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Pediatric transplantation in Europe during the COVID-19 pandemic: early impact on activity and healthcare

Short running title: Pediatric transplantation during the COVID-19 pandemic

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ABSTRACT

The current pandemic SARS-CoV-2 virus has required an unusual allocation of resources that can negatively impact of chronically ill patients and high-complexity procedures. Across the European reference network on pediatric transplantation (ERN-TransplantChild) we conducted a survey to investigate the impact of the COVID-19 outbreak on pediatric transplant activity and healthcare practices in both solid organ transplantation (SOT) and hematopoietic stem cell (HSCT) transplantation. The replies of 30 professionals from 18 centers in Europe were collected. Twelve of 18 centers (67%) showed a reduction in their usual transplant activity. Additionally, outpatient visits have been modified, restricted to selected ones and to the use of telemedicine tools has increased. Additionally, a total of 14 COVID-19 pediatric transplanted patients were identified at the time of the survey, including eight transplant recipients and six candidates for transplantation. Only two moderate-severe cases were reported, both in HSCT setting. These survey results demonstrate the limitations in healthcare resources for pediatric transplantation patients during early stages of this pandemic. COVID-19 disease is a major worldwide challenge for the field of pediatric transplantation, where there will be a need for systematic data collection, encouraging regular discussions to address the long-term consequences for pediatric transplantation candidates, recipients and their families.

Key Words: pediatric transplantation, solid organ transplantation, hematopoietic stem cell transplantation, SARS-CoV-2, coronavirus disease 2019, COVID-19, post-transplant management, children, young and adolescents.

Abbreviations:

COVID-19: Coronavirus disease 2019

ERN: European reference networks

EU: European Union

HSCT: hematopoietic stem cell transplant

ICU: intensive care unit

SOT: solid organ transplantation

WHO: World Health Organization

INTRODUCTION

The global outbreak of the new coronavirus SARS-CoV-2 infection is responsible for the current pandemic of systemic disease, mainly characterized by respiratory distress, known as coronavirus disease 2019 (COVID-19)[1], declared by the World Health Organization (WHO) as an emerging disease of international interest. According to WHO data[2], a total of 5.307.258 COVID-19 cases and 342.069 deaths have been reported globally on 25 of May 2020 (0:00 a.m. CET), of whom, 1.356.603 cases and 160.610 deaths were registered in Europe[3].

Although global data are not yet available, published studies suggest that children (0-17 years old) correspond to less of than 5% of the total number of patients affected by COVID-19 and that children seem to have a less severe disease in comparison to adults[4,5]. Indeed, although severe outcomes (including deaths) have been reported in the pediatric population[6], relatively fewer children with COVID-19 require hospitalization or admission to the intensive care unit (ICU)[7]. Those children with multiple co-morbidities are distinctively at a higher risk for severe illness. However, information on specific risk factors, forms of presentation and prognosis of COVID-19 in pediatric transplantation patients is scarce.

The emergence of COVID-19 has had a profound impact in transplantation worldwide, not only with respect to issues around donors or recipients, but also healthcare resources utilization as the magnitude of COVID-19 cases in certain regions exceeds the available capacity of the health system[8]. At this early stage in the pandemic very little information is available regarding the risk and burden of COVID-19 in pediatric transplant recipients as well as direction regarding protocols to be applied in this special population[9,10] Dealing with this situation, several interventions aligned with international recommendations[11–13] have been implemented in pediatric transplant centers. These include the application of protocols made for adult transplant

recipients[14,15] and the local adaptations of international guidelines[16–19] for the diagnosis, prevention and management of SARS-CoV-2 infection.

The aim of this study was to perform a multi-center comparative analysis among the members of the European Reference Network on Pediatric Transplantation (ERN-TransplantChild) to evaluate the impact of the COVID-19 outbreak on pediatric transplant activity, standard of care for patients in the transplant program, as well as gauging the current approach to patients on the waiting list and transplant recipients diagnosed with COVID-19.

Methods

ERN members of the University Hospital of Padova (Italy) in collaboration with the ERN-TransplantChild coordination team from Hospital Universitario La Paz (Madrid, Spain), prepared a survey for the other ERN-TransplantChild members in order to evaluate the impact of the COVID-19 outbreak on pediatric transplantation across Europe.

