ISSN 2220-3230 (online)

World Journal of *Transplantation*

World J Transplant 2023 February 18; 13(2): 25-57

Published by Baishideng Publishing Group Inc

World Journal of Transplantation

Contents

Monthly Volume 13 Number 2 February 18, 2023

World Journal of Transplantation

Monthly Volume 13 Number 2 February 18, 2023

Contents

ABOUT COVER

The Transplant Team of the University of Thessaloniki, Greece.

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

February 18, 2023

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 2023 February 18; 13(2): 25-27

DOI: 10.5500/wjt.v13.i2.25

ISSN 2220-3230 (online)

EDITORIAL

Translational research and innovation in modern transplant practice: Paradigms from Greece and around the world

Georgios Tsoulfas, Ioannis Boletis, Vassilios Papalois

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): C
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Cozzi M, Italy; Masaru T, Hungary

Received: November 30, 2022
Peer-review started: November 30, 2022
First decision: January 3, 2023
Revised: January 14, 2023
Accepted: February 7, 2023
Article in press: February 7, 2023
Published online: February 18, 2023

Georgios Tsoulfas, Department of Transplantation Surgery, Aristotle University School of Medicine, Thessaloniki 54124, Greece

Ioannis Boletis, Department of Nephrology, EKPA University, Athens 11527, Greece

Vassilios Papalois, Department of Transplant Surgery, Imperial College Renal and Transplant Centre, London W12 0HS, United Kingdom

Corresponding author: Georgios Tsoulfas, FACS, FICS, MD, PhD, Chief Doctor, Professor, Surgeon, Department of Transplantation Surgery, Aristotle University School of Medicine, Campus Aristotle University School of Medicine, Thessaloniki 54124, Greece.
tsoulfasg@gmail.com

Abstract

The continuous clinical and technological advances, together with the social, health and economic challenges that the global population faces, have created an environment where the evolution of the field of transplantation is essentially necessary. The goal of this special issue is to provide a picture of the current status of transplantation in Greece as well as in many other countries in Europe and around the world. Authors from Greece and several other countries provide us with valuable insight into their respective areas of transplant expertise, with a main focus on the field of translational research and innovation. The papers that are part of this Special Issue "Translational Research and Innovation and the current status of Transplantation in Greece" have presented innovative and meaningful approaches in modern transplant research and practice. They provide us with a clear overview of the current landscape in transplantation, including liver transplantation in the context of a major pandemic, the evolution of living donor kidney transplantation or the evolution of the effect of hepatitis C virus infection in transplantation, while at the same time explore more recent challenges, such as the issue of frailty in the transplant candidate and the changes brought by newer treatments, such as immunotherapy, in transplant oncology. Additionally, they offer us a glimpse of the effect that technological innovations, such as virtual reality, can have on transplantation, both in terms of clinical and educational aspects. Just as critical is the fact that this Special Issue emphasizes the multidisciplinary, collaborative efforts currently taking place that link transplant research and innovation with other cutting-edge disciplines such as bioengineering, advanced information technology and artificial intelligence. In this Special Issue, in addition to the clinical and research evolution of the field of

transplantation, we are witnessing the importance of interdisciplinary collaboration in medicine.

Key Words: Translational research; Non-alcoholic fatty liver disease; Immunotherapy; Pandemic; Liver transplantation; Bioengineering; Artificial intelligence; Immunosuppression; Transplant oncology; Living donor kidney transplantation

Core Tip: The goal of this special issue is to provide a picture of the current status of transplantation in Greece as well as in many other countries in Europe and around the world. The issue will focus on presenting innovative and meaningful approaches in modern transplant research and practice as well as to emphasize the multidisciplinary, collaborative efforts currently taking place that link transplant research and innovation with other cutting-edge disciplines such as bioengineering, advanced information technology and artificial intelligence.

Citation: Tsoulfas G, Boletis I, Papalois V. Translational research and innovation in modern transplant practice: Paradigms from Greece and around the world. *World J Transplant* 2023; 13(2): 25-27
URL: https://www.wjgnet.com/2220-3230/full/v13/i2/25.htm
DOI: https://dx.doi.org/10.5500/wjt.v13.i2.25

INTRODUCTION

Transplantation represents to all of us the "Field of Dreams". The reason is that this multidisciplinary vocation of modern medical practice combines the opportunity to significantly improve and, in most cases, save human lives, with adrenaline-filled surgical procedures, together with a constant need for innovation and improvement in a variety of areas including nephrology, hepatology, endocrinology, immunology, pharmacology, anesthesia, radiology and surgery. Most importantly, it is an area where most of the biggest questions have yet to be answered, such as those of achieving tolerance and avoiding immunosuppression. All of the above, make the field of transplantation an actively evolving science on many different levels, where every step forward counts, since human lives are at stake.

The goal of this special issue is to provide a picture of the current status of transplantation in Greece as well as in many other countries in Europe and around the world. The issue will focus on presenting innovative and meaningful approaches in modern transplant research and practice as well as to emphasize the multidisciplinary, collaborative efforts currently taking place that link transplant research and innovation with other cutting-edge disciplines such as bioengineering, advanced information technology and artificial intelligence. Furthermore, we wish to demonstrate that a negative national and international financial climate and the massive effect of the coronavirus disease 2019 pandemic, do not stop the advancement of the field of transplantation and, on certain occasions, they can be the drive for it.

The authors participating in this special issue provide us with a clear overview of the current landscape in transplantation, including liver transplantation in the context of a major pandemic, the evolution of living donor kidney transplantation or the evolution of the effect of hepatitis C virus infection in transplantation, while at the same time explore more recent challenges, such as the issue of frailty in the transplant candidate and the changes brought by newer treatments, such as immunotherapy, in transplant oncology[1]. Additionally, they offer us a glimpse of the effect that technological innovations, such as virtual reality, can have on transplantation, both in terms of clinical and educational aspects.

Most importantly, the papers in this special issue stress the need for interdisciplinary and international collaboration in the field of transplantation and the fact that it remains our "Field of Dreams". Yesterday's dream is today's aspirational research and tomorrow's established practice.

CONCLUSION

The papers in this Special Issue[2-12] are evidence that global economic and health challenges cannot and should not stop the ongoing evolution of a scientific field as active and as necessary as transplantation.

FOOTNOTES

Author contributions: All authors contributed equally to the writing and editing of the manuscript.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Country/Territory of origin: Greece

ORCID number: Georgios Tsoulfas 0000-0001-5043-7962; Ioannis Boletis 0000-0003-4664-8921; Vassilios Papalois 0000-0003-1645-8684.

Corresponding Author's Membership in Professional Societies: American College of Surgeons; American Gastroenterological Association; American Society of Transplant Surgeons; American Society of Transplantation; European Society of Organ Transplantation; American HepaticoPancreaticoBiliary Association.

S-Editor: Fan JR
L-Editor: A
P-Editor: Fan JR

REFERENCES

1 **Rallis KS**, Makrakis D, Ziogas IA, Tsoulfas G. Immunotherapy for advanced hepatocellular carcinoma: From clinical trials to real-world data and future advances. *World J Clin Oncol* 2022; **13**: 448-472 [PMID: 35949435 DOI: 10.5306/wjco.v13.i6.448]
2 **Gyftopoulos A**, Ziogas IA, Montenovo MI. Liver transplantation during COVID-19: Adaptive measures with future significance. *World J Transplant* 2022; **12**: 288-298 [PMID: 36187879 DOI: 10.5500/wjt.v12.i9.288]
3 **Agrafiotis AC**, Karakasi KE, Poras M, Neiros S, Vasileiadou S, Katsanos G. Surgical chest complications after liver transplantation. *World J Transplant* 2022; **12**: 359-364 [PMID: 36437843 DOI: 10.5500/wjt.v12.i11.359]
4 **Karydis N**, Maroulis I. Changing landscape in living kidney donation in Greece. *World J Transplant* 2023; **13**: 28-35 [DOI: 10.5500/wjt.v13.i2.28]
5 **Ntakakis G**, Plomariti C, Frantzidis C, Antoniou PE, Bamidis PD, Tsoulfas G. Exploring the use of virtual reality in surgical education. *World J Transplant* 2023; **13**: 36-43 [DOI: 10.5500/wjt.v13.i2.36]
6 **Oikonomou IM**, Sinakos E, Antoniadis N, Goulis I, Giouleme O, Anifanti M, Katsanos G, Karakasi KE, Tsoulfas G, Kouidi E. Effects of an active lifestyle on the physical frailty of liver transplant candidates. *World J Transplant* 2022; **12**: 365-377 [PMID: 36437844 DOI: 10.5500/wjt.v12.i11.365]
7 **Alexandrou ME**, Ferro CJ, Boletis I, Papagianni A, Sarafidis P. Hypertension in kidney transplant recipients. *World J Transplant* 2022; **12**: 211-222 [PMID: 36159073 DOI: 10.5500/wjt.v12.i8.211]
8 **Vagiotas L**, Stangou M, Kasimatis E, Xochelli A, Myserlis G, Lioulios G, Nikolaidou V, Panteli M, Ouranos K, Antoniadis N, Maria D, Papagianni A, Tsoulfas G, Fylaktou A. Effect of panel reactive antibodies on T cell immunity reinstatement following renal transplantation. *World J Transplant* 2022; **12**: 313-324 [PMID: 36313234 DOI: 10.5500/wjt.v12.i10.313]
9 **Ouranos K**, Chatziioannou A, Goulis I, Sinakos E. Role of immunotherapy in downsizing hepatocellular carcinoma prior to liver transplantation. *World J Transplant* 2022; **12**: 331-346 [PMID: 36437845 DOI: 10.5500/wjt.v12.i11.331]
10 **Kalogirou MS**, Gioulemе O. Growing challenge of post-liver transplantation non-alcoholic fatty liver disease. *World J Transplant* 2022; **12**: 281-287 [PMID: 36187880 DOI: 10.5500/wjt.v12.i9.281]
11 **Theocharidou E**, Adebayo D. Challenges in liver transplantation in the context of a major pandemic. *World J Transplant* 2022; **12**: 347-358 [PMID: 36437846 DOI: 10.5500/wjt.v12.i11.347]
12 **Yuan Q**, Hong S, Leya G, Roth E, Tsoulfas G, Williams W, Madsen JC, Elias N. Analysis of the effects of donor and recipient hepatitis C infection on kidney transplant outcomes in the United States. *World J Transplant* 2023; **13**: 44-57 [DOI: 10.5500/wjt.v13.i2.44]

World Journal of Transplantation

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

World J Transplant 2023 February 18; 13(2): 28-35

DOI: 10.5500/wjt.v13.i2.28

ISSN 2220-3230 (online)

OPINION REVIEW

Changing landscape in living kidney donation in Greece

Nikolaos Karydis, Ioannis Maroulis

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): C, C
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Dayal C, South Africa; He GF, China; Sureshkumar KK, United States; Zhou ST, China

Received: September 3, 2022
Peer-review started: September 3, 2022
First decision: October 31, 2022
Revised: January 5, 2023
Accepted: January 8, 2023
Article in press: February 8, 2023
Published online: February 18, 2023

Nikolaos Karydis, Department of General Surgery and Transplantation, University of Patras, Patras 26504, Greece

Ioannis Maroulis, Department of General Surgery, University of Patras, Patras 26504, Greece

Corresponding author: Nikolaos Karydis, FEBS, FRCS, MD, PhD, Assistant Professor, Department of General Surgery and Transplantation, University of Patras, University Campus 26504 Rio Achaia, Patras 26504, Greece. npkaridis@gmail.com

Abstract

Patients with end-stage renal disease in Greece are facing long waiting times to receive a kidney transplant from a deceased donor. Living kidney donation offers a valuable alternative that provides optimal outcomes and significantly expands the donor pool but still remains relatively underutilised. Developments around the world in the field of kidney transplantation mandate a change in current practice to include additional options for living donation through paired exchange, antibody-incompatible transplantation and other strategies, following careful consideration of the cultural and ethical factors involved in these complex clinical decisions. An increase in living donation rates may be achieved in several ways, including targeted campaigning to overcome potential barriers. Educating clinicians on transplantation will prove as equally important as informing patients and prospective donors but requires training and resources. Adoption of established practices and implementation of new strategies must be tailored to the needs of the Greek donor and recipient population. Local beliefs about donation, perception of associated risk and other social characteristics must be considered in the design of future strategies. Facilitating living donation in a safe environment with appropriate donor and recipient education will form the solid foundation of a new era of kidney transplantation in Greece.

Key Words: Living kidney donation; Paired exchange; Incompatible transplantation; Unrelated donors; Greece

Core Tip: Living kidney donation is the driving force behind every successful kidney transplant programme worldwide. In Greece, in particular, it accounts for nearly half of performed transplants annually. Its role is of paramount importance since deceased donor kidney transplant waiting times are currently unacceptably long. Paired exchange and other options will form the basis to expand the donor pool and facilitate future developments in the field.

Citation: Karydis N, Maroulis I. Changing landscape in living kidney donation in Greece. *World J Transplant* 2023; 13(2): 28-35
URL: https://www.wjgnet.com/2220-3230/full/v13/i2/28.htm
DOI: https://dx.doi.org/10.5500/wjt.v13.i2.28

INTRODUCTION

Living kidney donation remains the optimal source of kidney transplants worldwide, despite advances in deceased donor organ utilisation and preservation. Living donor kidneys offer excellent long-term outcomes in terms of patient and graft survival[1,2]. Apart from this, living donation has gradually served as the basis for expansion and development of novel patient pathways in kidney transplantation. Antibody-incompatible transplant programmes have been largely successful, enabling discontinuation of dialysis and prolongation of survival in highly sensitised recipients[3,4]. Kidney exchange programmes have been met with great enthusiasm among physicians, surgeons, transplant coordinators and patients alike, dramatically reducing the need for more immunologically complex treatments[5]. Other areas of recent developments include the cross-linking between deceased donor and living donor pathways, providing new insights in the utilisation and optimal matching of available organs to the most suitable recipients[6].

