ISSN 2220-3230 (online)

World Journal of *Transplantation*

World J Transplant 2022 May 18; 12(5): 83-111

Published by Baishideng Publishing Group Inc

World Journal of Transplantation

Contents

Monthly Volume 12 Number 5 May 18, 2022

World Journal of Transplantation

Monthly Volume 12 Number 5 May 18, 2022

Contents

ABOUT COVER

Editor-in-Chief of *World Journal of Transplantation*, Maurizio Salvadori, MD, Professor, Department of Transplantation Renal Unit, Careggi University Hospital, Florence 50139, Italy. maurizio.salvadori1@gmail.com

AIMS AND SCOPE

The primary aim of *World Journal of Transplantation* (*WJT*, *World J Transplant*) is to provide scholars and readers from various fields of transplantation with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJT mainly publishes articles reporting research results obtained in the field of transplantation and covering a wide range of topics including bone transplantation, brain tissue transplantation, corneal transplantation, descemet stripping endothelial keratoplasty, fetal tissue transplantation, heart transplantation, kidney transplantation, liver transplantation, lung transplantation, pancreas transplantation, skin transplantation, *etc*..

INDEXING/ABSTRACTING

The *WJT* is now abstracted and indexed in PubMed, PubMed Central, Scopus, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Transplantation

ISSN
ISSN 2220-3230 (online)

LAUNCH DATE
December 24, 2011

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Maurizio Salvadori, Sami Akbulut, Vassilios Papalois, Atul C Mehta

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2220-3230/editorialboard.htm

PUBLICATION DATE
May 18, 2022

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

World Journal of Transplantation

Submit a Manuscript: https://www.f6publishing.com

World J Transplant 2022 May 18; 12(5): 83-87

DOI: 10.5500/wjt.v12.i5.83

ISSN 2220-3230 (online)

EDITORIAL

Multiorgan retrieval and preservation of the thoracic and abdominal organs in Maastricht III donors

Daniel Casanova, Federico Castillo, Eduardo Miñambres

Specialty type: Transplantation

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: He K, China

Received: April 5, 2021
Peer-review started: April 5, 2021
First decision: July 29, 2021
Revised: October 10, 2021
Accepted: April 26, 2022
Article in press: April 26, 2022
Published online: May 18, 2022

Daniel Casanova, Federico Castillo, Department of Surgery, University Hospital Marqués de Valdecilla University Cantabria, Santander 39008, Cantabria, Spain

Eduardo Miñambres, Intensive Care Unit, Transplant Office, University Hospital Marques de Valdecilla University of Cantabria Medical School, Santander 39008, Cantabria, Spain

Corresponding author: Daniel Casanova, FRCS (Hon), MD, PhD, Full Professor, Professor, Surgeon, Department of Surgery, University Hospital Marqués de Valdecilla University Cantabria, Chairman Board Europeo de Trasplante, President Section Surgery UEMS, Servicio de Cirugía General y Digestiva Hospital Universitario Marqués de Valdecilla, Santander 39008, Cantabria, Spain. daniel.casanova@unican.es

Abstract

This editorial describes the indications and technical aspects of the simultaneous retrieval of thoracic and abdominal organs in Maastricht III donors as well as the preservation of such organs until their implantation.

Key Words: Multiorgan retrieval; Abdominal organs; Thoracic organs; Maastricht III; Preservación; Transplantation

Core Tip: Every year approximately 100000 transplants are performed worldwide, which together with good success rates and the improvement of immunosuppressive medication means that indications for transplant are continually increasing. However, the imbalance between supply and demand of organs for transplantation means that the existing number of donors is insufficient for the large number of patients on waiting lists. Donation of organs after death needs to become an integral consideration as part of end-of-life care.

Citation: Casanova D, Castillo F, Miñambres E. Multiorgan retrieval and preservation of the thoracic and abdominal organs in Maastricht III donors. *World J Transplant* 2022; 12(5): 83-87
URL: https://www.wjgnet.com/2220-3230/full/v12/i5/83.htm
DOI: https://dx.doi.org/10.5500/wjt.v12.i5.83

INTRODUCTION

Organ transplantation is one of the most important advances in modern medicine, making it possible to increase the longevity and quality of life of transplant recipients, with patient and graft survival rates that were unimaginable just a few decades ago.

Every year approximately 100000 transplants are performed worldwide, which together with good success rates and the improvement of immunosuppressive medication means that indications for transplant are continually increasing. However, the imbalance between supply and demand of organs for transplantation means that the existing number of donors is insufficient for the large number of patients on waiting lists. Donation of organs after death needs to become an integral consideration as part of end-of-life care.

In Spain, due to efficient organization and public trust in the system and management of available resources, donation rates stand at 49 per million population (the highest in the world), although this supply still does not meet existing needs. There is, therefore, a need to further optimize the management of donation by tapping into new sources of organs. Currently, the most common type of donor for transplantation is the brain-dead donor, although in some centres, living donor transplantation programmes have been developed as an alternative, primarily for the kidney and liver.

Currently, we are witnessing renewed interest in organ procurement from donors after cardiocirculatory arrest. This type of donor was not previously accepted by most transplant teams due to the prolonged periods of ischaemia after cardiac arrest resulting in significant cell damage due to hypoxia. It should be remembered that before the brain death law was implemented in 1968, many organ donors were of this type, as it was necessary to wait for cardiocirculatory arrest to occur before harvesting organs.

In the 1980s transplant groups, especially in the United States and northern European countries, began including donation after cardiocirculatory arrest into their programmes. Kidneys were obtained either from living donors or from donors in asystole, who in English-language terminology have been called Non Heart Beating Donors, Donors after Cardiac Death or more recently and due to considerations related to the diagnosis of death Donors after the Circulatory Determination of Death (DCDD). Controlled Donation after Circulatory Determination of Death (cDCDD) is gradually becoming an important source of organs in countries with active programmes[1-4]. In Spain from 2010-2019, cDCDD accounted for up to 28% of total organ procurement activity[5].

In 1995, the first symposium on donation after cardiocirculatory arrest was held in Maastricht (The Netherlands), where three fundamental aspects were agreed upon: (1) Classification of donors after cardiac arrest (Non Heart Beating Donors) into four categories (Table 1); (2) Criteria for determining death after irreversible cardiac arrest; and (3) The period of time to wait between cardiac arrest and the start of organ harvesting.

In 1998, the United States Institute of Medicine published the consensus on transplantation with donors in irreversible cardiac arrest, recommending a non-touch time of 5 min, which became the standard time period for most groups[6]. However, a "no-touch period" attempts and varies widely between countries-protocols, ranging from 5 to 20 min[7].

Therefore, potential type III asystole donors are those patients with no apparent contraindications for donation who due to their admission pathology and subsequent evolution are expected to go into cardiorespiratory arrest after withdrawal of life-support measures within a period of time compatible with organ donation. The selection of donors is decided jointly with the family.

MAJORITY OF POTENTIAL MAASTRICHT TYPE III DONORS

The majority of potential Maastricht type III donors are patients with severe neurological pathology with a catastrophic functional prognosis and in whom progression to brain death is not foreseeable. Other patients may come from respiratory and/or cardiological medical pathologies with unfavourable evolution and prognosis, in whom the therapeutic measures applied have proved ineffective. There is no absolute age limit for controlled asystole donation, but it tends to be more restrictive than for brain death donation. In general, it depends on the organ to be transplanted, but a limit of 65-70 years has been established, although this limit is likely to be re-evaluated as experience is gained with this type of donation.

Current protocol recommendations are that the time elapsed between extubation and cardiorespiratory arrest should not exceed 2 h, although this time is debatable, as the haemodynamic and respiratory conditions of the patient after extubation are potentially more important.

The medical criteria for organ selection do not differ from the general criteria for brain death donation, although they are usually more restrictive. With regard to family consent, specific consent must be obtained for femoral vessel cannulation, heparin administration as well as administration of organ preservation drugs prior to death. Once mechanical ventilation has been withdrawn, periods of hypotension, hypoxia or anuria should be recorded. Sedation should be administered as necessary to ensure the patient's comfort and well-being, in accordance with recommendations on the management

Table 1 Donors after Cardiac Death Maastricht classification

Category	Type	Circumstances
1	Uncontrolled	Dead on arrival
2	Uncontrolled	Unsuccessful resuscitation
3	Controlled	Cardiac arrest follows planned withdrawal of life sustaining treatments
4	Either	Cardiac arrest in a patient who is brain dead

of the critically ill patient at the end of life from the relevant bioethics committee.

The death of the patient will be confirmed by a doctor responsible for the Critical Care Unit where the patient is admitted and who is not involved in the donation process, after confirming the absence of a curve in the arterial monitoring, the absence of breathing and the absence of response to stimuli for a period of 5 min. International recommendations on the type III donation procedure have recently been published that help define and clarify the most debated aspects of this type of donation[8].

In many hospitals, the multiorgan harvesting of abdominal organs in cDCDD is performed using a rapid harvesting technique. However, in recent years, the procurement of organs from asystole has developed significantly in Spain. Several centres are now pioneering the use of abdominal normothermic regional perfusion (NRP) with extracorporeal membrane oxygenation (ECMO) devices as a strategy for in situ blood reperfusion in both controlled and uncontrolled Donors after Cardiac Death [9-11]. Simultaneous thoracic and abdominal organ harvesting in controlled asystole type III donors is based on normothermic ECMO technology. NRP has the potential to decrease or ameliorate ischaemic injury and facilitate the testing of graft viability, reducing the percentage of organs discarded before transplantation.

One of the important advantages of the Spanish system is that it is legally authorised to initiate anticoagulation manoeuvres and placement of cannulae with consent.

Functional warm ischaemia time for abdominal grafts is defined as the time from systolic blood pressure < 60 mmHg to the onset of NRP (5 min of non-contact period included). For functional warm ischaemia time, an upper time limit of 30 min is set for the liver, pancreas and heart and 60 min for lungs and kidneys. In the intensive care unit, heparin administration (300-500 units/kg) and cannulation of the femoral vessels is performed prior to withdrawal of life support therapies. The femoral artery and femoral vein are cannulated, and an aortic balloon occlusion is placed in the contralateral groin to prevent cerebral and coronary perfusion during NRP. The goal of performing abdominal NRP is to maintain a pump flow of 2.0-2.4 L/min. A continuous pressure of 60-65 mmHg and a temperature of 37 °C should be maintained at the femoral arterial cannula; bicarbonate is administered after NRP is initiated to maintain a pH of 7.35-7.45, and a haematocrit > 25% is targeted.

Whilst NRP appears to be the ideal method for abdominal grafts, the lungs are removed from the donor in controlled asystole using the rapid extraction technique, by lowering the lung temperature with topical cooling as quickly as possible. This combined method was first described in the United Kingdom[12]. Our group has proposed a variant of the technique with premortem interventions, in which the risk of possible trans-diaphragmatic cooling of the liver is minimized[13]. However, there is still some reluctance among practitioners to combine the lung cooling and rapid retrieval technique with NRP for abdominal grafts. This method increases the complexity of the procurement procedure and might injure the grafts due to double temperature (low temperature affecting the liver and normothermia affecting the lungs) or due to inadequate perfusion pressure in the pump as a result of bleeding in the thorax after removal of the cardiopulmonary block or after vena cava clamping. From a technical point of view, once death is determined and NRP is initiated, a rapid sternotomy is performed. At the same time, the donor is reintubated and ventilated 5 min after NRP with 100% oxygen and a positive end-expiratory pressure of 5 cm H2O. The pulmonary artery is cannulated for cold lavage perfusion with Perfadex® (50 mL/kg). One litre of saline at 4 °C is administered in both hemithoraces for topical cooling, and the superior vena cava is ligated to separate the thoracic and abdominal compartments. Once the lungs are preserved with Perfadex® solution, lung extraction is performed using the same technique as for Donors after Cardiac Death donors.

To avoid low blood flow in the pump due to the absence of venous return from the thorax and head, 1.0-1.5 L of saline are administered to the cDCDD donor just before ligation of the vena cava. After perfusing the pulmonary artery with preservation solution, a laparotomy is performed to assess the appearance of the abdominal grafts by placing a cannula in the inferior mesenteric vein. After 2 h of NRP, the ECMO device is stopped, and a rapid dual cold organ perfusion is performed.

The retrieval of the kidneys, pancreas and liver is performed in the conventional way with the same surgical technique used in brain death donation, as haemodynamic stabilisation due to perfusion with NRP allows a completely controlled sequence of dissection and extraction. Perfusion with preservation solutions allows the kidneys, pancreas and liver to be obtained in optimal conditions for implantation.

Blood samples are taken from the ECMO device immediately after starting the NRP and at least every 30 min. Biochemistry, serum lactate levels and haematocrit are analysed. If alanine transaminase or aspartate transaminase exceed four times the upper limit of normal during NRP, the liver and pancreas are ruled out, even with a normal macroscopic appearance. Lactate levels are also monitored during NRP.

Ethical questions have been raised about the use of abdominal NRP and premortem interventions in cDCDD such as the possibility of restoring cerebral circulation after declaration of death if the aortic balloon occlusion technique fails. A specific methodology to avoid restoration of cerebral circulation after determination of death when using NRP and antemortem cannulation has recently been described and validated in a multicentre study[14]. This approach avoids the aforementioned ethical concern by guaranteeing the absence of cerebral resuscitation.

In the last 5 years the use of thoraco-abdominal NRP (TA-NRP) has made heart transplantation feasible and allows practitioners to assess heart function before organ procurement without any negative impact on the preservation of abdominal organs. The combined retrieval of lungs, heart and abdominal grafts using TA-NRP has been performed successfully in our centre. The use of TA-NRP in cDCDD heart donors in conjunction with cold storage following retrieval can eliminate the need to use *ex situ* machine perfusion devices, making cDCDD heart transplantation economically possible in other countries[15-17].

CONCLUSION

In summary, the use of TA-NRP for heart, lung and abdominal grafts or the combined approach (rapid recovery of the lungs and NRP for abdominal grafts) offers a remarkable recovery rate and is safe for thoracic organs (heart and lungs). Furthermore, abdominal grafts can benefit from the use of NRP as a preservation procedure. As this is a promising initial experience, further studies are needed to confirm our findings in the combined thoracic and abdominal procurement procedure.

FOOTNOTES

Author contributions: Casanova D designed the research, analysed the data and wrote the paper; Castillo F performed the research and analysed the data; Miñambres E performed the research and analysed the data; All authors wrote, read and approved the final manuscript.

Conflict-of-interest statement: All authors have nothing to disclose.

Country/Territory of origin: Spain

ORCID number: Daniel Casanova 0000-0003-3863-5039; Federico Castillo 0000-0002-5092-8830; Eduardo Miñambres 0000-0002-0466-044X.

S-Editor: Wang LL
L-Editor: Filipodia
P-Editor: Wang LL

REFERENCES

1 **Kootstra G**, Daemen JH, Oomen AP. Categories of non-heart-beating donors. *Transplant Proc* 1995; **27**: 2893-2894 [PMID: 7482956]
2 **Heineman E**, Daemen JH, Kootstra G. Non-heart-beating donors: methods and techniques. *Transplant Proc* 1995; **27**: 2895-2896 [PMID: 7482957]
3 **Kootstra G**. The asystolic, or non-heartbeating, donor. *Transplantation* 1997; **63**: 917-921 [PMID: 9112339 DOI: 10.1097/00007890-199704150-00001]
4 **Wijnen RM**, Booster MH, Stubenitsky BM, de Boer J, Heineman E, Kootstra G. Outcome of transplantation of non-heart-beating donor kidneys. *Lancet* 1995; **345**: 1067-1070 [PMID: 7715337]
5 **Andreeva VA**, Egnell M, Stoś K, Przygoda B, Talati Z, Touvier M, Galan P, Hercberg S, Pettigrew S, Julia C. Polish Consumers' Understanding of Different Front-of-Package Food Labels: A Randomized Experiment. *Foods* 2022; **11**: 134

[PMID: 35010260 DOI: 10.3390/foods11010134]

6 **Institute of Medicine (US) Committee on Non-Heart-Beating Transplantation II: The Scientific and Ethical Basis for Practice and Protocols**. Non-Heart-Beating Organ Transplantation: Practice and Protocols. Washington (DC): National Academies Press (US), 2000 [PMID: 25077239 DOI: 10.17226/9700]

7 **Grunfeld Eva**. Implementing cancer survivorship care planning: workshop summary. Institute of Medicine, National Academies Press, Washington, DC, 2007. *Psycho-oncology* 2007; **16**: 1054-1055 [DOI: 10.1002/pon.1237]

8 **Ortega-Deballon I**, Hornby L, Shemie SD. Protocols for uncontrolled donation after circulatory death: a systematic review of international guidelines, practices and transplant outcomes. *Crit Care* 2015; **19**: 268 [PMID: 26104293]

9 **Domínguez-Gil B**, Ascher N, Capron AM, Gardiner D, Manara AR, Bernat JL, Miñambres E, et al Expanding controlled donation after the circulatory determination of death: statement from an International collaborative. Intensive Care Med 2021; 47: 265-281 [DOI: 10.1007/s00134-020-06341-7]

