contacted the Republican Clinical Infectious Diseases Hospital named after A.F. Agafonov, as the high temperature persisted, shortness of breath appeared with little physical activity and a feeling of congestion in the chest.

On admission: body temperature — 38.5 °C, saturation — 86 %, respiratory rate — 22/min, blood pressure — 102/61 mmHg, heart rate and pulse — 86 beats/min. Height — 163 cm, body weight — 54 kg, body mass index — 20.3 kg/m$^2$. Skin: darkening of the skin, dry skin, reduced turgor, with scratching on the back, chest, shoulders. Pronounced icterus of the sclera and visible mucous membranes. There was no peripheral edema. The breathing in the lungs was harsh, no wheezing. Heart sounds were rhythmic and muffled. The abdomen was soft, not tense, participated in the act of breathing, and was painless. The liver was enlarged — protruded 2 cm from under the edge of the costal arch. The spleen was not palpable. PCR swab for the COVID-19 pathogen — positive. According to computed tomography (CT) of the chest, there are signs of bilateral polysegmental pneumonia. In both lungs, areas of infiltration, zonal, linear compaction of the "frosted glass" type were determined. The degree of lung damage is CT-2 (damage to the lung parenchyma up to 40–45 %).

Diagnosis: New coronavirus infection (virus identified) severe: bilateral polysegmental pneumonia, respiratory failure of the 2nd degree, CT-2. Liver cirrhosis as a result of stage 4 PBC overlap syndrome and AIH, Child — Pugh class B, minimal activity. Varicose veins of the esophagus of the 1st degree. Portal gastropathy. Autoimmune thyroiditis. Euthyroidism. Cysts of the right kidney. Urolithiasis, right kidney stone.

On the day of admission, the patient was prescribed respiratory support with low-flow oxygen up to 7 L/min, interleukin-6 blocker olokizumab 192 mg, dexamethasone 20 mg/day, enoxaparin, and therapy for liver cirrhosis. On the 12th day of illness (October 23, 2021), due to the increasing severity of respiratory failure, which required increased respiratory support, with persistent low-grade fever, an increase in the level of C-reactive protein (up to 70 mg/mL) and bilirubin, the patient was transferred to temporary Infectious Diseases Hospital of the Republican Clinical Hospital. According to the CT results (October 23, 2021), negative dynamics were observed: CT signs of viral pneumonia (CT-3), the volume of the lesion on the right — 70 %, on the left — 60 % (Fig. 1).

The patient was transferred to non-invasive artificial ventilation, the interleukin-6 blocker levilimab was administered at a dose of 324 mg intravenously, and therapy with dexamethasone 24 mg, enoxaparin, and pathogenetic therapy for liver cirrhosis was continued. A day later, the patient experienced stable normothermia, respiratory function stabilized, the level of C-reactive protein normalized (4.8 mg/L), and the level of lymphocytes rose to 9.5 %. Subsequently, during therapy, the respiratory function was completely restored, the body temperature did not increase, and the patient was discharged under the supervision of doctors at the place of residence, despite the deterioration of some indicators of the liver condition. Table 1 shows the results of the patient's blood tests during her stay in the temporary infectious diseases hospital of the Republican Clinical Hospital.

During November 2021 — February 2022, there was a gradual deterioration in the patient's condition, which required her hospitalization in the gastroenterology department of the Russian Clinical Hospital on February 25, 2022. Upon admission, she complained of severe weakness, drowsiness, lethargy, increasing jaundice of the

