LETTER TO THE EDITORS

The COVID-19 second wave risk and liver transplantation: lesson from the recent past and the unavoidable need of living donors

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September 2020 signed the beginning of the second wave of COVID-19 outbreak in Italy (Figure S1) [1]. Since the dramatic experience learned during the first epidemic wave a significant decline of liver transplantations (LTs) will be expected. Every year, approximatively 1200 LTs are performed in Italy [2]. The majority of these are concentrated within four northern regions (Lombardia, Veneto, Piemonte, Emilia-Romagna, *LoVePiER*), accounting about more than the half of the overall LT performed per year (749/1277 LT, 58.6%, in 2019). Nowadays, *LoVePiER* was the most involved areas by the COVID-19 outbreak, with a total of 75 738 (71.5%) documented cases until March 31st and 10 174 (81.8%) deaths (Table S1) [1].

Considering the period of the first outbreak month (March 1st–March 31st), a dramatic decrease of about 35% of LT was registered in Italy, compared to the same period in 2019 and comparing the trend of January and February 2020 [2]. Before COVID-19, the average rate of donor availability in *LoVePiER* was 52.7 donors per million people (PMP/2019), showing the high virtuosity of the transplantation system and people, similar to the highest rates recorded in the world [3]. However, in March 2020 only 43 donors were alerted in *LoVePiER*, significantly lower compared to the 64 in March 2019 (−33%), as well as in the whole country with a donor decrease of 43% (143 in March 2019 vs. 82 in March 2020) [2]. Donors' numbers turned growing up since June 2020, near to the numbers of 2019; however, probably, a new sudden decrease will occur during the next months [2].

The average rate of donor availability in *LoVePiER* was 47.9 donors per million people (PMP/until July 2020), and projections for the entire year would be lower due to the second wave beginning in the autumn [2].

The dramatic impact of the COVID-19 outbreak in Italy gave a frightening perspective for LT candidates (Fig. 1). Considering a virtual cohort of 1000 patients listed on March 1st, 2020, the probability of these patients to be transplanted within the first year was 64%, significantly worst compared to the 80% of the pre-COVID-19 scenario. Similarly, the dropout risk of the 1,000 patients considered in the virtual cohort appeared to progressively increase from the COVID-19 outbreak compared to the pre-COVID-19 scenario (5% vs. 7% at 1 year and 8% vs. 13% at 2 years, respectively, for pre- and post-COVID-19) (Fig. 1).

A mix of multiple causes related to *missing potential donors*, *health system crisis*, and *socio-emotional predisposition* may be considered. Concerning the *missing potential donors*, the numbers of all traumas were significantly reduced due to the isolation of people at home; more people died at home of cardiovascular causes without access to emergency services and the possibility of resuscitation and consequently brain death diagnosis. The *National health system* was suddenly under stress by the admission of hundreds of symptomatic patients every day for an unpredictable period of time. Many of these needed isolation, ventilatory support, and much nurse and physician support, especially by anesthesiologists, infectivologists, and pneumologists. The Italian donation system is organized from the top down by a Central National Coordination, macroregional allocation areas, regional coordination, and local coordination. All the coordinators are mainly anesthesiologists and healthcare managers, essentially the leading physicians involved in the COVID-19 emergency. This meant less propensity for donation rather

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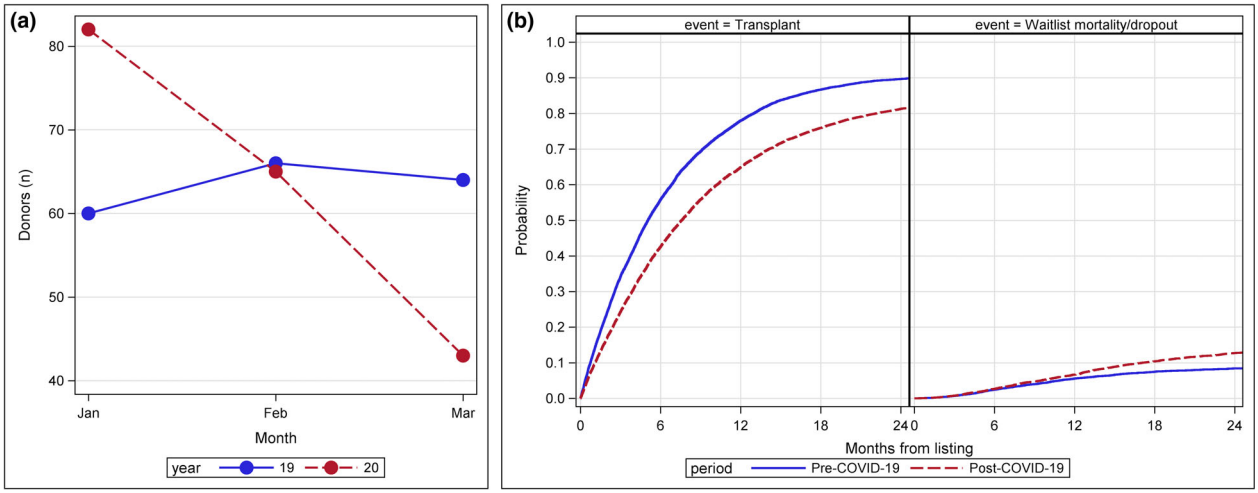