Professionals from all transplant programs, both hematopoietic stem cell transplantation (HSCT) and solid organ transplantation (SOT), including kidney, lung, heart, pancreas, intestine, multi-visceral or multi-organic, of the all 18 centers members of ERN TransplantChild distributed in 11 EU countries were invited to participate. The survey included relevant questions to: i) assess pediatric transplantation activity, including living-donation issues; ii) identify the protocols adopted to prevent and manage SARS-CoV-2 infection at the hospital level; iii) evaluate the impact of these practices on the healthcare of transplanted children; and iv), describe the management of confirmed COVID-19 cases among the special population of pediatric transplant recipients and candidates. The complete questionnaire is available online (https://ec.europa.eu/eusurvey/runner/TransplantChild_COVID19).

The survey focused on information from the centers during the 30 days since case reporting (Day 1) began in the participating countries. Total case and cumulative incidence data were obtained from the COVID interactive dashboard from the European Centre for Disease Prevention and Control (available online: https://qap.ecdc.europa.eu/public/extensions/COVID-19/COVID-19.html).

A confirmed case was defined by laboratory testing of SARS-CoV-2 by reverse transcription polymerase chain reaction (RT-PCR). Cases were grouped by the manifestations of the disease by

their severity: mild disease (from asymptomatic to mild symptoms: fever, dry cough, tiredness, muscle aches or headache, sore throat or runny nose), and moderate/severe disease (pneumonia with dyspnea, respiratory frequency ≥ 30/min, blood oxygen saturation (SpO2) ≤ 93%, respiratory failure, septic shock, and/or multiple organ dysfunction).

The survey, published on the EU official web site, was accessible from April 8, 2020 until April 14, 2020 when all ERN-TransplantChild members completed the questionnaire. The survey results were summarized by a descriptive analysis using R statistical software, version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

COVID-19 situation in Europe and participants

All the 18 ERN-TransplantChild centers from 11 countries (Spain, France, Germany, Italy, Lithuania, Netherlands, Poland, Portugal, Sweden, United Kingdom and Belgium) answered the survey. Five of 18 hospitals operate as freestanding pediatric hospitals, while thirteen are within general hospitals including pediatric and adult patients. A total of thirty professionals, representing forty pediatric transplant programs (Table 1), completed the questionnaire: twenty pediatricians in charge of SOT programs, five pediatricians in charge of HSCT programs and five pediatric surgeons. Figure 1A shows the distribution of cases by country in the EU. On April 14 in the EU the number of cases reported was 811,747, with 742,404 cases (91.4%) corresponding to the 11 countries of the centers that participated in the survey. All of them, had a cumulative incidence of cases per 100,000 inhabitants for a period of 30 days at the time of the survey (Figure 1B), with Italy starting the detection of cases on February 23, 2020, and all countries on March 14, 2020, when Lithuania began the D1 of reported cases.

Pediatric transplant activity during the COVID-19 outbreak

As concerns pediatric transplant activity, 10 out of 18 centers (55%) remained active during the month of March 2020, while seven limited their activity to urgent cases and one completely suspended pediatric transplant programs. Besides COVID-19 transmission issues, in 4/7 centers where only urgent transplants were performed, the limitation was also due to limited resources, especially to the lack of availability of ICU beds for transplant patients. Overall, 12 of 18 centers

(67%) experienced a reduction (from 25 to 75%) of their usual workload during the study period (Table 1). Only 3 programs (2 kidney and 1 liver) were not available to perform living donor transplantation; however, in the rest of the centers, the living donor was reserved for urgent cases. Cadaveric donors were available with specific local adaptations of the protocols for COVID-19 screening, although their accessibility was considerably reduced. In HSCT programs the problem was reflected in the unrelated donors from other countries, being influenced by quarantine mobility restrictions, since the limitations of the donor's displacement to the donation centers, to decreased shipping capacity.

Outpatient visits of pediatric transplanted patients were also affected by the COVID-19 outbreak in 17 out of 18 centers (96%). One center entirely suspended outpatient activity (Table 1), nine centers limited the visits to selected patients, and seven centers started or increased the use of telemedicine. In eight centers (44%) outpatient visits were performed only after a telephone pre-triage excluding epidemiological (e.g., close contact with a known COVID-19 case) and clinical risk factors (e.g., ongoing fever or respiratory symptoms in the patient or in the caregiver) for SARS-CoV-2 infection. This telephone pre-triage was extended to hospital admissions in 15 centers (83%). A negative nasopharyngeal swab for SARS-CoV-2 was also required before planned hospitalizations or procedures in 10 centers (55%).