National living donor programmes share many common features but also differ in many ways, even among countries with obvious geographical and cultural similarities. The plausible explanation lies in the complexities of healthcare systems to identify and utilise the maximum number of potential donors, both deceased and living. Furthermore, disparities in training and education may inevitably magnify the differences in donation and transplant rates. Greece is currently entering a new era in kidney transplantation, in particular living donor transplantation, with major new developments that could substantially increase the transplant rates.

LIVING DONATION IS THE DRIVING FORCE IN KIDNEY TRANSPLANTATION

Although donation and transplant rates are low in Greece at approximately five deceased donors per million population[7], the actual living donor kidney transplant rate, ranging between 38%-50% of all transplants the last 5 years, is easily comparable to countries with well-established deceased donor and living donor programmes[8]. This simple observation justifies the argument that an appropriate expansion of the living donor pool could, at least to some extent, "generate" many more high-quality kidney grafts. Additionally, it provides important clues regarding the intention of the Greek population to donate organs albeit usually within the limits of close or extended family.

Deceased donor kidney transplantation currently suffers from unacceptably long waiting times due to multifactorial long-standing issues that effectively limit the number of brain-dead donors who proceed to donation. The obvious advantage of living donation over deceased kidney donation is the relative independence from complicated donor pathways, lack of suitable infrastructure, staffing issues, limitations of laboratory workflows and cultural trends towards donation in general. The latter has been studied in a relatively small sample of an urban population but has provided very useful insight into the attitudes towards organ donation in Greece[9]. Although the vast majority (90.0%-98.0%) of participants demonstrated a high level of understanding around brain death, organ donation and transplantation, only 3.8% were formally registered with the national organ donor register. Half of the participants would be willing to donate the organs of a relative, however more than half would feel guilty doing so. Another emerging concern in this survey was the fear about the process of organ removal, which probably reflects a lack of trust in the processes and regulatory framework related to organ donation in general. Interestingly, religious beliefs did not emerge as significant potential obstacles to donation, and willingness to donate was actually higher among Greek Orthodox participants (63.7%) than the study sample average (48.3%).

Other significant advantages of living over deceased donation include shorter workup times for living donor pairs, presumably due to the willingness of donors and recipients alike to proceed with a transplant, improved immunological matching between family members, ability to proceed with incompatible transplants and finally the relative ease to manage logistical issues, from access to the

operating theatre to specialist perioperative and postoperative care. Deceased donation rates are expected to grow over the next few years in Greece, owing to changes in legislation and the investment of financial and staffing resources to national and local transplant coordination. Until then, living kidney donors will likely drive the country into the new era of transplantation by offering invaluable organs to their respective recipients and by acting as ambassadors of donation and transplantation in the general population. The latter may be more impactful on the public's attitude towards issues surrounding transplantation in general but also requires a coordinated approach led by donors and clinicians in equal parts. The United Network for Organ Sharing has developed a volunteer programme with the primary goal of raising awareness and educating prospective donors through real-life experiences of other donors[10]. Becoming an ambassador of living donation involves an initial orientation and education phase, after which living donors share their personal experience through local events, the United Network for Organ Sharing website and social media. Similar programmes are being developed around the world by national transplant organisations, such as the United Kingdom's National Health Service Blood and Transplant, and are expected to improve communication between transplant professionals and the public.

Highlighting the successes of living donation as well as the safety of modern techniques[11], *i.e.*, minimally invasive donor nephrectomy, quick recovery time, reduced postoperative pain, short length of hospital stay, minimal postoperative complications and excellent long-term outcomes in terms of general health and donor survival, is central to any communication relating to transplantation to strengthen the public's trust. Transparency and publication of interval donation and transplant-related statistics on a scheduled basis in an easily accessible public domain will eliminate suspicion and fear around unacceptable practices that have been reported elsewhere in the world from time to time.

OPTIONS FOR LIVING KIDNEY DONATION IN GREECE

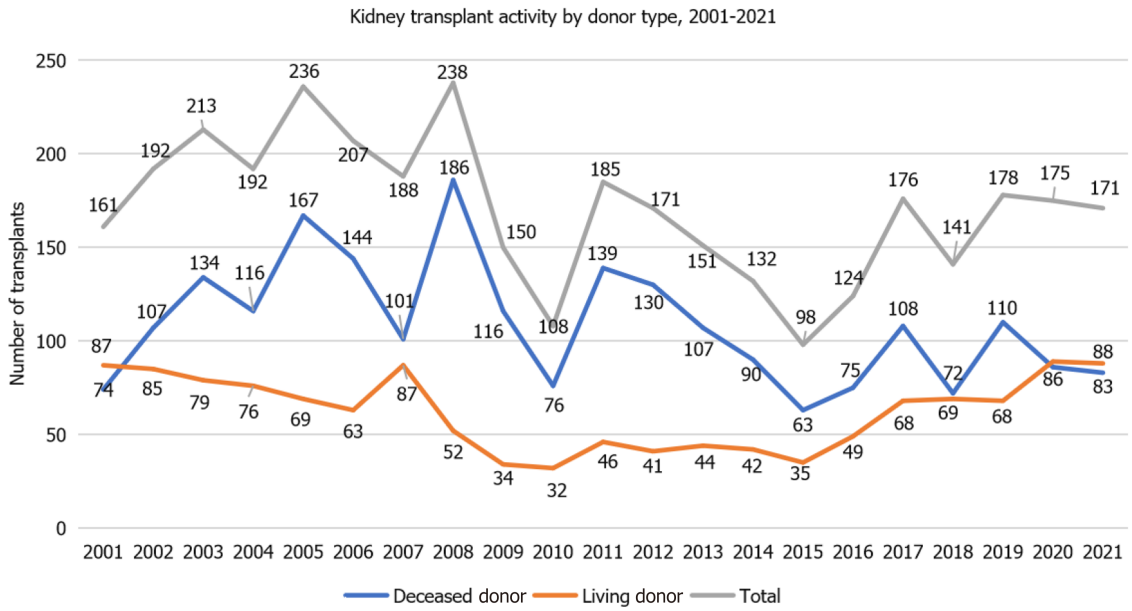
In the recent past, the norm in living kidney donation would be a donor who would come forward and donate to a specified, compatible recipient, usually a member of their close or extended family. Although life-changing behaviours as simple as the above literally transformed modern transplantation and taught clinicians many valuable lessons around modern immunology, we have since made huge progress in terms of living donor organ utilisation. A realistic approach to kidney transplantation dictates that every living donor should be encouraged and facilitated to donate within a safe and coercion-free environment after a fully informed consent process.

The boundaries of living donation have been pushed significantly to make every living donor kidney count for patients in need of an organ, either directly or indirectly[12]. In this context, every suitable living donor should proceed either with a direct or indirect transplant to their intended recipient, which has allowed the development of complex paired exchange networks, mostly but not exclusively geographically confined within their countries. In some instances, these complex networks "interact" with deceased donor pathways to create novel opportunities for highly sensitised or difficult-to-transplant patients who would otherwise not have any chance to receive a kidney transplant. The notion of a "donor-recipient" pair is becoming less clear in this reality, and programmes around the world are being challenged to keep up with developments.

The landscape of living kidney donation has significantly changed in Greece over the last few years, though there is still a long way to cover in certain areas. However, most efforts have concentrated on encouraging living donation, thus the conditions to allow living kidney transplantation to flourish are already in place. Official data from the National Transplant Organisation indicate a rising number of living donor kidney transplants (Figure 1), despite adverse circumstances such as the coronavirus disease 2019 pandemic.

A direct living donor transplant is in many ways the "gold" standard of care. It allows for an immunologically straightforward kidney transplant, in the context of blood group (ABO) and human leukocyte antigen (HLA) compatibility between donor and recipient. Until recently, such transplants were only allowed within extended families, excluding several other types of living donors. The last decade has seen significant legislative changes that have permitted directed donation from unrelated donors, following a formal approval process, which has also been further simplified in the last few years. We consider this change a fundamentally positive step into the new era of transplantation, although official data on its practical applicability so far are lacking. To our knowledge, unrelated undirected, *i.e.*, altruistic, kidney donation, has not yet taken place in Greece due to legislative restrictions. From a practical perspective, the extent to which such donation would make an actual difference in transplant rates is probably very limited, based on cultural perceptions. Indeed, a quite thorough study on the patterns of blood donation in Greece revealed that the concept of "need" is a stronger motivator than the sense of altruistic "offer" for blood donors[13].

The emergence of unrelated donors has inevitably introduced new challenges for the transplant community. Quite a few donors will have an incompatible blood group with the recipient and/or a positive immunological crossmatch. There is sufficient evidence and experience worldwide to suggest that ABO-incompatible kidney transplants have comparable graft and patient outcomes and should be



DOI: 10.5500/wjt.v13.i2.28

Figure 1 Annual deceased and living donor kidney transplant activity in Greece, 2001-2021.

routinely considered as a valid option in suitable pairs[14]. Blood group-incompatible kidney transplants are performed in only one of the transplant units in Greece, although we believe that recipients with relatively low anti-A or anti-B titres could be managed successfully in smaller centres as well. Anecdotal evidence suggests that such donors may have been discouraged from donation due to lack of expertise or suitable infrastructure, and alternative donors may have been sought instead. However, the availability of multiple living donor options is realistically a luxury for the majority of patients, partly due to widely prevalent cultural views that limit living donation from certain age groups. The bottom line is that occasionally living donors may exist but are not able to proceed.

The issue of antibody-incompatible kidney transplantation has a few possible solutions, all of which are available in Greece, albeit still underdeveloped to a variable extent. These solutions include paired exchange or kidney sharing schemes (programmes of kidney exchange between incompatible donor-recipient pairs) and have transformed living donor kidney transplantation over the last two decades[15, 16]. Despite several points of criticism and concerns from both patients and clinicians, the huge success of these programmes has established their role in daily practice. Even well-established and active antibody-incompatible programmes have now shrunk to serve only a small number of patients that cannot be transplanted through paired exchange. In the United Kingdom, for example, the combined number of ABO- and HLA-incompatible kidney transplants has declined gradually from 171 in 2012 to 25 in 2021, as shown graphically in the most recent annual activity report[17].

Engagement from all participating units in a country is obviously of paramount importance to allow the creation of a candidate pool large enough to facilitate ABO and HLA matching. Long chains of such pairs are possible, although logistical issues should be considered to minimise ischaemia times and optimise outcomes. The combination of kidney exchange with altruistic donation has enabled kidney transplantation for highly sensitised or difficult-to-match patients at the end of commonly long chains. In-centre kidney exchange has taken place in Greece in the recent past, however this is potentially more complicated from a logistical perspective, *e.g.*, access to operating theatres, where nephrectomies and transplants all take place on the same day. Between-centres kidney exchange poses its own challenges, but certainly still remains an underutilised option. With appropriate communication and standardisation of donor and recipient procedures, as well as HLA typing and matching, transplant units in Greece could easily transition into a new era of collaboration.

Building a large enough pool possibly requires a radically new approach to living donation altogether. Donors that may have previously been discouraged or misinformed should be given a second chance to consider donation and participate in paired exchange. Our experience shows that donors and recipients are open to the idea of paired exchange and are willing to consider all possibilities in order to avoid long waiting times on the deceased donor waiting list.

Incompatible donors are legally allowed to donate to the deceased donor waiting list, in exchange for their recipient to be prioritised on the waiting list to receive the first available deceased donor kidney. Although there are reasonable concerns around matching the quality of a living donor kidney to a kidney from a deceased donor, in terms of age, medical background, cause of death and terminal kidney function, it remains a valid option for some recipients, compared to a long average waiting time of 8

years. Recipients that fall into this prioritisation list are also allowed to turn down an offer that does not "match" their living donor. Although this is a relatively new option, it is becoming increasingly popular among incompatible pairs, and 17 pairs have been successfully transplanted so far through this scheme.

Antibody-incompatible transplantation remains a popular option, particularly for ABO-incompatible pairs. The literature clearly supports ABO-i kidney transplantation over remaining on haemodialysis [18], thus we believe every transplant unit in Greece could develop an ABO-i programme to enable transplantation for the relatively small number of patients that will proceed with this form of transplant, at least until a robust national paired exchange programme becomes established. Clearly, some centres will accumulate greater expertise in this field, but smaller units could enable transplants with lower anti-A or anti-B titres at the early stages of their development[19]. HLA-incompatible transplantation, although proven superior to haemodialysis[4], remains a challenging procedure with significant risks for the recipients. Early antibody-mediated rejection possibly contributes to inferior graft survival up to 5 years post-transplant[20]. Enhanced immunosuppression may lead to serious bacterial and viral complications that may threaten both graft and patient survival[14]. Indeed, a recent meta-analysis showed increased mortality risk in ABO-i recipients up to 8 years post-transplant[20]. At the same time, the actual number of potential ABO-incompatible transplants in Greece may not adequately justify the risks at this point in time.

FUTURE PROSPECTS

Transplant units need to adapt and invest in the novel options that are now available to our recipients, particularly under the burden of very long waiting times on the deceased donor list. Direct or "indirect" living kidney donation is key to the existence and development of all the above options. Clearly, the kind intentions of every living donor should be honoured in the best possible way after detailed discussion with both the donor and the recipient[21]. The mental and psychological process involved in every aspect of living donation deserves dedication in time and resources to ensure donors will not be discouraged by logistical complexities or delays. Training and education of all staff involved is of utmost importance to provide a seamless and positive experience to donors, who will become advocates of living donation in the community. Emphasizing the safety and quick recovery after living donation with minimally invasive techniques as well as the excellent long-term health outcomes for donors compared to the age-matched general population are also essential to reassure the public and promote living donation[22].

Introducing new concepts around living kidney donation in Greece should also start early to allow for adequate public discussion and engagement. Donation from offspring to parent rarely takes place in Greece. Although any adult individual may be considered for donation by law, there is reluctance even among transplant clinicians to consider young donors. Donation at an early age is a well-established and accepted practice in other countries, with excellent psychological and medical outcomes for both donors and recipients. In 2021 in the United Kingdom, 20% of all living donors were aged 18-34[17]. During the same period, only one donor (1%) was younger than 30 years in Greece. The age distribution of living donors over the last few years is depicted in Table 1, where it becomes evident that most donors are middle-aged or older. Clearly, widening the age criteria for donation in transplant units with appropriate consenting of younger donors will enable more transplants in the future.

