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Letters from the Frontline

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List of Abbreviations: LRLT = Living-related liver transplant; LT = Liver transplantation; (SARS-CoV-2 = Severe acute respiratory syndrome Coronavirus 2;

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ABSTRACT

Liver Transplant Programs in Italy have faced a sequela of management and clinical decision-making problems due to the high incidence in some regions of the country of severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2). The Italian Society for Organ Transplantation (SITO) and the Board of Liver Transplant Program Directors issued a survey to assess the initial impact of this pandemic event on the routine activity of 22 Italian Liver Transplant Programs. One hundred percent of participants completed the survey within a few days. The analysis is presented dividing the centers in two macro-areas: north-central Italy and south-central Italy. The reason for this is that the two areas had a different incidence of the infection and because they have distinctive rates of cadaveric donation. Overall, all centers remained open although a reduction in the activity was noted. Transplant Programs reduced their outpatient activity both in terms of pre-transplant evaluation (68% of the centers) and transplant recipient follow-up (100%); a reduction in transplant activity was observed in the first two weeks of March only in the north-central macro area (23 LTs vs 39 in 2018 and 60 in 2019); overall, SARS-CoV-2 infection was registered for 24 liver transplant recipients and 37 health care providers in liver transplant units. In the perspective of the increasing magnitude of the epidemic, more data will be required to define appropriate strategies for the increasingly complex management of liver transplant patients.

Since the first occurrence of the Coronavirus 2 (SARS-CoV-2) pandemic outbreak at the end of last year (1), it was immediately clear that immune compromised patients, such as transplant recipients, would be at a greater risk of death and developing serious respiratory complications (2). In a similar setting, Liver Transplant Programs in Italy had to face a sequela of management and clinical decision-making problems due to the extremely high incidence of Coronavirus in some regions of the country (Figure 1) (3). Moreover, while the Italian Transplant Authority (Centro Nazionale Trapianti) promptly released guidelines on donor management (4), the Liver Transplant Programs were left to pursue their own policies, even in the light of multiple logistic scenarios deriving from the different incidence of infection across the country (Figure 1b). Within a similar scenario, on March 16, 2020, the Italian Society for Organ Transplantation (SITO) and the Board of Liver Transplant Program Directors issued a survey to assess the initial impact of this pandemic event on the routine activity of 22 Italian Liver Transplant Programs. One hundred percent of participants completed the survey in a few days.

The survey included nine questions mainly focusing on three aspects:

- 1) Analysis of the center's volume of activity in February and in the first two weeks of March 2020 compared with the same period in 2018 and 2019.
- 2) Assessment of COVID-19 infections in patients and health care providers in each center.
- 3) Similar evaluation in the setting of the individual Living-Related Liver Transplant Programs.

The results of the survey are summarized in Table 1.

The analysis is presented dividing all centers into two macro-areas: north-central Italy and south-central Italy. The reason for this is that the two areas had a different incidence of the infection and because they have distinctive rates of cadaveric donation.

Overall, all centers remained open although a reduction in the activity was noted due to the donor shortage resulting from the different patient allocation needs in Italian intensive care units, now almost exclusively dedicated to the care of COVID-19 patients (5). In the period between February 15 and March 15, all Transplant Programs reduced their outpatient activity both in terms of pre-transplant evaluation (64% 15 out of 22 centers, 68%) and transplant recipient follow-up (100%). In terms of transplant activity, in the north-central Italy macro-area only a reduction can be seen in the

Accepted Article

first two weeks of March compared with the same period in 2018 and 2019 (23 LTs vs 39 in 2018 and 60 in 2019), while activity in the south-central area has not been impacted. Up to March 15, 2020, in the north-central Italy macro-area only we registered 24 liver transplant recipients positive to COVID-19 infection, of which 3 (13%) were admitted in the intensive care unit and 5 (21%) died. Seventeen physicians among the 37 health care providers resulted positive to the infection, the majority of which (94%) was of course in the northern macro-area. Eighty-two percent of the Programs performed the nasopharyngeal swab evaluation on all potential recipients upon admission for transplant, regardless of the presence of clinical suspicion or respiratory symptoms. The final section of the survey focused on Living-Related Liver Transplants: of the 7 centers performing LRLT, three temporarily suspended their program while the remaining ones reduced their activity.

The survey paints a picture of how Liver Transplant Programs are managing this pandemic event in Italy and how routine activity has been impacted. Some considerations can therefore be made based on this preliminary analysis: the Italian system, based on a network of relationship among centers and between centers and the Italian Transplant Authority, holds well despite the aggressiveness of this major event. Donor teams were provided by the Program nearest to the donor's hospital, regardless of where the organ was allocated, thus resulting in a limited exposure of surgeons to the epidemic widespread. Centers located in the red zone were able, with extraordinary efforts, to ensure liver transplants be performed for the sickest patients.

However, in the perspective of the exponentially increasing magnitude of the epidemic (Figure 1a), other problems remain and more time will be required to appropriately manage them. A more detailed analysis will be performed shortly adding data of the second half of March and April, when the peak of the infection is expected.