Strategies to prevent and manage SARS-CoV-2 infection at the hospital level

Only four out of 18 ERN-TransplantChild centers reported the availability of specific COVID-19 protocols for pediatric transplant patients in their countries at the time of the survey. Nevertheless, twelve out of 30 respondents belonging to seven centers had an adapted local protocol based on scientific society guidelines. In relation to the hospitalization decision of a COVID-19 patient, we asked about ward resources or critical care available to hospitalize pediatric transplant patients. Half of the respondents considered that clinically stable pediatric transplant patients could be admitted to a dedicated room in an isolated room (with or without negative pressure). Additionally, 91% respondents reported the capacity to admit critically ill SOT/HSCT pediatric patients with suspected or confirmed COVID-19 in a pediatric ICU. Hospital admission criteria for pediatric transplant patients with SARS-CoV-2 infection varied among respondents. Twelve of 18 centers decided to follow COVID-19 cases with mild symptoms at

home through telemedicine, and to hospitalize only suspected cases with moderate-severe symptoms; three centers admitted for observation suspected cases for COVID-19 confirmation to all pediatric patients, regardless of symptoms severity; the other three centers decided on a case-by-case basis, depending on the patient's symptoms and requirements, as well as the available hospital resources.

With respect to caregiver policy during hospital stays, 17/18 centers allowed only one caregiver per patient, equipped with protective personal equipment (i.e. surgical mask); Moreover, at least 4 centers considered nasopharyngeal swab testing for SARS-CoV-2 in the caregiver to support the decision of which caregiver will stay with the child during admission.

We ask about the material that professionals use during their daily activity in the hospital. For the healthcare of non-COVID patients-19, a total of 16 centers (88%) reported the use of a mask (14 centers surgical mask and 2 with FFP2 mask) and gloves. In relation to the surveillance of healthcare workers, only one center reported that all pediatric professionals at their center were periodically tested for SARS-CoV-2 infection independently of clinical symptoms and from the exposure to known COVID-19 cases. No active surveillance was reported by the remaining respondents in the other ERN-TransplantChild centers.

COVID-19 cases among pediatric population, transplant candidates and recipients

To determine whether participating centers had attended patients with COIVD-19, we initially asked for the number of pediatric patients who have been reported to the hospital. More than half of the participant ERN-TransplantChild centers (10/18) reported less than 10 COVID-19 had treated pediatric patients at the hospital level, six centers reported less than 30 cases, and only two centers reported more than 40 total cases in the pediatric population during the study period. Among affected children, the rate of ICU admission was less than 5% and no deaths were reported.

From the cases followed up by the respondent centers, until April 14, 2020, a total of 14 COVID-19 confirmed cases were reported among pediatric transplant candidates (kidney=2, liver=2, HSCT=2) and recipients (kidney=2, liver=3, HSCT=3) by five ERN-TransplantChild centers (Figure 2). All the six children on the transplant waiting list and six out of 8 transplanted children experienced a mild disease, while two out of 8 pediatric transplant recipients (both HSCT)

presented a moderate/severe disease (Figure 1). Although these are still preliminary data, the treatment strategy varied among centers. Children with mild COVID-19 received supportive therapy for pediatric patients with COVID-19, without any modification of previous immunosuppressive treatment. The HSCT patients with moderate/severe COVID-19 were not on immunosuppressive treatment and received standard support treatment without complications. No patients required admission to the ICU and no deaths were reported.

Discussion

This is the first study offering a European snapshot of the large variations in healthcare organizations, early practices, and perceptions of health care workers actively working in the field of pediatric SOT and HSCT during the COVID-19 pandemic. Pediatric transplantation (0-17 years old) is a highly complex procedure that requires the coordination of resources and specialized professionals[20]. Pediatric transplants represent approximately 10% of the total number of transplants performed worldwide[21]. The 18 ERN-TransplantChild members reported an activity of approximately 1900 pediatric transplants from 2017 to 2019, and of over 5900 outpatient visits in 2019; this number is considerable considering that the participating are national references centers, although at this moment it is not possible to determine the real impact on the health care of this group of patients. Also, it is possible that the reduction will be higher in those centers with programs where more cadaveric donors are performed, or in those centers where resources for living donor donation are compromised by the internal hospital adaptations during this period. As highlighted by the survey, pediatric transplantation activity as well as outpatient visits were substantially negatively affected by the COVID-19 pandemic across Europe. The fear of SARS-CoV-2 transmission risk, shortage of hospital bed capacity and staff, might be the main determinants of this reduction[22,23]. The long-term continuation of these limitations in healthcare resources may have severe consequences both for children on the transplant waiting list and for pediatric transplant recipients due to reduced access to close monitoring and diagnostic testing[23].

