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ORIGINAL ARTICLE

Carrying on with liver transplantation during the COVID-19 emergency: Report from piedmont region



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KEYWORDS

SARS-CoV-2;
 Outbreak;
 Transplant activity;
 Tertiary healthcare;
 Team working

Summary

Background: The COVID-19 pandemic is an emergency worldwide. In Italy, liver transplant activity was carried on, but despite all efforts, a 25% reduction of procured organs has already been observed during the first 4 weeks of the outbreak.

Aims: To analyze if our strategy and organization of LT pathway during the first two months of the COVID-19 emergency succeeded in keeping a high level of LT activity, comparing the number of LT in the first two months with the same period of time in 2019.

Methods: We compared the liver transplants performed in our Center between February 24th and April 17th, 2020 with liver transplants performed in the same period in 2019.

Abbreviations: AIH, autoimmune hepatitis; ALF, acute liver failure; ASSLD, American Association for the Study of Liver Disease; BAL, bronchoalveolar lavage; CIT, cold ischemia time; CNT, Italian Transplant Authority; EAD, early allograft dysfunction; EASL, European Association for the Study of the Liver; HCC, hepatocellular carcinoma; HOPE, Hypothermic Oxygenated Machine Perfusion; ICU, intensive care unit; LT, liver transplant; MELD, Model for the End-stage Liver Disease; NASH, non-alcoholic steatohepatitis; NPS, nasopharyngeal swab; WHO, World Health Organization.

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Results: In 2020, 21 patients underwent liver transplantation from deceased donors, exactly as the year before, without statistically significant difference. All patients survived in both groups, and the rate of early graft dysfunction was 24% in 2020 and 33% in 2019. In 2020 Median MELD was higher (17 vs 13). We were able to perform 3 multiorgan transplants and one acute liver failure. Nobody died on waiting list. The performance of our Center, despite the maxi-emergency situation, was steady and this was the result of a tremendous team working within the hospital and in our region.

Conclusions: Team working allowed our Center to maintain its activity level, taking care of patients before and after liver transplantation. Sharing our experience, we hope to be helpful to other Centers that are facing the pandemic and, if another pandemic comes, to be more prepared to deal with it.

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Introduction

The COVID-19 pandemic caused by SARS-CoV-2 virus is a public health emergency affecting all aspects of medical care. On January 30th, 2020, the World Health Organization (WHO) declared it to be a global health emergency and since March 13th Europe became the epicenter of the pandemic. By the end of February 2020, Italy had experienced a rapid spread of the virus, starting from its Northern regions, with a daily increase in the number of cases and deaths. On February 24th, 2020 a WHO-led team of experts arrived in Italy in order to assist the local health authorities. On the 8th of March the Italian government instituted a containment red zone enclosing the most affected areas and in the following days further decrees extended strict lockdown measures to the whole country in order to contrast SARS-CoV-2 spread. All non-urgent and non-oncological activities were suspended in national health service hospitals and planned surgeries were postponed. A growing number of wards and intensive care unit (ICU) beds were quickly dedicated to the care of COVID-19 patients. On April 17th, in Italy there were 172.434 confirmed cases, 42.727 healed and 22.745 deaths and the Piedmont alone counted 450 cases per 100.000 inhabitants with 19.803 confirmed cases, 3.634 healed and 2.171 deaths [1]. According to the European Association for the Study of the Liver (EASL) [2] and American Association for the Study of Liver Disease (AASLD) [3] liver transplant (LT) activity, as an acute care treatment, should not be postponed, even in the COVID-19 era. Preliminary data in post-LT patients [4,5] did not show an increased risk of severe COVID-19 disease, despite immunosuppression may prolong viral shedding [6]. Cirrhotic patients might be more susceptible to virus infection because of their dysfunctional immune response and transplantation in SARS-CoV-2 positive recipients is currently not recommended [2,3]. Consequently, the Italian Transplant Authority (CNT) recommends that all pauci/symptomatic recipients and all donors ought to be tested for SARS-CoV-2 RNA (nasopharyngeal swab, NPS or bronchoalveolar lavage, BAL) [7] immediately pre-LT and those who test positive are to be considered medically ineligible for transplantation/donation; screening of asymptomatic recipients of deceased donors will depend on local resources availability. Despite all efforts to preserve transplant activity, a 25% reduction of procured organs has already been observed in Italy during the first 4 weeks of the outbreak [8].

Our working hypothesis is that our organization of LT pathway during the first two months of the COVID-19 emergency succeeded in keeping a high level of LT activity, despite the reduction of procured organs.

We aimed to analyze the number of LT performed between February 24th, 2020 and April 17th, 2020 with the same period of time in 2019, in our high-volume transplant Center (median 150 LT/year).