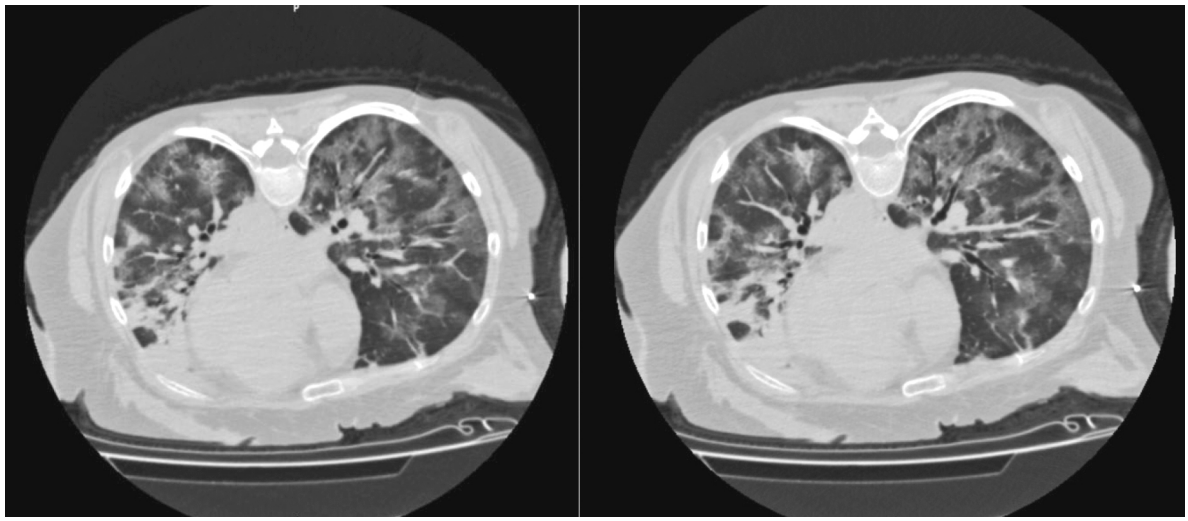

***Figure 1.*** Computed tomography of the lungs of Patient L. (October 23, 2021, 12th day of illness)

***Рисунок 1.*** Компьютерная томография легких пациентки Л. (23.10.2021 г., 12-й день болезни)

***Table 1.*** Dynamics of laboratory parameters of Patient L. during COVID-19 infection
***Таблица 1.*** Динамика лабораторных показателей пациентки Л. во время инфекции COVID-19

| **Parameter** ***Показатель*** | **October 23, 2021** ***23.10.2021 г.*** | **October 25, 2021** ***25.10.2021 г.*** | **November 7, 2021** ***07.11.2021 г.*** | **Norm** ***Норма*** |
|---|---|---|---|---|
| Leukocytes ($\times 10^9$/L) *Лейкоциты ($\times 10^9$/л)* | 2.5 | 2.9 | 6.5 | 4–9 |
| Hemoglobin, g/L *Гемоглобин, г/л* | 86 | 84 | 111 | 120–140 |
| Platelets, ($\times 10^9$/L) *Тромбоциты ($\times 10^9$/л)* | 86 | 94 | 72 | 180–400 |
| Lymphocytes, % *Лимфоциты, %* | 4.3 | 9.5 | 9.5 | 18–40 |
| Lymphocytes, ($\times 10^9$/L) *Лимфоциты ($\times 10^9$/л)* | 0.11 | 0.3 | – | 1–4.8 |
| Lactate dehydrogenase, U/L *Лактатдегидрогеназа, Ед./л* | – | 652.64 | – | 55–155 |
| ALT, U/L *АЛТ, Ед./л* | 58 | 97 | 204.4 | < 40 |
| AST, U/L *АСТ, Ед./л* | 104.3 | 130.4 | 97 | < 40 |
| Total protein, g/L *Белок общий, г/л* | – | – | 59.9 | 64–83 |
| Total bilirubin, μmol/L *Общий билирубин, мкмоль/л* | 76.7 | 68 | 118.3 | 3.5–21 |
| C reactive protein, mg/L *С-реактивный белок, мг/л* | 75 | 21.2 | 1.9 | < 5 |
| Quick's value, % *Протромбин по Квику, %* | 67 | 64.2 | 81 | 78–142 |
| Albumin, % *Альбумин, %* | 30 | 29 | 29 | 35–50 |

***Note:*** ALT — alanine aminotransferase; AST — aspartate aminotransferase.
***Примечание:*** АЛТ — аланинаминотрансфераза; АСТ — аспартатаминотрансфераза.

***Table 2.*** Dynamics of laboratory parameters of Patient L. before liver transplantation
***Таблица 2.*** Динамика лабораторных показателей пациентки Л. перед трансплантацией печени

| **Parameter** ***Показатель*** | **February 28, 2022** ***28.02.2022 г.*** | **March 2, 2022** ***02.03.2022 г.*** | **March 3, 2022** ***03.03.2022 г.*** | **Norm** ***Норма*** |
|---|---|---|---|---|
| ALT, U/L *АЛТ, Ед./л* | 371.5 | 290.6 | 230 | < 40 |
| AST, U/L *АСТ, Ед./л* | 270.2 | 140.5 | 104.5 | < 40 |
| Alkaline phosphatase, U/L *Щелочная фосфатаза, Ед./л* | 488.8 | 382.5 | 345 | 35–105 |
| GGTP, U/L *ГГТП, Ед./л* | 328 | 235.3 | 201 | 6–42 |
| Total bilirubin, μmol/L *Общий билирубин, мкмоль/л* | 340 | 396.7 | 216.8 | 3.5–21 |
| Creatinine, U/L *Креатинин, Ед./л* | 44 | 55 | 20 | 44–80 |
| Urea, mmol/L *Мочевина, ммоль/л* | 3.6 | 3.3 | 3.1 | 2.6–6.7 |
| Total protein, g/L *Белок общий, г/л* | 43.9 | 33.6 | 33 | 64–83 |

