

Hepatic transplant during SARS-CoV-2 (COVID-19) pandemic. A literature review

Trasplante hepático durante la pandemia del SARS-CoV-2 (COVID-19). Revisión de la literatura

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Abstract

Background: In December 2019, a new beta coronavirus, SARS-CoV-2, was identified in the city of Wuhan, China, as a causative agent of severe pneumonia, known as COVID-19, which has led to strict isolation measures, closure of liver transplantation programs and the need to modify treatment protocols. **Objective:** Document the information published so far on the impact of COVID-19 in the population with a history of liver transplantation and establish a treatment protocol. **Method:** MeSH terms were searched for "SARS-CoV-2", "COVID-19", "liver transplantation" and "treatment". **Results:** Up to now, a greater ease in acquiring the virus has been shown in the liver transplant population, without a difference in mortality when compared to the general population. Immunosuppression should continue at the minimum tolerated levels, without suspending calcineurin inhibitors. Of the specific treatment, steroids are those that have shown the greatest clinical benefit and decreased mortality. **Conclusion:** Liver transplantation is not independently associated with higher mortality. Factors other than transplantation must be taken into account when considering the risk of severity.

Keywords: COVID-19. Liver transplant. Treatment.

Resumen

Antecedentes: En diciembre de 2019 se identificó en la ciudad de Wuhan, China, un nuevo beta coronavirus, el SARS-CoV-2, como agente causal de neumonía grave, conocida como COVID-19, lo cual ha provocado medidas estrictas de aislamiento, cierre de programas de trasplante hepático y la necesidad de modificar los protocolos de tratamiento. **Objetivo:** Documentar la información publicada sobre el impacto de la COVID-19 en la población con antecedente de trasplante hepático y establecer un protocolo de tratamiento. **Método:** Se buscaron en PubMed los términos MeSH "SARS-CoV-2", "COVID-19", "trasplante hepático" y "tratamiento". **Resultados:** Hasta el momento se ha demostrado en la población con trasplante hepático una

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mayor facilidad para adquirir el virus, sin una diferencia en la mortalidad al compararla con la población general. La inmunosupresión debe continuar, sin suspender los inhibidores de la calcineurina. Del tratamiento específico, los esteroides son los que han demostrado el mayor beneficio clínico y una disminución de la mortalidad. **Conclusión:** El trasplante hepático no se asocia de manera independiente a una mayor mortalidad. Otros factores, además del trasplante, deben tomarse en cuenta al momento de establecer la gravedad.

Palabras clave: COVID-19. Trasplante hepático. Tratamiento.

Introduction

The group of coronaviruses belongs to the Coronaviridae family, of the Nidovirales order, which are viruses made up of an RNA structure. There are two subfamilies that infect the human being: alpha and beta¹. The alpha subfamily infects the upper airways and causes mild symptoms, while beta viruses, such as SARS-CoV and MERS-CoV, are highly pathogenic and capable of causing severe acute respiratory syndrome (SARS)². In December 2019, in Wuhan, Hubei, China, a new beta coronavirus, SARS-CoV-2, was identified, which was associated with an outbreak of severe pneumonia that the World Health Organization (WHO) later named Coronavirus Disease 2019 (COVID-19)³.

COVID-19 clinical spectrum can range from mild, defined by the WHO as absence of pneumonia or hypoxia, to severe, when it occurs as pneumonia with hypoxemia, which sometimes can progress to acute respiratory distress syndrome⁴⁻⁶.

Since the pandemic onset, a frequently questioned topic has been the role of immunosuppression in transplant recipient patients with regard to the influence on COVID-19 severity or outcome^{7,8}. One study demonstrated that patients with chronic immunosuppression due to transplantation have a higher probability of acquiring the virus, but lower likelihood to develop severe disease⁹. The purpose of this work is to review so far existing evidence on liver transplantation during the COVID-19 pandemic, taking into account the effect of immunosuppression on the course of the disease, its adjustment in case of acquiring the infection, the protocol to be followed for patients on the waiting list and transplant program reactivation in the near future.

Method

A search was carried out in PubMed using the following MeSH terms: "SARS-CoV-2", "COVID-19", "trasplante hepático" (liver transplant) and "tratamiento"

(treatment) and, subsequently, the articles considered to be the most relevant from January to August 2020 were identified and selected. No data analysis of any kind was performed.