Materials and methods

Study population

In this observational cohort study, we consecutively enrolled all patients who underwent LT in our Center, between the 24th of February 2020 and the 17th of April 2020. In addition, we retrospectively analyzed the LTs performed in 2019, in the same period of time. The variables assessed in the study population and their donors are shown in Table 1.

Pursuant to Italian law, Regional Transplantation Centers are the custodians of donor/recipient biomedical data also for research purposes. All study procedures complied with the ethical standards of the 2000 Declaration of Helsinki and the Declaration of Istanbul 2008.

Clinical protocol

By the end of February 2020, the number of patients coming to our transplant clinic was limited to subjects with urgent issues and phone visits or telemedicine as appropriate replaced in-person appointments. Arrival times were staggered in order to avoid patients congregating in the waiting areas. Before entry, all patients were screened for COVID-19 symptoms or recent exposure and each patient's temperature was checked. A pre-triage form had to be filled out before every procedure. Outpatient LT diagnostic workups were carried out by using COVID-free pathways. As already published, we recommended to our patients frequent handwashing and sanitization, avoid public places and overcrowded situations and wear a surgical mask to prevent of SARS-CoV-2 infection [9–11].

In our hospital 7 wards (5 internal medicine, pneumology and cardiology), 4 out of 5 ICUs and 1 out of 4 Radiology Unit were progressively dedicated to COVID patients; On

Table 1 Recipient and donor characteristics.

	2020 (n = 21)	2019 (n = 21)	P-value
Recipient characteristics			
Male	16 (76%)	15 (71%)	.99
Age, years	56 [51–65]	58 [56–62]	.72
Etiology of cirrhosis			.15
Viral	4 (20%)	11 (52%)	
Alcoholic	7 (35%)	5 (24%)	
AIH and cholestatic disorders	5 (25%)	1 (5%)	
NASH	2 (10%)	1 (5%)	
Others	2 (10%)	3 (14%)	
Etiology of ALF			
Viral	1 (5%)	0	
HCC in cirrhotic patients	9 (45%)	8 (38%)	.75
Blood type			.63
A	12 (57%)	11 (52%)	
B	2 (10%)	5 (24%)	
AB	1 (5%)	1 (5%)	
O	6 (29%)	4 (19%)	
Multiple organs transplant	3 (14%)	1 (5%)	.61
MELD at LT	17 [12–22]	13 [9–18]	.13
Donor characteristic			
Age, years	58 [38–72]	60 [51–63]	.45
Donor after cardiac death	1 (5%)	0	.99
Suboptimal graft	10 (48%)	7 (33%)	.53
Regional donors	18 (86%)	16 (76%)	.69
Transplant operation			
Ex vivo machine perfusion	4 (19%) ^a	6 (29%)	.72
Cold Ischemia Time, minutes	452 [346–473]	431 [393–495]	.99
Post-transplant course			
EAD	5 (24%)	7 (33%)	.73
ICU-stay, days	5 [4–7]	4 [3–6]	.69
Hospital-stay, days	11 [10–17]	13 [8–21]	.82
Discharge home	20 ^b (95%)	21 (100%)	1

Abbreviations: AIH, autoimmune hepatitis; EAD, early graft dysfunction, according to Olthoff; HCC, hepatocellular carcinoma; ICU, intensive care unit; LT, liver transplantation; MELD, Model for the End-stage Liver Disease; NASH, non-alcoholic steato-hepatitis.

^a One out of four with normothermic machine perfusion.

^b One still hospitalized (combined lung-liver-pancreas transplant).

April 17th in the district of Turin there were 9.503 confirmed cases.

In our liver sub-intensive unit, we were allowed to continue to admit patients with severe decompensated liver disease, and from March 31st every patient before admission was tested for SARS-CoV-2 RNA by NPSs in order to guarantee a COVID-free unit. Furthermore, among the 5 intensive care units of our hospital, the one dedicated to transplants was maintained COVID-free, by testing each transplant recipient in advance with SARS-CoV-2 RNA in NPS or BAL, starting from the 22nd of March.

The only source of our donors are deceased donors after brain or cardiac death and all of them were screened for SARS-CoV-2, according to CNT guidelines. A deceased donor graft was defined suboptimal if donor age was ≥ 65 years and/or had macrovesicular steatosis $\geq 15\%$ [12]. The degree of fatty infiltration of the graft were assessed on liver biopsies routinely obtained at the end of transplant surgery. In our center, from 2016, grafts from brain death donors char-

acterized by increased risk profile (donors >80 years and/or obese donors) as well as from donors after cardiac death undergo Hypothermic Oxygenated Machine Perfusion (HOPE) before implantation, to reduce ischemia-reperfusion injury. Recently, normothermic machine perfusion (OrganOx) was also used.