Transplant candidates are often reluctant to approach and recruit living donors. Separating the advocate from the patient has proved to be an effective strategy but needs appropriate training[23]. The introduction of programmes aiming to facilitate identification of potential donors and elicit their interest to proceed with donation should form a part of a national strategy. Examples of successful implementation include the Live Donor Champion Program at Johns Hopkins[24], the University of Pittsburgh Medical Center Living Donor Champion Program[25] and more recently the Kidney Coach Program at Mount Sinai Hospital[26]. These programmes have achieved a substantial increase in donor inquiries and a modest increase in donor evaluations and number of living donor transplants.

Donating indirectly to someone *via* a waiting list "voucher" is an emerging concept worldwide that still remains to be validated but certainly shows the direction of modern transplantation and proves the concept that every living donor deserves to be "utilised" in the best possible way. This approach usually applies to donors that would probably be too old to donate when their recipient would actually need a kidney transplant, *e.g.*, a grandfather donating to their grandchild *via* the general waiting list. Simply put, transplant vouchers provide a means to overcome chronological incompatibility between donation and transplantation. The donor donates in the deceased donor list and the prospective recipient receives a "voucher" or a "priority ticket" that can be redeemed for a future transplant that will probably take place years later[27].

Reducing financial barriers for living donation and accounting for potential income losses remains a matter of debate for many years across the globe. Despite concerns around commercialisation of donation, a rational approach to protect and support prospective donors in their decision was proposed a few years ago by the American Society of Transplantation's Live Donor Community of Practice after careful and systematic exploration of factors such as employment, insurance and medical cost of

Table 1 Age distribution of living donors in Greece, 2016-2021, *n* (%)

Age group	Number of living donors by year					
	2016	2017	2018	2019	2020	2021
20-30	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
31-40	2 (4)	4 (6)	5 (7)	2 (3)	1 (1)	8 (9)
41-50	9 (18)	9 (13)	16 (23)	19 (28)	19 (21)	12 (13)
51-60	14 (29)	24 (35)	16 (23)	22 (32)	34 (38)	34 (37)
61-70	19 (39)	22 (32)	27 (40)	20 (3)	23 (26)	24 (27)
71-90	5 (10)	9 (14)	5 (7)	5 (7)	12 (14)	12 (13)
Total	49 (100)	68 (100)	69 (100)	68 (100)	89 (100)	91 (100)

donation. It became clear that the creation of a standardised financial toolkit for donors, adapted to each country's requirements and limitations is a perfectly actionable way to encourage living donation and remove any sense of insecurity in the process before and after donation[28].

Lastly, but equally important, we believe that further research is needed to understand living donation trends and perceptions in the public. These may vary significantly between different parts of the world. Therefore, extrapolation of conclusions from previous work elsewhere should be done with caution. Focus groups with patients and donors at a local level will shed light on various cultural barriers that could be potentially resolved with appropriate targeted campaigns. Additionally, transplant clinicians will have a unique opportunity to understand what matters most for living donors and how to better support them through the journey of donation[29,30].

CONCLUSION

Living donor kidney transplantation is undergoing a phase of transformation in Greece. New legislation and crucial changes in transplant policies pave the way for expansion of the donor pool, especially through living donation. The role of transplant professionals in this process of change and adaptation is to lead the developments in a safe and productive way for the benefit of patients. We have a duty to campaign for all the above and extend this knowledge to all parts involved in transplantation, from central organisation to local patient groups. Through living donation we have a unique opportunity to make progress and catch up with the growing need for more transplants in Greece by creating a positive environment in the community around transplantation in general. Every prospective living donor deserves to receive education, delivered responsibly, and high-quality care in every step of the way to donation, knowing that their generous offer will be fully appreciated. Clinicians on the other hand need to continue to explore ways that will encourage living donors to come forward. Identifying potential barriers to donation is the first important step into the future.

FOOTNOTES

Author contributions: Karydis N drafted the original manuscript and its revision; Maroulis I contributed to the final editing of the original and revised manuscript.

Conflict-of-interest statement: The authors declare that they have no conflicts of interest with the contents of this article.

Country/Territory of origin: Greece

ORCID number: Nikolaos Karydis 0000-0002-5729-552X; Ioannis Maroulis 0000-0002-6221-6099.

S-Editor: Liu GL
L-Editor: Filipodia

P-Editor: Liu GL

REFERENCES

1 **Hart A**, Lentine KL, Smith JM, Miller JM, Skeans MA, Prentice M, Robinson A, Foutz J, Booker SE, Israni AK, Hirose R, Snyder JJ. OPTN/SRTR 2019 Annual Data Report: Kidney. *Am J Transplant* 2021; **21** Suppl 2: 21-137 [PMID: 33595191 DOI: 10.1111/ajt.16502]

2 **Medin C**, Elinder CG, Hylander B, Blom B, Wilczek H. Survival of patients who have been on a waiting list for renal transplantation. *Nephrol Dial Transplant* 2000; **15**: 701-704 [PMID: 10809814 DOI: 10.1093/ndt/15.5.701]

3 **Montgomery RA**. Renal transplantation across HLA and ABO antibody barriers: integrating paired donation into desensitization protocols. *Am J Transplant* 2010; **10**: 449-457 [PMID: 20121749 DOI: 10.1111/j.1600-6143.2009.03001.x]

4 **Orandi BJ**, Luo X, Massie AB, Garonzik-Wang JM, Lonze BE, Ahmed R, Van Arendonk KJ, Stegall MD, Jordan SC, Oberholzer J, Dunn TB, Ratner LE, Kapur S, Pelletier RP, Roberts JP, Melcher ML, Singh P, Sudan DL, Posner MP, El-Amm JM, Shapiro R, Cooper M, Lipkowitz GS, Rees MA, Marsh CL, Sankari BR, Gerber DA, Nelson PW, Wellen J, Bozorgzadeh A, Gaber AO, Montgomery RA, Segev DL. Survival Benefit with Kidney Transplants from HLA-Incompatible Live Donors. *N Engl J Med* 2016; **374**: 940-950 [PMID: 26962729 DOI: 10.1056/NEJMoa1508380]

5 **Furian L**, Nicolò A, Di Bella C, Cardillo M, Cozzi E, Rigotti P. Kidney exchange strategies: new aspects and applications with a focus on deceased donor-initiated chains. *Transpl Int* 2020; **33**: 1177-1184 [PMID: 32772429 DOI: 10.1111/tri.13712]

6 **Wall AE**, Veale JL, Melcher ML. Advanced Donation Programs and Deceased Donor-Initiated Chains-2 Innovations in Kidney Paired Donation. *Transplantation* 2017; **101**: 2818-2824 [PMID: 28574902 DOI: 10.1097/TP.0000000000001838]

7 **European Parliamentary Research Service (EPRS)**. Organ donation and transplantation. Facts, figures and European Union action-April 2020 briefing. [Internet] [cited 20 December 2022]. Available from: https://www.europarl.europa.eu/thinktank/en/document/EPRS_BRI(2020)649363

8 **NHS Blood and Transplant (NHSBT)**. Annual report on kidney transplantation 2020-2021. [Internet] [cited 20 December 2022]. Available from: https://www.odt.nhs.uk/statistics-and-reports/organ-specific-reports/

9 **Georgiadou E**, Sounidakis N, Mouloudi E, Giaglis P, Giasnetsova T, Marmanidou K, Gritsi-Gerogianni N. Attitudes and behavior toward organ donation in Greece. *Transplant Proc* 2012; **44**: 2698-2701 [PMID: 23146497 DOI: 10.1016/j.transproceed.2012.09.017]

10 **United Network for Organ Sharing (UNOS)**. UNOS ambassadors. [Internet] [cited 15 December 2022]. Available from: https://unos.org/community/unos-ambassadors/

11 **Liyanage L**, Muzaale A, Henderson M. The true risk of living kidney donation. *Curr Opin Organ Transplant* 2019; **24**: 424-428 [PMID: 31145155 DOI: 10.1097/MOT.0000000000000654]

12 **Kute VB**, Prasad N, Shah PR, Modi PR. Kidney exchange transplantation current status, an update and future perspectives. *World J Transplant* 2018; **8**: 52-60 [PMID: 29988896 DOI: 10.5500/wjt.v8.i3.52]

13 **Kalargirou AA**, Beloukas AI, Kosma AG, Nanou CI, Saridi MI, Kriebardis AG. Attitudes and behaviours of Greeks concerning blood donation: recruitment and retention campaigns should be focused on need rather than altruism. *Blood Transfus* 2014; **12**: 320-329 [PMID: 24887229 DOI: 10.2450/2014.0203-13]

14 **de Weerd AE**, Betjes MGH. ABO-Incompatible Kidney Transplant Outcomes: A Meta-Analysis. *Clin J Am Soc Nephrol* 2018; **13**: 1234-1243 [PMID: 30012630 DOI: 10.2215/CJN.00540118]

15 **Kher V**, Jha PK. Paired kidney exchange transplantation - pushing the boundaries. *Transpl Int* 2020; **33**: 975-984 [PMID: 32634850 DOI: 10.1111/tri.13693]

16 **Biró P**, Haase-Kromwijk B, Andersson T, Ásgeirsson EI, Baltesová T, Boletis I, Bolotinha C, Bond G, Böhmig G, Burnapp L, Cechlárová K, Di Ciaccio P, Fronek J, Hadaya K, Hemke A, Jacquelinet C, Johnson R, Kieszek R, Kuypers DR, Leishman R, Macher MA, Manlove D, Menoudakou G, Salonen M, Smeulders B, Sparacino V, Spieksma FCR, Valentín MO, Wilson N, van der Klundert J; ENCKEP COST Action. Building Kidney Exchange Programmes in Europe-An Overview of Exchange Practice and Activities. *Transplantation* 2019; **103**: 1514-1522 [PMID: 30247314 DOI: 10.1097/TP.0000000000002432]

17 **NHS Blood and Transplant (NHSBT)**. Annual Activity Report 2021-2022. [Internet] [cited 15 December 2022]. Available from: https://www.odt.nhs.uk/statistics-and-reports/annual-activity-report/

18 **Massie AB**, Orandi BJ, Waldram MM, Luo X, Nguyen AQ, Montgomery RA, Lentine KL, Segev DL. Impact of ABO-Incompatible Living Donor Kidney Transplantation on Patient Survival. *Am J Kidney Dis* 2020; **76**: 616-623 [PMID: 32668318 DOI: 10.1053/j.ajkd.2020.03.029]

19 **Lo P**, Sharma A, Craig JC, Wyburn K, Lim W, Chapman JR, Palmer SC, Strippoli GF, Wong G. Preconditioning Therapy in ABO-Incompatible Living Kidney Transplantation: A Systematic Review and Meta-Analysis. *Transplantation* 2016; **100**: 933-942 [PMID: 26425876 DOI: 10.1097/TP.0000000000000933]

20 **Scurt FG**, Ewert L, Mertens PR, Haller H, Schmidt BMW, Chatzikyrkou C. Clinical outcomes after ABO-incompatible renal transplantation: a systematic review and meta-analysis. *Lancet* 2019; **393**: 2059-2072 [PMID: 31006573 DOI: 10.1016/S0140-6736(18)32091-9]

21 **Lentine KL**, Lam NN, Segev DL. Risks of Living Kidney Donation: Current State of Knowledge on Outcomes Important to Donors. *Clin J Am Soc Nephrol* 2019; **14**: 597-608 [PMID: 30858158 DOI: 10.2215/CJN.11220918]

22 **Krishnan N**, Mumford L, Lipkin G, Gill P, Fletcher S, Dasgupta I, Ryan R, Raymond NT. Comparison of Medium-term Outcomes of Living Kidney Donors With Longitudinal Healthy Control in the United Kingdom. *Transplantation* 2020; **104**: e65-e74 [PMID: 31895342 DOI: 10.1097/TP.0000000000003082]

23 **Garonzik-Wang JM**, Berger JC, Ros RL, Kucirka LM, Deshpande NA, Boyarsky BJ, Montgomery RA, Hall EC, James NT, Segev DL. Live donor champion: finding live kidney donors by separating the advocate from the patient.