10 **Miñambres E**, Suberviola B, Dominguez-Gil B, Rodrigo E, Ruiz-San Millan JC, Rodríguez-San Juan JC, Ballesteros MA. Improving the Outcomes of Organs Obtained From Controlled Donation After Circulatory Death Donors Using Abdominal Normothermic Regional Perfusion. *Am J Transplant* 2017; **17**: 2165-2172 [PMID: 28141909 DOI: 10.1111/ajt.14214]

11 **Hessheimer AJ**, Coll E, Torres F, Ruíz P, Gastaca M, Rivas JI, Gómez M, Sánchez B, Santoyo J, Ramírez P, Parrilla P, Marín LM, Gómez-Bravo MÁ, García-Valdecasas JC, López-Monclús J, Boscá A, López-Andújar R, Fundora-Suárez J, Villar J, García-Sesma Á, Jiménez C, Rodríguez-Laíz G, Lladó L, Rodríguez JC, Barrera M, Charco R, López-Baena JÁ, Briceño J, Pardo F, Blanco G, Pacheco D, Domínguez-Gil B, Sánchez Turrión V, Fondevila C. Normothermic regional perfusion vs. super-rapid recovery in controlled donation after circulatory death liver transplantation. *J Hepatol* 2019; **70**: 658-665 [PMID: 30582980 DOI: 10.1016/j.jhep.2018.12.013]

12 **Miñambres E**, Rodrigo E, Suberviola B, Valero R, Quintana A, Campos F, et al Strict selection criteria in uncontrolled donation after circulatory death provide excellent long-term kidney graft survival. Clin Transplant 2020; 34: e14010 [DOI: 10.1111/ctr.14010]

13 **Oniscu GC**, Siddique A, Dark J. Dual temperature multi-organ recovery from a Maastricht category III donor after circulatory death. *Am J Transplant* 2014; **14**: 2181-2186 [PMID: 25056864 DOI: 10.1111/ajt.12808]

14 **Miñambres E**, Ruiz P, Ballesteros MA, Álvarez C, Cifrián JM, Atutxa L, Ventoso A, Castillo F, Gastaca M. Combined lung and liver procurement in controlled donation after circulatory death using normothermic abdominal perfusion. Initial experience in two Spanish centers. *Am J Transplant* 2020; **20**: 231-240 [PMID: 31265753 DOI: 10.1111/ajt.15520]

15 **Perez-Villares JM**, Rubio JJ, Del Río F, Miñambres E. Validation of a new proposal to avoid donor resuscitation in controlled donation after circulatory death with normothermic regional perfusion. *Resuscitation* 2017; **117**: 46-49 [PMID: 28591558 DOI: 10.1016/j.resuscitation.2017.05.030]

16 **Messer S**, Page A, Colah S, Axell R, Parizkova B, Tsui S, Large S. Human heart transplantation from donation after circulatory-determined death donors using normothermic regional perfusion and cold storage. *J Heart Lung Transplant* 2018; **37**: 865-869 [PMID: 29731238 DOI: 10.1016/j.healun.2018.03.017]

17 **Miñambres E**, Royo-Villanova M, Pérez-Redondo M, Coll E, Villar-García S, Canovas SJ. Spanish experience with heart transplants from controlled donation after the circulatory determination of death using thoraco-abdominal normothermic regional perfusion and cold storage. *Am J Transplant* 2021; **21**: 1597-1602 [PMID: 33319435 DOI: 10.1111/ajt.16446]

World Journal of Transplantation

Submit a Manuscript: https://www.f6publishing.com

World J Transplant 2022 May 18; 12(5): 88-99

DOI: 10.5500/wjt.v12.i5.88

ISSN 2220-3230 (online)

MINIREVIEWS

Pediatric transplantation during the COVID-19 pandemic

Christos Dimitrios Kakos, Ioannis A Ziogas, Georgios Tsoulfas

Specialty type: Transplantation

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Al-Ani RM, Iraq; Jin X, China

Received: December 13, 2021
Peer-review started: December 13, 2021
First decision: March 13, 2022
Revised: March 16, 2022
Accepted: April 20, 2022
Article in press: April 20, 2022
Published online: May 18, 2022

Christos Dimitrios Kakos, Ioannis A Ziogas, Surgery Working Group, Society of Junior Doctors, Athens 15123, Greece

Ioannis A Ziogas, Division of Hepatobiliary Surgery and Liver Transplantation, Department of Surgery, Vanderbilt University Medical Center, Nashville, TN 37232, United States

Georgios Tsoulfas, Department of Transplantation Surgery, Aristotle University School of Medicine, Thessaloniki 54622, Greece

Corresponding author: Georgios Tsoulfas, FACS, FICS, MD, PhD, Professor, Department of Transplantation Surgery, Aristotle University School of Medicine, 66 Tsimiski Street, Thessaloniki 54622, Greece. tsoulfasg@gmail.com

Abstract

Children infected by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) seem to have a better prognosis than adults. Nevertheless, pediatric solid organ transplantation (SOT) has been significantly affected by the unprecedented coronavirus disease 2019 (COVID-19) pandemic during the pre-, peri-, and post-transplant period. Undoubtedly, immunosuppression constitutes a real challenge for transplant clinicians as increased immunosuppression may prolong disease recovery, while its decrease can contribute to more severe symptoms. To date, most pediatric SOT recipients infected by SARS-CoV-2 experience mild disease with only scarce reports of life-threatening complications. As a consequence, after an initial drop during the early phase of the pandemic, pediatric SOTs are now performed with the same frequency as during the pre-pandemic period. This review summarizes the currently available evidence regarding pediatric SOT during the COVID-19 pandemic.

Key Words: Pediatric; Transplantation; SARS-CoV-2; COVID-19; Immunosuppression

Core Tip: Pediatric patients experience milder symptoms of coronavirus disease 2019 (COVID-19). Pediatric solid organ transplantation during the COVID-19 pandemic represents a real challenge not only for the solid organ transplantation candidates and recipients but also for the transplant clinicians. Immunosuppression increases the risk of COVID-19 but may also provide a benefit against possible infection, as it lowers the risk of a catastrophic hyperinflammatory response from the host. We herein review the currently available evidence regarding pediatric solid organ transplantation during the COVID-19 pandemic.

Citation: Kakos CD, Ziogas IA, Tsoulfas G. Pediatric transplantation during the COVID-19 pandemic. *World J Transplant* 2022; 12(5): 88-99
URL: https://www.wjgnet.com/2220-3230/full/v12/i5/88.htm
DOI: https://dx.doi.org/10.5500/wjt.v12.i5.88

INTRODUCTION

Coronavirus disease 2019 (COVID-19) has impacted all people worldwide and particularly people with chronic underlying comorbidities. Specifically, people with weakened immunity either due to an underlying disease or due to immunosuppression are at high risk. Although children represent just 2%-10% of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) diagnostic cases and seem to have less severe disease when compared with adults[1], pediatric solid organ transplantation (SOT) candidates and recipients have been significantly afflicted by the pandemic. The aim of this review is to summarize and discuss the currently available data regarding pediatric SOT during the COVID-19 pandemic.

CHILDREN AND COVID-19

It is well known now that children experience milder COVID-19 when compared with adults and a lower proportion of children require hospitalization[2,3]. The most frequently reported symptoms are cough and fever, while some pediatric patients may also present with gastrointestinal symptoms[4]. Although fatalities are rare in the pediatric population, 2%-8% of children with COVID-19 will eventually require admission to an intensive care unit[5]. Pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 is a post-infectious consequence of pediatric SARS-CoV-2 infection presenting with gastrointestinal, cardiac, renal, or neurologic manifestations[6].

There has been excessive research on why adults experience a more severe form of COVID-19. A key concept is the difference between the pediatric and adult immune systems. Except for the most severe SARS-CoV-2 cases, children appear to preserve CD8+ cytotoxic response[6-8], as they do not face the immunosenescence that normally occurs with aging. Data have also shown that children might have more powerful adaptive immunity[9]. For example, pediatric SARS-CoV-2 patients do not present with either lymphopenia or high neutrophil/lymphocyte ratio[6]. In addition, adults have higher levels of circulating proinflammatory cytokines [interleukin-1β (IL-1β), IL-6, IL-10, IL-12, interferon-γ, tumor necrosis factor-α (TNF-α), C-reactive protein] than pediatric SARS-CoV-2 patients[10-12]. Although in a study from New York City, IL-6 and TNF-α values did not differ from adults[13].

A finding that needs further investigation is the potential role of angiotensin-converting enzyme 2 (ACE2) receptor, which is the main binding protein of SARS-CoV-2 on host cells[14]. ACE2 has been described as an anti-fibrotic and anti-inflammatory agent against pulmonary leak and inflammation, thus higher expression of ACE2 that has been observed in children may contribute to the fact that children are more resistant to SARS-CoV-2[7].

Furthermore, the fact that children typically do not have significant comorbidities, such as arterial hypertension, diabetes mellitus, or congestive heart failure, may contribute to the milder cases of COVID-19 observed. Associated factors that predispose a negative outcome in children with SARS-CoV-2 have not been well defined[15]. Nevertheless, previous studies have identified obesity, hypoxemia at clinical presentation, asthma, congenital heart disease, inherited metabolic syndrome, chromosomal disorders, and ethnicity as risk factors for severe SARS-CoV-2 infection in children[16-19]. Last but not least, another theory suggests that common childhood infections (respiratory syncytial virus, mycoplasma pneumoniae) can carry out cross protection, so children who have recently recovered from these infections may have higher immunoglobin G titers than adults[20,21].

SARS-COV-2 AND HEPATIC/RENAL MANIFESTATIONS IN CHILDREN

SARS-CoV-2 enters the liver parenchyma through the ACE2 receptor. However, the liver is only rarely affected seriously by the disease, most probably due to its tolerogenic environment[22,23]. The most common hepatic manifestation is an elevation of hepatic transaminases in 6%-27% of pediatric cases and a mild elevation of γ-glutamyl transferase, alkaline phosphatase, and total bilirubin, yet their clinical significance remains unclear[24]. The liver damage may be directly caused by viral infection of the liver cells from medications like remdesivir or lopinavir/ritonavir or from chronic hypoxia[25-27]. High levels of IL-6 and IL-10 are associated with severe SARS-CoV-2 infection but not with SARS-CoV-2-related abnormal liver enzymes[28].

A cohort study from the United States and the United Kingdom demonstrated that adults with chronic liver disease and cirrhosis are prone to increased risk of adverse outcomes following SARS-CoV-2[29]. A study from northern Italy also noted that adults and children with autoimmune liver disease maintained satisfactory health status despite their imbalanced immune system[30]. Another Italian multicenter study that included both cirrhotic and non-cirrhotic liver disease patients demonstrated that 84% of children with chronic liver disease remained healthy during the outbreak[9]. It remains unclear whether children with chronic liver disease experience more severe symptoms.

SARS-CoV-2 can also present with renal manifestations, while several studies suggest that kidney transplantation should be continued during the COVID-19 pandemic under certain precautions[31-34]. Acute kidney injury is mostly associated with immune alterations and direct cytopathic lesions by SARS-CoV-2[35]. Acute tubular injury is also a common yet typically mild manifestation[36]. Comorbidities, such as diabetes mellitus and cardiovascular disease, can delay recovery from acute kidney injury[37]. A multicenter study from Turkey revealed that the incidence of SARS-CoV-2 is higher in pediatric patients on dialysis or after kidney transplantation, yet the authors reported that regional factors, such as the high population, the crowded households, and socioeconomic status in Istanbul, may have contributed to this particular observation in that cohort[38]. They also found that the hospitalization rate was higher in dialysis patients compared with kidney transplantation recipients, potentially due to a higher proportion of asymptomatic disease in kidney transplantation recipients[38].

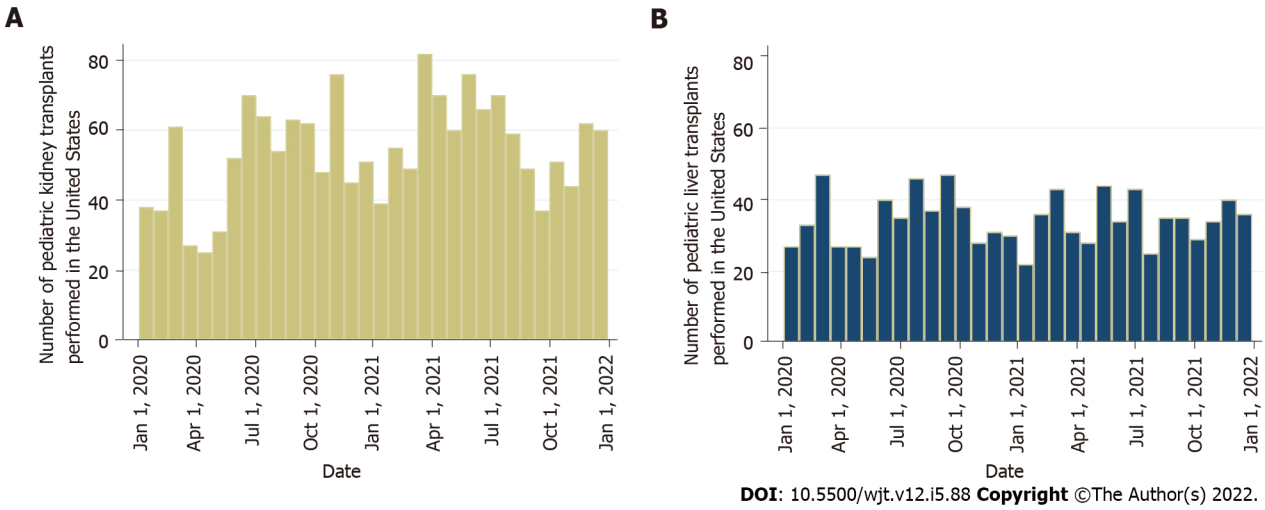
IMPACT OF SARS-COV-2 ON PEDIATRIC TRANSPLANTATION

It was inevitable that the COVID-19 pandemic would affect the transplant activity worldwide. A multicenter analysis of the European Reference Network on Pediatric Transplantation showed a substantial reduction of pediatric transplants across Europe[39]. This was related to the precautions and measures to minimize SARS-CoV-2 transmission, the shortage of hospital beds and staff, the restrictions in operation room availability, and a notable decline in the recovery of deceased donor organs, especially during the early phase of the pandemic[40]. Additionally, United States data from the Scientific Registry of Transplant Recipients showed an initial decrease in pediatric kidney transplants from both deceased and living donors by 47% and 82%, respectively[41]. Subsequently, there was a continual increase with numbers reaching the expected pre-pandemic levels by May 2020[41]. The authors also reported a 189% increase in waitlist removal due to mortality or deterioration[41]. Kemme *et al*[42] used the same registry studying pediatric liver transplantation. They found a decrease in waitlist addition by 25% between March and May of 2020, with Black candidates being affected the most. During the early phase of the pandemic there was a 38% reduction in pediatric liver transplantation, with Black children experiencing an 81% decline in living donor liver transplantation in contrast to White children who faced no change in this category. Overall, White children had a 30% drop in liver transplantation during the pandemic[42]. Figure 1 depicts the number of pediatric kidney and liver transplants performed in the United States between January 1, 2020 and January 1, 2022.

PEDIATRIC TRANSPLANTATION DURING THE COVID-19 PANDEMIC

Except for universal recommendations from transplant societies worldwide, there are no mandatory guidelines specific to pediatric SOT during the pandemic. The decision for SOT depends on the urgency of the need for a new organ and the risk-to-benefit ratio. Both pediatric SOT candidates and living donors should follow prevention strategies to reduce potential exposure to SARS-CoV-2 in the pretransplant period. Self-quarantine for 14 d prior to living donation is important, while a negative swab test for both the candidate and the donor upon admission to the hospital should also be required. Particularly in cases of pediatric SOT, the caregiver should also be asymptomatic and have a negative swab test prior to transplant. Further, most transplant societies strongly mandate universal SARS-CoV-2 screening of potential deceased donors before organ procurement[43].

There is no consensus about the optimal time for transplantation when the potential donor had a SARS-CoV-2 infection. In general, it is recommended to avoid grafts from donors with active SARS-CoV-2 infection[44], while there are different acceptance criteria for donors who have recently recovered



DOI: 10.5500/wjt.v12.i5.88

Figure 1 Number of pediatric transplants performed in the United States between January 1, 2020 and January 1, 2022 (data from the United Network for Organ Sharing database). A: Kidney transplants; B: Liver transplants.

from the infection[43]. Some transplant societies recommend using a graft from a living donor at least 28 d after symptom resolution irrespective of real-time reverse transcriptase polymerase chain reaction (RT-PCR) positivity. Due to the pulmonary and renal dysfunction associated with SARS-CoV-2 infection, additional considerations may be appropriate when the procedure involves transplantation of lungs or kidneys from a previously infected donor.

There is a scarcity of data regarding the optimal time of SOT if a pediatric candidate is infected by SARS-CoV-2. Ideally, the candidate should be both asymptomatic and have a negative test. Notably, Goss *et al*[45] reported an uncomplicated liver transplantation in a child positive for SARS-CoV-2 on a nasopharyngeal swab test just 4 wk before transplant. The immunoglobin G specific antibodies persisted for 6 wk after liver transplantation, with unaltered immunosuppression per the center's standard protocol[45]. Until additional data are available, the risk of the procedure must always be weighed against the risk of deferring SOT.