After LT, immunosuppression consisted of tacrolimus, mycophenolate mofetil and steroids, as per our standard protocol. Early allograft dysfunction (EAD) was defined according to Olthoff [13]: total bilirubin level ≥ 10 mg/dL or international normalized ratio ≥ 1.6 on postoperative day 7 or aspartate aminotransferase or alanine aminotransferase level >2000 IU/L within the first 7 days after transplant.

Statistical analysis

Categorical variables were represented as number (n) and percentage (%) and compared using Fisher's exact test

or Chi-square test. Quantitative variables were shown as median and interquartile range (25th–75th percentiles, IQR) and their distribution was evaluated with D’Agostino & Pearson test; parametric data were evaluated by t-test, non-parametric data were evaluated by Mann–Whitney U test. $P < 0.05$ in a two-tailed test was considered statistically significant.

Results

Between February 24th, 2020 and April 17th, 2020, among 22 admissions in our 7-bed sub-intensive liver unit, a 40-year-old woman, who was listed during hospitalization, developed fever during hospitalization and tested positive for SARS-CoV-2 RNA in NPSs. Immediately transferred to a COVID unit, she came back to our unit after 7 days and 2 negative SARS-CoV-2 RNA in NPS and underwent LT the day after readmission to our unit.

At the beginning and at the end of the enrollment period 51 and 52 patients, respectively, were actively on the LT waiting list. None of the patients on the LT waiting list had to be admitted to hospital for COVID-19 and the on-list mortality rate was 0%. During the study period, 21 first LTs were consecutively performed in our Center. The majority of the recipients were male, with a median age of 56 years (IQR 51–65). The median biochemical Model for end-stage Liver disease (MELD) at LT was 17 (IQR 12–22). Twenty patients were affected by cirrhosis (20% viral-, 35% alcohol-, 25% autoimmune/cholestatic-related) and 45% of them also by hepatocellular carcinoma (HCC). Two out of the twenty patients underwent combined liver-kidney transplant and one combined lung-liver-pancreas transplant. One patient was transplanted for HBV-related acute liver failure (ALF) (Table 1). Four out of 21 patients (19%) were hospitalized at the time of LT and the ALF patient was in the ICU on ventilator/respiratory support. Looking at the donors: 86% of the graft were recruited in our regional area. The median donor age was 58 years (IQR 38–72) and 48% of the grafts were suboptimal. The median cold ischemia time was 452 min (IQR 346–473). *Ex vivo* normothermic machine perfusion was employed for one graft, and hypothermic perfusion for 3 grafts. 95% of livers came from brain-dead donors and one from a donor after cardiac death. After LT, 1 out of the 21 recipients was found positive for SARS-CoV2 on NPS on his 5th day post-LT, after his bed neighbor, who was recovering from liver resection, had tested positive the day before. His oxygen saturation was persistently normal and CT scan was negative for pneumonia. We transferred the patient immediately to the COVID unit, where precautionary hydroxychloroquine 400 mg twice daily was administered for 16 days. Mycophenolate mofetil dosing was reduced from 1500 mg/day to 1000 mg/day and target tacrolimus trough level was set at 5–7 ng/ml. He was discharged after 18 uneventful days in COVID unit, and the SARS-CoV2 on NPS is still positive, without specific symptoms.

In 2019, over the same period of time, at the beginning and at the end of the enrollment period 60 and 71 patients, respectively, were actively on the LT waiting list; the mortality rate on the LT waiting list was 0% and we performed the same number of LTs (19 first transplant and 2 re-transplants), compared with 2020. 71% of the patients was male, with a

median age of 58 years (IQR 56–62). The median biochemical MELD at LT was 13 (IQR 9–18) with an HCC rate of 38%. The etiology of liver cirrhosis was viral for 52% of the cases, alcohol related for 24%. The median donor age was 60 years (IQR 51–63), all of them were brain-dead and 76% of the graft were recruited into our regional area. The median cold ischemia time was 431 min (IQR 393–495) and 33% of the grafts were suboptimal. *Ex-vivo* hypothermic machine perfusion was used in 29% of the grafts.

All patients survived in both groups, and the rate of EAD was 24% in 2020 and 33% in 2019 (Table 1). We did not find any statistically significant difference between the two cohorts.