Given the absence of guidelines regarding the management of pediatric transplant recipient and candidates during the COVID-19 pandemic, members of the ERN-TransplantChild network devised interdisciplinary strategies to optimize available resources at individual centers. In

almost half of pediatric transplant centers, a negative SARS-CoV-2 swab was also required as an additional admission criterion. Caregiver testing before admission was considered in some centers to allow them to decide who parent stay with the child, but in most cases, the caregiver's lack of symptoms was considered sufficient to contain the possible SARS-CoV-2 in-hospital spread. Moreover, even though the protection of healthcare workers is considered a priority, the test for SARS-CoV-2 infection was periodically performed in only one center, while no active surveillance was reported by the remaining respondents. Although professional screening was not common at this early stage of the pandemic, it will be important to be considered later phases, especially for those professionals who may have contact with higher risk patients with COVID-19, such as immunocompromised patients, to ensure that both healthcare personnel and patients are not put at risk.

A telephone pre-triage to exclude COVID-19 epidemiologic and clinical risk factors, could be a cost-effective strategy and was widely implemented before outpatient visits and hospital admissions. It is also important to highlight how, to overcome the issues related to lockdown, telemedicine technologies have been rapidly introduced to support some activities such as remote patient monitoring and management. This technology was already reported as a potentially valuable tool for the follow up of transplant patients, but experience is limited only to the outpatients setting[24]. Therefore, pediatric transplant centers need to be prepared for difficult and extraordinary situations, such as deciding which patients should be transplanted when resources are limited and the best care for those patients after transplant[8]. Indeed, each donor-recipient scenario may have different considerations in terms of resource limitations, potential benefits and risks[9,25,26]. It is also important to define an appropriate pathway to avoid post-transplant infection[27]. In epidemic regions, transplant centers need to carefully balance the costs and benefits in performing a transplant during the COVID-19 pandemic.

We also reported the occurrence and the outcome of SARS-CoV-2 infection in six children awaiting transplantation and eight pediatric transplant recipients. None of the candidates in the SOT waiting list, nor any of the SOT recipients presented a severe COVID-19 syndrome. The moderate-severe cases described were HSCT patients who were not being treated with immunosuppressive drugs but with probable impairment of their immune system either due to the transplant procedure itself or by the underlying disease[28]. Therefore, even if it seems that the

immunosuppressive treatment in immunocompromised children may not increase the risk of severe COVID-19 disease[29], at present it is not possible to determine whether the post-transplant status could modify the risk for COVID-19 due to the limited number of affected children, or not. Despite being the epicenter of the pandemic at the beginning, the Italian centers had not reported confirmed symptomatic cases at the time of the survey. Recently, NiCastro et. al informed about the adoption of protocols for the early detection of cases in the pediatric population attended in pediatric Hospital in Bergamo[30]. During this study, there were no admitted patients who tested positive for SARS-CoV-2 from the pediatric transplant unit.

Although data are limited at the time of writing, published data is available in 2 pediatric transplant patients with COVID-19, a 13-year-old child with multiple comorbidities who acquired COVID-19 (mild presentation) five years post kidney transplant[31], and 55-month-old girl with COVID-19 pneumonia (moderate presentation) after 5 months undergoing liver transplantation[32]. The treatment of these cases included immunosuppressors reduction, in addition to supportive measures; none of these cases required ICU, and the outcome was favorable, with no reported mortality.

Some limitations of the study methodology should be considered, including those inherent in a survey-based study. This survey reflects the practices adopted by professionals in each center, and while these are major national centers it does not necessarily reflect the situation at a national level. The availability of resources at each center also limits the ability to make universal recommendations in the care of pediatric transplant patients. Due to lack of experience in treating affected pediatric transplant patients, hospital admission criteria for suspected and confirmed COVID-19 cases varied between ERN-TransplantChild centers.