Transplantation 2012; **93**: 1147-1150 [PMID: 22461037 DOI: 10.1097/TP.0b013e31824e75a5]

24 Live Donor Champion Program. [Internet] [cited 15 December 2022]. Available from: https://www.hopkinsmedicine.org/transplant/patient_information/Live-donor-program.html

25 **Caruso C**, Zell C, Swaytha G, Angela B, Sarah S, Elaine L, Susan P, Travis W, Abhinav H. UPMC Living Donor Champion Program [abstract]. [Internet] [cited 15 December 2022]. Available from: https://atcmeetingabstracts.com/abstract/upmc-living-donor-champion-program/

26 **LaPointe Rudow D**, Geatrakas S, Armenti J, Tomback A, Khaim R, Porcello L, Pan S, Arvelakis A, Shapiro R. Increasing living donation by implementing the Kidney Coach Program. *Clin Transplant* 2019; **33**: e13471 [PMID: 30588663 DOI: 10.1111/ctr.13471]

27 **Veale JL**, Nassiri N, Capron AM, Danovitch GM, Gritsch HA, Cooper M, Redfield RR, Kennealey PT, Kapur S. Voucher-Based Kidney Donation and Redemption for Future Transplant. *JAMA Surg* 2021; **156**: 812-817 [PMID: 34160572 DOI: 10.1001/jamasurg.2021.2375]

28 **Tushla L**, Rudow DL, Milton J, Rodrigue JR, Schold JD, Hays R; American Society of Transplantation. Living-Donor Kidney Transplantation: Reducing Financial Barriers to Live Kidney Donation--Recommendations from a Consensus Conference. *Clin J Am Soc Nephrol* 2015; **10**: 1696-1702 [PMID: 26002904 DOI: 10.2215/CJN.01000115]

29 **Hanson CS**, Ralph AF, Manera KE, Gill JS, Kanellis J, Wong G, Craig JC, Chapman JR, Tong A. The Lived Experience of "Being Evaluated" for Organ Donation: Focus Groups with Living Kidney Donors. *Clin J Am Soc Nephrol* 2017; **12**: 1852-1861 [PMID: 28993303 DOI: 10.2215/CJN.03550417]

30 **Burnapp L**, Van Assche K, Lennerling A, Slaats D, Van Dellen D, Mamode N, Citterio F, Zuidema W, Weimar W, Dor FJMF. Raising awareness of unspecified living kidney donation: an ELPAT view. *Clin Kidney J* 2020; **13**: 159-165 [PMID: 32296519 DOI: 10.1093/ckj/sfz067]

World Journal of Transplantation

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

World J Transplant 2023 February 18; 13(2): 36-43

DOI: 10.5500/wjt.v13.i2.36

ISSN 2220-3230 (online)

MINIREVIEWS

Exploring the use of virtual reality in surgical education

Georgios Ntakakis, Christina Plomariti, Christos Frantzidis, Panagiotis E Antoniou, Panagiotis D Bamidis, 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): A
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Frascio M, Italy; Ma Y, China

Received: September 5, 2022
Peer-review started: September 5, 2022
First decision: October 31, 2022
Revised: November 14, 2022
Accepted: January 3, 2023
Article in press: January 3, 2023
Published online: February 18, 2023

Georgios Ntakakis, Christina Plomariti, Panagiotis E Antoniou, Panagiotis D Bamidis, Department of Medicine, School of Health Sciences, Aristotle University of Thessaloniki, Thessaloniki 54124, Greece

Christos Frantzidis, School of Computer Science, University of Lincoln, Lincoln LN6 7TS, United Kingdom

Georgios Tsoulfas, Department of Surgery, Aristotle University of Thessaloniki, Thessaloniki 54124, Greece

Corresponding author: Georgios Ntakakis, MSc, Research Scientist, Department of Medicine, School of Health Sciences, Aristotle University of Thessaloniki, Building D, Entrance 8, 3rd Floor Aristotle University of Thessaloniki, Thessaloniki 54124, Greece.
gntakakis@outlook.com

Abstract

Virtual reality (VR) technologies have rapidly developed in the past few years. The most common application of the technology, apart from gaming, is for educational purposes. In the field of healthcare, VR technologies have been applied in several areas. Among them is surgical education. With the use of VR, surgical pathways along with the training of surgical skills can be explored safely, in a cost-effective manner. The aim of this mini-review was to explore the use of VR in surgical education and in the 3D reconstruction of internal organs and viable surgical pathways. Finally, based on the outcomes of the included studies, an ecosystem for the implementation of surgical training was proposed.

Key Words: Surgical education; Virtual reality; Abdominal surgery; Simulation

Core Tip: This mini-review aims to explore the use of virtual reality in surgical education and in the 3D reconstruction of internal organs and viable surgical pathways. For this purpose, a non-systematic literature review was conducted and three highly influential scientific papers were selected and discussed. The main topics addressed are the use of technologies in surgical education, the methodologies for the implementation of the training systems, the evaluation approaches and the strengths and limitations of the studies. Finally, the review concluded with a comparative synthesis of the main findings and a discussion on the proposal of a system for implementing these findings on surgical education in the field of organ transplantation.

Citation: Ntakakis G, Plomariti C, Frantzidis C, Antoniou PE, Bamidis PD, Tsoulfas G. Exploring the use of virtual reality in surgical education. *World J Transplant* 2023; 13(2): 36-43
URL: https://www.wjgnet.com/2220-3230/full/v13/i2/36.htm
DOI: https://dx.doi.org/10.5500/wjt.v13.i2.36

INTRODUCTION

During the past few years, the use of virtual reality (VR) has increased rapidly in a number of sectors, like education[1,2] transportation[3,4] and healthcare[5]. In the case of education, the main advantage of using VR, is the immersion it provides, by using personalized experiences, promoting engagement, and providing hints that it may enhance learning[6], through the motivation aligned with the active participation of students.

As the immersion of the system increases, the effectiveness of the training module increases [7,8]. Additionally, the level of immersion of VR has been found to be proportional to the number of modalities involved[9].

VR has also found numerous applications in medical education[10-12]. More specifically, in the case of surgical education, the use of VR has been favored, due to many reasons, such as lack of mentors, reduction in training hours and various issues concerning operative procedures[13]. In order to exploit all these advantages, many solutions have been implemented, like the da Vinci Skills Simulator[14] and the LAP Mentor VR laparoscopic surgical simulator[15].

The aim of the present mini-review was to explore the use of VR simulators either alone or in combination with head-mounted displays (HMDs) in surgical education and in the construction of 3D models of internal organs[16]. For this purpose, three highly influential scientific papers were selected and discussed. The main topics addressed were the use of technologies in surgical education, the methodologies for the implementation of the training systems, the evaluation approaches and the strengths and limitations of the studies. Finally, the review concluded with a comparative synthesis of the main findings and a discussion on the proposal of a system for implementing these findings on surgical education in the field of organ transplantation.

METHODOLOGY

In April 2022, we performed a non-systematic literature search on the Google Scholar database using the terms “Virtual Reality”, “surgical education”, “surgery”, “medical education” to identify peer-reviewed articles, written in the English language, published after 2016, that seemingly explored the area of interest. The selected articles adhered to the following inclusion criteria: (1) Implement training in surgical skills with the use of VR technology; (2) Perform skill or full procedure training in abdominal surgeries; and (3) Include participants who were either surgical trainees or experienced surgeons.

All the information of interest was extracted from the selected articles. The information was used for the authors to identify main opportunities and limitations in the use of VR systems in surgical education and finally propose an infrastructure for extended reality (XR) technologies in order to implement a surgical training ecosystem.

TECHNOLOGIES

The devices used for promoting surgical education with the use of VR are mostly expensive[17,18] simulators (LapSim and Lap Mentor), often combined with some additional HMDs[18,19], like HTC Vive 360 or Google VR, to create an immersive and engaging user experience. Most simulation technologies include special controllers (some with haptic feedback) that accurately simulate the use of surgical instruments[17]. The LapSim emulator includes Simball 4D Joystick hardware and the Lap

Mentor includes a syringe allowing realistic fluid delivery and BAL performance, while a wide variety of bronchoscopy instruments, such as biopsy forceps, cytology brush, suction and more can also be simulated. Both simulators offer a high-resolution display of the virtual environment (VE). The combination of VR HMDs and the VR simulators promotes immersiveness and enhances the interaction between the participants and the VE (Table 1).

While the aforementioned devices offer a unique interactive experience, their cost can be extremely high. During the past years, there has been a rapid shift in the exploration of low-cost devices, offering the possibility of a larger market to the creators of any application. Such devices are the Oculus Rift, Meta Quest, HTC Vive, Pico[18,19]. The cost of these devices does not exceed $500, making surgical training more accessible to any hospital setting and open to more participants. Sampogna *et al*[19] used the Oculus Rift device combined with the Leap Motion sensor. The Oculus Rift requires a wired computer connection as well as the installation of the Oculus software on the computer and then through screencast displays the 3D VE on the glasses of the Rift device. The device includes two controllers, but in this study, they used the Leap Motion in order to keep the participants' hands free. Leap Motion is a motion sensor that recognizes users' actions and translates them into commands on a VR device or computer.

IMPLEMENTATION METHODS

When implementing surgical training in VR, the simulation can include either some basic tasks that are performed during specific surgeries[17,18], or full surgical procedures[17]. Simulators that specialize in specific surgeries, like the LAP simulator, have already integrated most of the corresponding tasks and require no further configurations in order to be ready for use. Huber *et al*[18] combined such a VR laparoscopic simulator with a 360° video depicting an operating room, thus creating a highly immersive scenario, and offering, for the first time, a structured surrounding environment for the simulation to be accumulated in.

All the images and 3D models contained in the aforementioned simulators, are based on magnetic resonance imaging (MRI) and recordings of *in vivo* procedures. In order to create realistic 3D models of internal organs, a collection of computed tomography scans and MRIs are required. Sampogna *et al*[19] described in detail the procedure of recreating 3D reconstructions based on medical imaging.

EVALUATION AND OUTCOME MEASURES

When implementing an evaluation of the efficacy of new training methodologies, usually the learning impact of the new method needs to be compared to traditional methods. In the selected studies there was heterogeneity in the outcome measures, which did not follow a common evaluation protocol (Table 2).

There are some common measurements between the study of Beyer-Berjot *et al*[17] and Huber *et al*[18] such as the completion time of each task and the number of errors, but other than that, the focus of the evaluation was shifted in opposite directions.

The outcome measures used in the study of Beyer-Berjot *et al*[17] were: (1) Time taken to complete the task; (2) Time spent *per* hand; (3) Accuracy of the surgical procedure; (4) Depth of incisions; (5) Number of errors; (6) Number of ripped and burned vessels; and (7) Overall score of the LapSim system based on the calculation of all the components. Questionnaires were also administered, evaluating the degree of interaction, concentration and realism.

In the study of Huber *et al*[18], different outcome measures were considered, focusing on the degree of interaction of clipping and grasping, 2-handed maneuvers (time, number of movements, and path length) in 4 tasks, medial dissection, lateral dissection, anastomosis and full large single copy. The fidelity and content validity were measured on a Likert scale.

Sampogna *et al*[19] developed questionnaires to measure simplicity, precision and fidelity, guidance, satisfaction, 3D reconstruction quality, VR immersiveness.

CRITICAL REVISIT

As mentioned before, the main advantage of using VR in surgical education is the immersiveness the technology provides. This advantage was exploited in full when VR was implemented with the use of HMD, as described by Huber *et al*[18], Sampogna *et al*[19]. Furthermore, Huber *et al*[18] introduced noise cancelling headphones for increasing immersion. Haptic feedback is a modality often used in VR environments in order to engage the sense of touch. Beyer-Berjot *et al*[17] used a simulator that integrated with haptic feedback.

Table 1 Comparison of technologies

	Beyer-Berjot *et al*[17], 2016–Lap Mentor VR	Huber *et al*[18], 2017-LapSim	Sampogna *et al*[19], 2017-Oculus Rift and Leap motion
Technology used for training	Virtual reality		
Equipment used for training	Custom hardware and software-Lap Mentor VR	Custom hardware and software-LapSim	Windows 10-Oculus Quest Rift S
Additional technology used for training	Haptic		
Additional equipment used for training	Lap Mentor realistic tactile surgical tools	LapSim realistic tactile surgical tools	Oculus gestures + Leap Motion
Operating system	Lap Mentor software	LapSim software	Windows 10

VR: Virtual reality.

Table 2 Beyer-Berjot *et al*[17], 2016 and Huber *et al*[18], 2017 outcome measures

Beyer-Berjot *et al*[17], 2016–Lap Mentor VR		Huber *et al*[18], 2017-LapSim	
Tasks	**Outcome measures**	**Tasks**	**Outcome measures**
Initial assessment	Time (s)	Peg transfer	Time (s)
Clipping and grasping	No. of movements	Fine dissection	Left time (s)
2-Handed maneuvers	Path length (cm)	Cholecystectomy	Right time (s)
Full laparoscopic sigmoid colectomy			Time (z-score)
Median dissection			Left path length (m)
Lateral dissection			Left angular path (degree)
Anastomosis			Left grasps (*n*)
Full LSC			Right path length (m)
			Right angular path (degree)
			Right grasps (*n*)
			Economics (z-score)
			Maximum drops (*n*)
			Errors (z-score)
			Total (z-score)

VR: Virtual reality; LSC: Large single copy.

The enrolment of participants of different gaming and surgical skills can prove beneficial when evaluating a VR surgical education application. Huber *et al*[18] used participants of 3 different laparoscopic experience levels, while about half of them had never played video games or had any exposure to VR. Beyer-Berjot *et al*[17] implemented a similar design for the selection of the participants, but additionally they recruited a small number of video game players. The fact that the participants of these two studies had varying gaming skills, can offer a more subjective view on the usability and acceptability of the system, while the different surgical levels can assess the effectiveness of the system in terms of education.

LIMITATIONS

Despite the great advantages of using VR technology in surgical education, there are also a couple of limitations that need to be considered. The use of VR simulators implemented without the use of HMDs, as described by Beyer-Berjot *et al*[17], did not exploit the full potential of the technology, lacking in immersion and users' engagement. Furthermore, the limited number of participants when performing a

feasibility study along with the non-comparison of a new teaching method versus the traditional one[17-19] can lead to barriers in evaluating the impact on learning and skill development. Also, limitations of the use of VR may appear in older adults due to lack of acquittance with the technology. Finally, as Sampogna *et al*[19] pointed out, if the first operators have rich experience on the skills the new systems aspire to train, the effect of the developed applications on speeding-up the learning curve cannot be evaluated properly. The aforementioned limitations should be considered in terms of the publishing date and in the context of the technological advances of the time. Since then, VR technology has made major progress and the scope of its capabilities has improved vastly.

COMPARATIVE SYNTHESIS

Among the selected studies, two used high-end VR simulation equipment and performed their study with precision sensors[17,18]. In the two studies, during each simulated task, a variety of data were collected, and they were displayed after the completion of the simulation. Some of them were time-on-task, and number of errors as well as some other indicators were designed during the implementation of the systems. The main difference between the simulators used the surgical task they focus on. LipSim can perform fine dissection, peg transfer, and cholecystectomy while LapMentor offers the option of training in sigmoid colectomy. In the study of Sampogna *et al*[19], MRIs were collected from different patients and then reconstruction of the internal organs was performed. The 3D models were imported in the Unity3D environment, and an application was created for Oculus Rift.

In all selected studies, the participants were either surgeons or surgical residents. Beyer-Berjot *et al*[17] and Huber *et al*[18] divided their participants into experimental groups based on the number of operations they had carried out in their careers and on their expertise, while Sampogna *et al*[19] did not categorize their participants. In all three studies, before the beginning of the studies, participants had the opportunity to perform some warm-up tasks in order to get acquainted with the VR technology. The main aim of this exercise was to minimize the errors caused due to difficulties in operating the simulators and the HDMs.