Management of immunosuppression in liver transplant recipients

Liver transplant recipient population is generally considered to be at high risk for the development of serious infectious diseases, due to immunosuppressant drugs chronic use, either monoclonal antibodies such as basiliximab, or steroids and anti-proliferative drugs such as mycophenolate mofetil and calcineurin inhibitors; all this, depending on the time elapsed since transplantation and the necessary degree of immunosuppression^{5,10}. Initially, prophylactic immunosuppression reduction is not recommended in asymptomatic patients. This may increase the risk of graft rejection and not necessarily translate into less severity should they contract COVID-19¹¹. Currently, data on COVID-19 in transplant recipients is scarce, but prolonged immunosuppression is known to increase vulnerability for acquiring the disease, and leads to having a high viral load at diagnosis, as well as to a higher probability of fatal outcomes¹². This contrasts with the impossibility for immunosuppression to be discontinued due to the risk of graft rejection^{5,8,13}. In a study of a multicenter cohort of 151 liver transplant recipients infected with COVID-19, who were compared with 627 patients who were also infected but had no transplant history, the main outcome measure, mortality, was not different between both groups, but on multivariate logistic regression analysis, a mortality increase was identified in the group of transplant recipients as age increased (odds ratio [OR]: 1.6 for each year), and the same was observed with creatinine increase (OR: 1.57 for each 1 mg/dL) and with the presence of non-liver cancer (OR: 18.3). Other adverse findings in liver transplant recipients were a higher number of admissions to intensive care units and higher need for invasive mechanical ventilation¹⁴.

Taking into account the studies published so far, case reports and the experience of each center, COVID-19 behavior and prognosis in the population with liver transplantation are observed to be similar to those of the general population^{15,16}. In case of acquiring COVID-19 and having a history of liver transplantation, the recommendations will depend on the severity of the infection clinical presentation. The first suggested change is to reduce or discontinue mycophenolate mofetil and keep only calcineurin inhibitors at the lowest possible doses. In patients who receive prednisone on a chronic basis, it should be continued at the pre-admission dose, orally or at its intravenous equivalent, while assessing the risk of secondary adrenal insufficiency and, if necessary, starting stress doses with steroids that have mineralocorticoid effect¹¹. Regardless of immunosuppression management, it is important to know that 14-53% of patients with COVID-19 may develop liver chemistry anomalies, especially with a hepatocellular pattern. Elevation is usually transient, less than five times the upper limit of normal and self-limiting. This does not contraindicate implementation of specific experimental treatments for the virus¹⁷, but it does require frequent monitoring of liver chemistry and watching for potential drug interactions, particularly with calcineurin inhibitors and mammalian target of rapamycin (m-TOR) inhibitors¹¹.

COVID-19 treatment in liver transplant recipients

GENERAL MEASURES

The WHO recommends for patients with mild COVID-19 to be isolated and receive only symptomatic and supportive treatment, without prophylactic antibiotics being prescribed, and the same for patients with moderate disease, but in them with close surveillance. For patients with severe disease, it is recommended to hospitalize and monitor them continuously, administer them supplemental oxygen and prophylactic, intermediate or therapeutic anticoagulation, as required, and to start prophylactic antibiotics, daily de-escalating or escalating according to evolution and culture results⁴.

As for specific treatment, there are many investigational drugs for the treatment of COVID-19, all with limited evidence, and the vast majority still regarded as experimental.

CORTICOSTEROIDS

Although the use of steroids for patients with severe COVID-19 was initially controversial, due to a virus clearance probable delay and hospital stay prolongation¹⁸, in severely ill patients, they are currently known to have an impact on 28-day mortality reduction. The recommended corticosteroid is dexamethasone at a dose of 6 mg/day for 10 days¹⁹, but its equivalent in methylprednisolone or hydrocortisone may be used²⁰.

REMDESIVIR

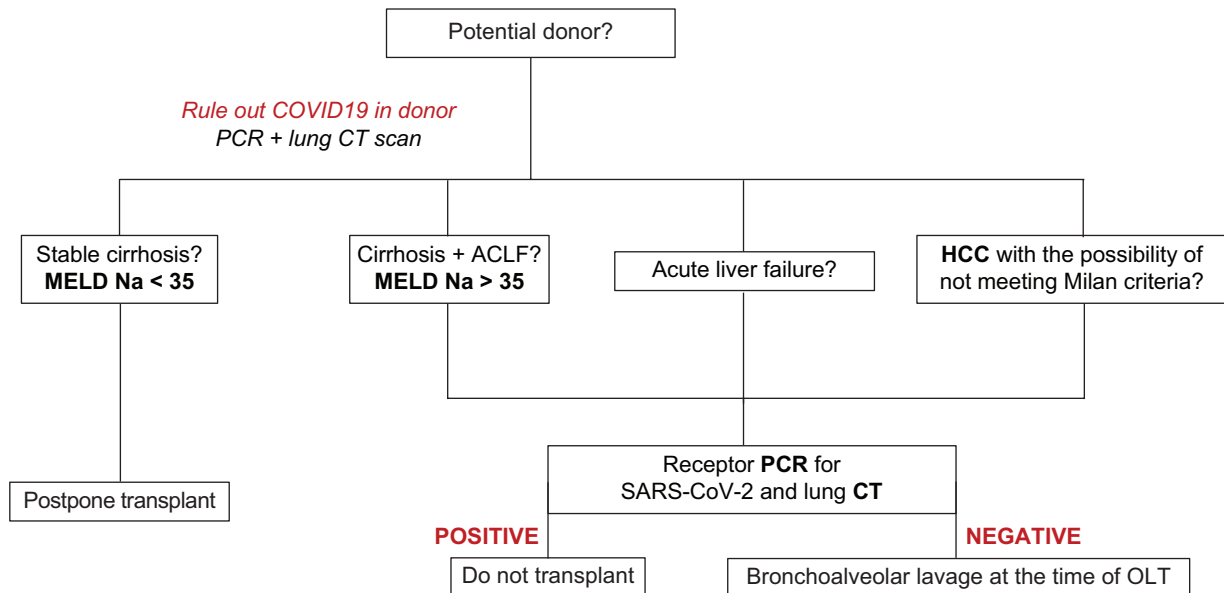
Remdesivir is a direct-acting antiviral, with in vitro inhibitory effect on SARS-CoV 1 and 2, as well as on MERS-CoV, RNA polymerase^{21,22}. Although it is not yet approved by the Food and Drug Administration (FDA) of the United States of America, there is an emergency use authorization for patients with severe COVID-19^{23,24}. In patients with liver disease or liver transplant recipients, liver chemistry should be daily monitored during remdesivir administration because it can raise transaminases, and if they do increase more than fivefold above their normal value, discontinuing the drug is recommended²⁵.

