



DR. MICHELE COLLEDAN (Orcid ID : 0000-0002-3880-4763)

DR. LORENZO D'ANTIGA (Orcid ID : 0000-0001-7150-3148)

Article type : Letters from the Frontline

Impact of the SARS-CoV-2 outbreak on pediatric liver transplant recipients residing in Lombardy, Northern Italy

Emanuele Nicastro¹, Angelo Di Giorgio¹, Marco Zambelli², Marco Ginammi¹, Michela Bravi¹, Paola Stroppa¹, Valeria Casotti¹, Raffaele Palladino³, Michele Colledan², Lorenzo D'Antiga¹

1) Pediatric Hepatology, Gastroenterology and Transplantation Unit, Hospital Papa Giovanni XXIII, Bergamo, Italy; 2) Surgery, Hospital Papa Giovanni XXIII, Bergamo, Italy; 3) Department of Public Health, University "Federico II" of Naples, Naples, Italy

Author for correspondence: Lorenzo D'Antiga, MD

Paediatric Hepatology, Gastroenterology and Transplantation
Hospital Papa Giovanni XXIII

Piazza OMS1, 24127

Bergamo (Italy)

E-mail: ldantiga@asst-pg23.it

Phone: +390352673856

Text word count: 1488

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1002/LT.25840](https://doi.org/10.1002/LT.25840)

This article is protected by copyright. All rights reserved

N. of tables: 1

N. of Figures: 1

The Authors declare no conflict of interest

Funding: Authors' own work; no financial support was received for this work

Key words: Liver Transplantation, Immunosuppression, Coronavirus, COVID-19, SARS-CoV-2, children.

To the Editor:

The novel Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2) disease (COVID-19) represents an unprecedented public health issue for the general population and for patients with underlying chronic conditions (1). Compared to adults, children seem to have a milder course of the disease, with very few requiring medical attention (2).

Reports of critical disease in adults and children with cancer have raised concern about the risk of severe COVID-19 course in patients with immune system impairment, including recipients of solid organ transplants on long term immune suppression (3).

Since severe COVID-19 represents an immune-inflammatory over-response to SARS-CoV-2, immune suppression might not represent an issue or even be protective against lung injury (4). Recent reports by our team are reassuring, based on direct experience and lack of any evidence that immunosuppression was an additional risk factor for the disease in previous Coronaviruses epidemics (5,6).

Thousands of children are living worldwide with a liver transplant, but no report have been released about the impact of COVID-19 in such population, especially due to the difficulties to obtain clinical information during the pandemic.

Lombardy, as the most affected Italian region, in a country where true infections certainly exceed by orders of magnitude those detected, can be considered one of the areas with highest COVID-19 prevalence worldwide (7). The Hospital Papa Giovanni XXIII in Bergamo – which is located in the epicenter of the outbreak – is also the largest Italian pediatric liver transplant (PLT) center.

To overcome the limitations in patients' access to healthcare during the outbreak, we designed a telephone survey aiming to collect information on the health status and the exposure risk during the SARS-CoV-2 pandemic of children followed at our PLT center, and residing in a high-prevalence area in Northern Italy.

Data records of all patients who underwent liver transplantation between 0 and 17 years of age, as a part of the Bergamo program from 1997 to 2019, and residing in Lombardy between January 2020 and April 2020, were selected. Between April 6 and April 17, 2020 a 18-question phone interview to the patients or patients' caregivers was carried out to address: demographic features, patient medical history and immunosuppressive (IS) treatment, history of contacts with suspected or confirmed COVID-19 cases, occurrence of symptoms suggestive for COVID-19, referral to hospital for any reason and testing for SARS-CoV-2 infection, presence of suspected or confirmed COVID-19 among family members or relatives (Supplementary material).

Suspected case of COVID-19 was defined by at least one of the following two conditions: *i*) episode of acute respiratory tract infection (RTI) (sudden onset of at least one of the following: cough, fever, shortness of breath); *ii*) close contact with a confirmed or highly probable case of SARS-CoV-2 infection (1).