On another note, technology overall has significantly changed the way people communicate during the COVID-19 pandemic, and thus telemedicine can have a pivotal role on transplant follow-up as it facilitates the general rules for social distancing[46]. However, a German study showed that most young adults who underwent liver transplantation in childhood were afraid to attend medical appointments and 40% reported lower appointment adherence[47]. Additionally, although video consultations might be helpful for follow-up, their acceptance by liver transplantation recipients was lower than expected [47]. It is important that pediatric patients adhere to follow-up appointments after SOT, and their parents should notify the transplant provider of any suspected or proven SARS-CoV-2 exposure and discuss whether additional measures are needed. Careful hand hygiene and avoidance of crowds during the period of high immunosuppression are key strategies for prevention of a possible infection [48].

Finally, several studies have evaluated the SARS-CoV-2 vaccine safety and efficacy in SOT recipients and children, with nearly all of them supporting that the administration of at least two vaccine doses in these patients is safe and efficient[49-55]. There is also an ongoing study approved by Johns Hopkins University examining the levels of SARS-CoV-2 antibodies in children who are organ transplant candidates or recipients before and after they get the SARS-CoV-2 vaccine (IRB00248540).

MANAGEMENT OF SARS-COV-2 POSITIVE PEDIATRIC TRANSPLANT RECIPIENTS

A confirmed SARS-CoV-2 case requires laboratory evidence of viral detection. The testing strategies vary by geographical location and testing capacity. A nasopharyngeal RT-PCR test is the recommended gold standard. However, a negative RT-PCR test does not definitively exclude SARS-CoV-2 infection, and the reported rates of false negative results vary between 2%-29%[56]. If symptoms persist, a second nasopharyngeal RT-PCR test should be performed after 48-72 h. Depending on the time of the year, an evaluation for other respiratory viruses should be considered. An alternative diagnosis would reduce but not eliminate the possibility of COVID-19, while the detection of another respiratory pathogen may require additional management (*e.g.*, antiviral treatment in case of influenza infection).

Antibody tests should not be used to diagnose acute SARS-CoV-2 infection, while their application to assess the host response after an infection is an area under investigation. It is unknown if pediatric SOT recipients mount a robust serologic response to SARS-CoV-2, and even if they have protective

antibodies, the length of this protection is unknown[53-55]. Single center studies from Saudi Arabia and Brazil have shown a relatively high seroprevalence of SARS-CoV-2 in the pediatric kidney transplantation population[57,58]. However, there are concerns for possible false positive antibody results due to cross-reactivity with other coronaviruses[59].

The management of a confirmed case of SARS-CoV-2 in a pediatric SOT recipient is mainly supportive, with supplemental oxygen, nonsteroidal anti-inflammatory drugs, remdesivir, dexamethasone, and SARS-CoV-2 convalescent plasma being the only proven measures that can significantly affect the outcome[26,60,61]. Lopinavir, ritonavir, and hydroxychloroquine have not shown any significant benefit in mortality and morbidity, including the need for mechanical ventilation[60].

A crucial aspect in this group of patients is immunosuppression, which is generally considered a double-edged sword[62]. Increased immunosuppression may increase the viral load and delay recovery, whereas low immunosuppression may contribute to severe COVID-19 forms due to a more robust immune response[63]. In fact, SARS-CoV-2-induced pulmonary injury is mainly driven by excessive activation of the innate immune inflammatory response of the host[64]. Despite that notion, it has been proposed that immunosuppression in immunocompromised children may not actually increase the risk for severe SARS-CoV-2 disease[65]. On the contrary, SOT recipients may benefit from immunosuppressive drugs, as they will dampen the cytokine storm[66,67]. Immunosuppression has not been reported as a stronger risk factor than obesity, chronic comorbidities, or increased age. One possible explanation is that in SARS-CoV-2, unlike other viral agents (*e.g.*, adenovirus, rhinovirus, norovirus, influenza), the host immune response is the main driver of lung tissue damage during infection[65]. Interestingly, a systematic review showed that immunosuppressed patients have a lower incidence of SARS-CoV-2 infection when compared with the general population, and they may exhibit relatively favorable outcomes as compared to other comorbidities[68].

The impact of immunosuppression on COVID-19 severity in pediatric SOT recipients remains unclear. Although complete withdrawal of immunosuppression might not be the optimal approach, individual modifications may be necessary in cases of moderate-to-severe SARS-CoV-2 infection[69]. It seems that some immunosuppression may allow for control of the dysregulated immune response, which is commonly observed in severe SARS-CoV-2 infection[65,69]. Comparative data on immunosuppression management strategies are not yet available. Some authors recommend decreasing or discontinuing cell cycle inhibitors and cautiously reducing calcineurin inhibitors (*i.e.*, cyclosporine, tacrolimus) in moderate-to-severe COVID-19 in adult SOT recipients, while others recommend continuing calcineurin inhibitors and steroids and stopping anti-proliferative medication[70]. It is also thought that calcineurin inhibitors might exert an antiviral effect and inhibit IL-6 and IL-10 pathways, which are involved in the immune dysregulation observed in COVID-19 patients[71]. In addition, certain immunosuppression therapies like mammalian target of rapamycin inhibitors may even have biologic activity against SARS-CoV-2[72].

Transplant centers follow their own strategies based on their institutional experiences. Although the data for pediatric patients are scarce, Colmenero *et al*[73] observed no adverse outcome with the use of calcineurin inhibitors and mammalian target of rapamycin inhibitors in adult patients. On the other hand, mycophenolate mofetil was associated with severe SARS-CoV-2 infection in a dose-dependent manner[74]. This can be explained by its mechanism of action, as mycophenolate mofetil produces a cytostatic effect on activated lymphocytes[74]. It is well known that SARS-CoV-2 is associated with lymphopenia, so mycophenolate mofetil may exert a synergic and deleterious effect on depleting peripheral lymphocytes[74]. On the contrary, mammalian target of rapamycin inhibitors increase the quality and functionality of memory T cells and reduce the replication of multiple viruses including cytomegalovirus, Epstein-Barr virus and human immunodeficiency virus[75]. Regarding calcineurin inhibitors, some studies have shown *in vitro* antiviral effects against coronaviruses and that they can ameliorate the cytokine storm[76]. Randomized clinical trials comparing the different immunosuppressive schemas would help us guide management of both adult and pediatric SOT recipients.

If there is strong suspicion for bacterial superinfection, the administration of antibiotics, such as moxifloxacin, levofloxacin, ceftriaxone, vancomycin, or amikacin, can be considered[77-79]. Azithromycin should be used with caution in SOT recipients as it can increase the levels of tacrolimus [80]. These medications have been prescribed mainly in unresponsive cases, which precludes us from deducing meaningful conclusions in the absence of high-quality data.

OUTCOMES IN SARS-COV-2 POSITIVE PEDIATRIC TRANSPLANT RECIPIENTS

There are several recent reports of pediatric SOT recipients who have been infected by SARS-CoV-2 (Table 1)[38,57,58,66,77-79,81-98]. For example, Heinz *et al*[81] reported mild symptoms in a 6-mo-old recipient just 4 d after liver transplantation, while the infection was probably transmitted from the mother-donor. Neither the donor nor the recipient were tested pretransplant due to low availability of rapid testing at the early phase of the pandemic[81]. A multicenter study documented no mortality due to COVID-19 but a high rate of acute liver injury in pediatric liver transplantation recipients[83]. Morand *et al*[82] reported a coinfection of SARS-CoV-2 and Epstein-Barr virus in a pediatric liver

Table 1 Pediatric solid organ transplantation recipients with severe acute respiratory syndrome coronavirus 2 infection in 25 previously published studies

Ref.	Organ	Number of recipients	Diagnosis method	Center	Outcome	Cause of death
Sin *et al*[83]	Liver	110	N/A	International	All alive	N/A
Kehar *et al*[88]	Liver	47	RT-PCR test: 39. Serum antibodies: 8	International	All alive	N/A
Fonseca *et al*[89]	Liver	12	RT-PCR test	Hospital Sírio-Libanês, São Paulo, Brazil	All alive	N/A
Yuksel *et al*[90]	Liver	10	RT-PCR test	Koç University Hospital, Istanbul, Turkey	All alive	N/A
Ali Malekhosseini *et al*[84]	Liver	4	RT-PCR test or chest computed tomography scan	Shiraz Transplant Center, Abu Ali Sina Hospital, Shiraz, Iran	All died	Liver failure
Duvant *et al*[79]	Liver	1	Serum antibodies	Hospital Timone Enfants, Marseille, France	Alive	N/A
Heinz *et al*[81]	Liver	1	RT-PCR test	Columbia University Vagelos College of Physician and Surgeons, New York, United States	Alive	N/A
Morand *et al*[82]	Liver	1	RT-PCR test	La Timone Children Hospital, Marseille, France	Alive	N/A
Nikoupour *et al* [78]	Liver	1	RT-PCR test	Shiraz Transplant Center, Abu Ali Sina Hospital, Shiraz, Iran	Dead	Multiorgan failure
Soin *et al*[91]	Liver	1	RT-PCR test	Medanta the Medicity, Gurgaon, Delhi, India	Alive	N/A
Petters *et al*[85]	Liver	1	RT-PCR test	Baylor College of Medicine, Houston, United States	Alive	N/A
Canpolat *et al*[38]	Kidney	29	RT-PCR test	Multicenter, Turkey	All alive	N/A
Varnell *et al*[92]	Kidney	24	RT-PCR test	Multicenter (United States)	All alive	N/A
Alshami *et al*[57]	Kidney	9	RT-PCR test	King Fahad Specialist Hospital Dammam, Saudi Arabia	All alive	N/A
Berteloot *et al*[86]	Kidney	5	RT-PCR test	Hospital Universitaire Necker Enfants Maladies, Paris, France	All alive	N/A
Singer *et al*[93]	Kidney	5	RT-PCR test	Cohen Children Medical Center, New York, United States	All alive	N/A
Solomon *et al*[94]	Kidney	4	RT-PCR test	Maria Fareri Children's Hospital, New York, United States	All alive	N/A
Levenson *et al*[87]	Kidney	1	RT-PCR test	Louisiana State University Health Sciences Center, New Orleans, Louisiana, United States	Alive	N/A
Bush *et al*[77]	Kidney	1	RT-PCR test	University of Florida, Gainesville, United States	Alive	N/A
Bock *et al*[95]	Heart	20	RT-PCR test	Loma Linda Children's Hospital, California, United States	All alive	N/A
Lee *et al*[96]	Heart	4	RT-PCR test: 3. Serum antibodies: 1	Columbia University Irving Medical Center, New York, United States	All alive	N/A
Russell *et al*[97]	Heart	1	RT-PCR test	UCLA, California, United States	Alive	N/A
Goss *et al*[66]	Liver, kidney, heart, lung	26	RT-PCR test	Multicenter (United States)	All alive	N/A
Cleto-Yamane *et al*[58]	Liver, kidney	25	RT-PCR test	Hospital Estadual da Crianca, Rio de Janeiro, Brazil	All alive	N/A
Talgam-Horshi *et al*[98]	Liver, kidney, combined (liver and pancreas)	25	RT-PCR test	Schneider Children's hospital of Israel, Tel Aviv, Israel	All alive	N/A

N/A: Not applicable; RT-PCR: Real-time reverse transcriptase polymerase chain reaction.

transplantation recipient that was managed with slight reduction of tacrolimus. Nikoupour *et al*[78] reported a fatal outcome in a 3-year-old liver transplantation recipient after multiorgan failure and cardiorespiratory arrest. Results from the same transplant center reported a 100% death rate in 4 pediatric liver transplantation recipients due to liver failure, implying an increased mortality risk in children[84]. A case report from Texas described a case of multisystem inflammatory syndrome with features of Kawasaki disease in a 3-year-old African American female liver transplantation recipient [86]. The patient did not require transfer to the intensive care unit and was effectively managed with tacrolimus titration[85].

There are also some interesting findings in pediatric kidney transplantation recipients. Berteloot *et al* [86] presented 9 pediatric cases, 7 of whom developed graft arterial stenosis during early follow-up after kidney transplantation. It was reported as immune post viral graft vasculitis triggered by SARS-CoV-2 [86]. Levenson *et al*[87] reported acute kidney injury in an adolescent male kidney transplantation recipient following SARS-CoV-2 infection, with biopsy showing segmental glomerulosclerosis on a background of chronic active antibody-mediated rejection. The case was treated with an overall reduction of immunosuppression, along with anti-inflammatory treatment, which proved to be effective in preserving allograft function while attaining recovery[87]. Finally, a multicenter, multiorgan case series from five transplant centers across the United States demonstrated favorable outcomes in pediatric SOT recipients with COVID-19, which may mirror those of immunocompetent children, with infrequent hospitalizations and minimal additional treatment requirements[66].

CONCLUSION

Pediatric transplantation is a complex process that requires a combination of resources and specialized professionals and has been significantly impacted by the COVID-19 pandemic. Overall, there was a substantial decrease in pediatric SOT during the early phase of the pandemic, yet recent findings show that pediatric SOT outcomes during the pandemic were favorable. The results on the safety and efficacy on vaccines have been promising, yet further research is required to draw more solid conclusions on the optimal immunosuppressive management of pediatric SOT recipients.

ACKNOWLEDGEMENTS

The data reported here have been supplied by the United Network for Organ Sharing as the contractor for the Organ Procurement and Transplantation Network. The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy of or interpretation by the OPTN or the United States Government.

FOOTNOTES

Author contributions: Kakos CD, Ziogas IA, and Tsoulfas G designed the research study; Kakos CD and Ziogas IA performed the research, analyzed the data, and wrote the manuscript; Tsoulfas G critically revised the manuscript; and all authors have read and approved the final manuscript.

Conflict-of-interest statement: The authors declare no conflict of interests for this article.

Country/Territory of origin: Greece

ORCID number: Christos Dimitrios Kakos 0000-0002-2269-9014; Ioannis A Ziogas 0000-0002-6742-6909; Georgios Tsoulfas 0000-0001-5043-7962.

S-Editor: Wang JJ
L-Editor: Filipodia
P-Editor: Wang JJ

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 [PMID: 32091533 DOI: 10.1001/jama.2020.2648]

2 **Lee PI**, Hu YL, Chen PY, Huang YC, Hsueh PR. Are children less susceptible to COVID-19? *J Microbiol Immunol Infect* 2020; **53**: 371-372 [PMID: 32147409 DOI: 10.1016/j.jmii.2020.02.011]

3 **Liguoro I**, Pilotto C, Bonanni M, Ferrari ME, Pusiol A, Nocerino A, Vidal E, Cogo P. SARS-COV-2 infection in children and newborns: a systematic review. *Eur J Pediatr* 2020; **179**: 1029-1046 [PMID: 32424745 DOI: 10.1007/s00431-020-03684-7]

4 **CDC COVID-19 Response Team**. Coronavirus Disease 2019 in Children - United States, February 12-April 2, 2020. *MMWR Morb Mortal Wkly Rep* 2020; **69**: 422-426 [PMID: 32271728 DOI: 10.15585/mmwr.mm6914e4]

5 **Götzinger F**, Santiago-García B, Noguera-Julián A, Lanaspa M, Lancella L, Calò Carducci FI, Gabrovska N, Velizarova S, Prunk P, Osterman V, Krivec U, Lo Vecchio A, Shingadia D, Soriano-Arandes A, Melendo S, Lanari M, Pierantoni L, Wagner N, L'Huillier AG, Heininger U, Ritz N, Bandi S, Krajcar N, Roglić S, Santos M, Christiaens C, Creuven M, Buonsenso D, Welch SB, Bogyi M, Brinkmann F, Tebruegge M; ptbnet COVID-19 Study Group. COVID-19 in children and adolescents in Europe: a multinational, multicentre cohort study. *Lancet Child Adolesc Health* 2020; **4**: 653-661 [PMID: 32593339 DOI: 10.1016/S2352-4642(20)30177-2]

6 **Wu H**, Zhu H, Yuan C, Yao C, Luo W, Shen X, Wang J, Shao J, Xiang Y. Clinical and Immune Features of Hospitalized Pediatric Patients With Coronavirus Disease 2019 (COVID-19) in Wuhan, China. *JAMA Netw Open* 2020; **3**: e2010895 [PMID: 32492165 DOI: 10.1001/jamanetworkopen.2020.10895]

7 **Dhochak N**, Singhal T, Kabra SK, Lodha R. Pathophysiology of COVID-19: Why Children Fare Better than Adults? *Indian J Pediatr* 2020; **87**: 537-546 [PMID: 32410003 DOI: 10.1007/s12098-020-03322-y]

8 **Miri SM**, Noorbakhsh F, Mohebbi SR, Ghaemi A. Higher prevalence of asymptomatic or mild COVID-19 in children, claims and clues. *J Med Virol* 2020; **92**: 2257-2259 [PMID: 32470174 DOI: 10.1002/jmv.26069]

9 **Di Giorgio A**, Hartleif S, Warner S, Kelly D. COVID-19 in Children With Liver Disease. *Front Pediatr* 2021; **9**: 616381 [PMID: 33777864 DOI: 10.3389/fped.2021.616381]

10 **Han H**, Ma Q, Li C, Liu R, Zhao L, Wang W, Zhang P, Liu X, Gao G, Liu F, Jiang Y, Cheng X, Zhu C, Xia Y. Profiling serum cytokines in COVID-19 patients reveals IL-6 and IL-10 are disease severity predictors. *Emerg Microbes Infect* 2020; **9**: 1123-1130 [PMID: 32475230 DOI: 10.1080/22221751.2020.1770129]

