Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

COVID-19 in long-term liver transplant patients: preliminary experience from an Italian transplant centre in Lombardy

Coronavirus disease 2019 (COVID-19) is a public health emergency and a pandemic of international concern.[1] Italy has witnessed, in the past month, an unexpectedly high rate of infection, with more than 100 000 patients testing positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and a case-fatality rate close to 10% (as of March 31, 2020)[2] and therefore faces a worse scenario than in China, where the disease was first reported.

Data on COVID-19 in liver transplant patients are scarce. We report the experience in our transplant centre, in the midst of the current outbreak in Lombardy, Italy (10 million inhabitants; 25 124 ascertained infections, and 7199 virus-related deaths as of March 31, 2020).[2] Three of our 111 long-term liver transplant survivors (transplanted more than 10 years ago) have died in the past 3 weeks (between March 5 and March 18) following severe COVID-19 disease. All three were male, older than 65 years, receiving antihypertensive drugs, overweight (BMI >28 kg/m^2), with hyperlipidaemia, and diabetes (median HbA_{1c} of 6·9%). The post-transplant course had been uneventful for all three patients, and their immunosuppressive regimen had been gradually tapered off, with very low trough concentrations of calcineurin inhibitors (two patients receiving ciclosporin [28 and 35 ng/mL, respectively] and one receiving tacrolimus [2·1 ng/mL]). All three patients died after admission to hospital for community-acquired pneumonia, and were in need of supplementary oxygen at admission but rapidly developed severe respiratory distress syndrome that required mechanical ventilation. The patients died between 3 and 12 days after the onset of pneumonia; all three patients had tested positive for SARS-CoV-2 by nasopharyngeal swabs. By contrast, three of our 40 recently transplanted (ie, within the past 2 years) patients have tested SARS-CoV-2 positive, and although quarantined, are all experiencing an uneventful course of disease.

Available data regarding COVID-19 suggest that tissue damage might be mediated by a direct virus-induced cytopathogenic effect or could be due to an immunomediated inflammatory response to the virus.[3] Whether liver transplant recipients are more susceptible to SARS-CoV-2 infection is a matter of concern, but so far there have been no specific recommendations from major societies. A case series from Italy showed that children who had received liver transplants, despite being immunosuppressed, were not at increased risk of severe pulmonary disease compared with the general population.[4]

All three COVID-19-related deaths observed in our centre were long-term patients on minimal immunosuppressive regimens, rather than recently transplanted, fully immunosuppressed patients. We examined clinical and demographic data of our patients (table). In keeping with the paediatric data,[4] immunosuppression did not seem to increase the risk of severe COVID-19 disease. Given that a reactive innate immune response might be responsible for severe clinical manifestations, immunosuppression might be protective, although this needs further clarification. Conversely, the presence of metabolic-related comorbidities, which are known to increase with time since transplant,[5] might be associated with an increased risk of severe COVID-19 disease. However, the number of COVID-19-related deaths in our series is small, and these observations can only be considered preliminary.

Post-transplant metabolic complications (eg, arterial hypertension, chronic renal insufficiency, diabetes, hyperlipidaemia, and weight gain) might outweigh immunosuppression as a risk factor for development of severe COVID-19 disease in patients who have received liver transplants, in line with data from China, which suggest that comorbidities are associated with a worse prognosis.[6] Of these metabolic complications, diabetes might be of particular concern, given its high prevalence (20–40%) in patients undergoing solid organ transplantation.[7]

Notably, a comparison of the 3% COVID-19-associated mortality observed in our long-term transplant

	Long-term liver transplant recipient (>10 years, n=111)	Short-term liver transplant recipient (<2 years, n=40)	p value
Age older than 65 years	55 (50%)	12 (30%)	0·04
Overweight or obesity (body mass index >25 kg/m^2)	89 (80%)	24 (60%)	0·02
Diabetes	67 (60%)	9 (23%)	0·0001
Hyperlipidaemia	50 (45%)	7 (18%)	0·002
Arterial hypertension	111 (100%)	27 (68%)	0·0001
History of cardiovascular event	39 (35%)	2 (5%)	0·0015
Chronic kidney disease	44 (40%)	8 (20%)	0·03
Full immunosuppression*	11 (10%)	28 (70%)	0·0001
COVID-19-related deaths	3 (3%)	0	0·57

COVID-19=coronavirus disease 2019. *Ciclosporin concentration more than 150 ng/mL or tacrolimus concentration more than 5 ng/mL.

