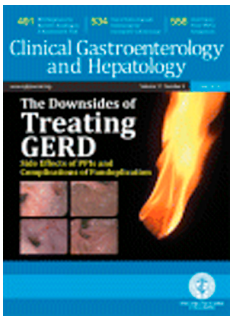

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HEALTH STATUS OF LIVER TRANSPLANTED PATIENTS DURING THE CORONAVIRUS OUTBREAK IN ITALY: A LARGE SINGLE CENTER EXPERIENCE FROM MILAN

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Study concept and design (MFD, FI); acquisition of data (MFD, FI); analysis and interpretation of data (MFD, FI); drafting of the manuscript (MFD); critical revision of the manuscript for important intellectual content (PL, MFD); statistical analysis (FI); study supervision (GR)

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Background

Coronavirus 2 (SARS-CoV-2), infection was declared a pandemic by the World Health Organization on March 11 2020 **(1).** This virus is responsible of a clinical condition, defined as coronavirus disease 2019 (COVID-19) with a clinical spectrum from mild respiratory and/or gastrointestinal symptoms to interstitial pneumonia with acute respiratory distress syndrome, possible multi-organ failure and death **(2).** COVID-19 severity directly correlates with patient's age and presence of comorbidities **(3).** Pro-inflammatory cytokines may play an important role, especially in the more severe form of COVID-19. As a consequence, patients undergoing immunosuppressive therapy might be to some extent protected from the SARS-CoV-2 infection and its complications **(4).** Indeed, COVID-19 has not been described in solid organ transplant recipients so far **(5).** Current AASLD recommendations acknowledge that post-transplant immunosuppression is not a risk factor for mortality associated with SARS-CoV-2 infection "per se" but the recommendations underline that post-transplant recipients older than 60 years are more likely to acquire SARS-CoV-2 infection. Therefore, the AASLD suggests adoption of stringent prevention measures for liver transplant recipients **(6).**

In this paper, we report the results of a survey administered to a large series of transplanted patients followed at the Maggiore Hospital Policlinico, Milan.

Material and methods

At the beginning of the outbreak in Italy, we recommended to all liver transplant recipients the following measures to prevent of SARS-CoV-2 infection: frequent handwashing and sanitization; avoid public places and overcrowded situations; and wear a surgical mask in every public place. We later minimized in-person visits by improving the use of telemedicine.

In March, we performed a survey of our liver transplant patients to verify adherence to the preventive measures against SARS-CoV-2 and compliance with the seasonal anti-flu vaccination. We also inquired about possible symptoms or signs of COVID-19. All suspected cases were further investigated for a diagnosis.

Results

In total, 640 patients completed the survey. The epidemiological and clinical features of this population are reported in Supplementary Table 1. From the beginning of the pandemic in Italy as of April 4 2020, our data show that 516 recipients (81%) adhered to at least two preventive measures and 455 (71%) received the seasonal anti-flu vaccination. Thirty-four (5.3%) patients experienced a flu-like syndrome, complicated by bronchitis or bacterial pneumonia in 6, all recovered with antibiotic therapy. COVID-19 was diagnosed in 8 symptomatic recipients (overall prevalence 1.25%,) including one patient previously classified as having a flu-like syndrome. Epidemiological and clinical features are reported in Table 1.

Discussion

In this study we report a real life "snapshot" of a large cohort of liver transplanted patients during the SARS-CoV-2 outbreak in Italy. Our data show an excellent adherence rate to the recommended preventive measures (84%); this high compliance with preventive strategies might have contributed to the relatively low prevalence of SARS-CoV-2 infection in our population. Nevertheless, some patients from our cohort of liver transplant recipients developed COVID-19, with an observed 1.25% infection rate so far. Noteworthy, most of the cases (75%) had a mild disease (3 quarantined and 3 rapidly discharged) while 2 patients are still hospitalized.

These findings slightly differ from those reported by D'Antiga in which some infected patients but no cases of COVID-19 were described **(7).** The different populations investigated by the two groups could explain the disparities: our cohort in Milano concerns only adult patients, while D'Antiga's cohort in Bergamo mainly included pediatric transplanted patients. Results may also be affected also by the different time frames in the two reports. However, both studies showed that transplant settings may differ from the general population, possibly in regards to a high degree of surveillance at individual patient level and a milder disease expression which could be related to immune-suppressed status of liver transplant patients. Notably, all patients with COVID-19 live in Lombardy (Supplementary Figure 1), the region with the highest prevalence of infection in Italy: 10 million inhabitants with 63.094 ascertained infected people and 11.608 virus-related deaths. However, these data are not exhaustive for a correct estimation of the virus spreading in the general population due to the limited number of diagnosis performed (overall nasopharingeal swabbing: 232.674) (8)

The main merit of this preliminary study is the large sample size, with a homogeneous collection of data from a single Center. The main limitations are related to the observational nature of the study and the short duration of follow-up. Overall, our study provides support for the use of telemedicine to deliver care to liver transplant recipients. Long-term clinical and epidemiological studies in the transplant setting will be of great utility in the field.

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Legend to Supplementary Figure 1: Geographical distribution of the 8 transplanted recipients with a diagnosis of COVID-19 in Lombardy

Table 1. Epidemiological and Clinical features of the 8 liver transplant recipients with a diagnosis of COVID-19

	#1	**#2**	**#3**	**#4**	**#5**	**#6**	**#7**	**#8**
Age, yrs	60	78	65	57	57	62	75	50
Sex	M	M	M	M	M	F	M	F
Region Province	Lombardy Brescia	Lombardy Brescia	Lombardy Lecco	Lombardy Lecco	Lombardy Milano	Lombardy Milan	Lombardy Brescia	Lombardy Milan
Time since LT, months	36	230	65	187	96	137	211	3
Immunosuppression	CNI +MMF	CNI+MMF	Steroids	CNI+MMF	CNI+MMF	CNI+MMF	CNI+MMF	CNI+ Steroids
Seasonal anti-Flu vax	Yes	Yes	No	No	yes	Yes	No	No
Cardio-pulmonary comorbidities	No/No	Yes/No	No/Yes	Yes/Yes	No/No	No/Yes	Yes/No	Yes/Yes
Start of symtoms	February 28th	March 11th	March 15th	March 15th	March 18th	March 23th	March 24th	March 25th
COVID-19 diagnosis	Nasal Swab Chest X-Ray	Nasal Swab Chest-CT scan	- Chest-CT scan	Nasal Swab Chest X-ray	Nasal Swab Chest-x-Ray	Nasal Swab Chest-CT scan	Nasal Swab Chest X-Ray	Nasal Swab Chest-CT scan
Fever Respiratory sympt. Diarrhea Pneumonia	Yes Yes No No	Yes Yes No Yes	Yes Yes No Yes (mild)	Yes Yes No No	Yes Yes No Yes (mild)	Yes Yes No Yes (mild)	Yes No Yes Yes (mild)	Yes Yes No Yes
Hospitalization	No	Yes (non invasive ventilation)	No	No	Yes (discharged)	Yes (discharged)	Yes (discharged)	Yes (non invasive ventilation)

* Liver transplantation (LT), Corona Virus Disease-19 (COVID-19), Calcineurine inhibitor (CNI), Mycophenolate (MMF)