***Note:*** ALT — alanine aminotransferase; AST — aspartate aminotransferase; GGTP — gamma-glutamyl transpeptidase.
***Примечание:*** АЛТ — аланинаминотрансфераза; АСТ — аспартатаминотрансфераза; ГГТП — гамма-глутамилтранспептидаза.

skin and sclera, decreased appetite, and weight loss of 5 kg in 2 months. Objectively: upon admission, the condition was of moderate severity, inhibited. Due to severe weakness, the patient was admitted in a wheelchair. The skin and visible mucous membranes were icteric in color, dry, and there were scratches. Peripheral lymph nodes were not enlarged. Auscultation: breathing is harsh, no wheezing, respiratory rate — 18/min, heart sounds were rhythmic and clear, blood pressure was 104/70 mmHg, pulse — 68/min. When palpated, the abdomen was soft, painless, and participated in the act of breathing. The liver was compacted, Kurlov dimensions — 10, 9 and 8 cm. The spleen was not enlarged in size.

In the analyzes over time from November 2021, an increase in changes in the biochemical blood test was noted (Table 2).

To the therapy with methylprednisolone 6 mg in the morning, ursodeoxycholic acid 750 mg per

***Figure 2.*** Removed liver

***Рисунок 2.*** Удаленная печень

day, omeprazole 20 mg in the morning, L-ornithine aspartate was added intravenously daily. The patient was in the department and was first on the waiting list for liver transplantation.

On March 3, 2022, orthotopic liver transplantation was performed. The duration of the operation was 7 hours 35 minutes. An upper-median laparotomy was performed with extension to the right to the 12th rib. The liver was mobilized. The right and left hepatic arteries were isolated and crossed at the level of the lobar branches. The hepaticocholedochus was isolated and crossed at the porta hepatis. Hepatectomy was performed with preservation of the retrohepatic portion of the inferior vena cava. The donor liver was implanted, and vein anastomoses were subsequently formed. Arterial and biliary reconstruction was carried out sequentially. Figure 2 shows the lower surface of the explant with the gallbladder. The consistency of the liver was dense, the surface of the organ was uneven and lumpy. The sizes of regenerated nodes varied from 3 to 10 mm. Between the regenerated nodes there were layers of dense grayish tissue. Macroscopic picture of mono-multibular cirrhosis of the liver. Histological examination revealed portal cirrhosis of the liver.

The postoperative period proceeded without complications. The results of laboratory tests are presented in Table 3.

Diagnosis upon discharge from the surgical department: condition after orthotopic liver transplantation (March 3, 2022) for liver cirrhosis as a result of overlap syndrome (stage 4 PBC and AIH), antibodies to ANA, AMA — positive, Child — Pugh class C, minimal activity. MELD-Na score — 28.8 points (2nd degree esophageal varicose veins, splenomegaly). Normochromic anemia of mild severity. Autoimmune thyroiditis. Euthyroidism. Cysts of the right kidney. Urolithiasis (right kidney stone 6 mm). Hepatic encephalopathy with cognitive impairment. Polyneuropathy (during tacrolimus therapy) in the form of flaccid lower paraparesis. The patient was recommended: observation by a therapist at her place of residence, a gastroenterologist at the Republican Clinical Hospital. Tacrolimus extended-release capsules 10 mg once daily for a week, followed by possible adjustment of immunosuppressive therapy (target tacrolimus concentration in venous blood — 8–12 ng/mL), Mycophenolate mofetil 500 mg twice daily. Prednisolone tablets 5 mg, 4 tablets (20 mg) in the morning after meals, with a dose reduction of 1 tablet per week until completely canceled. Valganciclovir 450 mg once daily for 3 months.

***Table 3.*** Dynamics of laboratory tests of Patient L. after liver transplantation
***Таблица 3.*** Динамика лабораторных исследований пациентки Л. после проведенной трансплантации печени