Confirmed case of COVID-19 was defined by a positive nasal-pharyngeal swab (NPS) for SARS-CoV-2 nucleic acid using real-time reverse-transcriptase polymerase chain reaction (RT-PCR) assay (1). The severity of illness was classified as in previous studies (1,2).

For the epidemiological assumptions, we based on a recently published SARS-CoV-2 prevalence model, that estimated that 13.3% of the Lombardy population has been infected (corresponding to approximately 1,338,056 cases) (8). To minimize the proportion of undetected SARS-CoV-2 in pediatric age range given the little symptoms severity, we selected population data from the Veneto region, with the highest number of diagnostic tests performed in relation to the population (9). Assuming that the age distribution of true cases in our region is close to that of Veneto region (10.3% of the cases in the age group 0-19 years), considering local census data (10), we calculated that approximately 137,820 cases of COVID-19 occurred in Lombardy in the 0-29 years age group. With the over mentioned assumptions, the estimated prevalence in our population should be as high as 4,873 (95%CI: 4,847 – 4899) COVID-19 cases per 100,000 inhabitants by the first week of April 2020.

Out of 519 patients, 364 residing outside the region of Lombardy during the study period were excluded (Figure 1). One hundred and fifty-five patients (150 Italian residing in Lombardy, 5 cross-border patients temporarily residing in Bergamo) were included in the study [M:F = 85:70; mean age 13.6 years (IQR 12.4 – 14.8 years)].

Questionnaires were administered by telephone to the caregivers or to the patients themselves in 138 cases (response rate = 89%). One hundred and fifty-six PLT were performed in these 138 patients at a mean age of 3.5 years (IQR 2.8 – 4.3 years), in three cases combined with kidney transplants, and in one case in the context of a multivisceral transplant. Biliary atresia was the primary disease leading to PLT in 55% of patients. The level of completeness of each question was high (overall percentage of received answers = 99.6%). All patients (100%) were on IS treatment (data on 148 patients, PRA 100%). Patients' characteristics are displayed in Table 1.

Of 138 patients, 5 (4%) had a close contact with a confirmed case of COVID-19, that was a parent in three of them. None of the patients developed symptoms suggestive of COVID-19, nor required oxygen

administration or hospitalization for reasons related to COVID-19. A NPS was performed in three of these patients and yielded negative results.

Another 13 patients (9%) had a contact with a suspected case of COVID-19, that was a household in 5. Eight patients (61%) developed symptoms compatible with COVID-19, which were fever and cough in 7 (87%), fatigue in 2 (25%) and anosmia, dysgeusia and loss of appetite in one. None of these patients received a diagnostic NPS or chest imaging for suspected pneumonia since none required to come to medical attention for respiratory illness.

Forty-four patients (32%) developed respiratory symptoms including fever (54%), cough (54%), sore throat (11%), associated with fatigue (11%), vomiting (11%) and diarrhea (9%). Two patients presented gastrointestinal symptoms in absence of respiratory illness. Overall, one third of the surveyed patients had symptoms compatible with COVID-19 in the study period, occurring 38 ± 26 days before the interview. Only one patient was tested by NPS, which was negative for SARS-CoV-2.

None of the patients had respiratory failure, developed pneumonia, needed oxygen administration nor required hospital admission. No patient reduced or withdrew IS. Thirty-nine of them (85%) had a full recovery by the time of the interview, the others were at home in good general conditions.

No confirmed COVID-19 case occurred in our surveyed population.

With the over mentioned epidemiological assumptions, (estimated prevalence in our population = 4,873 SARS-CoV-2 cases/100,000), 7 cases were expected to occur in our population.

Considering cases of SARS-CoV-2 infection all patients reporting respiratory symptoms and the two with history of close contact with confirmed COVID-19 patients, a total number of 48 patients can be defined as suspected.