11 **Jacques FH**, Apedaile E. Immunopathogenesis of COVID-19: Summary and Possible Interventions. *Front Immunol* 2020; **11**: 564925 [PMID: 33072103 DOI: 10.3389/fimmu.2020.564925]

12 **Coperchini F**, Chiovato L, Croce L, Magri F, Rotondi M. The cytokine storm in COVID-19: An overview of the involvement of the chemokine/chemokine-receptor system. *Cytokine Growth Factor Rev* 2020; **53**: 25-32 [PMID: 32446778 DOI: 10.1016/j.cytogfr.2020.05.003]

13 **Pierce CA**, Preston-Hurlburt P, Dai Y, Aschner CB, Cheshenko N, Galen B, Garforth SJ, Herrera NG, Jangra RK, Morano NC, Orner E, Sy S, Chandran K, Dziura J, Almo SC, Ring A, Keller MJ, Herold KC, Herold BC. Immune responses to SARS-CoV-2 infection in hospitalized pediatric and adult patients. *Sci Transl Med* 2020; **12** [PMID: 32958614 DOI: 10.1126/scitranslmed.abd5487]

14 **Gheblawi M**, Wang K, Viveiros A, Nguyen Q, Zhong JC, Turner AJ, Raizada MK, Grant MB, Oudit GY. Angiotensin-Converting Enzyme 2: SARS-CoV-2 Receptor and Regulator of the Renin-Angiotensin System: Celebrating the 20th Anniversary of the Discovery of ACE2. *Circ Res* 2020; **126**: 1456-1474 [PMID: 32264791 DOI: 10.1161/CIRCRESAHA.120.317015]

15 **Shekerdemian LS**, Mahmood NR, Wolfe KK, Riggs BJ, Ross CE, McKiernan CA, Heidemann SM, Kleinman LC, Sen AI, Hall MW, Priestley MA, McGuire JK, Boukas K, Sharron MP, Burns JP; International COVID-19 PICU Collaborative. Characteristics and Outcomes of Children With Coronavirus Disease 2019 (COVID-19) Infection Admitted to US and Canadian Pediatric Intensive Care Units. *JAMA Pediatr* 2020; **174**: 868-873 [PMID: 32392288 DOI: 10.1001/jamapediatrics.2020.1948]

16 **Fernandes DM**, Oliveira CR, Guerguis S, Eisenberg R, Choi J, Kim M, Abdelhemid A, Agha R, Agarwal S, Aschner JL, Avner JR, Ballance C, Bock J, Bhavsar SM, Campbell M, Clouser KN, Gesner M, Goldman DL, Hammerschlag MR, Hymes S, Howard A, Jung HJ, Kohlhoff S, Kojaoghlanian T, Lewis R, Nachman S, Naganathan S, Paintsil E, Pall H, Sy S, Wadowski S, Zirinsky E, Cabana MD, Herold BC; Tri-State Pediatric COVID-19 Research Consortium. Severe Acute Respiratory Syndrome Coronavirus 2 Clinical Syndromes and Predictors of Disease Severity in Hospitalized Children and Youth. *J Pediatr* 2021; **230**: 23-31.e10 [PMID: 33197493 DOI: 10.1016/j.jpeds.2020.11.016]

17 **Williams N**, Radia T, Harman K, Agrawal P, Cook J, Gupta A. COVID-19 Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in children and adolescents: a systematic review of critically unwell children and the association with underlying comorbidities. *Eur J Pediatr* 2021; **180**: 689-697 [PMID: 32914200 DOI: 10.1007/s00431-020-03801-6]

18 **Brisca G**, Mariani M, Andrea Rotulo G, Pirlo D, Romanengo M, Castagnola E, Piccotti E, Moscatelli A. Clinical course of COVID-19 in children with pre-existing medical conditions. *Acta Paediatr* 2021; **110**: 1291-1292 [PMID: 33351207 DOI: 10.1111/apa.15730]

19 **Harman K**, Verma A, Cook J, Radia T, Zuckerman M, Deep A, Dhawan A, Gupta A. Ethnicity and COVID-19 in children with comorbidities. *Lancet Child Adolesc Health* 2020; **4**: e24-e25 [PMID: 32473663 DOI: 10.1016/S2352-4642(20)30167-X]

20 **Orange JS**, Du W, Falsey AR. Therapeutic Immunoglobulin Selected for High Antibody Titer to RSV also Contains High Antibody Titers to Other Respiratory Viruses. *Front Immunol* 2015; **6**: 431 [PMID: 26379667 DOI: 10.3389/fimmu.2015.00431]

21 **Mi B**, Chen L, Panayi AC, Xiong Y, Liu G. Serum Mycoplasma pneumoniae IgG in COVID-19: A protective factor. 2020 Preprint. Available from: medRxiv 2020.04.12.20060079 [DOI: 10.1101/2020.04.12.20060079]

22 **Chai X**, Hu L, Zhang Y, Han W, Lu Z, Ke A, Zhou J, Shi G, Fang N, Fan J, Cai J, Lan F. Specific ACE2 Expression in

Cholangiocytes May Cause Liver Damage After 2019-nCoV Infection. 2020 Preprint. Available from: bioRxiv 2020.02.03.931766 [DOI: 10.1101/2020.02.03.931766]

23 **Li N**, Hua J. Immune cells in liver regeneration. *Oncotarget* 2017; **8**: 3628-3639 [PMID: 27690296 DOI: 10.18632/oncotarget.12275]

24 **Qiu H**, Wu J, Hong L, Luo Y, Song Q, Chen D. Clinical and epidemiological features of 36 children with coronavirus disease 2019 (COVID-19) in Zhejiang, China: an observational cohort study. *Lancet Infect Dis* 2020; **20**: 689-696 [PMID: 32220650 DOI: 10.1016/S1473-3099(20)30198-5]

25 **Zhang C**, Shi L, Wang FS. Liver injury in COVID-19: management and challenges. *Lancet Gastroenterol Hepatol* 2020; **5**: 428-430 [PMID: 32145190 DOI: 10.1016/S2468-1253(20)30057-1]

26 **Beigel JH**, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, Hohmann E, Chu HY, Luetkemeyer A, Kline S, Lopez de Castilla D, Finberg RW, Dierberg K, Tapson V, Hsieh L, Patterson TF, Paredes R, Sweeney DA, Short WR, Touloumi G, Lye DC, Ohmagari N, Oh MD, Ruiz-Palacios GM, Benfield T, Fätkenheuer G, Kortepeter MG, Atmar RL, Creech CB, Lundgren J, Babiker AG, Pett S, Neaton JD, Burgess TH, Bonnett T, Green M, Makowski M, Osinusi A, Nayak S, Lane HC; ACTT-1 Study Group Members. Remdesivir for the Treatment of Covid-19 - Final Report. *N Engl J Med* 2020; **383**: 1813-1826 [PMID: 32445440 DOI: 10.1056/NEJMoa2007764]

27 **Bertolini A**, van de Peppel IP, Bodewes FAJA, Moshage H, Fantin A, Farinati F, Fiorotto R, Jonker JW, Strazzabosco M, Verkade HJ, Peserico G. Abnormal Liver Function Tests in Patients With COVID-19: Relevance and Potential Pathogenesis. *Hepatology* 2020; **72**: 1864-1872 [PMID: 32702162 DOI: 10.1002/hep.31480]

28 **Zhou YH**, Zheng KI, Targher G, Byrne CD, Zheng MH. Abnormal liver enzymes in children and infants with COVID-19: A narrative review of case-series studies. *Pediatr Obes* 2020; **15**: e12723 [PMID: 32875680 DOI: 10.1111/ijpo.12723]

29 **Marjot T**, Moon AM, Cook JA, Abd-Elsalam S, Aloman C, Armstrong MJ, Pose E, Brenner EJ, Cargill T, Catana MA, Dhanasekaran R, Eshraghian A, García-Juárez I, Gill US, Jones PD, Kennedy J, Marshall A, Matthews C, Mells G, Mercer C, Perumalswami PV, Avitabile E, Qi X, Su F, Ufere NN, Wong YJ, Zheng MH, Barnes E, Barritt AS 4th, Webb GJ. Outcomes following SARS-CoV-2 infection in patients with chronic liver disease: An international registry study. *J Hepatol* 2021; **74**: 567-577 [PMID: 33035628 DOI: 10.1016/j.jhep.2020.09.024]

30 **Di Giorgio A**, Nicastro E, Speziani C, De Giorgio M, Pasulo L, Magro B, Fagiuoli S, D' Antiga L. Health status of patients with autoimmune liver disease during SARS-CoV-2 outbreak in northern Italy. *J Hepatol* 2020; **73**: 702-705 [PMID: 32413378 DOI: 10.1016/j.jhep.2020.05.008]

31 **López V**, Vázquez T, Alonso-Titos J, Cabello M, Alonso A, Beneyto I, Crespo M, Díaz-Corte C, Franco A, González-Roncero F, Gutiérrez E, Guirado L, Jiménez C, Jironda C, Lauzurica R, Llorente S, Mazuecos A, Paul J, Rodríguez-Benot A, Ruiz JC, Sánchez-Fructuoso A, Sola E, Torregrosa V, Zárraga S, Hernández D; Grupo de Estudio GREAT (Grupo Español de Actualizaciones en Trasplante). [Recommendations on management of the SARS-CoV-2 coronavirus pandemic (Covid-19) in kidney transplant patients]. *Nefrologia (Engl Ed)* 2020; **40**: 265-271 [PMID: 32278616 DOI: 10.1016/j.nefro.2020.03.002]

32 **Akalin E**, Azzi Y, Bartash R, Seethamraju H, Parides M, Hemmige V, Ross M, Forest S, Goldstein YD, Ajaimy M, Liriano-Ward L, Pynadath C, Loarte-Campos P, Nandigam PB, Graham J, Le M, Rocca J, Kinkhabwala M. Covid-19 and Kidney Transplantation. *N Engl J Med* 2020; **382**: 2475-2477 [PMID: 32329975 DOI: 10.1056/NEJMc2011117]

33 **Coates PT**, Wong G, Drueke T, Rovin B, Ronco P; Associate Editors, for the Entire Editorial Team. Early experience with COVID-19 in kidney transplantation. *Kidney Int* 2020; **97**: 1074-1075 [PMID: 32354635 DOI: 10.1016/j.kint.2020.04.001]

34 **Vistoli F**, Furian L, Maggiore U, Caldara R, Cantaluppi V, Ferraresso M, Zaza G, Cardillo M, Biancofiore G, Menichetti F, Russo A, Turillazzi E, Di Paolo M, Grandaliano G, Boggi U; Italian National Kidney Transplantation Network; the Joint Committee of the Italian Society of Organ Transplantation and the Italian Society of Nephrology. COVID-19 and kidney transplantation: an Italian Survey and Consensus. *J Nephrol* 2020; **33**: 667-680 [PMID: 32495231 DOI: 10.1007/s40620-020-00755-8]

35 **Bitencourt L**, Pedrosa AL, de Brito SBCS, Fróes ACF, de Carvalho ST, Fonseca GG, Ferreira GC, Fradico PF, Simões E Silva AC. COVID-19 and Renal Diseases: An Update. *Curr Drug Targets* 2021; **22**: 52-67 [PMID: 33050860 DOI: 10.2174/1389450121999201013151300]

36 **Legrand M**, Bell S, Forni L, Joannidis M, Koyner JL, Liu K, Cantaluppi V. Pathophysiology of COVID-19-associated acute kidney injury. *Nat Rev Nephrol* 2021; **17**: 751-764 [PMID: 34226718 DOI: 10.1038/s41581-021-00452-0]

37 **Yende S**, Parikh CR. Long COVID and kidney disease. *Nat Rev Nephrol* 2021; **17**: 792-793 [PMID: 34504319 DOI: 10.1038/s41581-021-00487-3]

38 **Canpolat N**, Yıldırım ZY, Yıldız N, Taşdemir M, Göknar N, Evrengül H, Gülmez R, Aksu B, Dursun H, Özçelik G, Yavaşcan Ö, Çiçek RY, Tülpar S, Hacıhamdioğlu DÖ, Nayır A, Alpay H. COVID-19 in pediatric patients undergoing chronic dialysis and kidney transplantation. *Eur J Pediatr* 2022; **181**: 117-123 [PMID: 34218318 DOI: 10.1007/s00431-021-04191-z]

39 **Doná D**, Torres Canizales J, Benetti E, Cananzi M, De Corti F, Calore E, Hierro L, Ramos Boluda E, Melgosa Hijosa M, Garcia Guereta L, Pérez Martínez A, Barrios M, Costa Reis P, Teixeira A, Lopes MF, Kaliciński P, Branchereau S, Boyer O, Debray D, Sciveres M, Wennberg L, Fischler B, Barany P, Baker A, Baumann U, Schwerk N, Nicastro E, Candusso M, Toporski J, Sokal E, Stephenne X, Lindemans C, Miglinas M, Rascon J, Jara P; ERN TransplantChild. Pediatric transplantation in Europe during the COVID-19 pandemic: Early impact on activity and healthcare. *Clin Transplant* 2020; **34**: e14063 [PMID: 32786120 DOI: 10.1111/ctr.14063]

40 **Merola J**, Schilsky ML, Mulligan DC. The Impact of COVID-19 on Organ Donation, Procurement and Liver Transplantation in the United States. *Hepatol Commun* 2020; **5**: 5-11 [PMID: 33043228 DOI: 10.1002/hep4.1620]

41 **Charnaya O**, Chiang TP, Wang R, Motter J, Boyarsky B, King E, Werbel W, Durand CM, Avery R, Segev D, Massie A, Garonzik-Wang J. Effects of COVID19 Pandemic on Pediatric Kidney Transplant in the United States. *Res Sq* 2020 [PMID: 32935089 DOI: 10.21203/rs.3.rs-72427/v1]

42 **Kemme S**, Yoeli D, Sundaram SS, Adams MA, Feldman AG. Decreased access to pediatric liver transplantation during the COVID-19 pandemic. *Pediatr Transplant* 2022; **26**: e14162 [PMID: 34633127 DOI: 10.1111/petr.14162]

43 **L'Huillier AG**, Danziger-Isakov L, Chaudhuri A, Green M, Michaels MG, M Posfay-Barbe K, van der Linden D, Verma

A, McCulloch M, Ardura MI. SARS-CoV-2 and pediatric solid organ transplantation: Current knowns and unknowns. *Pediatr Transplant* 2021; **25**: e13986 [PMID: 33689201 DOI: 10.1111/petr.13986]

44 **American Society of Transplantation**. SARS-CoV-2 (Coronavirus, 2019-nCoV): Recommendations and Guidance for Organ Donor Testing. [cited 5 December 2021]. Available from: https://www.myast.org/sites/default/files/Donor%20Testing_100520_revised_ReadyToPostUpdated10-12.pdf

45 **Goss MB**, Munoz FM, Ruan W, Galván NTN, O'Mahony CA, Rana A, Cotton RT, Moreno NF, Heczey AA, Leung DH, Goss JA. Liver transplant in a recently COVID-19 positive child with hepatoblastoma. *Pediatr Transplant* 2021; **25**: e13880 [PMID: 32979013 DOI: 10.1111/petr.13880]

46 **Hussain T**, Nassetta K, Badawy SM. Adherence to Immunosuppression Medications among Heart Transplant Recipients: Challenges, Opportunities, and Potential Role of Digital Approaches in the COVID-19 Era. *J Cardiovasc Dev Dis* 2021; **8** [PMID: 34200823 DOI: 10.3390/jcdd8060068]

47 **Kröncke S**, Lund LK, Buchholz A, Lang M, Briem-Richter A, Grabhorn EF, Sterneck M. Psychosocial situation, adherence, and utilization of video consultation in young adult long-term pediatric liver transplant recipients during COVID-19 pandemic. *Pediatr Transplant* 2021; **25**: e14121 [PMID: 34428322 DOI: 10.1111/petr.14121]

48 **Gonzalez BE**, Michaels MG. Safe living after transplantation or chemotherapy. *Pediatr Transpl Oncol Infect Dis* 2021; 90-96.e2 [DOI: 10.1016/B978-0-323-64198-2.00022-1]

49 **Qin CX**, Auerbach SR, Charnaya O, Danziger-Isakov LA, Ebel NH, Feldman AG, Hsu EK, McAteer J, Mohammad S, Perito ER, Thomas AM, Chiang TPY, Garonzik-Wang JM, Segev DL, Mogul DB. Antibody response to 2-dose SARS-CoV-2 mRNA vaccination in pediatric solid organ transplant recipients. *Am J Transplant* 2022; **22**: 669-672 [PMID: 34517430 DOI: 10.1111/ajt.16841]

50 **Strauss AT**, Hallett AM, Boyarsky BJ, Ou MT, Werbel WA, Avery RK, Tobian AAR, Massie AB, Hamilton JPA, Garonzik-Wang JM, Segev DL. Antibody Response to Severe Acute Respiratory Syndrome-Coronavirus-2 Messenger RNA Vaccines in Liver Transplant Recipients. *Liver Transpl* 2021; **27**: 1852-1856 [PMID: 34407309 DOI: 10.1002/lt.26273]