CONVALESCENT PLASMA

This type of treatment is not recommended by the WHO⁴. The Infectious Diseases Society of America only recommends it for patients with severe COVID-19 and who are included in a clinical trial. So far, there is only one controlled clinical trial that has shown probable clinical improvement in severely ill patients²⁶; case series have not demonstrated sufficient evidence for evaluating an effect on mortality²⁷.

HYDROXYCHLOROQUINE AND AZITHROMYCIN

The use of hydroxychloroquine or chloroquine has not been shown to reduce the risk of intubation or death in hospitalized patients²⁸, and neither the rate of viral load negativization²⁹. Association with azithromycin has not demonstrated to reduce mortality, but it has shown an increase in the risk of cardiac arrest secondary to QT prolongation³⁰, and the FDA has withdrawn the authorization for its use³¹.



Appendix: The donor should not have had respiratory symptoms for at least 14 days prior to death; the same criteria apply to the recipient prior to OLT

Figure 1. Liver transplant algorithm during the COVID-19 pandemic. The donor should not have had respiratory symptoms for at least 14 days prior to death; the same criteria apply to the recipient. ACLF: Acute-on-Chronic Liver Failure; CT, computed tomography; HCC: hepatocellular carcinoma; MELD Na: Model for End-Stage Liver Disease considering natremia; OLT: orthotopic liver transplantation; PCR: polymerase chain reaction.

TOCILIZUMAB

Tocilizumab is a monoclonal antibody that inhibits interleukin 6, which is one of the main mediators of the inflammation caused by COVID-19. By blocking this inflammatory cascade in patients with severe disease and persistent fever, it could reduce secondary organ damage, but the evidence so far is not conclusive and the reported studies are case series that, although in some of them an improvement in the radiological pattern has been shown, as well as a decrease in fever and inflammatory markers, and in the probability of requiring invasive mechanical ventilation³², no benefit in 14-day survival has been observed on other occasions³³.

Liver transplant during the COVID-19 pandemic

At this moment, most transplant centers in the world have closed their programs due to the COVID-19 pandemic³⁴. This implies the death of many patients on waiting list, follow-up loss of those already transplanted and, in the event programs are reopened, risk of contagion of health personnel and their close circle³⁵. We can anticipate that liver transplant recipients will

become infected, but little is known about SARS-CoV-2 transmission from donor to recipient and to medical personnel³⁶. The probability for the donor to be a potential source of transmission depends not only on exposure factors and incubation period (2-14 days), but also on viremia and viability of the virus in blood and in certain organs^{37,38}. During the 2002 SARS pandemic, cases of infection were identified in liver transplant recipients and surgical team members³⁹.

TRANSFUSION OF BLOOD PRODUCTS DURING TRANSPLANTATION

Coronavirus has not been found to be transmitted through blood products transfusion, but the FDA recommends not to receive transfusions from patients with respiratory symptoms, and the European Centre for Disease Prevention and Control recommends waiting 21 to 28 days to donate blood after having had contact with infected patients or having traveled to risky areas³⁷.

PATIENTS ON WAITING LIST

Given that the kinetics of the virus are unknown, and that there is the possibility of false-negative nasal

swab results⁴⁰, liver transplants should be limited to the most urgent cases (Model for End-stage Liver Disease [MELD] > 35, acute liver failure or hepatocellular carcinoma close to failing to meet the Milan criteria)⁴¹. All recipients should be screened for COVID-19, have a lung CT scan performed, and transplants will not be carried out in those who are infected. In case the donor has been at risk of exposure, but without having experienced respiratory symptoms or fever prior to death, his/her organs can be used as long as they are not the lungs or intestine³⁷ (Fig. 1).

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Ethical disclosures

Protection of people and animals. The authors declare that no experiments were performed on humans or animals for this research.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Conflicts of interest

There are no conflicts of interest involving the authors of this article.

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