| **Parameter** ***Показатель*** | **April 1, 2022** ***01.04.2022 г.*** | **April 4, 2022** ***04.04.2022 г.*** | **April 11, 2022** ***11.04.2022 г.*** | **April 15, 2022** ***15.04.2022 г.*** | **9 months after transplantation** ***9 мес. после исплантации*** | **Norm** ***Норма*** |
|---|---|---|---|---|---|---|
| ALT, U/L *АЛТ, Ед./л* | 31.9 | 22.0 | 14.0 | 23.8 | 7 | < 40 |
| AST, U/L *АСТ, Ед./л* | 27.2 | 8.0 | 13.0 | 17.1 | 14 | < 40 |
| Alkaline phosphatase, U/L *Щелочная фосфатаза, Ед./л* | 399.4 | 290.0 | 172.0 | 118.3 | 85 | 35–105 |
| GGTP, U/L *ГГТП, Ед./л* | 102 | 67 | 42 | 43 | 14 | 6–42 |
| Total bilirubin, μmol/L *Общий билирубин, мкмоль/л* | 14.40 | 14.40 | 10.20 | 8.2 | 8.3 | 3.5–21 |
| Creatinine, U/L *Креатинин, Ед./л* | 49.3 | 49.0 | 50.0 | 49 | 88 | 44–80 |
| Urea, mmol/L *Мочевина, ммоль/л* | 1.9 | 0.8 | 2.7 | 4.3 | 3.6 | 2.6–6.7 |
| Potassium, mmol/L *Калий, ммоль/л* | 3.39 | 3.60 | 4.30 | 4.11 | 3.78 | 3.4–5.4 |
| Total protein, g/L Б*елок общий, г/л* | 49.30 | 50.30 | 56.90 | 60.1 | 70 | 64–83 |
| Sodium, mmol/L *Натрий, ммоль/л* | 136 | 148 | 147 | 141 | 142 | 130–156 |

***Note:*** ALT — alanine aminotransferase; AST — aspartate aminotransferase; GGTP — gamma-glutamyl transpeptidase.
***Примечание:*** АЛТ — аланинаминотрансфераза; АСТ — аспартатаминотрансфераза; ГГТП — гамма-глутамилтранспептидаза.

After liver transplantation the patient notes positive dynamics: improvement of well-being, good mood, absence of weakness and itching. The patient has more energy for her family, time for a new hobby, and she plans to go back to work in the near future. Monthly controls the level of tacrolimus — range from 5.1 to 5.4 ng/mL.

## Discussion

Management of patients with autoimmune liver diseases during the SARS-CoV-2 pandemic is challenging. The liver is one of the targets of COVID-19 infection and the mechanism of liver damage is multifactorial [17, 18]. COVID-19 infection is known to impair liver function even in individuals without pre-existing organ damage, which represents a poor prognosis factor in previously healthy patients [18].

One of the predictors of an unfavorable course of COVID-19 is liver cirrhosis. SARS-CoV-2 has direct hepatotoxicity and enters the liver through cholangiocytes or through translocation from the intestine. Liver cells with cirrhosis express more receptors for SARS-CoV-2 than normal liver cells [19]. These receptors are expressed in large quantities in hepatocyte precursor cells, which in turn are responsible for liver regeneration in cirrhosis [20]. SARS-CoV-2 may cause indirect liver damage through systemic inflammation with immune dysregulation, hypoxia due to respiratory failure, ischemic injury due to coagulopathy or endotheliitis, right ventricular failure due to myocarditis, and worsening of pre-existing liver disease or drug-induced liver damage [17].

It is worth noting that patients with AIH needed hospitalization more often than patients without liver disease. But there was no increase in the risk of transfer to the intensive care unit or an increase in the number of deaths. The age and initial severity of liver disease were independent risk factors for death in patients with AIH, but not immunosuppressive therapy [21].

There is insufficient information in the literature about the features of liver transplantation during the COVID-19 pandemic. It is necessary to consider the presence or duration of COVID-19 in both donors and recipients. A.V. Kulkarni et al. described the experience of early liver transplantation 2 and 4 weeks after COVID-19 infection, which was due to worsening liver disease. In both options, donors and recipients before transplantation were required to have 2 negative smear results for COVID-19 using the PCR method with an interval of 3 days between them [22]. The International Society for Heart and Lung Transplantation recommends waiting at least 14 days after the initial diagnosis of COVID-19 and two negative swabs for COVID-19 with an interval of 48 hours before transplantation [23].

## Conclusion

The presented clinical observation shows the course of overlap syndrome in a patient whose disease began at a young, working age. At the time of diagnosis, she had a detailed clinical and laboratory-instrumental picture at the stage of cirrhosis in the outcome of AIH/PBC.

Against the background of therapy, almost constant disease activity, and the presence of stage 1 varicose vein disease, the patient, aged 40 years, was able to become pregnant, carry and give birth to a child. In the fall of 2021, the patient suffered from severe COVID-19. Against the background of the underlying chronic disease, the course of COVID-19 was severe and long-lasting. The experience of COVID-19 led to decompensation of cirrhosis within two months, and the patient underwent orthotopic liver transplantation. Recovery after the operation was without complications, with positive clinical and laboratory dynamics.

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