FUTURE STEPS

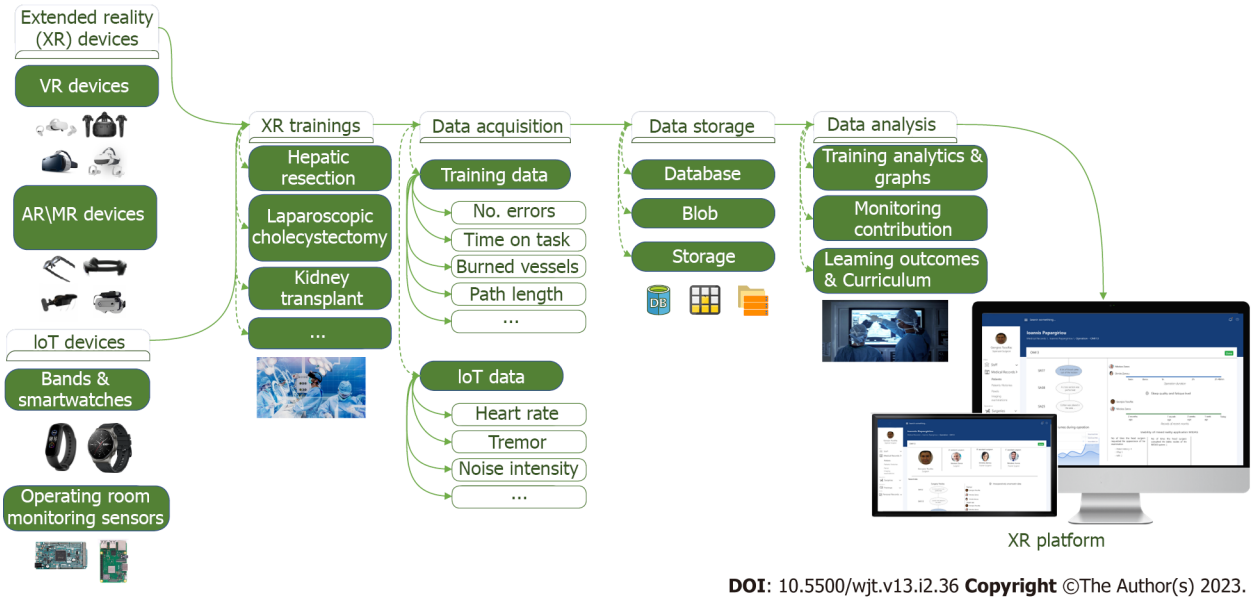
In the past few years, expensive devices and applications have been used in the field of surgical education and surgical procedure, which imposes significant limitations to their extensive use. So, it is important to explore the use of less expensive XR technologies (augmented reality, VR, mixed reality). It is also important to explore the difficulties in co-surgery and in team surgery, due to cooperation problems that may arise. There is also a lack of intra-operative applications that focus on surgeon interactions. In addition, although some studies have been conducted on VR applications in the field of transplantation in general, there is a lack of studies on abdominal transplantations. Also, it will be useful to explore XR not only in surgical training but also during the surgical procedure.

Based on the findings of the comparative synthesis of the already existing approaches, we proposed a roadmap and its application could foster the training of surgeries (Figure 1). A 5-layered system could be constructed according to the following paradigm.

The first layer includes low-cost devices XR. More specifically, future studies should investigate VR devices such as Meta Quest 2, Pico and AR devices such as NReal Light, Toshiba DynaEdge, which cost no more than $500 each and are affordable for not only surgeons but also mass purchases by hospitals and universities. Also, within the same layer we propose the inclusion of IoT devices such as bands and smartwatches as well as Arduino and Raspberry devices that allow sensorial, real-world, big data acquisition, like speech and motion capture analysis. The second layer focuses on co-designing and co-creating virtual and augmented surgeons' training, based on participatory activities that will take place among healthcare and technology-oriented professionals[20]. In the third layer, a big data acquisition system is designed during the training activities. Data are gathered from heterogeneous sources such as training metrics, biomarkers, and sensory recordings[21] that could help assess the quality of the surgical procedure. In the fourth layer, biosensors are programmed to collect periodic data from the surgeons, which are uploaded on a cloud-based infrastructure where they are stored in a suitable database for analysis. Additional factors could be studied, such as the noise in the virtual surgery as well as the fatigue of the surgeon during the sessions. The analysis of these data is likely to create new approaches to deal with medical errors in operating rooms. In the fifth layer a platform is constructed that graphically presents the training analytics and the course of the surgeries for each surgeon.

CONCLUSION

VR technologies are becoming more accessible and are a potential cognitive enhancer in the field of



DOI: 10.5500/wjt.v13.i2.36

Figure 1 Extended reality proposed ecosystem[21-27]. XR: Extended reality; VR: Virtual reality; AR: Augmented reality; MR: Mixed reality.

surgical education. The findings of this mini-review offer insight into the devices and systems used to train surgeons, as well as to low-cost devices that are rapidly being developed to offer a solution in surgical training. Interestingly, we found a lack of VR training in the field of organ transplantation. In order to tackle this, an ecosystem for promoting learning through XR systems is proposed to be implemented for use in training for transplantation. In order to assess the proposed architecture, a feasibility study along with a cost-effectiveness analysis should be performed. The implementation and evaluation of the system falls outside the scope of this mini-review. Nevertheless, it could prove to be a valuable tool in the field of surgical and more specifically transplantation training, especially if evaluated against a transplantation simulator.

ACKNOWLEDGEMENTS

We thank our colleagues from Laboratory Medical Physics and Digital Innovation lab, Faculty of Health Sciences, School of Medicine, Aristotle University of Thessaloniki who provided insight and expertise that greatly assisted the research.

FOOTNOTES

Author contributions: Ntakakis G search the database; Ntakakis G and Plomariti C check the articles against the inclusion criteria; Ntakakis G, Plomariti C, Frantzidis C, and Antoniou PE wrote the manuscript; All authors have read and approved the final version to be submitted.

Supported by Hellenic Foundation for Research and Innovation (HFRI) Under The 3rd Call for HFRI PhD Fellowships, No. 6232; "Evaluating Novel Tangible and Intangible Co-creative Experiential Medical Education" (ENTICE) Knowledge Alliances for Higher Education Project, Co-funded By The Erasmus + Program of The European Union, No. 612444-EPP-1-2019-1-CY-EPPKA2-KA.

Conflict-of-interest statement: George Ntakakis is an employee of Laboratory of Medical Physics and Digital Innovation, Faculty of Health Sciences, School of Medicine, Aristotle University of Thessaloniki, Thessaloniki, Greece. Christina Plomariti is an employee of Laboratory of Medical Physics and Digital Innovation, Faculty of Health Sciences, School of Medicine, Aristotle University of Thessaloniki, Thessaloniki, Greece. Christos A. Frantzidis is a senior lecturer of School of Computer Science, University of Lincoln, Lincoln, UK. Panagiotis Antoniou is an employee of Laboratory of Medical Physics and Digital Innovation, Faculty of Health Sciences, School of Medicine, Aristotle University of Thessaloniki, Thessaloniki, Greece. Panagiotis Bamidis is a professor of Laboratory of Medical Physics and Digital Innovation, Faculty of Health Sciences, School of Medicine, Aristotle University of Thessaloniki, Thessaloniki, Greece. Georgios Tsoulfas is a professor of Department of Transplantation and Surgery, Aristotle University of Thessaloniki, Thessaloniki, Greece.

Country/Territory of origin: Greece

ORCID number: Georgios Ntakakis 0000-0002-0902-9905; Christina Plomariti 0000-0002-3871-5912; Panagiotis D Bamidis 0000-0002-9936-5805; Georgios Tsoulfas 0000-0001-5043-7962.

S-Editor: Fan JR
L-Editor: Ma JY
P-Editor: Fan JR

REFERENCES

1 **Kavanagh S**, Luxton-Reilly A, Wuensche B, Plimmer B. A systematic review of virtual reality in education. *Themes Sci Tech Edu* 2017; 10: 85-119
2 **Konstantinidis ST**, Bamidis PD, Zary N. Introduction to digital innovation in healthcare education and training. *InDigital Innovations in Healthcare Education and Training* 2021; 3-15
3 **Jin M**, Lam SH. A virtual-reality based integrated driving-traffic simulation system to study the impacts of intelligent transportation system (ITS). InProceedings. *2003 Interna Confer Cyberworlds* 2003; 158-165 [DOI: 10.1109/CYBER.2003.1253449]
4 **Kreimeier J**, Ullmann D, Kipke H, Götzelmann T. Initial Evaluation of Different Types of Virtual Reality Locomotion Towards a Pedestrian Simulator for Urban and Transportation Planning. *InExtended Abstracts of the 2020 CHI Conference on Human Factors in Computing Systems* 2020; 1-6 [DOI: 10.1145/3334480.3382958]
5 **Lányi CS**. Virtual reality in healthcare. InIntelligent paradigms for assistive and preventive healthcare. Berlin, Heidelberg: Springer, 2006: 87-116
6 **Pantelidis VS**. Reasons to use virtual reality in education and training courses and a model to determine when to use virtual reality. *Themes Sci Tech Edu* 2010; **2**: 59-70 [DOI: 10.1007/bf02763872]
7 **Regenbrecht HT**, Schubert TW, Friedmann F. Measuring the sense of presence and its relations to fear of heights in virtual environments. *Int J Hum Comput Interact* 1998; **10**: 233-249 [DOI: 10.1207/s15327590ijhc1003_2]
8 **Robillard G**, Bouchard S, Fournier T, Renaud P. Anxiety and presence during VR immersion: a comparative study of the reactions of phobic and non-phobic participants in therapeutic virtual environments derived from computer games. *Cyberpsychol Behav* 2003; **6**: 467-476 [PMID: 14583122 DOI: 10.1089/109493103769710497]
9 **Andreano J**, Liang K, Kong L, Hubbard D, Wiederhold BK, Wiederhold MD. Auditory cues increase the hippocampal response to unimodal virtual reality. *Cyberpsychol Behav* 2009; **12**: 309-313 [PMID: 19500000 DOI: 10.1089/cpb.2009.0104]
10 **Pickering JD**, Panagiotis A, Ntakakis G, Athanassiou A, Babatsikos E, Bamidis PD. Assessing the difference in learning gain between a mixed reality application and drawing screencasts in neuroanatomy. *Anat Sci Educ* 2022; **15**: 628-635 [PMID: 34157219 DOI: 10.1002/ase.2113]
11 **Baniasadi T**, Ayyoubzadeh SM, Mohammadzadeh N. Challenges and Practical Considerations in Applying Virtual Reality in Medical Education and Treatment. *Oman Med J* 2020; **35**: e125 [PMID: 32489677 DOI: 10.5001/omj.2020.43]
12 **Dyer E**, Swartzlander BJ, Gugliucci MR. Using virtual reality in medical education to teach empathy. *J Med Libr Assoc* 2018; **106**: 498-500 [PMID: 30271295 DOI: 10.5195/jmla.2018.518]
13 **Bilimoria KY**, Chung JW, Hedges LV, Dahlke AR, Love R, Cohen ME, Hoyt DB, Yang AD, Tarpley JL, Mellinger JD, Mahvi DM, Kelz RR, Ko CY, Odell DD, Stulberg JJ, Lewis FR. National Cluster-Randomized Trial of Duty-Hour Flexibility in Surgical Training. *N Engl J Med* 2016; **374**: 713-727 [PMID: 26836220 DOI: 10.1056/NEJMoa1515724]
14 **ASVIDE**. Da Vinci Skills Simulator. [cited 10 August 2022]. Available from: https://www.asvide.com/article/view/28232
15 **Ayodeji ID**, Schijven M, Jakimowicz J, Greve JW. Face validation of the Simbionix LAP Mentor virtual reality training module and its applicability in the surgical curriculum. *Surg Endosc* 2007; **21**: 1641-1649 [PMID: 17356944 DOI: 10.1007/s00464-007-9219-7]
16 **Athanasiou A**, Meling TR, Brotis A, Moiraghi A, Fountas K, Bamidis PD, Magras I. 3D printing in neurosurgery. *Appli Med Sur* 2022; **2**: 159-194 [DOI: 10.1016/b978-0-323-66193-5.00008-3]
17 **Beyer-Berjot L**, Berdah S, Hashimoto DA, Darzi A, Aggarwal R. A Virtual Reality Training Curriculum for Laparoscopic Colorectal Surgery. *J Surg Educ* 2016; **73**: 932-941 [PMID: 27342755 DOI: 10.1016/j.jsurg.2016.05.012]
18 **Huber T**, Paschold M, Hansen C, Wunderling T, Lang H, Kneist W. New dimensions in surgical training: immersive virtual reality laparoscopic simulation exhilarates surgical staff. *Surg Endosc* 2017; **31**: 4472-4477 [PMID: 28378077 DOI: 10.1007/s00464-017-5500-6]
19 **Sampogna G**, Pugliese R, Elli M, Vanzulli A, Forgione A. Routine clinical application of virtual reality in abdominal surgery. *Minim Invasive Ther Allied Technol* 2017; **26**: 135-143 [PMID: 28084141 DOI: 10.1080/13645706.2016.1275016]
20 **Antoniou P**, Bamidou A, Tartanis I, Vrellis I, Bamidis P. Antoniou P, Bamidou A, Tartanis I, Vrellis I, Bamidis P. From Expert Consulting to Co-creation in Medical Education; Co-creating an Exploratory Educational Space for Orthopedic Medical Education. *InInternational Conference on Technology and Innovation in Learning, Teaching and Education* 2018;