While an epidemiological criterion for suspicion of COVID-19 was present in 18 (13%), only 4 (22%) developed mild symptoms after being in contact with a confirmed or suspected case of COVID-19 and – interestingly – none of the 5 household contacts of confirmed COVID-19 developed symptoms or was found positive for SARS-CoV-2 on diagnostic NPS. This raises questions about whether children are less susceptible to SARS-CoV-2 infection and not only to its more severe clinical implications.

On the other hand, one third of our patients reported mild/moderate respiratory symptoms possibly compatible with SARS-CoV-2 infection in the study period. Due to the reduced diagnostic capability and to limited diagnostic policies, NPS was not performed in such patients. However, so-defined suspected COVID-19 cases in liver-transplanted children and young adults exceeded by 7 folds the estimated number of infections in the age-matched general population (34,782 vs 4,873 cases per 100,000). The most likely hypothesis to explain this difference is that the vast majority of mild respiratory syndromes are due to other etiologies than SARS-CoV-2. In line with this, 18 children admitted to our Pediatric Hepatology ward for all causes in the study period had a negative SARS-CoV-2 screening NPS. Conversely, the calculated number of infections in the young general population could be still underestimated, as an effect of the poor diagnostic effort at community-level (11).

The main finding of this research is that our liver-transplanted young patients did not experience any severe respiratory infection, despite residing in one of the earliest and hardest-hit areas worldwide, where first

cases likely date long before any distancing or isolation measure. This raises the question whether immunosuppression could be irrelevant or even protective against SARS-CoV-2 infection and its complications, mainly driven by a well-documented pro-inflammatory state.

Similar results were obtained in children receiving anticancer chemotherapy and in those taking immune suppressant medications for inflammatory bowel disease (6,12).

In conclusion, children – even when immunosuppressed – remain at low risk of severe or complicated COVID-19 disease. In this emerging public health context, there are no reasons to delay or interrupt oncological treatments or withdraw immune suppression, as well as to postpone life-saving treatments in liver-transplanted patients, or to suspend transplant programs as an *a priori* preventative measure.

Further research will be needed to understand the actual incidence of SARS-CoV-2 infection in children at-risk and in the general paediatric population.

REFERENCES

1. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. *JAMA*. 2020;323:1239–1242.
2. Dong Y, Mo X, Hu Y, Qi X, Jiang F, Jiang Z, et al. Epidemiology of COVID-19 Among Children in China. *Pediatrics* [Internet]. 2020 [cited 2020 Apr 27]; Available from: <https://pediatrics.aappublications.org/content/early/2020/03/16/peds.2020-0702.1>
3. Zhang L, Zhu F, Xie L, Wang C, Wang J, Chen R, et al. Clinical characteristics of COVID-19-infected cancer patients: a retrospective case study in three hospitals within Wuhan, China. *Ann. Oncol. Off. J. Eur. Soc. Med. Oncol*. 2020;
4. Li X, Geng M, Peng Y, Meng L, Lu S. Molecular immune pathogenesis and diagnosis of COVID-19. *J. Pharm. Anal*. 2020;
5. D'Antiga L. Coronaviruses and Immunosuppressed Patients: The Facts During the Third Epidemic. *Liver Transplant. Off. Publ. Am. Assoc. Study Liver Dis. Int. Liver Transplant. Soc*. 2020;
6. Norsa L, Indriolo A, Sansotta N, Cosimo P, Greco S, D'Antiga L. Uneventful course in IBD patients during SARS-CoV-2 outbreak in northern Italy. *Gastroenterology*. 2020;
7. Flaxman S, Mishra S, Gandy A, Unwin H, Coupland H, Mellan T, et al. Report 13: Estimating the number of infections and the impact of non-pharmaceutical interventions on COVID-19 in 11 European countries [Internet]. Imperial College London; 2020 [cited 2020 Apr 27]. Available from: <http://spiral.imperial.ac.uk/handle/10044/1/77731>
8. Signorelli C, Scognamiglio T, Odone A. COVID-19 in Italy: impact of containment measures and prevalence estimates of infection in the general population. *Acta Bio-Medica Atenei Parm*. 2020;91:175–179.
9. Ministero della Salute. Nuovo coronavirus [Internet]. [cited 2020 Apr 27]; Available from: <http://www.salute.gov.it/nuovocoronavirus>
10. Indicatori demografici [Internet]. [cited 2020 Apr 27]; Available from:

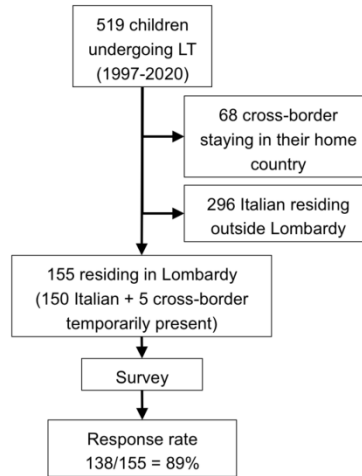
<http://dati.istat.it/Index.aspx?QueryId=18462>

11. Goumenou M, Sarigiannis D, Tsatsakis A, Anesti O, Docea AO, Petrakis D, et al. COVID-19 in Northern Italy: An integrative overview of factors possibly influencing the sharp increase of the outbreak (Review). *Mol. Med. Rep.* 2020;
12. Hrusak O, Kalina T, Wolf J, Balduzzi A, Provenzi M, Rizzari C, et al. Flash survey on severe acute respiratory syndrome coronavirus-2 infections in paediatric patients on anticancer treatment. *Eur. J. Cancer Oxf. Engl.* 1990. 2020;132:11–16.

Table 1. Characteristics of 138 pediatric liver transplant recipients exposed to SARS-CoV-2 during the outbreak in Northern Italy

Number of patients	138
Female, n (%)	60 (43.5 %)
Age (years) at PLT, median (range)	1.5 (0.3-17.9)
Age (years) at survey, median (range)	14.9 (1.2 – 34.8)
- 0-9 years, n (%)	44 (32%)
- 10-19 years, n (%)	75 (54%)
- 20-29 years, n (%)	17 (12%)
- ≥ 30 years, n (%)	2 (1%)
Type of graft, n (%)	
- Whole liver	21 (15%)
- II + III segment	100 (73%)
- I, IV-VIII segment	10 (7%)
- Other	7 (5%)
Patients on IS treatment	138 (100%)
- Tacrolimus monotherapy	103 (75%)
- Tacrolimus + prednisone	13 (9%)
- Tacrolimus + mycophenolate	12 (9%)
- Tacrolimus + prednisone + mycophenolate	5 (4%),
- Cyclosporine monotherapy	3 (2%)
- Tacrolimus + azathioprine	1 (0.5%)
- Sirolimus monotherapy	1 (0.5%)
Contact with suspected case of COVID-19, n (%)	16 (12%)
Contact with confirmed case of COVID-19, n (%)	5 (4%)
Suspected COVID-19 as per symptoms, n (%)	46 (33%)
- Fever	24 (43%)
- Cough	24 (43%)
- Fatigue	5 (8%)
- Sore throat	5 (8%)
- Diarrhea and/or vomiting	5 (8%)
- Loss of appetite	1
- Anosmia	1
- Dysgeusia	1
- Shortness of breath	1
- Myalgia	1
Suspected COVID-19 as per contact with confirmed case	2 (1%)
Total suspected COVID-19	48 (35%)
Confirmed cases of COVID-19, n (%)	0
Discontinuation of IS therapy, n (%)	0
Outcome	
- survived	138 (100%)
- hospitalized for suspected COVID-19, n (%)	0
- died	0

PLT: pediatric liver transplant; IS: immunosuppression



lt_25840_f1.tif