An increasingly complex management of sick patients waiting for an organ and an elevated risk of drop out and mortality on the waiting list are the two major concerns of the Italian Liver Transplant community. With the commitment of intensive care units to primarily provide care to COVID-19 patients, the rate of deceased donations is not expected to improve in the short term.

In addition, the wrong perception of more stable clinical individuals on the waiting list, such as oncologic patients, may be the reason of some denials reported after a call for a potential transplant.

Priorities include solving logistical problems such as defining safe pathways for transplant patients inside the hospitals, and identifying appropriate strategies to deliver informed consent and all information related the potential increased risk of infection to transplant patients.

In conclusion, while we are optimistic on the overall approach of the Italian Liver Transplant community to this violent outbreak, we are aware that additional critical data analysis and work are required to continue ensuring a lifesaving procedure such as Liver Transplant to many sick patients.

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Table legend

Table 1. Impact of the SARS-CoV-2 epidemic on the routine activity of 22 Italian Liver Transplant Programs.

Figure legend

Figure 1. SARS-CoV-2 epidemic outbreak in Italy. A: Number of COVID-19 confirmed cases as reported by the Italian Government on March 15, 2020. **B:** Cartogram reporting total number of COVID-19 cases in each region and number of cases per 100,000 population at March 15, as reported by Italian Government and Superior Institute of Health Care (institutional organ of the Ministry of Health). Black dots represent all liver transplant centers across the country. The detailed list of contributing centers is available in Supplementary Table S1.

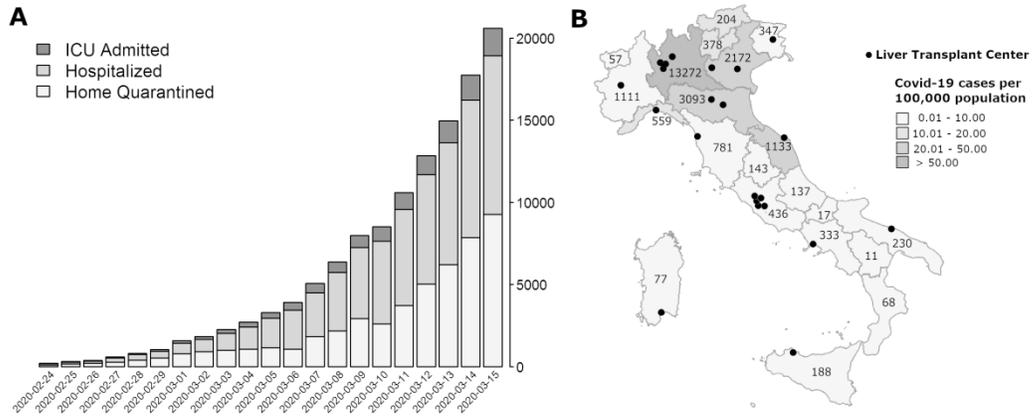
	North- Central	South- Central	Overall
Number of LT Centers	14	8	22
Center Policy on Liver Transplantation, no. (%)			
Regular activity	11 (79)	6 (75)	17 (77)
Reduced activity	3 (21)	2 (25)	5 (23)
Center Policy on Transplant Recipient Follow-up, no (%)			
Reduced activity	14 (100)	8 (100)	22 (100)
Center Policy on Pre-transplant Evaluation, no (%)			
Regular activity	4 (29)	3 (38)	7 (32)
Reduced activity	9 (64)	5 (62)	14 (64)
Suspended activity	1 (7)	0 (0)	1 (5)
Center Policy on Nasopharyngeal Swab Evaluation for LT candidates, no (%)			
For all potential recipients	12 (86)	6 (75)	18 (82)
In presence of clinical suspicion or respiratory symptoms	2 (14)	2 (25)	4 (18)
Center Volume of Activity from February 1 to March 15			
Number of Liver Transplants			
2018	128	29	157
From February 1 to February 28	68	18	86
From March 1 to March 15	60	11	71
2019	134	34	168
From February 1 to February 28	95	22	117
From March 1 to March 15	39	12	51
2020	121	35	156
From February 1 to February 29	98	21	119
From March 1 to March 15	23	14	37
Assessment of the COVID-19 Infection in Transplant Recipients			
Total Positive to COVID-19, no (%)	24	0	24
Transplanted in 2020	5 (21)	0	5 (21)
Required hospitalization	17 (71)	0	17 (71)
Required ICU admission	3 (13)	0	3 (13)
Dead	5 (21)	0	5 (21)
Assessment of the COVID-19 Infection in Health Care Providers			
Total Positive to COVID-19, no (%)	35	2	37
Physicians	16 (46)	1 (50)	17 (46)
Other health care providers	19 (54)	1 (50)	20 (54)

Living-Related Liver Transplant (LRLT)

Total Number of Centers	4	3	7
Center Policy on Liver Transplantation, no (%)			
Regular activity	1 (25)	2 (67)	3 (43)
Reduced activity	1 (25)	0	1 (14)
Suspended activity	2 (50)	1 (33)	3 (43)

Center Volume of LRLT Activity from February 1 to March 15**Number of Living-Related Liver Transplants**

2018	0	5	5
2019	0	2	2
2020	0	3	3



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