622-631 [DOI: 10.1007/978-3-030-20954-4_47]
21 **Antoniou PE**, Arfaras G, Pandria N, Athanasiou A, Ntakakis G, Babatsikos E, Nigdelis V, Bamidis P. Biosensor Real-Time Affective Analytics in Virtual and Mixed Reality Medical Education Serious Games: Cohort Study. *JMIR Serious Games* 2020; **8**: e17823 [PMID: 32876575 DOI: 10.2196/17823]
22 **The Medical Futurist**. How Does Medical Virtual Reality Make Healthcare More Pleasant? [cited 24 April 2018]. Available from: https://medicalfuturist.com/how-does-medical-virtual-reality-make-healthcare-more-pleasant
23 **Sarah van Gelder**. To Regain People's Trust, the Democratic Party Must Support Single-Payer. [cited 10 May 2017]. Available from: https://www.yesmagazine.org/social-justice/2017/05/10/to-regain-peoples-trust-the-democratic-party-must-support-single-payer
24 **Greenwald W**. Meta Quest 2 Review. [cited 19 September 2022]. Available from: https://www.pcmag.com/reviews/oculus-quest-2
25 **Foster A**. VR Headsets prove popular with consumer. [cited 3 July 2017]. Available from: https://www.ibc.org/trends/vr-headsets-market-analysis-and-guide-to-devices/2030.article
26 **Siddiqui A**. Xiaomi Mi Band 5 Review: Fixing all the quirks from the Mi Band 4, and then some. [cited 25 October 2020]. Available from: https://www.xda-developers.com/xiaomi-mi-band-5-review
27 **Piltch A**. How to Set Up a Raspberry Pi for the First Time. [cited 21 September 2022]. Available from: https://www.tomshardware.com/how-to/set-up-raspberry-pi

World Journal of Transplantation

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

World J Transplant 2023 February 18; 13(2): 44-57

DOI: 10.5500/wjt.v13.i2.44

ISSN 2220-3230 (online)

ORIGINAL ARTICLE

Retrospective Cohort Study

Analysis of the effects of donor and recipient hepatitis C infection on kidney transplant outcomes in the United States

Qing Yuan, Shanjuan Hong, Gregory Leya, Eve Roth, Georgios Tsoulfas, WW Williams, Joren C Madsen, Nahel Elias

Specialty type: Transplantation

Provenance and peer review: Unsolicited 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): D
Grade E (Poor): 0

P-Reviewer: Balaban HY, Turkey; Wishahi M, Egypt

Received: September 21, 2022
Peer-review started: September 21, 2022
First decision: October 24, 2022
Revised: November 7, 2022
Accepted: December 21, 2022
Article in press: December 21, 2022
Published online: February 18, 2023

Qing Yuan, Department of Urology, Chinese PLA General Hospital, Beijing 100853, China

Qing Yuan, Shanjuan Hong, Gregory Leya, Eve Roth, WW Williams, Joren C Madsen, Nahel Elias, Transplant Center and Center for Transplantation Sciences, Massachusetts General Hospital, Boston, MA 02114, United States

Georgios Tsoulfas, Department of Surgery, Aristotle University of Thessaloniki, Thessaloniki 541 24, Greece

WW Williams, Department of Medicine, Massachusetts General Hospital, Boston, MA 02114, United States

Joren C Madsen, Division of Cardiac Surgery, Massachusetts General Hospital, Boston, MA 02114, United States

Nahel Elias, Division of Transplant Surgery, Massachusetts General Hospital, Boston, MA 02114, United States

Corresponding author: Nahel Elias, MD, Assistant Professor, Surgeon, Transplant Center and Center for Transplantation Sciences, Massachusetts General Hospital, 55 Fruit Street, Boston, MA 02114, United States. elias.nahel@mgh.harvard.edu

Abstract

BACKGROUND

As Hepatitis C virus infection (HCV+) rates in kidney donors and transplant recipients rise, direct-acting antivirals (DAA) may affect outcomes.

AIM

To analyze the effects of HCV+ in donors, recipients, or both, on deceased-donor (DD) kidney transplantation (KT) outcomes, and the impact of DAAs on those effects.

METHODS

The Organ Procurement and Transplantation Network data of adult first solitary DD-KT recipients 1994-2019 were allocated into four groups by donor and recipient HCV+ status. We performed patient survival (PS) and death-censored graft survival (DCGS) pairwise comparisons after propensity score matching to

assess the effects of HCV+ in donors and/or recipients, stratifying our study by DAA era to evaluate potential effect modification.

RESULTS

Pre-DAA, for HCV+ recipients, receiving an HCV+ kidney was associated with 1.28-fold higher mortality (HR $_{1.15}$1.28$_{1.42}$) and 1.22-fold higher death-censored graft failure (HR $_{1.08}$1.22$_{1.39}$) compared to receiving an HCV- kidney and the absolute risk difference was 3.3% (95%CI: 1.8%-4.7%) for PS and 3.1% (95%CI: 1.2%-5%) for DCGS at 3 years. The HCV dual-infection (donor plus recipient) group had worse PS (0.56-fold) and DCGS (0.71-fold) than the dual-uninfected. Donor HCV+ derived worse post-transplant outcomes than recipient HCV+ (PS 0.36-fold, DCGS 0.34-fold). In the DAA era, the risk associated with HCV+ in donors and/or recipients was no longer statistically significant, except for impaired PS in the dual-infected *vs* dual-uninfected (0.43-fold).

CONCLUSION

Prior to DAA introduction, donor HCV+ negatively influenced kidney transplant outcomes in all recipients, while recipient infection only relatively impaired outcomes for uninfected donors. These adverse effects disappeared with the introduction of DAA.

Key Words: Hepatitis C virus; Kidney transplantation; Direct-acting antiviral therapy; Propensity score matching

Core Tip: In this paper, using data from across 25 years, we demonstrate that the adverse effects of hepatitis C infection in donors and/or recipients on kidney transplant outcomes have disappeared since the introduction of direct-acting antiviral agents.

Citation: Yuan Q, Hong S, Leya G, Roth E, Tsoulfas G, Williams W, Madsen JC, Elias N. Analysis of the effects of donor and recipient hepatitis C infection on kidney transplant outcomes in the United States. *World J Transplant* 2023; 13(2): 44-57

URL: https://www.wjgnet.com/2220-3230/full/v13/i2/44.htm

DOI: https://dx.doi.org/10.5500/wjt.v13.i2.44

INTRODUCTION

By improving patients' quality of life and survival, kidney transplantation (KT) is the optimal treatment for advanced kidney disease, even for Hepatitis C virus infected (HCV+) dialysis patients[1,2]. HCV+ donor kidneys could alleviate transplant organ shortages[3], and most kidney waitlist patients favor accepting an HCV+ kidney over waiting longer for an uninfected (HCV-) kidney[4]. Nonetheless, likely driven by concerns over HCV transmission and transplant outcomes, HCV+ kidneys have traditionally been discarded rather than transplanted into HCV- recipients[5].

Since December 2013, direct-acting antivirals (DAA), including NS3/4A inhibitors (boceprevir, telaprevir, simeprevir, asunaprevir, grazoprevir and paritaprevir), NS5A inhibitors (ombitasvir, ledipasvir, daclatasvir, elbasvir and velpatasvir), NS5B inhibitors (sofosbuvir and dasabuvir)[6], have revolutionized HCV treatment by consistently achieving 95% or better sustained virologic responses[7]. Before the introduction of DAAs, a combination of interferon and ribavirin were the standard scheme for HCV treatment[8]. Concurrently, United States donors who died as a result of drug overdose, many of whom were HCV+, increased from 66 to 1263 between 2000 and 2016. Notably, these donors were young: median age of 31 years[3]. HCV+ kidneys' superior quality, the increased prevalence of HCV+ in donors and recipients, and DAA treatments, have contributed to soaring numbers of HCV+ donor and/or recipient transplants. In the DAA era, because of the promise of HCV treatment, waitlisted transplant candidates were 2.2 times more likely willing to accept an HCV+ kidney and HCV+ recipients were 1.95 times more likely to receive an HCV+ kidney when compared to the pre-DAA era[5].

Despite HCV antiviral advancements, the Organ Procurement and Transplantation Network (OPTN) deceased donor (DD) kidneys allocation algorithm uses the Kidney Donor Risk Index (KDRI), for which donor HCV+ status has the largest coefficient amongst dichotomous factors in the calculation[9]. This outdated system overestimates HCV+ kidneys' risk in the DAA era, depriving candidates of high-quality HCV+ kidneys if they, or their accepting center, decline kidney offers based on KDRI thresholds, thus contributing to HCV+ kidneys' high discard rate.

We sought to understand the effect of HCV+ in donors and recipients on DD-KT outcomes and discern whether those effects differed among various HCV+ donor and recipient combinations. We hypothesized that donor HCV status could modify HCV effect in recipients, recipient HCV status could modify HCV effect in donors, and those modifications would change favorably following DAA availability. We used national registry data with propensity score matching (PSM) to systematically characterize the effect of HCV+ on KT outcomes both prior to and following the introduction of DAAs.

MATERIALS AND METHODS

Data sources

We used the OPTN Analysis and Research file released in June 2019 based on data collected through March 2019. The content in this paper is the responsibility of the authors alone and does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the United States Government.

Study population

We identified all adult (age ≥ 18) first-time solitary KT recipients from ABO-compatible DD between January 1994 and March 2019 in the United States Patients with missing or uncertain HCV-antibody status in the donor or recipient were excluded. Patients were allocated into four groups according to HCV+ in the donor (D+) or recipient (R+): D-R-, D+R-, D-R+, and D+R+.

Outcome and exposure classification

The study outcomes were patient survival (PS) and death-censored graft survival (DCGS) following KT. DCGS was defined as time to re-transplantation or dialysis reinstatement, whichever came first. Recipient HCV status is reported but not necessarily confirmed or assessed at transplant. HCV+ status was defined as HCV Ab+ or HCV nucleic acid test (NAT) positive, while HCV- was defined as HCV Ab- without HCV NAT+.

PSM

We performed pairwise PS and DCGS comparisons after PSM to assess the effect of donor and recipient HCV+ status on outcomes. Briefly, transplantation of HCV (+) or (-) donors into HCV (-) recipients was used to assess the effect of HCV+ in naïve recipients, as compared to D+R+ *vs* D-R+ combinations to assess the effect of HCV donor status in HCV infected recipients. D+R- *vs* D-R- patients addressed HCV donor infection effect in uninfected recipients, while D+R+ *vs* D-R+ patients addressed the effect in HCV+ recipients. Similarly, D+R+ *vs* D+R- pairings were compared for the effect of recipient HCV+ on HCV+ donor kidneys' outcomes, and D-R+ *vs* D-R- pairings were compared for the effect in HCV- donor kidneys. Finally, D+R+ *vs* D-R- pairings addressed the effect of HCV+ in both donors and recipients on outcomes, and D+R- *vs* D-R+ pairings addressed whether HCV+ in donors or recipients alone was more detrimental.

Subject pairs were matched by the probability of positive HCV exposure based on a multivariable logistic regression model with 40 potential predictors from the donor, recipient, and transplant procedure. Supplementary Table 1 shows model variables and missingness. Variables were chosen based on The Scientific Registry of Transplant Recipients risk adjustment models[10]. We used complete-case analysis for categorical variables missing fewer than 1% of values and included a missing indicator in the initial step for those missing more than 1%. For continuous variables, the missing values were imputed with the median, and a missing indicator was also included for those missing percentage > 1% (Supplementary Table 1). The potential outliers of continuous variables were winsorized at 1 and 99 percentiles. By focusing on HCV exposure effect in a sample of subjects that resembles the exposed subjects, we estimated the average treatment effect in the treated. We used the nearest neighbor matching with 1:1 ratio, without replacement, and with a caliper of width equal to 0.2 of the standard deviation (SD) of the logit of the propensity score. We performed balance diagnosis comparing matched groups' characteristics. An SD greater than 0.1 was considered an imbalance sign, and the propensity score prediction model was refitted ensuring matched groups' balance (Supplementary Table 1). We further stratified our study by DAA era (before or after December 2013) to evaluate potential effect modification.

Statistical analysis

Survival rates were presented in Kaplan-Meier curves and analyzed by log-rank tests. Time to outcome was defined as the interval from date-of-transplant to date-of-outcome (death or graft failure) and censored for loss to follow-up or end of study period. Absolute and relative risk differences in mortality and death-censored graft failure (DCGF) were estimated using Austin's methods[11]. All analyses were performed using RStudio software, version 1.1.456 (R. RStudio, Inc., Boston, MA). A *P*-value of less than 0.05 identified statistical significance, and all confidence intervals used a 95% threshold.

RESULTS

Changing characteristics of KT relative to HCV in donors and recipients

We identified 166,160 D-R-, 6,251 D-R+, 3,854 D+R+, and 1,672 D+R- pairings during the study (Figure 1). D+R+ transplants increased at a similar rate to D-R- transplants in the pre-DAA era, while D+R- and D-R+ transplants remained stable for two decades. However, HCV+ kidney utilization surged in the DAA era, initially with the traditional operating paradigm (D+ to R+), which peaked in 2016 and soon shifted to more robust HCV+ kidneys utilization (D+ to R-) (Figure 2).

Tables 1-3 and Supplementary Table 2 and 3 detail all cohorts' donor, recipient, and transplant characteristics. The D+R- donors pre-DAA were predominantly male, white or African American, with low body mass index, who succumbed to head trauma, with relatively low serum creatinine, and low rates of donation after circulatory death (DCD), diabetes, and hypertension (Supplementary Table 2A). In contrast, D+R- recipients tended to be older (57 [IQR, 47, 65]) and had less dialysis time. Thirty-seven percent of D+R- and 38% of D+R+ were shared nationally, and D+R- had the longest cold ischemia time (CIT) at 20 h [IQR, 16.0, 26.0]. D+R- and D+R+ cohorts had higher HLA mismatch than D-R- and D-R+. However, the incidence of delayed graft function (DGF) in D+R- was 25.3%, lower than in the D-R+ or D+R+ cohorts and similar to the D-R- cohort (Supplementary Table 2C).