Figure 1 Number of donors in the first quarter of 2019 and 2020 in the LoVePiER area, by month (Panel a) and projected cumulative probabilities of being transplanted and of mortality/dropout in the pre- and post-COVID-19 emergency periods (Panel b). Cumulative probabilities depicted in Panel B were simulated in a competing risk framework. The cumulative probability of being transplanted in the pre-COVID-19 period was simulated via exponential distribution, assuming a median time to transplant of 5 months [1] and a constant event rate. The median time assumed in the post-COVID-19 period was 7.5 months, consistent with the observed 33% decrease of available donors in the LoVePiER area (March 2019 vs March 2020). The cumulative probability of waiting list mortality/dropout was simulated via the Weibull distribution, assuming event rates similar to those reported by Ishaque et al. (2019) [10] and based on US STSR data. A linear monthly increase of event rate was assumed.

than COVID-19-affected patients. More than double the number of intensive care beds available in the *LoVePiER* were used for COVID-19 patients. This sometimes forced physicians to apply an admission selection based on the survival benefits for the patients, reducing the chance of recovery of potential donors. Lastly, the *socio-emotional predisposition* of the people is a very weak toward donation, as they are extremely susceptible to all global occurrences. Indeed, continuous and effective social advertising campaigns increase the donation rate, in the same way as unfavorable events discourage organ donations.

Such an unexpected collapse of deceased donors (DDs) hit all transplant physicians who were unprepared for this event, without any immediate alternatives aimed at alleviating consequences on candidates. Living donor liver transplantation (LDLT) is the only available organ alternative to DDs. Many concerns about LDLT came to light in the first years of the 21st century, with a consequence of very low number of centers and cases performed in the last 20 years in the developed countries. In Italy, less than 20 LDLTs are performed per year and the majority of these are for pediatric recipients. Surgeons were particularly worried about donor safety and recipient results (Hepatocellular-Carcinoma outcome, vascular and biliary complications, rate of re-transplant, small-for-size and vascular outflow reconstructions) compared to DDLT [4]. However, in the same period the eastern countries, lacking DDs, developed a huge experience on LDLT with extraordinary results for both donors and recipients [5–7]. Over the last decade, a strong experience has been collected by HPB and transplant centers in Italy concerning all the most extreme liver surgeries, even in terms of surgical skills concerning the preoperative radiological assessment of the anatomy and future remnant liver as well as surgical planning [5–7]. The increasing experience in two-stage resections (ALPPS), robotic and laparoscopic liver surgery, ex situ resections, and complex vascular and biliary reconstruction during cancer liver surgery have contributed to significantly improve all the multidisciplinary skills in this field. Therefore, the majority of the concerns of the past may be overcome today. COVID-19 does not seem to be more risky for transplant recipients [8,9], moreover living donors are "super-healthy" people by definition, thus at the lowest risk of COVID-19 complications compared to the general population. Hospitals immediately need to create clean tracks for transplant recipients and donors, from hospital entrance to discharge. In line with these concepts, we developed a strict new policy for LDLT during the outbreak. Basically, donors need to be protected by an unpredictable risk of COVID-19 infection (likely very low) acquired during the overall procedure and hospital admission or due to that. The essential points of this

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policy are nasal swab 10 days before in-hospital admission and repeated the day before; a trustee at home quarantine since the first swab until admission; dedicated clean trucks into the hospital; no contacts with any visitors and all the hospital employers who have contacts with the donors should be tested for COVID-19 at least within the last 48 h; quick postoperative discharge and new nasal swab before discharge. According with these principles, two LDLTs have been safely performed since July 2020 at our Institution. Donors' and recipients' outcomes were uneventful and all of them are at home, alive and healthy.

From what has been stated above, we consider LDLT an essential resource that all the leading centers in developed countries should take into consideration to alleviate consequences of an unavoidable significant increase of LT candidate mortality in this global outbreak or in future similar conditions. Intra-hospital clean tracks and skilled teams may be the key to protect living donors and recipients.

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Conflict of interest

The authors have declared no conflicts of interest.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1 Graphic is extracted from the official Civil Protection Department website (Italian Internal Minister).

Table S1 Table reports the original daily report from the Italian Health Ministry concerning the outcome of Covid-19 contagion and deaths across the Italian regions and the whole country.

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