51 **Boyarsky BJ**, Werbel WA, Avery RK, Tobian AAR, Massie AB, Segev DL, Garonzik-Wang JM. Antibody Response to 2-Dose SARS-CoV-2 mRNA Vaccine Series in Solid Organ Transplant Recipients. *JAMA* 2021; **325**: 2204-2206 [PMID: 33950155 DOI: 10.1001/jama.2021.7489]

52 **Werbel WA**, Boyarsky BJ, Ou MT, Massie AB, Tobian AAR, Garonzik-Wang JM, Segev DL. Safety and Immunogenicity of a Third Dose of SARS-CoV-2 Vaccine in Solid Organ Transplant Recipients: A Case Series. *Ann Intern Med* 2021; **174**: 1330-1332 [PMID: 34125572 DOI: 10.7326/L21-0282]

53 **Freeman MC**, Rapsinski GJ, Zilla ML, Wheeler SE. Immunocompromised Seroprevalence and Course of Illness of SARS-CoV-2 in One Pediatric Quaternary Care Center. *J Pediatric Infect Dis Soc* 2021; **10**: 426-431 [PMID: 33049042 DOI: 10.1093/jpids/piaa123]

54 **Nailescu C**, Khalid M, Wilson AC, Amanat F, Arregui S, Canas J, Hooks J, Krammer F, Schwaderer AL, Hains DS. Assessment of Seroconversion to SARS-CoV-2 in a Cohort of Pediatric Kidney Transplant Recipients. *Front Pediatr* 2020; **8**: 601327 [PMID: 33194930 DOI: 10.3389/fped.2020.601327]

55 **Zhang Y**, Xu J, Jia R, Yi C, Gu W, Liu P, Dong X, Zhou H, Shang B, Cheng S, Sun X, Ye J, Li X, Zhang J, Ling Z, Ma L, Wu B, Zeng M, Zhou W, Sun B. Protective humoral immunity in SARS-CoV-2 infected pediatric patients. *Cell Mol Immunol* 2020; **17**: 768-770 [PMID: 32382126 DOI: 10.1038/s41423-020-0438-3]

56 **Woloshin S**, Patel N, Kesselheim AS. False Negative Tests for SARS-CoV-2 Infection - Challenges and Implications. *N Engl J Med* 2020; **383**: e38 [PMID: 32502334 DOI: 10.1056/NEJMp2015897]

57 **Alshami A**, Al Attas R, Azzam A, Mohammed A, Al-Quhaidan N. Detection of SARS-CoV-2 antibodies in pediatric kidney transplant patients. *BMC Nephrol* 2021; **22**: 123 [PMID: 33827461 DOI: 10.1186/s12882-021-02325-x]

58 **Cleto-Yamane TL**, Rodrigues-Santos G, de Magalhães-Barbosa MC, Moura PG, Vasconcelos RD, Gouveia JLS, de Oliveira AL, Ferreira FC, Shalders AL, de Oliveira MBG, Lima-Setta F, da Cunha AJLA, Prata-Barbosa A. Screening of COVID-19 in outpatient children with cancer or solid organ transplantation: preliminary report. *Eur J Pediatr* 2021; **180**: 3237-3241 [PMID: 33768332 DOI: 10.1007/s00431-021-04044-9]

59 **Lv H**, Wu NC, Tsang OT, Yuan M, Perera RAPM, Leung WS, So RTY, Chan JMC, Yip GK, Chik TSH, Wang Y, Choi CYC, Lin Y, Ng WW, Zhao J, Poon LLM, Peiris JSM, Wilson IA, Mok CKP. Cross-reactive Antibody Response between SARS-CoV-2 and SARS-CoV Infections. *Cell Rep* 2020; **31**: 107725 [PMID: 33500101 DOI: 10.1016/j.celrep.2020.107725]

60 **Siemieniuk RA**, Bartoszko JJ, Ge L, Zeraatkar D, Izcovich A, Kum E, Pardo-Hernandez H, Qasim A, Martinez JPD, Rochwerg B, Lamontagne F, Han MA, Liu Q, Agarwal A, Agoritsas T, Chu DK, Couban R, Cusano E, Darzi A, Devji T, Fang B, Fang C, Flottorp SA, Foroutan F, Ghadimi M, Heels-Ansdell D, Honarmand K, Hou L, Hou X, Ibrahim Q, Khamis A, Lam B, Loeb M, Marcucci M, McLeod SL, Motaghi S, Murthy S, Mustafa RA, Neary JD, Rada G, Riaz IB, Sadeghirad B, Sekercioglu N, Sheng L, Sreekanta A, Switzer C, Tendal B, Thabane L, Tomlinson G, Turner T, Vandvik PO, Vernooij RW, Viteri-García A, Wang Y, Yao L, Ye Z, Guyatt GH, Brignardello-Petersen R. Drug treatments for covid-19: living systematic review and network meta-analysis. *BMJ* 2020; **370**: m2980 [PMID: 32732190 DOI: 10.1136/bmj.m2980]

61 **Rahman F**, Liu STH, Taimur S, Jacobs S, Sullivan T, Dunn D, Baneman E, Fuller R, Aberg JA, Bouvier N, Rana MM. Treatment with convalescent plasma in solid organ transplant recipients with COVID-19: Experience at large transplant center in New York City. *Clin Transplant* 2020; **34**: e14089 [PMID: 32918761 DOI: 10.1111/ctr.14089]

62 **Ritchie AI**, Singanayagam A. Immunosuppression for hyperinflammation in COVID-19: a double-edged sword? *Lancet* 2020; **395**: 1111 [PMID: 32220278 DOI: 10.1016/S0140-6736(20)30691-7]

63 **Willicombe M**, Thomas D, McAdoo S. COVID-19 and Calcineurin Inhibitors: Should They Get Left Out in the Storm? *J Am Soc Nephrol* 2020; **31**: 1145-1146 [PMID: 32312797 DOI: 10.1681/ASN.2020030348]

64 **Ye Q**, Wang B, Mao J. The pathogenesis and treatment of the `Cytokine Storm' in COVID-19. *J Infect* 2020; **80**: 607-613 [PMID: 32283152 DOI: 10.1016/j.jinf.2020.03.037]

65 **D'Antiga L**. Coronaviruses and Immunosuppressed Patients: The Facts During the Third Epidemic. *Liver Transpl* 2020; **26**: 832-834 [PMID: 32196933 DOI: 10.1002/lt.25756]

66 **Goss MB**, Galván NTN, Ruan W, Munoz FM, Brewer ED, O'Mahony CA, Melicoff-Portillo E, Dreyer WJ, Miloh TA, Cigarroa FG, Ranch D, Yoeli D, Adams MA, Koohmaraie S, Harter DM, Rana A, Cotton RT, Carter B, Patel S, Moreno NF, Leung DH, Goss JA. The pediatric solid organ transplant experience with COVID-19: An initial multi-center, multi-organ case series. *Pediatr Transplant* 2021; **25**: e13868 [PMID: 32949098 DOI: 10.1111/petr.13868]

67 **Seminari E**, Colaneri M, Sambo M, Gallazzi I, Di Matteo A, Roda S, Bruno R; COVID19 IRCCS San Matteo Pavia Task Force. SARS Cov-2 infection in a renal-transplanted patient: A case report. *Am J Transplant* 2020; **20**: 1882-1884 [PMID: 32243672 DOI: 10.1111/ajt.15902]

68 **Minotti C**, Tirelli F, Barbieri E, Giaquinto C, Donà D. How is immunosuppressive status affecting children and adults in SARS-CoV-2 infection? *J Infect* 2020; **81**: e61-e66 [PMID: 32335173 DOI: 10.1016/j.jinf.2020.04.026]

69 **Romanelli A**, Mascolo S. Immunosuppression drug-related and clinical manifestation of Coronavirus disease 2019: A therapeutical hypothesis. *Am J Transplant* 2020; **20**: 1947-1948 [PMID: 32243698 DOI: 10.1111/ajt.15905]

70 **Kronbichler A**, Gauckler P, Windpessl M, Il Shin J, Jha V, Rovin BH, Oberbauer R. COVID-19: implications for immunosuppression in kidney disease and transplantation. *Nat Rev Nephrol* 2020; **16**: 365-367 [PMID: 32409782 DOI: 10.1038/s41581-020-0305-6]

71 **Siddiqi HK**, Mehra MR. COVID-19 illness in native and immunosuppressed states: A clinical-therapeutic staging proposal. *J Heart Lung Transplant* 2020; **39**: 405-407 [PMID: 32362390 DOI: 10.1016/j.healun.2020.03.012]

72 **Conti P**, Ronconi G, Caraffa A, Gallenga CE, Ross R, Frydas I, Kritas SK. Induction of pro-inflammatory cytokines (IL-1 and IL-6) and lung inflammation by Coronavirus-19 (COVI-19 or SARS-CoV-2): anti-inflammatory strategies. *J Biol Regul Homeost Agents* 2020; **34**: 327-331 [PMID: 32171193 DOI: 10.23812/CONTI-E]

73 **Colmenero J**, Rodríguez-Perálvarez M, Salcedo M, Arias-Milla A, Muñoz-Serrano A, Graus J, Nuño J, Gastaca M, Bustamante-Schneider J, Cachero A, Lladó L, Caballero A, Fernández-Yunquera A, Loinaz C, Fernández I, Fondevila C, Navasa M, Iñarrairaegui M, Castells L, Pascual S, Ramírez P, Vinaixa C, González-Dieguez ML, González-Grande R, Hierro L, Nogueras F, Otero A, Álamo JM, Blanco-Fernández G, Fábrega E, García-Pajares F, Montero JL, Tomé S, De la Rosa G, Pons JA. Epidemiological pattern, incidence, and outcomes of COVID-19 in liver transplant patients. *J Hepatol* 2021; **74**: 148-155 [PMID: 32750442 DOI: 10.1016/j.jhep.2020.07.040]

74 **Allison AC**, Eugui EM. Mycophenolate mofetil and its mechanisms of action. *Immunopharmacology* 2000; **47**: 85-118 [PMID: 10878285 DOI: 10.1016/s0162-3109(00)00188-0]

75 **Bowman LJ**, Brueckner AJ, Doligalski CT. The Role of mTOR Inhibitors in the Management of Viral Infections: A Review of Current Literature. *Transplantation* 2018; **102**: S50-S59 [PMID: 29369973 DOI: 10.1097/TP.0000000000001777]

76 **Tanaka Y**, Sato Y, Sasaki T. Suppression of coronavirus replication by cyclophilin inhibitors. *Viruses* 2013; **5**: 1250-1260 [PMID: 23698397 DOI: 10.3390/v5051250]

77 **Bush R**, Johns F, Acharya R, Upadhyay K. Mild COVID-19 in a pediatric renal transplant recipient. *Am J Transplant* 2020; **20**: 2942-2945 [PMID: 32406181 DOI: 10.1111/ajt.16003]

78 **Nikoupour H**, Kazemi K, Arasteh P, Ghazimoghadam S, Eghlimi H, Dara N, Gholami S, Nikeghbalian S. Pediatric liver transplantation and COVID-19: a case report. *BMC Surg* 2020; **20**: 224 [PMID: 33023552 DOI: 10.1186/s12893-020-00878-6]

79 **Duvant P**, Roquelaure B, Morand A, Bosdure E, Garaix F, Zandotti C, Fabre A. A second case of multisystem inflammatory syndrome associated with SARS-CoV-2 in a liver-transplanted child. *Pediatr Transplant* 2022; **26**: e14116 [PMID: 34414640 DOI: 10.1111/petr.14116]

80 **Mori T**, Aisa Y, Nakazato T, Yamazaki R, Ikeda Y, Okamoto S. Tacrolimus-azithromycin interaction in a recipient of allogeneic bone marrow transplantation. *Transpl Int* 2005; **18**: 757-758 [PMID: 15910307 DOI: 10.1111/j.1432-2277.2005.00135.x]

81 **Heinz N**, Griesemer A, Kinney J, Vittorio J, Lagana SM, Goldner D, Velasco M, Kato T, Lobritto S, Martinez M. A case of an Infant with SARS-CoV-2 hepatitis early after liver transplantation. *Pediatr Transplant* 2020; **24**: e13778 [PMID: 32559354 DOI: 10.1111/petr.13778]

82 **Morand A**, Roquelaure B, Colson P, Amrane S, Bosdure E, Raoult D, Lagier JC, Fabre A. Child with liver transplant recovers from COVID-19 infection. A case report. *Arch Pediatr* 2020; **27**: 275-276 [PMID: 32402433 DOI: 10.1016/j.arcped.2020.05.004]

83 **Sin P**, Díaz LA, Martínez M, Vizcaya C, D'Agostino D, Gana JC. Acute Liver Injury Among Pediatric Liver Transplantation Recipients With Coronavirus Disease 2019: An International Collaborative Study. *J Pediatr Gastroenterol Nutr* 2021; **73**: 391-394 [PMID: 34183614 DOI: 10.1097/MPG.0000000000003213]

84 **Ali Malekhosseini S**, Nikoupour H, Gholami S, Shamsaeefar A, Arasteh P, Kazemi K, Dehghani M, Eghlimi H, Raeisi Shahraki H, Roozbeh J, Rezaianzadeh A, Nikeghbalian S. A Report of 85 Cases of COVID-19 and Abdominal Transplantation From a Single Center: What Are the Associated Factors With Death Among Organ Transplantation Patients. *Transplantation* 2021; **105**: 90-99 [PMID: 32976364 DOI: 10.1097/TP.0000000000003470]

85 **Petters LM**, Vogel TP, Munoz FM, Hernandez JA, Koohmaraie S, Nowicki MJ, Zumbro CE, Mysore KR. Multisystem inflammatory syndrome in children associated with SARS-CoV-2 in a solid organ transplant recipient. *Am J Transplant* 2021; **21**: 2596-2599 [PMID: 33754452 DOI: 10.1111/ajt.16572]

86 **Berteloot L**, Berthaud R, Temmam S, Lozach C, Zanelli E, Blanc T, Heloury Y, Capito C, Chardot C, Sarnacki S, Garcelon N, Lacaille F, Charbit M, Pastural M, Rabant M, Boddaert N, Leruez-Ville M, Eloit M, Sermet-Gaudelus I, Dehoux L, Boyer O. Arterial abnormalities identified in kidneys transplanted into children during the COVID-19 pandemic. *Am J Transplant* 2021; **21**: 1937-1943 [PMID: 33346946 DOI: 10.1111/ajt.16464]

87 **Levenson E**, Shepherd TN, Aviles D, Craver R, Ehlayel A, Love GL, Simms K, Straatmann C, Ashoor IF. De novo collapsing glomerulopathy in a pediatric kidney transplant recipient with COVID-19 infection. *Pediatr Transplant* 2021; **25**: e14013 [PMID: 33773007 DOI: 10.1111/petr.14013]

88 **Kehar M**, Ebel NH, Ng VL, Baquero JER, Leung DH, Slowik V, Ovchinsky N, Shah AA, Arnon R, Miloh T, Gupta N, Mohammad S, Kogan-Liberman D, Squires JE, Sanchez MC, Hildreth A, Book L, Chu C, Alrabadi L, Azzam R, Chepuri B, Elisofon S, Falik R, Gallagher L, Kader H, Mogul D, Mujawar Q, Namjoshi SS, Valentino PL, Vitola B, Waheed N,

Zheng MH, Lobritto S, Martinez M. Severe Acute Respiratory Syndrome Coronavirus-2 Infection in Children With Liver Transplant and Native Liver Disease: An International Observational Registry Study. *J Pediatr Gastroenterol Nutr* 2021; **72**: 807-814 [PMID: 33605666 DOI: 10.1097/MPG.0000000000003077]

89 **Fonseca EA**, Feier F, Pugliese R, Freitas AF, Porta G, Miura I, Baggio V, Kondo M, Benavides M, Vincenzi R, Roda K, Oliveira CV, Chapchap P, Seda-Neto J. Pediatric liver transplantation activity in a high-volume program during the COVID-19 pandemic in Brazil. *Pediatr Transplant* 2021; **25**: e14112 [PMID: 34396644 DOI: 10.1111/petr.14112]

90 **Yuksel M**, Akturk H, Mizikoglu O, Toroslu E, Arikan C. A single-center report of COVID-19 disease course and management in liver transplanted pediatric patients. *Pediatr Transplant* 2021; **25**: e14061 [PMID: 34076953 DOI: 10.1111/petr.14061]

91 **Soin AS**, Choudhary NS, Yadav SK, Saigal S, Saraf N, Rastogi A, Bhangui P, Srinivasan T, Mohan N, Saha SK, Gupta A, Chaudhary RJ, Yadav K, Dhampalwar S, Govil D, Gupta N, Vohra V. Restructuring Living-Donor Liver Transplantation at a High-Volume Center During the COVID-19 Pandemic. *J Clin Exp Hepatol* 2021; **11**: 418-423 [PMID: 33052181 DOI: 10.1016/j.jceh.2020.09.009]

92 **Varnell C Jr**, Harshman LA, Smith L, Liu C, Chen S, Al-Akash S, Barletta GM, Belsha C, Brakeman P, Chaudhuri A, Fadakar P, Garro R, Gluck C, Goebel J, Kershaw D, Matossian D, Nailescu C, Patel HP, Pruette C, Ranabothu S, Rodig N, Smith J, Sebestyen VanSickle J, Weng P, Danziger-Isakov L, Hooper DK, Seifert M. COVID-19 in pediatric kidney transplantation: The Improving Renal Outcomes Collaborative. *Am J Transplant* 2021; **21**: 2740-2748 [PMID: 33452854 DOI: 10.1111/ajt.16501]