Discussion

We compared LT activity in our Center during the first 2 months of COVID-19 pandemic, starting since February 24th, with the same period of the year before. Italy has been the first European country to face the severe COVID-19 pandemic since February 2020 and our National Healthcare System, which offers universal access to health care to all residents, is facing a tremendous pressure. Hospitals and health workers were asked to suspend all non-urgent activities and to postpone all planned surgery in order to give over beds to the treatment of COVID-19 patients. In accordance with AASLD and EASL recommendations [2,3], transplant surgery was excluded from these limitations, in order not to compound the outbreak lethality with risking the lives of patients who need a life-saving LT. This requires stringent criteria for prioritizing patients who are more likely to die on the wait list and a delicate balance with the risk of hospital-acquired COVID-19. In order to optimize resource utilization and to avoid transplantation in virus-positive patients, every effort has been made to prevent SARS-CoV-2 infection in patients before and after LT and the SARS-CoV-2 molecular screening for donors and symptomatic recipients became mandatory.

In our Country deceased donors are the prevalent organ resource and a restriction in the number of available ICU beds necessarily influenced the donation activity; in fact, during the first 4 weeks of COVID-19 outbreak the number of procured organs dropped by 25%, as reported by CNT.

From 1990 more than 3000 LTs have been carried out at our Center and the annually LT volume is around 150. The Unit is located into a region strongly hit by COVID-19 (454 cases per 100,000 inhabitants and 50 deaths per 100,000). In our study we evidenced that, despite the emergency public health situation, we performed during the first 2 months the same number of LT of the year before, without mortality on the waiting list and early post-transplant. Median MELD was higher as well as the complexity of patients: we managed 3 multiorgan transplants and one acute liver failure, without significantly impacting on the ICU hospitalization days (median ICU-stay value: 5 days in 2020 vs 4 days in 2019, $P=0.69$) and all patients survived in both groups. Furthermore, the majority of the donors were recruited in our regional area, one of the hardest hits by the virus, and we were able to manage machine perfusion in 19% of the cases inside our hospital. We did not change our standard immunosuppression regimen, according to published data which show that immunosuppression was not a risk factor for mortality associated with SARS (2002–2003) or MERS

(2012-present) [3,4], even if it may prolong viral shedding in post-transplant patients with COVID-19 [3,6].

We strongly believe that the steady performance of our Center, despite the maxi-emergency situation, was the result of a tremendous team working within the hospital and in the Piedmont Region. Our healthcare Director (AS) rapidly switched in our tertiary referral hospital many medical doctors and departments previously dedicated to different specialties, into new COVID-19 units, progressively increasing in number and size. Our transplant hepatologists were spared from the full-time management of COVID-units, in order to take care of outpatient and inpatient transplant patients. Our liver sub-intensive care and transplant intensive unit were included into a COVID-free pathway within the hospital and a strong collaboration between transplant hepatologists and surgeons made possible the prioritization of patients more in need of transplant and to optimize the recipient/donor match. Furthermore, regional ICUs were able to preserve beds and intensivists for the management of a precious resource like a potential organ donor. Despite all our efforts to maintain a transplant COVID-free pathway, two transplant patients, one before and one after LT were tested SARS-CoV-2 virus positive during hospitalization and both were safely discharged home.

Some limitations need to be acknowledged. The small number of enrolled patients, limited period of the study and the monocentric experience. The experience of Maggi et al. [14] as well the preliminary analysis of Italian Society for Organ Transplantation [15] showed that there is a variability in the emergency management even between the Italian regions. Lombardy has 10.002.615 inhabitants [16] and four active liver transplant programs (Ospedale Niguarda in Milan, Fondazione IRCCS Policlinico in Milan, Istituto dei Tumori in Milan and Ospedali Riuniti in Bergamo). This is the region that was hit first, with the highest number of cases in Italy (On April 17th there were 64.135 confirmed cases and 11.851 deaths, 641 cases/100.000 inhabitants). Piedmont has 4.392.526 inhabitants [16] and the liver transplant activity is focused in a single center, in Turin. The COVID-19 outbreak arrived in Piedmont with a delay of around two weeks, and on April 17th, 2020 19.803 confirmed cases and 2.171 deaths were recorded, with 450 cases/100,000 inhabitants. The delay of the epidemic peak and the centralization of LT activity could explain the different results reported from the Lombardy centers and ours. Agopian et al. also reported a great variability in LT activity from different regions in US [17].

In conclusion, Italy is facing an unprecedented health care emergency situation due to the COVID-19 pandemic. Team working with close involvement of several specialties such as hepatologists, surgeons, anesthesiologists and radiologists allowed our single regional Center to maintain its activity level, taking care of patients before and after LT. We think that LT, being a life-saving procedure, should be not suspended when it is possible. Sharing our experience, we hope to be helpful to other Transplant Centers that are now facing the COVID-19 emergency.

Conflict of interest

All authors have no conflict of interest to declare.

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