

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

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Coronavirus disease 2019 (COVID-19) is a public health emergency and a pandemic of international concern.<sup>1</sup> 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)<sup>2</sup> 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).<sup>2</sup> 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<sup>2</sup>), with hyperlipidaemia, and diabetes (median

HbA<sub>1c</sub> 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.<sup>3</sup> 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.<sup>4</sup>

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,<sup>4</sup> 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,<sup>5</sup> 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.<sup>6</sup> Of these metabolic complications, diabetes might be of particular concern, given its high prevalence (20–40%) in patients undergoing solid organ transplantation.<sup>7</sup>

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

	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 <sup>2</sup> )	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

symptomatic patients.<sup>8</sup> 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.<sup>9</sup>

We declare no competing interests.

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## SARS-CoV-2 in wastewater: potential health risk, but also data source

Since the first publications reporting the detection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in faeces,<sup>1</sup> it became clear that human wastewater might contain the novel coronavirus. From Feb 17, 2020, onwards, we took 24-h 10 L samples once a week from human wastewater collected at Amsterdam Airport Schiphol (Haarlemmermeer, Netherlands) for virus analyses. Samples tested positive for virus RNA by quantitative RT-PCR methodology 4 days after the first cases of coronavirus disease 2019 (COVID-19) were identified in the Netherlands on Feb 27, 2020 (unpublished data). This could be explained by virus excretion from potentially symptomatic, asymptomatic, or presymptomatic individuals passing through the airport. Furthermore, human wastewater sampled near the first Dutch cases in Tilburg, Netherlands, also tested positive for the presence of viral RNA within a week of the first day of disease

onset (unpublished data).<sup>2</sup> These findings indicate that wastewater could be a sensitive surveillance system and early warning tool, as was previously shown for poliovirus.<sup>3</sup> To our knowledge, this detection in the Netherlands is the first report of SARS-CoV-2 in wastewater.

Whether SARS-CoV-2 is viable under environmental conditions that could facilitate faecal–oral transmission is not yet clear. However, evidence exists of potential community spread, with the virus spreading easily and sustainably in the community in some affected geographic areas such as China.<sup>4</sup> A case has also been reported in the USA in which the individual had not been exposed to anyone known to be infected with SARS-CoV-2 and had not travelled to countries in which the virus is circulating.<sup>5</sup> Potential enteric transmission also has implications for those working with human waste and wastewater, for whom WHO guidance has been developed specifically in relation to COVID-19. Overall, the provision of safe water, sanitation, and hygienic conditions can offer protection from any infectious disease, including COVID-19.

Enteric transmission of SARS-CoV-2 is possible and exposure to SARS-CoV-2 in wastewater could pose a health risk. But environmental surveillance of SARS-CoV-2 could serve as a data source, indicating if the virus is circulating in the human population. Previously, this tool has been successfully applied for preclinical identification of Aichi virus.<sup>6</sup> The possibility of faecal–oral transmission of COVID-19 has implications, especially in areas with poor sanitation where diagnostic capacity might be limited, such as Africa. Wastewater surveillance, especially in areas with a scarcity of data, might be informative, as we have previously shown in monitoring antibiotic resistance on a global scale.<sup>7</sup>

AMdRH is Director of the WHO Collaborating Centre for Risk Assessment of Pathogens in Food and Water. WL and AMdRH declare no competing interests.

For the WHO guidance on water, sanitation, hygiene and waste management see <https://www.who.int/publications-detail/water-sanitation-hygiene-and-waste-management-for-covid-19>

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