93 **Singer PS**, Sethna C, Molmenti E, Fahmy A, Grodstein E, Castellanos-Reyes L, Fassano J, Teperman L. COVID-19 infection in a pediatric kidney transplant population: A single-center experience. *Pediatr Transplant* 2021; **25**: e14018 [PMID: 33813782 DOI: 10.1111/petr.14018]

94 **Solomon S**, Pereira T, Samsonov D. An early experience of COVID-19 disease in pediatric and young adult renal transplant recipients. *Pediatr Transplant* 2021; **25**: e13972 [PMID: 33502074 DOI: 10.1111/petr.13972]

95 **Bock MJ**, Kuhn MA, Chinnock RE. COVID-19 diagnosis and testing in pediatric heart transplant recipients. *J Heart Lung Transplant* 2021; **40**: 897-899 [PMID: 34253455 DOI: 10.1016/j.healun.2021.06.009]

96 **Lee H**, Mantell BS, Richmond ME, Law SP, Zuckerman WA, Addonizio LJ, Lee TM, Lytrivi ID. Varying presentations of COVID-19 in young heart transplant recipients: A case series. *Pediatr Transplant* 2020; **24**: e13780 [PMID: 32542914 DOI: 10.1111/petr.13780]

97 **Russell MR**, Halnon NJ, Alejos JC, Salem MM, Reardon LC. COVID-19 in a pediatric heart transplant recipient: Emergence of donor-specific antibodies. *J Heart Lung Transplant* 2020; **39**: 732-733 [PMID: 32430156 DOI: 10.1016/j.healun.2020.04.021]

98 **Talgam-Horshi E**, Mozer-Glassberg Y, Waisbourd-Zinman O, Ashkenazi-Hoffnung L, Haskin O, Levi S, Hamdani G, Landau D, Alfandary H. Clinical Outcomes and Antibody Response in COVID-19-Positive Pediatric Solid Organ Transplant Recipients. *Pediatr Infect Dis J* 2021; **40**: e514-e516 [PMID: 34382612 DOI: 10.1097/INF.0000000000003293]

World Journal of Transplantation

Submit a Manuscript: https://www.f6publishing.com

World J Transplant 2022 May 18; 12(5): 100-111

DOI: 10.5500/wjt.v12.i5.100

ISSN 2220-3230 (online)

ORIGINAL ARTICLE

Observational Study

Simultaneous nephrectomy during kidney transplantation for polycystic kidney disease does not detrimentally impact comorbidity and graft survival

Tom Darius, Sébastien Bertoni, Martine De Meyer, Antoine Buemi, Arnaud Devresse, Nada Kanaan, Eric Goffin, Michel Mourad

Specialty type: Transplantation

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Jesus-Silva SG, Brazil

Received: March 31, 2021
Peer-review started: March 31, 2021
First decision: July 29, 2021
Revised: August 11, 2021
Accepted: April 9, 2022
Article in press: April 9, 2022
Published online: May 18, 2022

Tom Darius, Sébastien Bertoni, Martine De Meyer, Antoine Buemi, Michel Mourad, Surgical and Abdominal Transplantation Unit, University Clinics Saint Luc, Brussels 1200, Belgium

Arnaud Devresse, Nada Kanaan, Eric Goffin, Division of Nephrology, University Clinics Saint Luc, Brussels 1200, Belgium

Corresponding author: Tom Darius, FRCS (Gen Surg), MD, PhD, Doctor, Professor, Surgeon, Surgical and Abdominal Transplantation Unit, University Clinics Saint Luc, Avenue Hippocrate 10, Brussels 1200, Belgium. tom.darius@uclouvain.be

Abstract

BACKGROUND

The lack of space, as an indication for a native unilateral nephrectomy for positioning a future kidney graft in the absence of other autosomal dominant polycystic kidney disease-related symptoms, remains controversial.

AIM

To evaluate the surgical comorbidity and the impact on graft survival of an associated ipsilateral native nephrectomy during isolated kidney transplantation in patients with autosomal dominant polycystic kidney disease.

METHODS

One hundred and fifty-four kidney transplantations performed between January 2007 and January 2019 of which 77 without (kidney transplant alone (KTA) group) and 77 with associated ipsilateral nephrectomy (KTIN group), were retrospectively reviewed. Demographics and surgical variables were analyzed and their respective impact on surgical comorbidity and graft survival.

RESULTS

Creation of space for future graft positioning was the main reason (n = 74, 96.1%) for associated ipsilateral nephrectomy. No significant difference in surgical comorbidity (lymphocele, wound infection, incisional hernia, wound hematoma, urinary infection, need for blood transfusion, hospitalization stay, Dindo Clavien classification and readmission rate) was observed between the two study groups. The incidence of primary nonfunction and delayed graft function was comparable

in both groups [0% and 2.6% (P = 0.497) and 9.1% and 16.9% (P = 0.230), respectively, in the KTA and KTIN group]. The 1- and 5-year graft survival were 94.8% and 90.3%, and 100% and 93.8%, respectively, in the KTA and KTIN group (P = 0.774). The 1- and 5-year patient survival were 96.1% and 92.9%, and 100% and 100%, respectively, in the KTA and KTIN group (P = 0.168).

CONCLUSION

Simultaneous ipsilateral native nephrectomy to create space for graft positioning during kidney transplantation in patients with autosomal dominant polycystic kidney disease does not negatively impact surgical comorbidity and short- and long-term graft survival.

Key Words: Autosomal dominant polycystic kidney disease; Complications; Kidney transplantation; Graft survival; Unilateral nephrectomy; Surgical comorbidity

Core Tip: The associated surgical comorbidity and graft survival of an ipsilateral nephrectomy during isolated kidney transplantation in patients with autosomal dominant polycystic kidney disease was evaluated. One hundred and fifty-four patients were retrospectively evaluated, of which 77 did and 77 did not undergo associated ipsilateral nephrectomy during the transplantation. In a long-term follow-up, we observed no negative impact on surgical comorbidity and graft survival of a simultaneous ipsilateral native nephrectomy to create space for graft positioning during kidney transplantation in patients with autosomal dominant polycystic kidney disease.

Citation: Darius T, Bertoni S, De Meyer M, Buemi A, Devresse A, Kanaan N, Goffin E, Mourad M. Simultaneous nephrectomy during kidney transplantation for polycystic kidney disease does not detrimentally impact comorbidity and graft survival. *World J Transplant* 2022; 12(5): 100-111

URL: https://www.wjgnet.com/2220-3230/full/v12/i5/100.htm

DOI: https://dx.doi.org/10.5500/wjt.v12.i5.100

INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is one of the most frequent causes of renal failure in Europe and the USA and may affect 2.5% to 10% of dialysis patients. Renal failure is the result of the development and progressive expansion of multiple bilateral cysts in the renal parenchyma, leading to a progressive decline in renal function owing to compression of normal functioning parenchyma by enlarging cysts[1-3].

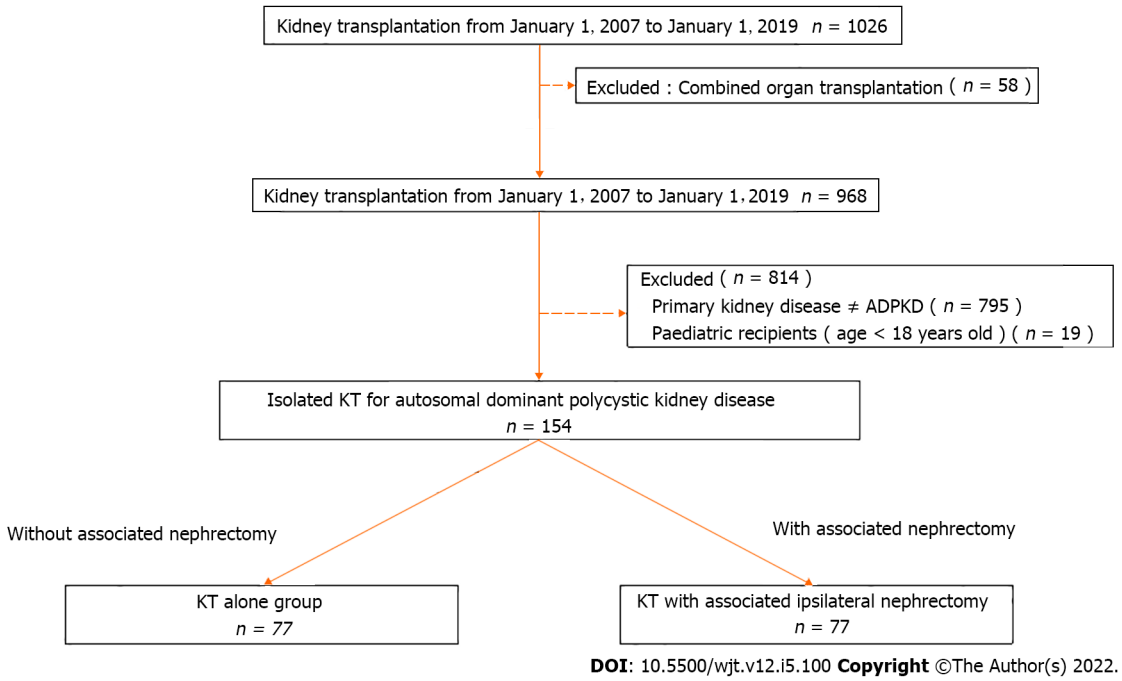
Clear indications for nephrectomy before transplantation include intractable pain and discomfort, ongoing hematuria, recurrent severe cyst infections, gastrointestinal symptoms such as early satiety, recurrent nephrolithiasis and risk of malignancy[1,2,4]. Unilateral native nephrectomy to create space for graft positioning in an otherwise asymptomatic ADPKD patient is quite often routinely performed in isolated kidney transplant candidates before their activation on the waiting list. This strategy is mainly driven by the fear of increased surgical comorbidity and the possible negative impact of prolonged cold ischemia time and short- and long-term graft survival related to the associated nephrectomy during transplantation. However, many controversies still exist concerning the indication and timing of a unilateral nephrectomy to create space for graft positioning in an asymptomatic kidney transplant candidate suffering from massive enlarged polycystic kidney[3,5,6].

Therefore, this retrospective study aimed to evaluate the surgical comorbidity and the impact on early and late graft survival of an associated ipsilateral native nephrectomy during isolated kidney transplantation in ADPKD patients. Based on these results a symptom-based algorithm is proposed to decide the timing and necessity of a unilateral or bilateral nephrectomy in ADPKD candidates waiting for, or during transplantation.

MATERIALS AND METHODS

Donor and recipient demographics

Figure 1 illustrates the selection flowchart of this retrospective study. Between January 1 2007 and January 1 2019, a total of 1026 kidney transplantations were performed at the University Clinics Saint-Luc (Brussels, Belgium) of which 154 patients underwent isolated kidney transplantation for ADPKD.



DOI: 10.5500/wjt.v12.i5.100 **Copyright** ©The Author(s) 2022.

Figure 1 Selection flowchart of this retrospective study. ADPKD: Autosomal dominant polycystic kidney disease; KT: Kidney transplantation.

This selection was obtained using the following inclusion criteria: isolated kidney transplant recipient, ADPKD as a primary cause of renal failure, age greater than 18 years old. The exclusion criteria were the following: multi-organ recipients, ADPKD not the primary kidney disease and pediatric recipients. No patients were lost from follow-up. From these 154 ADPKD patients, 77 underwent a kidney transplantation alone (KTA group) and 77 kidney transplantation with associated native ipsilateral nephrectomy (KTIN group) and were retrospectively reviewed. This study was approved by the institutional ethical committee. The following donor characteristics were analyzed: Age, gender, type of donor (living *vs* deceased) and type of deceased donor (donation after brain death or donation after circulatory death) and cytomegalovirus status. Recipient characteristics included: age, gender, body mass index (BMI), rank of transplant, time on dialysis and residual diuresis before transplantation, Human Leucocyte Antigen (HLA) mismatching, hemoglobin and albumin level before transplantation. Donor and recipient characteristics are presented in Table 1. Combined organ transplantation and ABO incompatible transplantations were excluded.

Surgical technique

A standard kidney transplant procedure was performed by a hockey stick incision with a classical vascular reconstruction on the iliac vessels and a ureterovesical anastomosis achieved according to the extravesical approach described by Lich-Gregoir[7-9]. A ureter stent was not routinely used but only according to the surgeon's preference and indication. An associated native ipsilateral nephrectomy was performed, if indicated, before implantation of the kidney graft with cranial extension up to the costal margin of the hockey stick incision by a retroperitoneal approach. Perioperative drainage of multiple renal cysts was frequently performed to facilitate surgical resection. The following surgical characteristics were collected: indications for associated ipsilateral native nephrectomy, total surgical time, anastomosis time (defined as the time from the start of vascular anastomosis to reperfusion of the kidney), cold ischemia time (defined as the time from the start of *in situ* cold perfusion of the kidney in the deceased donor or *ex vivo* cold perfusion of the kidney in a living donor to the start of *in situ* vascular anastomosis in the recipient) and weight of the removed native polycystic kidney.

Posttransplant immunosuppression

A triple-drug protocol consisting of tacrolimus (Advagraf, Astellas Pharma BV, Brussels, Belgium), methylprednisolone (Medrol, Pfizer NV, Brussels, Belgium) and mycophenolate mofetil (Cellcept, 2x500 mg/d, NV Roche SA, Brussels, Belgium) was used during the whole study period in all except one patient. Induction therapy with basiliximab (Simulect, Novartis Pharma GmbH, Neurenberg, Germany) on day 0 and 4 and thymoglobuline 1.25 mg/kg (Thymoglobulin, Sanofi Genzyme Europe B.V., Amsterdam, The Netherlands) day 1 until day 4 after transplantation was used in recipients of a living donor graft and a donor after circulatory death, respectively. Plasmapheresis was applied in highly immunized recipients until one month after transplantation. Tacrolimus trough levels (T_0) were between 10 and 14 ng/mL, 7 and 10 ng/mL and 5 and 7 ng/mL, during the first month, between the second and

Table 1 Donor and recipient characteristics of 154 kidney transplant recipients suffering from autosomal dominant polycystic kidney with or without associated ipsilateral nephrectomy during isolated kidney transplantation in a single center transplant program from January 2007 until January 2019

	KT alone group (*n* = 77)	KT with associated ipsilateral nephrectomy (*n* = 77)	*P* value
Donor characteristics			
Age, yr	46.23 ± 14.94	47.40 ± 14.86	NS
Gender, male/female, *n* (%)	42/35 (54.5/45.5)	37/40 (48.1/51.9)	NS
CMV status, negative/positive, *n* (%)	32/43 (55.2/47.8)	26/47 (35.6/64.4)	NS
Type of donor, living/deceased donor, *n* (%)	6/71 (7.8/92.2)	21/56 (27.3/72.7)	[a]
Type of deceased donor, DBD/DCD, *n* (%)	54/17 (76.1/23.9)	38/18 (67.9/32.1)	NS
Recipient characteristics			
Age, yr	57.40 ± 9.89	53.40 ± 9.12	NS
Gender, male/female, *n* (%)	48/29 (62.3/37.7)	47/30 (61.0/38.9)	NS
Body mass index, kg/m²	25.69 ± 4.00	25.33 ± 3.76	NS
Blood group, *n* (%)			NS
A	33 (42.9)	42 (54.5)	NS
B	5 (6.5)	4 (5.2)	NS
AB	0 (0)	3 (3.9)	NS
O	39 (50.6)	28 (36.4)	NS
Pretransplant dialysis versus preemptive kidney transplant, *n* (%)	65/12 (84.4/15.6)	55/22 (71.4/28.6)	NS
Residual urine diuresis before transplant, mL	1057.75 ± 852.84	1188.42 ± 818.65	NS
Rank of transplant			NS
First transplant, *n* (%)	73 (94.8)	76 (98.7)	NS
Second transplant, *n* (%)	3 (3.9)	1 (1.3)	NS
Third transplant, *n* (%)	1 (1.3)	0 (0)	NS
Time on dialysis before transplantation, d	1105 ± 1198	720 ± 757	NS
HLA Mismatching (MM), *n* (%)			NS
0 MM	11 (14.3)	6 (7.8)	
1 MM	8 (10.4)	7 (9.1)	
2 MM	30 (39.0)	16 (30.8)	
3 MM	23 (29.9)	30 (39)	
4 MM	2 (2.6)	7 (9.1)	
5 MM	3 (3.9)	6 (7.8)	
6 MM	0 (0.0)	5 (6.5)	
Hemoglobin before transplantation, g/dL	12.47 ± 1.72	12.69 ± 1.18	NS
Albumin before transplantation, g/dL	4.32 ± 0.40	4.24 ± 0.41	NS
Peritransplant plasmapheresis treatment, *n* (%)	14 (18)	3 (4)	[a]

[a]$P < 0.05$. Data are given as the mean ± SD. ADPKD: Autosomal dominant polycystic kidney disease; CMV: Cytomegalovirus; DBD: Donation after brain death; DCD: Donation after circulatory death; HLA: Human leukocyte antigen; KT: Kidney transplantation; MM: Mismatching; NS: No significance.

third month and from 3 mo after transplantation, respectively. Methylprednisolone was started immediately after transplant at 16 mg/d and tapered (minus 4 mg every 2 wk) to a fixed dose of 4 mg for all recipients at long-term. Co-trimoxazole prophylaxis was given to all patients during the first 6 mo after transplantation. Valganciclovir prophylaxis (900 mg/d for normal kidney function) was given to

Table 2 Surgical data of 154 recipients suffering from autosomal dominant polycystic kidney disease with or without associated ipsilateral nephrectomy during isolated kidney transplantation in a single-center transplant program from January 2007 until January 2019

	KT alone group (*n* = 77)	KT with associated ipsilateral nephrectomy (*n* = 77)	*P value*
Indications for associated nephrectomy, *n* (%)			
Creating space for graft positioning, *n* (%)		74 (96.1)	
Pain, *n* (%)		29 (37.7)	
Recurrent urinary tract infections, *n* (%)		11 (14.3)	
Hematuria, *n* (%)		30 (39.0)	
Digestive symptoms, *n* (%)		3 (3.9)	
Lithiasis, *n* (%)		9 (11.7)	
Anastomosis time[1], min	39.61 ± 9.782	36.96 ± 10.10	NS
Cold ischemia time, min	827.56 ± 446.12	767.87 ± 436.81	NS
Total surgical time, min	169.07 ± 44.31	223.29 ± 71.96	[a]
Weight of removed native kidney, g		2073.94 ± 1197.89	

[1]Time from kidney out of ice water until moment of *in vivo* blood reperfusion.