While the majority of centers considered admission of only moderate/severe COVID-19 cases and dealing with the milder ones through telephone calls or telemedicine, other centers preferred to admit all pediatric transplant patients regardless of symptoms. In contrast to adults, almost all ERN-TransplantChild centers had the capacity to admit critically ill pediatric transplant patients with suspected/confirmed COVID-19 into pediatric ICUs[33] as a low rate of severe COVID-19 was reported in children, however, this option may not be available at all centers that routinely perform pediatric transplantation.

In conclusion, the ongoing situation reflects the early impact of the COVID-19 spread, which seems to be a major worldwide challenge for the field of pediatric SOT and HSCT in the next future. The responses are diverse and dependent on local circumstances in the context of absence of prior knowledge. There is a need to expand collaborations and data collection efforts, encourage discussions among experts, clinical trials, and evidence-based practices leading to consensus in addressing the long-term consequences of COVID-19 in pediatric transplant recipients and their families.

Author's contributions

DD, JTC, EB, MC, FDC, LH and PJ contributed to the conception and design the study. DD and JTC performed the data analysis and wrote the manuscript All authors contributed to manuscript revision, read and approved the submitted version.

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Table I. Current situation of Survey Respondents

	n (%)
Participant centers	18
Pediatric transplant programs	40
Kidney	11 (28%)
Liver	13 (32%)
HSCT	6(16%)
Intestinal/MV	4(10%)
Lung	3(7%)
Heart	3(7%)
Current status:	
Active	10 (56%)
Only urgent cases	7(38%)
Stopped	1(6%)
Pediatric transplant activity in the last month:	
Decrease of 25%	2(11%)
Decrease of 50%	4(22%)
Decrease of 75% or more	6(33%)
No reduction	6(33%)
Outpatient visits for pediatric transplant patients:	
Only selected outpatient visits	9(52%)
Outpatient visits by telemedicine tools	7(40%)
All visits are cancelled	1(4%)
No modifications	1(4%)
COVID-19 cases in pediatric population per center:	
0-10	10(56%)
11-20	3(17%)

21-30	3(17%)
More than 40	2(11%)
Rate of COVID-19 pediatric patients requiring ICU per center:	
Below 5%	16(89%)
5-10%	2(11%)
Centers reporting COVID-19 cases in pediatric transplant programs:	5(27%)

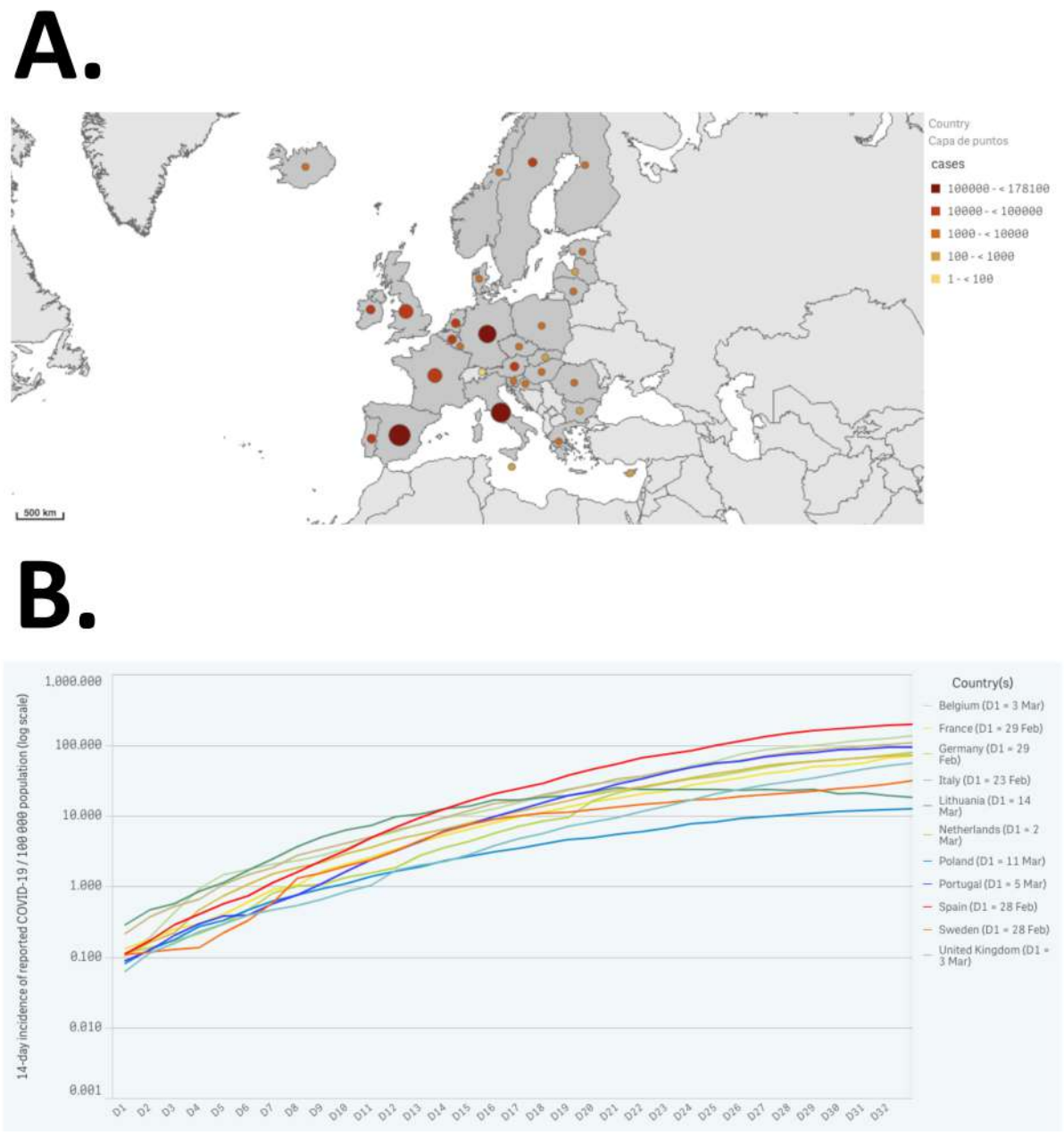
HSCT: Hematopoietic stem cell transplantation, MV: Multivisceral transplant