In the DAA era, HCV+ donors were younger than HCV- donors, with lower rates of diabetes and hypertension. D+R- donors were predominantly white (85.2%) and died primarily of anoxic brain injury (72%) (Supplementary Table 3A). D+R- recipients tended to be white (45.7%), highly educated (30.6% with post high school degree), and less likely to have hypertension as the etiology of renal failure (Supplementary Table 3B). Similar to the pre-DAA transplants, D+R- transplants had the lowest rate of DGF (20.5%) despite the longest CIT (18.4[IQR, 13.1, 23.8]) (Supplementary Table 3C).

The association between donor HCV+ and transplant outcome in the Pre-DAA era

Prior to the DAA era, D-R- patients had the best crude PS and DCGS, while D+R- patients had the worst crude PS and DCGS (Figure 3A and B). The crude 3-year PS was 89.6%, 73.1%, 86.7% and 84.8% for D-R-, D+R-, D-R+ and D+R+, respectively. The crude 3-year DCGS was 88.8%, 80.1%, 84.2% and 82% for D-R-, D+R-, D-R+ and D+R+, respectively (Table 4).

After matching, 1272 pairs of HCV+ and 528 pairs of HCV- recipients were generated. Among the HCV+ recipients, receiving an HCV+ DD kidney was associated with 1.28-fold higher mortality (HR $_{1.15}$1.28$_{1.42}$) and 1.22-fold higher DCGF (HR $_{1.08}$1.22$_{1.39}$) compared to receiving an HCV- kidney over the observed period (Figure 4A). The absolute risk difference (aRD) was 3.3% (95%CI: 1.8%, 4.7%) for PS and 3.1% (95%CI: 1.2%, 5%) for DCGS at 3 years (Table 4).

Among HCV- recipients, receiving an HCV+ kidney was associated with 1.55-fold higher mortality (HR $_{1.33}$1.55$_{1.80}$) and 1.64-fold higher DCGF (HR $_{1.33}$1.64$_{2.02}$) compared to an HCV- kidney (Figure 4A). The aRD was 8% (95%CI: 5.2%, 10.9%) for PS and 7.4% (95%CI: 4.3%, 10.5%) for DCGS at 3 years (Table 4).

The association between donor HCV+ and transplant outcome in the DAA era

In the DAA era, comparable crude PS and DCGS were observed among all four cohorts (Figure 3C and D). The crude 3-year PS were 91%, 86.1%, 88.1% and 89.8% for D-R-, D+R-, D-R+ and D+R+, respectively. The crude 3-year DCGS were 92.5%, 92.6%, 92.4% and 94.2% for D-R-, D+R-, D-R+ and D+R+, respectively (Table 4). After matching, there were 290 pairs of HCV+ and 791 pairs of HCV- recipients. In contrast with pre-DAA era risks, the risks for PS and DCGS associated with receiving an HCV+ kidney in either HCV+ or HCV- recipients were not statistically significantly different in the DAA era (Figure 4B).

The association between recipient HCV+ and transplant outcome

Pre-DAA, HCV+ in recipients of HCV- donor kidneys corelated with significant declines in both crude PS and DCGS. However, HCV+ in recipients of HCV+ donors demonstrated a relative protective effect on mortality by 22% (D+R- *vs* D+R+, adjusted $P < 0.001$ for log-Rank test, HR$_{0.69}$0.78$_{0.87}$), despite the DCGS remaining comparable between two groups (D+R- *vs* D+R+, adjusted $P = 0.988$ for log-Rank test) (Figure 3A and B).

After matching, we generated 461 pairs of HCV+ and 4646 pairs of HCV- DD. HCV+ in recipients of HCV- donor kidneys was associated with 1.25-fold higher mortality (HR $_{1.18}$1.25$_{1.33}$) and 1.31-fold higher DCGF (HR $_{1.22}$1.31$_{1.41}$). The aRD between D-R- and D-R+ was 2.6% (95%CI: 1.9%, 3.2%) for PS and 3.5% (95%CI: 2.6%, 4.4%) for DCGS at 3 years (Table 4). In contrast, HCV+ and HCV- recipients of HCV+ donors demonstrated comparable outcomes (HR $_{0.86}$1$_{1.18}$ for mortality, $_{0.87}$1.01$_{1.31}$ for DCGS) (Figure 4A).

In the DAA era, we generated 508 pairs of HCV+ and 1440 pairs of HCV- recipients after matching. The risk associated with recipient's HCV+ when receiving either HCV+ or HCV- kidneys was not statistically significantly different in PS or DCGS (Figure 4B).

The association between donor plus recipient HCV+ and post-transplant outcome

Pre-DAA, HCV+ in the donor and recipient significantly impaired both PS and DCGS (D-R- *vs* D+R+, adjusted $P < 0.001$ for log-Rank test) (Figure 3A and B). There were 2150 pairs of D-R- and D+R+

Table 1 Characteristics of donors in the pre-direct-acting antivirals era and the post-direct-acting antivirals era

Characteristics		D-R-	D-R+	D+R-	D+R+	*P* value
n	Pre	116108	4646	550	2455	
	Post	46099	1443	1082	1303	
Age (median [IQR])	Pre	40.0 [23.0, 51.0]	40.0 [24.0, 51.0]	41.0 [34.0, 46.0]	42.0 [33.0, 49.0]	< 0.001
	Post	40.0 [27.0, 52.0]	42.0 [29.0, 52.0]	35.0 [29.0, 44.0]	32.0 [26.0, 39.0]	< 0.001
Gender = M (%)	Pre	69042 (59.5)	2762 (59.4)	380 (69.1)	1574 (64.1)	< 0.001
	Post	28136 (61.0)	853 (59.1)	617 (57.0)	818 (62.8)	0.012
BMI (median [IQR])	Pre	25.6 [22.4, 29.7]	25.6 [22.3, 29.4]	24.8 [22.1, 28.0]	25.1 [22.3, 28.6]	< 0.001
	Post	27.1 [23.4, 31.9]	27.5 [23.7, 32.2]	26.3 [23.3, 30.5]	25.6 [22.8, 29.4]	< 0.001
Race (%)						
White	Pre	83490 (71.9)	3209 (69.1)	409 (74.4)	1824 (74.3)	< 0.001
African American		14085 (12.1)	698 (15.0)	91 (16.5)	341 (13.9)	
Hispanic		14482 (12.5)	574 (12.4)	45 (8.2)	260 (10.6)	
Other		4051 (3.5)	165 (3.6)	5 (0.9)	30 (1.2)	
White	Post	31238 (67.8)	929 (64.4)	922 (85.2)	1103 (84.7)	< 0.001
African American		6325 (13.7)	273 (18.9)	44 (4.1)	58 (4.5)	
Hispanic		6421 (13.9)	187 (13.0)	94 (8.7)	116 (8.9)	
Other		2115 (4.6)	54 (3.7)	22 (2.0)	26 (2.0)	
Cause of death (%)						
Anoxia	Pre	19852 (17.1)	750 (16.1)	67 (12.2)	470 (19.1)	< 0.001
Cerebrovascular/stroke		44318 (38.2)	1800 (38.7)	196 (35.6)	985 (40.1)	
Head trauma		48450 (41.7)	1926 (41.5)	281 (51.1)	960 (39.1)	
Other		3488 (3.0)	170 (3.7)	6 (1.1)	40 (1.6)	
Anoxia	Post	18056 (39.2)	574 (39.8)	779 (72.0)	882 (67.7)	< 0.001
Cerebrovascular/stroke		12337 (26.8)	397 (27.5)	109 (10.1)	127 (9.7)	
Head trauma		14151 (30.7)	430 (29.8)	176 (16.3)	272 (20.9)	
Other		1555 (3.4)	42 (2.9)	18 (1.7)	22 (1.7)	
DCD = yes (%)	Pre	10101 (8.7)	368 (7.9)	11 (2.0)	105 (4.3)	< 0.001
	Post	10519 (22.8)	329 (22.8)	151 (14.0)	128 (9.8)	< 0.001
SCR (median [IQR])	Pre	1.0 [0.7, 1.3]	1.0 [0.7, 1.3]	0.9 [0.7, 1.2]	0.9 [0.7, 1.1]	< 0.001
	Post	0.9 [0.7, 1.4]	1.0 [0.7, 1.4]	0.9 [0.7, 1.3]	0.9 [0.7, 1.1]	< 0.001
History of diabetes = yes (%)	Pre	6712 (5.8)	254 (5.5)	14 (2.5)	95 (3.9)	< 0.001
	Post	3616 (7.8)	123 (8.5)	41 (3.8)	30 (2.3)	< 0.001
History of hypertension = yes (%)	Pre	28967 (24.9)	1137 (24.5)	114 (20.7)	576 (23.5)	0.038
	Post	13638 (29.6)	453 (31.4)	226 (20.9)	173 (13.3)	< 0.001
Smoking history = no (%)	Pre	78484 (67.6)	3039 (65.4)	234 (42.5)	1068 (43.5)	< 0.001
	Post	36564 (79.3)	1154 (80.0)	723 (66.8)	953 (73.1)	< 0.001

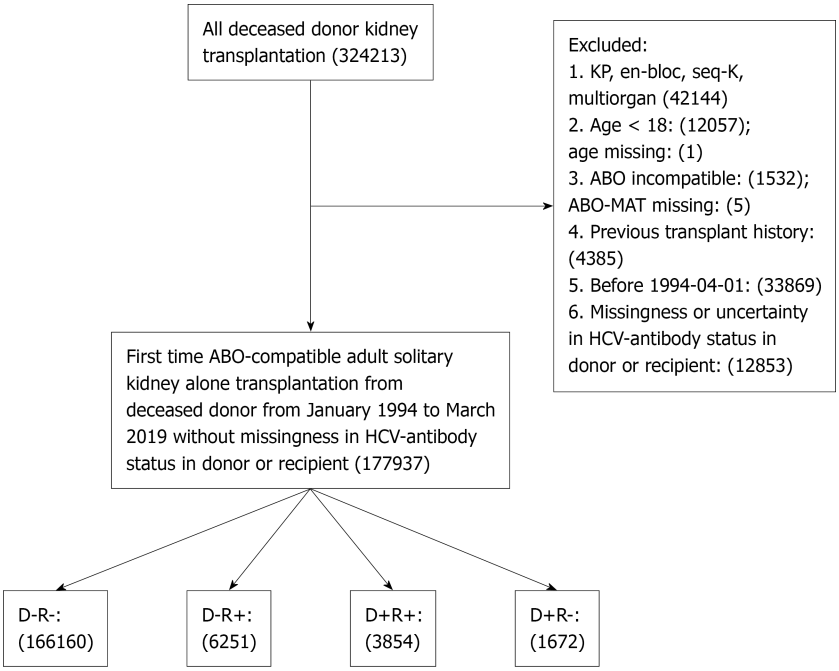
D(-/+) R(-/+), hepatitis C virus (-) or (+) donors into hepatitis C virus (-) or (+) recipients. BMI: Body mass index; DCD: Donation after circulatory death; IQR: Interquartile range; M: male; Pre: Pre-direct-acting antivirals era; Post: Post-direct-acting antivirals era; SCR: Serum creatinine.

transplants after matching. HCV+ in donor and recipient was associated with 1.56-fold higher mortality (HR $_{1.43}1.56_{1.7}$) and 1.71-fold higher DCGF (HR $_{1.54}1.71_{1.9}$) compared to the D-R- transplants. The aRD between D-R- and D+R+ were 5.3% (95%CI: 4.3%, 6.4%) for PS and 7.1% (95%CI: 5.7%, 8.5%) for DCGS

Table 2 Characteristics of recipients in the pre-direct-acting antivirals era and the post-direct-acting antivirals era

Characteristics		D-R-	D-R+	D+R-	D+R+	*P* value
n	Pre	116108	4646	550	2455	
	Post	46099	1443	1082	1303	
Age (median [IQR])	Pre	53.0 [42.0, 61.0]	51.0 [44.0, 58.0]	57.0 [47.0, 65.0]	53.0 [47.0, 59.0]	< 0.001
	Post	55.0 [44.0, 64.0]	59.0 [52.0, 64.0]	60.0 [52.0, 67.0]	60.0 [55.5, 65.0]	< 0.001
Gender = M (%)	Pre	69448 (59.8)	3251 (70.0)	406 (73.8)	1995 (81.3)	< 0.001
	Post	27135 (58.9)	994 (68.9)	739 (68.3)	1017 (78.1)	< 0.001
BMI (median [IQR])	Pre	26.8 [23.6, 30.9]	26.1 [23.0, 29.9]	26.5 [23.6, 29.4]	26.4 [23.3, 29.8]	< 0.001
	Post	28.6 [24.9, 32.8]	27.8 [24.4, 31.6]	29.1 [25.7, 33.3]	27.8 [24.5, 31.5]	< 0.001
Race (%)						
White	Pre	56376 (48.6)	1383 (29.8)	211 (38.4)	404 (16.5)	< 0.001
African American		34683 (29.9)	2447 (52.7)	290 (52.7)	1789 (72.9)	
Hispanic		15940 (13.7)	517 (11.1)	27 (4.9)	201 (8.2)	
Other		9109 (7.8)	299 (6.4)	22 (4.0)	61 (2.5)	
White	Post	16501 (35.8)	334 (23.1)	494 (45.7)	267 (20.5)	< 0.001
African American		15762 (34.2)	784 (54.3)	392 (36.2)	855 (65.6)	
Hispanic		9079 (19.7)	226 (15.7)	117 (10.8)	137 (10.5)	
Other		4757 (10.3)	99 (6.9)	79 (7.3)	44 (3.4)	
Insurance = nonprivate (%)	Pre	83051 (71.5)	3733 (80.3)	418 (76.0)	1831 (74.6)	< 0.001
	Post	37085 (80.4)	1265 (87.7)	831 (76.8)	993 (76.2)	< 0.001
Education level (%)						
High school	Pre	44906 (38.7)	1923 (41.4)	222 (40.4)	1195 (48.7)	< 0.001
Technical		22531 (19.4)	931 (20.0)	86 (15.6)	450 (18.3)	
Post high school degree		18972 (16.3)	494 (10.6)	59 (10.7)	254 (10.3)	
High school	Post	19085 (41.4)	741 (51.4)	403 (37.2)	680 (52.2)	< 0.001
Technical		11577 (25.1)	369 (25.6)	280 (25.9)	318 (24.4)	
Post high school degree		10687 (23.2)	230 (15.9)	331 (30.6)	214 (16.4)	
ESRD (%)						
Diabetes	Pre	32208 (27.7)	1193 (25.7)	178 (32.4)	783 (31.9)	< 0.001
Hypertension		30368 (26.2)	1745 (37.6)	221 (40.2)	1108 (45.1)	
Other		53532 (46.1)	1708 (36.8)	151 (27.5)	564 (23.0)	
Diabetes	Post	14439 (31.3)	477 (33.1)	438 (40.5)	601 (46.1)	< 0.001
Hypertension		12513 (27.1)	543 (37.6)	270 (25.0)	444 (34.1)	
Other		19147 (41.5)	423 (29.3)	374 (34.6)	258 (19.8)	
Dialysis time, day, (median [IQR])	Pre	1143 [708, 1691]	1344 [889, 2164]	976 [580, 1388]	1118 [603, 1596]	< 0.001
	Post	1661 [1043, 2373]	1999 [1364, 2988]	1257 [637, 1674]	1065 [593, 1661]	< 0.001
CPRA (median [IQR])	Pre	0.0 [0.0, 2.0]	0.0 [0.0, 2.0]	0.0 [0.0, 0.0]	0.0 [0.0, 0.0]	< 0.001
CPRA (mean [SD])	Post	19.3 (32.8)	20.5 (33.5)	9.4 (21.9)	9.3 (21.3)	< 0.001
PVD = yes (%)	Pre	5374 (4.6)	210 (4.5)	26 (4.7)	111 (4.5)	< 0.001
	Post	4590 (10.0)	186 (12.9)	118 (10.9)	148 (11.4)	0.001
Diabetes = yes (%)	Pre	38827 (33.4)	1491 (32.1)	225 (40.9)	1014 (41.3)	< 0.001
	Post	17213 (37.3)	583 (40.4)	521 (48.2)	714 (54.8)	< 0.001