[a]$P < 0.05$. Data are given as the mean ± SD. ADPKD: Autosomal dominant polycystic kidney disease; NT: Not significant; KT: Kidney transplantation; NS: No significance.

all patients during the first 6 mo after transplantation with the exception of cytomegalovirus donor seronegative/recipient seronegative patients. Biopsy-proven acute cellular rejection and humoral rejections were treated with methylprednisolone boluses for 3 d and plasmapheresis, respectively.

Follow-up

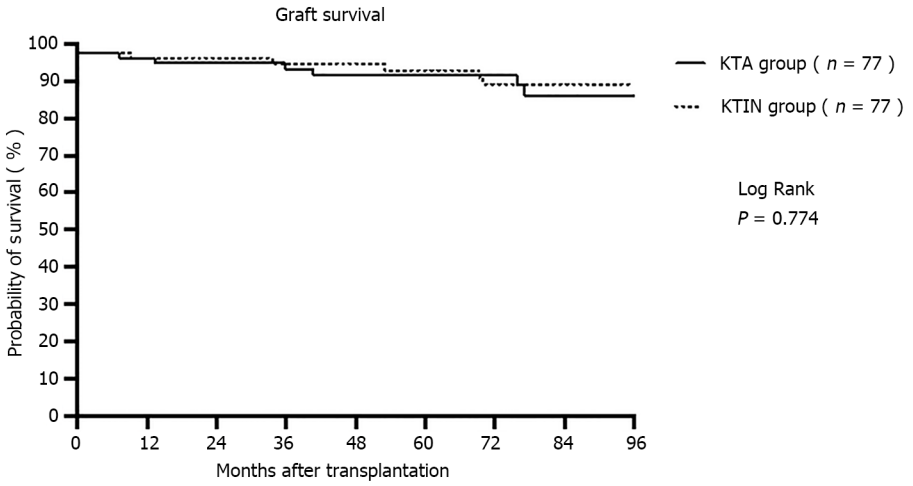
During the transplant hospitalization, the patients were monitored daily to evaluate comorbidity and kidney function was evaluated by serum creatinine and urine analysis. If primary nonfunction (PNF), delayed graft function (DGF) or vascular problems of the kidney graft were suspected, an urgent ultrasound was performed. Otherwise, a baseline ultrasound was performed at the end of the transplant hospitalization. Ambulatory follow-up of the kidney graft function (measured by serum creatinine and urine analysis) and surgical comorbidity was performed according to local center practice. No protocol, only indication biopsies of the kidney graft were performed after the preceding ultrasound. Every year after transplantation, an ultrasound of the kidney graft and the native kidneys was performed. If malignancy of the native kidneys was suspected, nuclear magnetic resonance was carried out.

Endpoints

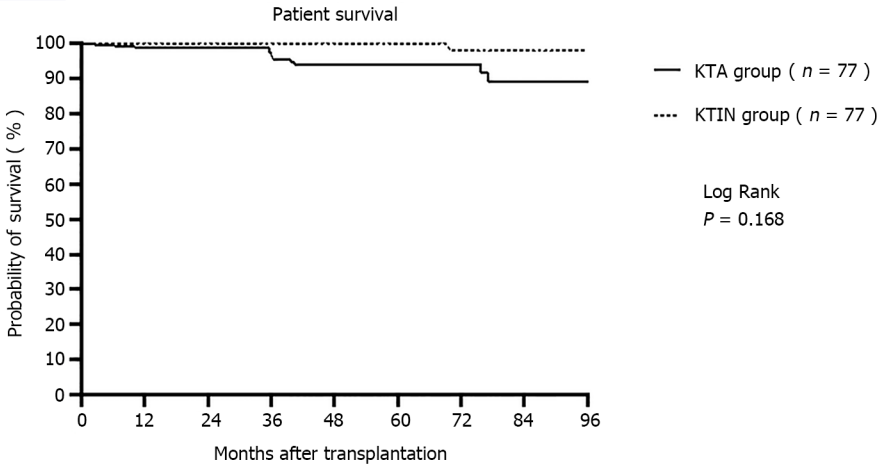
The primary endpoint was surgical comorbidity, measured as the incidence of postoperative lymphocele, wound infection, incisional hernia, wound hematoma, urinary infection, need for peritransplant (during and after transplantation) blood transfusion, pulmonary embolism, total hospital stay, readmission rate and surgical complications classified according to the Dindo Clavien classification [10]. Secondary endpoints were the incidence of PNF, DGF (defined as the need for dialysis during the first week after transplantation), venous or arterial kidney graft thrombosis, acute rejection incidence and type of rejection (cellular *vs* humoral) during the first year after transplantation and the 1- and 5-year patient- and graft survival rate.

Statistical analysis

Characteristics of the donor, the recipient and the transplant outcome were compared using the chi-square test for categorical variables and the t-test for continuous variables. Continuous variables are provided as means and standard deviations. Log-rank statistics were used with the Kaplan-Meier product-limit method to evaluate the associations of individual covariates with allograft survival. $P < 0.05$ was considered statistically significant. Statistical analysis and plots were accomplished with SPSS 24.0 statistical software (SPSS, Chicago, IL, USA) and Prism 8.2.0 (Graphpad Software, San Diego, CA, USA).



	Months after transplantation	12	24	36	48	60	72	84	96
KTA group (*n* = 77)	Graft survival rate (%)	94.8	93.5	92	90.3	90.3	90.3	85	85
	Patients at risk (*n*)	73	67	58	48	43	37	30	21
KTIN group (*n* = 77)	Graft survival rate (%)	96	96	94.6	94.6	92.8	89.2	89.2	89.2
	Patients at risk (*n*)	74	72	62	55	51	47	42	34



	Months after transplantation	12	24	36	48	60	72	84	96
KTA group (*n* = 77)	Graft survival rate (%)	100	98.7	97	93.8	93.8	93.8	88.7	88.7
	Patients at risk (*n*)	77	71	61	50	44	40	32	22
KTIN group (*n* = 77)	Graft survival rate (%)	100	100	100	100	100	98	98	98
	Patients at risk (*n*)	77	75	66	59	56	52	46	38

DOI: 10.5500/wjt.v12.i5.100

Figure 2 The graft and patient survival of 154 isolated kidney transplant recipients suffering from autosomal dominant polycystic kidney disease with or without associated ipsilateral nephrectomy during transplantation performed in a single center transplant program from January 2007 until January 2019. KT: Kidney transplantation.

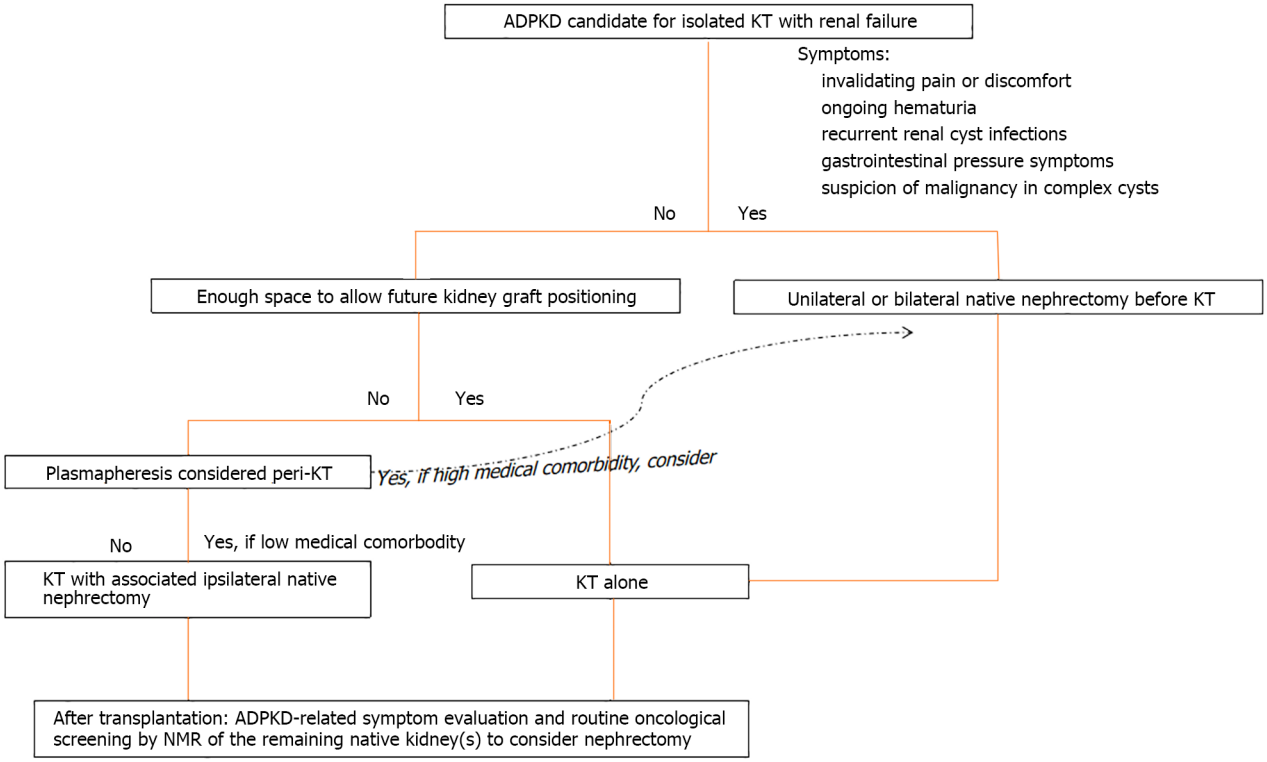
RESULTS

Donor and recipient characteristics

Donor and recipient characteristics of both study groups were comparable, with the exception of the incidence of living donation, which was significantly higher in the KTIN group compared with the KTA group [21 (27.3%) *vs* 6 (7.8%), *P* = 0.003] (Table 1). Peritransplant plasmapheresis was performed in 14 (18%) and 3 (4%) immunized recipients in the KTA and the KTIN group, respectively (*P* = 0.008).

Operative data

The main indications for performing an associated ipsilateral native nephrectomy at the same site as the kidney transplantation were lack of space for graft positioning (*n* = 74; 96.1%), pain (*n* = 29; 37.7%) and



DOI: 10.5500/wjt.v12.i5.100

Figure 3 Clinical algorithm to decide the optimal timing of a native nephrectomy in patients with autosomal dominant polycystic kidney disease, candidate for isolated kidney transplantation. ADPKD: Autosomal dominant polycystic kidney disease; NMR: Nuclear magnetic resonance; KT: Kidney transplantation.

hematuria (n = 30; 39.0%). Pain, as the only reason for ipsilateral nephrectomy, was present in 3 (3.9%) patients. The decision not to perform an associated ipsilateral native nephrectomy was taken by the surgeon during the transplant procedure if enough space for graft positioning in combination with the absence of other ADPKD-related symptoms was estimated at the moment of transplantation. No difference in anastomosis and cold ischemia time was observed between the two study groups (Table 2). The total surgical time was significantly longer in the KTIN group as compared with the KTA group (223.29 ± 71.96 *vs* 169.07 ± 44.31, respectively; P = 0.005). The mean weight of the removed polycystic kidney was 2073.94 ± 1197.89 g.

Comorbidity after transplantation

No significant difference in surgical comorbidity (lymphocele, wound infection, incisional hernia, wound hematoma, pulmonary embolism, urinary infection, need for peritransplant blood transfusion, hospitalization stay, readmission rate and Dindo Clavien classification) was observed between the two study groups (Table 3).

Graft function and patient survival

The incidence of PNF and DGF was comparable in both groups [0% *vs* 2.6% (P = 0.497) and 9.1% *vs* 16.9% (P = 0.230), respectively, in the KTA and KTIN group] (Table 3). No significant difference in renal artery and vein thrombosis of the kidney graft was observed between the two study groups. In addition, the incidence of acute rejection within one year after transplantation was comparable among the groups.

The 1- and 5-year graft survival were 94.8% and 90.3, and 100% and 93.8%, respectively, in the KTA and KTIN group (P = 0.774) (Figure 2). The 1- and 5-year patient survival were 96.1% and 92.9%, and 100% and 100%, respectively, in the KTA and KTIN group (P = 0.168) (Figure 2).

DISCUSSION

This retrospective single-center study is one of the largest series to demonstrate the absence of a negative impact on surgical comorbidity and short- and long-term kidney graft function following an associated ipsilateral native nephrectomy to create space for graft positioning during isolated kidney transplantation in ADPKD patients compared with ADPKD kidney transplant recipients without simultaneous nephrectomy.

Table 3 Surgical comorbidity and clinical outcomes of 154 isolated kidney transplant recipients suffering from autosomal dominant polycystic kidney disease with or without associated ipsilateral nephrectomy during transplantation in a single center transplant program from January 2007 until January 2019

	KT alone group (*n* = 77)	KT with associated ipsilateral nephrectomy (*n* = 77)	*P* value
Surgical comorbidity			
Lymphocele, *n* (%)	5 (6.5)	7 (9.1)	NS
Wound infection, *n* (%)	6 (7.8)	2 (2.6)	NS
Incisional hernia, n%)	0 (0)	3 (3.9)	NS
Wound hematoma, *n* (%)	6 (7.8)	3 (3.9)	NS
Pulmonary embolism, *n* (%)	1 (1.3)	0 (0)	NS
Urinary infection, *n* (%)	14 (18.2)	8 (10.4)	NS
Need for blood transfusion, *n* (%)	22 (28.6)	34 (44.2)	NS
Hospital stay after transplantation, d	15.22 ± 6.662	14.81 ± 6.44	NS
Readmission rate during whole follow-up, *n* (%)	42 (46.2)	49 (63.6)	NS
Dindo Clavien classification			NS
Class I	36 (46.8)	33 (42.9)	NS
Class II	22 (28.6)	32 (41.6)	NS
Class III	7 (9.1)	3 (3.9)	NS
Class IV	12 (15.6)	9 (11.7)	NS
Clinical outcomes			
Primary nonfunction, *n* (%)	0 (0)	2 (2.6)	NS
Delayed graft function, *n* (%)	7 (9.1)	13 (16.9)	NS
Renal artery thrombosis of kidney graft, *n* (%)	2 (2.6)	0 (0)	NS
Renal vein thrombosis of kidney graft, *n* (%)	2 (2.6)	0 (0)	NS
Acute rejection episode within 1 year after transplantation, *n* (%)	5 (6.5)	5 (6.5)	NS
Cellular, *n* (%)	5 (100)	2 (40)	
Humoral, *n* (%)	0 (0)	3 (60)	

Data are given as the mean ± SD. ADPKD: Autosomal dominant polycystic kidney disease; NT: Not significant; KT: Kidney transplantation; NS: No significance.