Figures legends:

Figure 1. A) Distribution of cumulative confirmed COVID-19 cases across European Union. B) Cumulative incidence of reported cases (logarithmic scale) from the 11 countries of members of the ERN TransplantChild. Source: European Centre for Disease Prevention and Control.

Figure 2. Representation of COVID-19 cases in transplants programs of 18 ERN-TransplantChild centers. Blue dots represent the 18 participants centers from 11 countries. In red the 5 centers reporting confirmed COVID-19 cases (5 centers= Hôpital Necker-Enfants Malades - Paris, France; La Paz University Hospital - Madrid, Spain; Cliniques Universitaires Saint-Luc - Brussels, Belgium; Prinsesmaxima centrum - Utrecht, Netherlands; Karolinska University Hospital Stockholm, Sweden).

* Moderate-severe COVID-19 cases. ** Two of 3 cases were moderate-severe COVID-19 cases.



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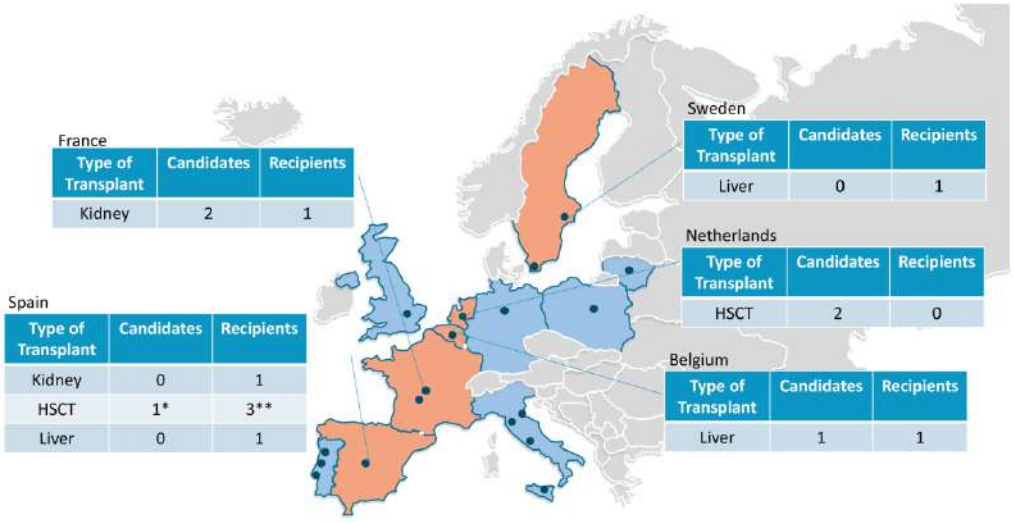

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