***Table*: Characteristics of liver transplant recipients in Istituto Nazionale Tumori, Milan**

Lancet Gastroenterol Hepatol 2020

Published **Online** April 9, 2020 https://doi.org/10.1016/S2468-1253(20)30116-3

recipients with the 10% case-fatality rate noted in Italy at present is difficult, since the case-fatality rate is known to be biased because nasopharyngeal swabbing is only done in highly symptomatic patients.[8] This limitation also applies to our population of liver transplant recipients—the total number who could be SARS-CoV-2 positive (but who remain asymptomatic or who have only mild symptoms, and who have thus not been tested), is not known. Nonetheless, given the short observation period (3 weeks) which we report here, the observed death rate is of concern.

We recognise the intrinsic limitations of this case series (ie, the small sample size, the unavailability of the exact number of COVID-19 positive patients, and the associated difficulty in accurately calculating the case-fatality rate) and the consequent urgent need of collecting data for further studies to draw more solid conclusions. However, according to this initial observation, we suggest that great attention is paid to long-term liver transplant recipients with metabolic comorbidities. In keeping with clinical insights from the American Association for the Study of Liver Diseases we suggest that immunosuppression should not be reduced or stopped in asymptomatic liver transplant recipients.[9]

We declare no competing interests.

*Sherrie Bhoori, Roberta Elisa Rossi, Davide Citterio, *Vincenzo Mazzaferro*
vincenzo.mazzaferro@istitutotumori.mi.it

Department of Hepatology, Hepato Pancreatic Biliary Surgery and Liver Transplantation, Istituto Nazionale Tumori, Foundation IRCCS, 20133 Milan, Italy (SB, RER, DC, VM); and Department of Pathophysiology and Organ Transplant (RER) and Department of Oncology (VM), University of Milan, Milan, Italy

1 WHO. Coronavirus disease 2019 (COVID-19) situation report—50. 2020. https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200310-sitrep-50-covid-19.pdf?sfvrsn=55e904fb_2 (accessed April 2, 2020).

2 Ministry of Health. COVID-19, situation in Italy. 2020. http://www.salute.gov.it/portale/nuovocoronavirus/dettaglioContenutiNuovoCoronavirus.jsp?lingua=english&id=5367&area=nuovoCoronavirus&menu=vuoto (accessed April 2, 2020).

3 Xu L, Liu J, Lu M, Yang D, Zheng X. Liver injury during highly pathogenic human coronavirus infections. *Liver Int* 2020; published online March 14. DOI: 10·1111/liv.14435.

4 D'Antiga L. Coronaviruses and immunosuppressed patients. The facts during the third epidemic. *Liver Transpl* 2020; published online March 20; DOI:10·1002/lt.25756.

5 Barnard A, Konyn P, Saab S. Medical management of metabolic complications of liver transplant recipients. *Gastroenterol Hepatol (N Y)* 2016; **12:** 601–08.

6 Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020; published online Feb 28. DOI: 10·1056/NEJMoa2002032.

7 Jenssen T, Hartmann A. Post-transplant diabetes mellitus in patients with solid organ transplants. *Nat Rev Endocrinol* 2019; **15:** 172–88.

8 Rajgor DD, Lee MH, Archuleta S, Bagdasarian N, Quek SC. The many estimates of the COVID-19 case fatality rate. *Lancet Infect Dis* 2020; published online March 27; http://dx.doi.org/10·1016/S1473–3099(20)30244–9.

9 American Association for the Study of Liver Diseases. Clinical insights for hepatology and liver transplant providers during the COVID-19 pandemic. 2020. https://www.aasld.org/sites/default/files/2020-03/AASLD-COVID19-ClinicalInsights-3.23.2020-FINAL-v2.pdf (accessed April 3, 2020).