The lifetime nephrectomy rate of at least one kidney is approximately 20-30% for patients with ADPKD[11,12]. Maintaining native kidneys in ADPKD transplant candidates may help to prevent renal osteodystrophy, anemia, uremia, fluid overload, congestive heart failure, and hyperkalemia[4,13,14]. The advantage of maintaining total native urine output is important for dialysis comfort in patients on the waiting list for transplantation and confers some survival benefits on the waiting list[15]. Even today, the indications and timing for a native unilateral or bilateral nephrectomy in ADPKD candidates for isolated kidney transplantation remain controversial and are quite often center-dependent and based on historical routine and experience. Clear indications for unilateral or bilateral native nephrectomy before transplantation are: (1) Invalidating pain and discomfort; (2) Ongoing hematuria; (3) Recurrent renal cyst infections and gastrointestinal pressure symptoms (*e.g.*, early satiety); (4) recurrent nephrolithiasis (rare); (5) The suspicion of malignancy in those with complex cysts; and (6) Combined liver and kidney transplantation. In the absence of these clear indications, the lack of space for positioning a future kidney graft remains controversial as an indication for performing a unilateral native nephrectomy before transplantation. We agree that a simultaneous ipsilateral nephrectomy to create space during isolated kidney transplantation can be technically challenging, even in the hands of an experienced surgeon. A review of the literature, as illustrated in Table 4, does not demonstrate a significant negative impact of an associated ipsilateral or bilateral nephrectomy during isolated kidney transplantation on surgical comorbidity and early and late allograft and patient survival[16-20]. The advantage of performing the nephrectomy simultaneous with the transplantation is the avoidance of an

Table 4 Overview of studies investigating the surgical comorbidity of a simultaneous native unilateral or bilateral nephrectomy during isolated kidney transplantation for autosomal dominant polycystic kidney disease

Ref.	Study group (n)	Type of donor	Isolated KT with simultaneous native bilateral or unilateral nephrectomy		KT alone	Study conclusions
			Bilateral	Unilateral		
Nunes P *et al*[13], 2007	1 (143)	LD (6%) + DD (94%)		+		Comparable overall complication rate and graft survival after 5 years if unilateral nephrectomy is performed for creation of space for a renal allograft
	2 (16)	LD (2%) + DD (98%)			+	
Kramer A *et al*[14], 2009	1 (20)	LD (100%)	+			Minimal morbidity of an associated bilateral nephrectomy during transplantation and graft and patient survival of 100% during 5-year follow-up
Skauby MH *et al*[15], 2012	1 (79); 2 (78)	LD (100%)	+		+	Associated bilateral nephrectomy results in a longer hospital stay and more postoperative complications. No difference in 1- and 5-year patient and graft survival
Neeff HP *et al*[16], 2013	1 (100)	LD (38%) + DD (62%)		+		Routine ipsilateral nephrectomy, independent of volume of polycystic kidney, during transplantation is a safe procedure without endangering patient or graft survival. The death of 3 patients in the first year post-transplant is a concern
Ahmad SB *et al*[17], 2016	1 (66)	LD (100%)	+			In symptomatic patients with ADPKD, the combined procedure is advantageous, especially in terms of patient satisfaction
	2 (52)				+	
Current study	1 (77)	LD (7.8%) + DD (92.2%)		+		Comparable surgical comorbidity and 1- and 5-year patient and graft survival
	2 (77)	LD (27.3%) + DD (72.7%)			+	

ADPKD: Autosomal dominant polycystic kidney disease; DD: Deceased donor; LD: Living donor; KT: Kidney transplantation.

extra anesthetic/surgical procedure and possible oliguria when performed before transplantation during the time on the waiting list. In line with these previous studies, the risk of losing a kidney graft, in relation to native nephrectomy is extremely low.

The proposed algorithm to decide the optimal timing of a native nephrectomy in candidates for isolated kidney transplantation is mainly based on ADPKD-related symptoms (Figure 3). In general, we do not perform a native nephrectomy to create space for graft positioning in the absence of ADPKD-related symptoms before transplantation but by preference during the transplantation. Patients with a pretransplant clinical examination showing a polycystic kidney below the level of the umbilicus or a radiological image showing a polycystic kidney extending into the iliac fossa, are very likely to need an ipsilateral native nephrectomy during transplant. Our center policy is to add peritransplant plasmapheresis to the standard immunosuppressive therapy in all high-immunized patients. Therefore, only for high-immunized patients with an expected long waiting time on the transplant list and high associated medical comorbidity, we consider a unilateral nephrectomy to create space for future kidney graft positioning before transplantation with the aim to decrease the risk of plasmapheresis-related surgical complications (bleeding, incisional hernias, blood transfusions, ...) during transplantation. This might explain the difference in the numbers of patients receiving peritransplant plasmapheresis in favor of the KTA group in our study. For high-immunized patients with low associated medical comorbidity, our preference is to perform the associated nephrectomy during the transplantation.

Also, our strategy is to avoid an unnecessary nephrectomy after transplantation. Today, it is unusual for ADPKD patients to require nephrectomies for complications related to their native kidney (< 20%) after transplantation[5]. Nuclear magnetic resonance of the abdomen is routinely performed after transplantation to screen for malignancies in the native polycystic kidney(s). Conflicting data exists regarding the risk of renal cell carcinomas in ADPKD-affected kidneys. While case studies report the occurrence of renal cell carcinomas in ADPKD-affected kidneys[21,22], these tumors may be partly due to acquired renal cystic disease resulting from long-term dialysis[23]. In contrast, data from the Scientific Registry of Transplant Recipients observed a lower cancer risk in polycystic kidney disease recipients. This might be explained by the ADPKD mutations causing clear cyst formation, but it is also possible that these mutations trigger protective cellular mechanisms that prevent cells from undergoing malignant transformation[24]. Ward CJ *et al*[25] demonstrated that germline mutations in polycystic kidney and hepatic disease 1 were protective against colorectal cancer. However, the observed lower

risk of renal cancer in the Scientific Registry of Transplant Recipients can also be explained by the higher incidence of nephrectomies in ADPKD recipients in contrast with their non-ADPKD counterparts[24].

We recognize some limitations in the present study. First, this a retrospective study. Second, in recipients with associated nephrectomy during isolated kidney transplantation, the lower incidence of peritransplant plasmapheresis and higher incidence of living donors could have underestimated the surgical comorbidity in this study group.

CONCLUSION

In conclusion, simultaneous native ipsilateral nephrectomy to create space for graft positioning during kidney transplantation in ADPKD patients does not detrimentally impact surgical comorbidity and short- and long-term graft survival.

ARTICLE HIGHLIGHTS

Research background

The lack of space, as an indication for a native unilateral nephrectomy for positioning a future kidney graft in the absence of other autosomal dominant polycystic kidney disease (ADPKD)-related symptoms, remains controversial.

Research motivation

Unilateral native nephrectomy to create space for graft positioning in an otherwise asymptomatic ADPKD patient is quite often routinely performed in isolated kidney transplant candidates before their activation on the waiting list. This strategy is mainly driven by the fear of increased surgical comorbidity and the possible negative impact of prolonged cold ischemia time and short- and long-term graft survival related to the associated nephrectomy during transplantation.

Research objectives

To evaluate the surgical comorbidity and the impact on graft survival of an associated ipsilateral native nephrectomy during isolated kidney transplantation in patients with ADPKD.

Research methods

One hundred and fifty-four kidney transplantations performed between January 2007 and January 2019 of which 77 without (kidney transplant alone (KTA) group) and 77 with associated ipsilateral nephrectomy (KTIN group), were retrospectively reviewed. Demographics and surgical variables were analyzed and their respective impact on surgical comorbidity and graft survival.

Research results

No significant difference in surgical comorbidity (lymphocele, wound infection, incisional hernia, wound hematoma, urinary infection, need for blood transfusion, hospitalization stay, Dindo Clavien classification and readmission rate) was observed between the two study groups. The 1- and 5-year graft survival were 94.8% and 90.3%, and 100% and 93.8%, respectively, in the KTA and KTIN group (P = 0.774). The 1- and 5-year patient survival were 96.1% and 92.9%, and 100% and 100%, respectively, in the KTA and KTIN group (P = 0.168).

Research conclusions

Simultaneous ipsilateral native nephrectomy to create space for graft positioning during kidney transplantation in patients with ADPKD does not negatively impact surgical comorbidity and short- and long-term graft survival.

Research perspectives

More kidney transplant candidates suffering from ADPKD when activated on the waiting list should be proposed for an associated ipsilateral nephrectomy during the transplantation instead of routinely programmed pretransplant nephrectomy.

FOOTNOTES

Author contributions: Darius T and De Meyer M designed the research; Bertoni S, De Meyer M and Darius T performed the research; Darius T analyzed the data; Darius T wrote the paper.

Institutional review board statement: This study was approved by the Institutional Board of our University Hospital on July 6, 2020.

Informed consent statement: All study participants provided informed written consent regarding personal and medical data collection prior to study enrolment.

Conflict-of-interest statement: All the authors have no conflict of interest related to the manuscript.

Data sharing statement: The original anonymous dataset is available on request from the corresponding author at tom.darius@uclouvain.be

STROBE statement: The manuscript was prepared according to the STROBE statement - checklist of items.

Country/Territory of origin: Belgium

ORCID number: Tom Darius 0000-0002-8151-4286; Sébastien Bertoni 0000-0001-8066-0639; Martine De Meyer 0000-0003-2002-6163; Antoine Buemi 0000-0001-9341-7902; Arnaud Devresse 0000-0003-4943-788X; Nada Kanaan 0000-0001-7903-8631; Eric Goffin 0000-0001-9242-7148; Michel Mourad 0000-0002-0372-275X.

Corresponding Author's Membership in Professional Societies: Belgian Transplant Society; European Society for Organ Transplantation; The Transplantation Society.

S-Editor: Wang LL
L-Editor: Webster JR
P-Editor: Cai YX

REFERENCES

1 **Torres VE**, Harris PC, Pirson Y. Autosomal dominant polycystic kidney disease. *Lancet* 2007; **369**: 1287-1301 [PMID: 17434405 DOI: 10.1016/S0140-6736(07)60601-1]
2 **Kanaan N**, Devuyst O, Pirson Y. Renal transplantation in autosomal dominant polycystic kidney disease. *Nat Rev Nephrol* 2014; **10**: 455-465 [PMID: 24935705 DOI: 10.1038/nrneph.2014.104]
3 **Akoh JA**. Current management of autosomal dominant polycystic kidney disease. *World J Nephrol* 2015; **4**: 468-479 [PMID: 26380198 DOI: 10.5527/wjn.v4.i4.468]
4 **Kirkman MA**, van Dellen D, Mehra S, Campbell BA, Tavakoli A, Pararajasingam R, Parrott NR, Riad HN, McWilliam L, Augustine T. Native nephrectomy for autosomal dominant polycystic kidney disease: before or after kidney transplantation? *BJU international* 2011; **108**: 590-594 [PMID: 21166760 DOI: 10.1111/j.1464-410X.2010.09938.x]
5 **Gebicki JM**. Classic redox. Garrison WM, Jayko ME, Bennett W. Radiation-induced oxidation of protein in aqueous solution. Radiat Res 1962; 16: 483-502. *Redox Rep* 2000; **5**: 15-16 [PMID: 10905538 DOI: 10.1179/rer.2000.5.1.15]
6 **Argyrou C**, Moris D, Vernadakis S. Tailoring the 'Perfect Fit' for Renal Transplant Recipients with End-stage Polycystic Kidney Disease: Indications and Timing of Native Nephrectomy. *In Vivo* 2017; **31**: 307-312 [PMID: 28438856 DOI: 10.21873/invivo.11060]
7 **Gregoir W**. [Congenital vesico-ureteral reflux]. *Acta urologica Belgica* 1962; **30**: 286-300 [PMID: 13901619]
8 **Lich R**, Jr. , Howerton LW, Davis LA. Childhood urosepsis. *J Kentucky Medical Association* 1961; **59**: 1177-1179 [DOI: 10.1016/s0022-5347(17)65219-4]
9 **Woodruff MF**, Nolan B, Robson JS, MacDonald MK. Renal transplantation in man. Experience in 35 cases. *Lancet* 1969; **1**: 6-12 [PMID: 4178807 DOI: 10.1016/s0140-6736(69)90982-9]
10 **Clavien PA**, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, de Santibanes E, Pekolj J, Slankamenac K, Bassi C, Graf R, Vanlanthen R, Padbury R, Cameron JL, Makuuchi M. The Clavien-Dindo classification of surgical complications: five-year experience. *Annals of surgery* 2009; **250**: 187-196 [DOI: 10.1097/sla.0b013e3181b13ca2]
11 **Sulikowski T**, Tejchman K, Zietek Z, Rózański J, Domański L, Kamiński M, Sieńko J, Romanowski M, Nowacki M, Pabisiak K, Kaczmarczyk M, Ciechanowski K, Ciechanowicz A, Ostrowski M. Experience with autosomal dominant polycystic kidney disease in patients before and after renal transplantation: a 7-year observation. *Transplant Proc* 2009; **41**: 177-180 [PMID: 19249508 DOI: 10.1016/j.transproceed.2008.10.034]
12 **Patel P**, Horsfield C, Compton F, Taylor J, Koffman G, Olsburgh J. Native nephrectomy in transplant patients with autosomal dominant polycystic kidney disease. *Ann R Coll Surg Engl* 2011; **93**: 391-395 [PMID: 21943464 DOI: 10.1308/003588411X582690]
13 **Brazda E**, Ofner D, Riedmann B, Spechtenhauser B, Margreiter R. The effect of nephrectomy on the outcome of renal transplantation in patients with polycystic kidney disease. *Ann Transplant* 1996; **1**: 15-18 [PMID: 9869924]

14 **Pirson Y**, Christophe JL, Goffin E. Outcome of renal replacement therapy in autosomal dominant polycystic kidney disease. Nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association. *European Renal Association* 1996; **11** Suppl 6: 24-28 [DOI: 10.1093/ndt/11.supp6.24]

15 **Termorshuizen F**, Dekker FW, van Manen JG, Korevaar JC, Boeschoten EW, Krediet RT. Relative contribution of residual renal function and different measures of adequacy to survival in hemodialysis patients: an analysis of the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD)-2. *J Am Soc Nephrol* 2004; **15**: 1061-1070 [DOI: 10.1097/01.asn.0000117976.29592.93]

16 **Nunes P**, Mota A, Alves R, Figueiredo A, Parada B, Macário F, Rolo F. Simultaneous renal transplantation and native nephrectomy in patients with autosomal-dominant polycystic kidney disease. *Transplant Proc* 2007; **39**: 2483-2485 [PMID: 17954154 DOI: 10.1016/j.transproceed.2007.07.035]

17 **Kramer A**, Sausville J, Haririan A, Bartlett S, Cooper M, Phelan M. Simultaneous bilateral native nephrectomy and living donor renal transplantation are successful for polycystic kidney disease: the University of Maryland experience. *J Urol* 2009; **181**: 724-728 [PMID: 19091353 DOI: 10.1016/j.juro.2008.10.008]

18 **Skauby MH**, Øyen O, Hartman A, Leivestad T, Wadström J. Kidney transplantation with and without simultaneous bilateral native nephrectomy in patients with polycystic kidney disease: a comparative retrospective study. *Transplantation* 2012; **94**: 383-388 [PMID: 22828736 DOI: 10.1097/TP.0b013e31825812b9]

19 **Neeff HP**, Pisarski P, Tittelbach-Helmrich D, Karajanev K, Neumann HP, Hopt UT and Drognitz O. One hundred consecutive kidney transplantations with simultaneous ipsilateral nephrectomy in patients with autosomal dominant polycystic kidney disease. Nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association. *European Renal Association* 2013; **28**: 466-471 [DOI: 10.1093/ndt/gfs118]

20 **Ahmad SB**, Inouye B, Phelan MS, Kramer AC, Sulek J, Weir MR, Barth RN, LaMattina JC, Schweitzer EJ, Leeser DB, Niederhaus SV, Bartlett ST, Bromberg JS. Live Donor Renal Transplant With Simultaneous Bilateral Nephrectomy for Autosomal Dominant Polycystic Kidney Disease Is Feasible and Satisfactory at Long-term Follow-up. *Transplantation* 2016; **100**: 407-415 [PMID: 26262506 DOI: 10.1097/TP.0000000000000838]

21 **Hajj P**, Ferlicot S, Massoud W, Awad A, Hammoudi Y, Charpentier B, Durrbach A, Droupy S, Benoît G. Prevalence of renal cell carcinoma in patients with autosomal dominant polycystic kidney disease and chronic renal failure. *Urology* 2009; **74**: 631-634 [PMID: 19616833 DOI: 10.1016/j.urology.2009.02.078]

22 **Jilg CA**, Drendel V, Bacher J, Pisarski P, Neeff H, Drognitz O, Schwardt M, Gläsker S, Malinoc A, Erlic Z, Nunez M, Weber A, Azurmendi P, Schultze-Seemann W, Werner M, Neumann HP. Autosomal dominant polycystic kidney disease: prevalence of renal neoplasias in surgical kidney specimens. *Nephron Clin Pract* 2013; **123**: 13-21 [PMID: 23752029 DOI: 10.1159/000351049]

23 **Ishikawa I**, Hayama S, Morita K, Nakazawa T, Yokoyama H, Honda R, Satoh K, Kakuma T. Long-term natural history of acquired cystic disease of the kidney. *Ther Apher Dial* 2010; **14**: 409-416 [PMID: 20649762 DOI: 10.1111/j.1744-9987.2010.00819.x]

24 **Wetmore JB**, Calvet JP, Yu AS, Lynch CF, Wang CJ, Kasiske BL, Engels EA. Polycystic kidney disease and cancer after renal transplantation. *J Am Soc Nephrol* 2014; **25**: 2335-2341 [PMID: 24854270 DOI: 10.1681/ASN.2013101122]

25 **Ward CJ**, Wu Y, Johnson RA, Woollard JR, Bergstralh EJ, Cicek MS, Bakeberg J, Rossetti S, Heyer CM, Petersen GM, Lindor NM, Thibodeau SN, Harris PC, Torres VE, Hogan MC, Boardman LA. Germline PKHD1 mutations are protective against colorectal cancer. *Hum Genet* 2011; **129**: 345-349 [PMID: 21274727 DOI: 10.1007/s00439-011-0950-8]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com