D(-/+) R(-/+), hepatitis C virus (-) or (+) donors into hepatitis C virus (-) or (+) recipients. BMI: Body mass index; ESRD: End stage renal disease; IQR: Interquartile range; M: Male; Pre: Pre-direct-acting antivirals era; Post: Post-direct-acting antivirals era; CPRA: Calculated panel reaction antibody; PVD: Peripheral vascular disease.



DOI: 10.5500/wjt.v13.i2.44

Figure 1 Flowchart of study cohorts identification. We identified all adult (age ≥ 18) first-time solitary kidney transplantation recipients from an ABO-compatible deceased donor between January 1994 and March 2019 in the United States Patients with missing or uncertain hepatitis C virus (HCV)-antibody status in the donor or recipient were excluded. Patients were allocated into four groups according to HCV infection in the donor (D+) or recipient (R+): D-R-, D+R-, D-R+, and D+R+. KP: Kidney-pancreas; HCV: Hepatitis C virus; ABO-MAT: ABO-blood type match.

at 3 years (Figure 4A, Table 4).

In the DAA era, 803 pairs of D-R- and D+R+ transplants were generated after matching. HCV+ in donor and recipient marginally significantly increased the mortality (P = 0.049 for log-rank test). The cox proportional hazard model showed a mortality increase by 1.43-fold (HR $_{1.0}$1.43$_{2.04}$) as compared to the D-R- transplants, with an aRD of 3.3% (95%CI: 0, 6.7%) at 3 years. The 3-year PS were 91.8% and 88.4% for D-R- and D+R+ recipients, respectively. HCV+ in donor and recipient did not statistically significantly affect DCGS (Figure 4B, Table 4).

The association between donor or recipient HCV+ and post-transplant outcome

In the pre-DAA era, HCV+ in the donor had more impact on patient survival than did infection in the recipient (D+R- *vs* D-R+, adjusted P < 0.001 for log-Rank test, HR$_{1.49}$1.69$_{1.83}$) (Figure 3A and B). After matching, there were 444 pairs of D+R- and D-R+ transplants. Donor HCV+ was associated with 1.36-fold higher mortality (HR $_{1.16}$1.36$_{1.61}$) and 1.34-fold higher DCGF (HR $_{1.08}$1.34$_{1.67}$) than recipient HCV+. The aRD between D+R- and D-R+ were 5.4% (95%CI: 2.6%, 8.6%) for PS and 4.8% (95%CI: 1.4%, 8.2%) for DCGS at 3 years (Figure 4A, Table 4).

In the DAA era, 253 pairs of D-R+ and D+R- transplants were identified after matching, with both PS (HR$_{0.52}$1.28$_{2.87}$) and DCGS (HR$_{0.58}$1.73$_{4.91}$) in the matched cohorts being comparable (Figure 4B, Table 4).

DISCUSSION

In our national study of 177937 DD KT across 25 years, we found a marked increase in HCV+ kidney utilization after DAA availability, initially with KTs of HCV+ kidneys to HCV+ recipients in 2014, followed by a dramatic shift towards transplants into HCV- recipients. This shift in 2016 likely reflects knowledge around the safety of HCV transplants with concurrent use of DAA. Pre-DAA D+R- recipients, despite generally being older, with less dialysis time and higher malignancy prevalence, received younger donors' kidneys. Interestingly, in the DAA era, recipients' education level was highest in the D+R- cohort, suggesting superior health literacy potentially facilitating informed consent and

Table 3 Characteristics of transplantation in the pre-direct-acting antivirals era and the post-direct-acting antivirals era

Characteristics		D-R-	D-R+	D+R-	D+R+	*P* value
n	Pre	116108	4646	550	2455	
	Post	46099	1443	1082	1303	
TX year (median [IQR])	Pre	2005 [2000, 2010]	2004 [1999, 2009]	2001 [1997, 2007]	2006 [2001, 2010]	< 0.001
	Post	2016 [2015, 2018]	2016 [2015, 2018]	2018 [2017, 2018]	2016 [2015, 2017]	< 0.001
Region (%)						
1	Pre	4694 (4.0)	167 (3.6)	11 (2.0)	74 (3.0)	< 0.001
2		14123 (12.2)	661 (14.2)	112 (20.4)	823 (33.5)	
3		17507 (15.1)	704 (15.2)	64 (11.6)	235 (9.6)	
4		10816 (9.3)	414 (8.9)	29 (5.3)	136 (5.5)	
5		17680 (15.2)	655 (14.1)	63 (11.5)	260 (10.6)	
6		4356 (3.8)	156 (3.4)	6 (1.1)	7 (0.3)	
7		9360 (8.1)	403 (8.7)	54 (9.8)	137 (5.6)	
8		7738 (6.7)	252 (5.4)	23 (4.2)	55 (2.2)	
9		7150 (6.2)	355 (7.6)	29 (5.3)	222 (9.0)	
10		10186 (8.8)	457 (9.8)	104 (18.9)	192 (7.8)	
11		12498 (10.8)	422 (9.1)	55 (10.0)	314 (12.8)	
1	Post	1601 (3.5)	62 (4.3)	35 (3.2)	65 (5.0)	< 0.001
2		5404 (11.7)	182 (12.6)	151 (14.0)	349 (26.8)	
3		6590 (14.3)	221 (15.3)	181 (16.7)	150 (11.5)	
4		4526 (9.8)	173 (12.0)	45 (4.2)	67 (5.1)	
5		8107 (17.6)	238 (16.5)	101 (9.3)	144 (11.1)	
6		1911 (4.1)	55 (3.8)	13 (1.2)	6 (0.5)	
7		3192 (6.9)	110 (7.6)	37 (3.4)	45 (3.5)	
8		3130 (6.8)	86 (6.0)	5 (0.5)	44 (3.4)	
9		3057 (6.6)	85 (5.9)	125 (11.6)	174 (13.4)	
10		3507 (7.6)	79 (5.5)	195 (18.0)	84 (6.4)	
11		5074 (11.0)	152 (10.5)	194 (17.9)	175 (13.4)	
Shared (%)						
Local	Pre	85197 (73.4)	3464 (74.6)	223 (40.5)	931 (37.9)	< 0.001
Regional		9559 (8.2)	377 (8.1)	124 (22.5)	591 (24.1)	
National		21352 (18.4)	805 (17.3)	203 (36.9)	933 (38.0)	
Local	Post	35095 (76.1)	1115 (77.3)	337 (31.1)	379 (29.1)	< 0.001
Regional		5349 (11.6)	157 (10.9)	345 (31.9)	348 (26.7)	
National		5655 (12.3)	171 (11.9)	400 (37.0)	576 (44.2)	
CIT (median [IQR])	Pre	18.0 [13.0, 23.1]	18.0 [13.0, 23.5]	20.0 [16.0, 26.0]	19.0 [15.0, 25.0]	< 0.001
	Post	16.7 [11.4, 22.6]	16.5 [11.0, 22.0]	18.4 [13.1, 23.8]	18.0 [12.3, 23.5]	< 0.001
HLA mismatch = 4-6 (%)	Pre	76253 (65.7)	3238 (69.7)	452 (82.2)	2151 (87.6)	< 0.001
	Post	35126 (76.2)	1170 (81.1)	894 (82.6)	1154 (88.6)	< 0.001
DGF = yes (%)	Pre	28919 (24.9)	1440 (31.0)	139 (25.3)	756 (30.8)	< 0.001
	Post	13468 (29.2)	496 (34.4)	222 (20.5)	284 (21.8)	< 0.001

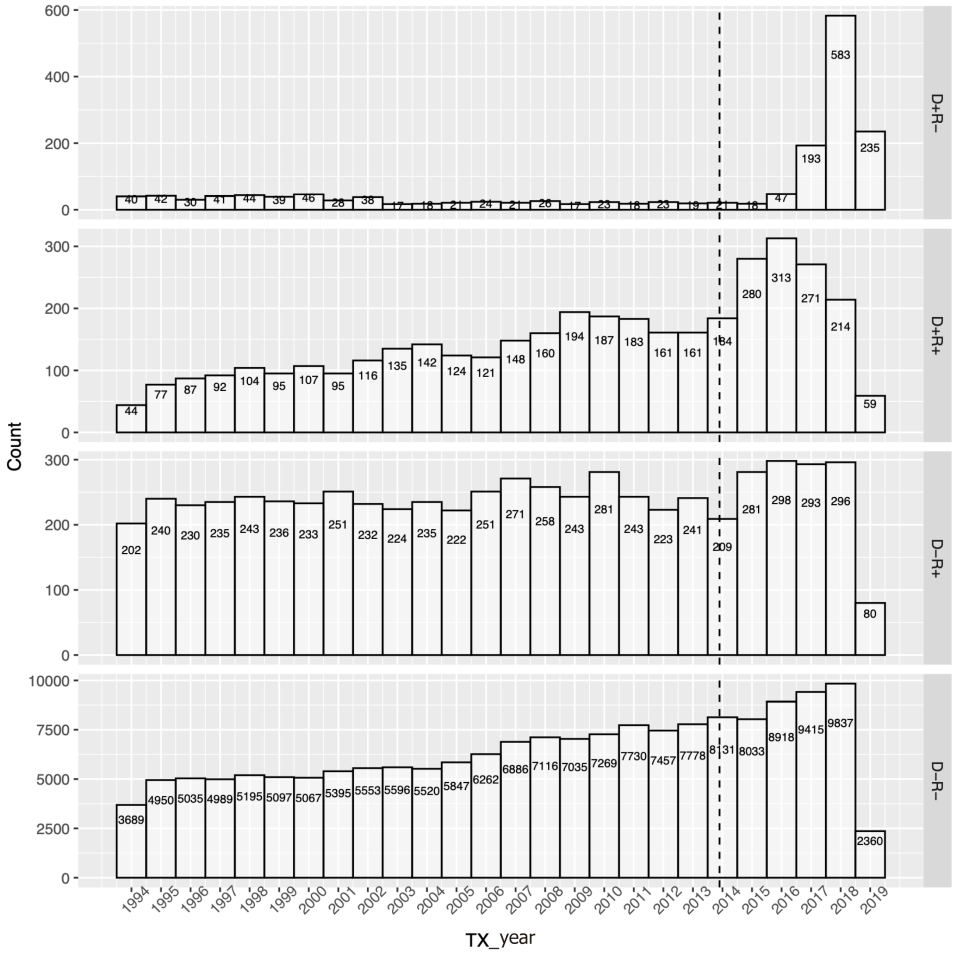
D(-/+) R(-/+), hepatitis C virus (-) or (+) donors into hepatitis C virus (-) or (+) recipients. CIT: Cold ischemia time; DGF: Delayed graft function; HLA: Human leukocyte antigen; IQR: Interquartile range; Pre: Pre-direct-acting antivirals era; Post: Post-direct-acting antivirals era; TX: Transplantation.

Table 4 Patient survival and death-censored graft survival at 3 years in the pre-direct-acting antivirals era and the post-direct-acting antivirals era

Cohorts in comparison (%)			D-R+	D+R+	D-R-	D+R-	Absolute risk difference
Crude	Patient survival	Pre	86.7 (85.8, 87.7)	84.8 (83.4, 86.3)	89.6 (89.5, 89.8)	73.1 (69.4, 76.9)	-
		Post	88.1 (85.7, 90.5)	89.8 (87.7, 92)	91 (90.6, 91.3)	86.1 (77.6, 95.6)	-
	Death-censored graft survival	Pre	84.2 (83.1, 85.3)	82 (80.4, 83.6)	88.8 (88.6, 89)	80.1 (76.6, 83.7)	-
		Post	92.4 (90.6, 94.2)	94.2 (92.5, 96)	92.5 (92.2, 92.8)	92.6 (87.3, 98.3)	-
D+ *vs* D- in R+	Patient survival	Pre	86.3 (84.4, 88.2)	84.8 (82.8, 86.8)	-	-	3.3 (1.8, 4.7)
		Post	90.2 (85.5, 95)	88.7 (84, 93.7)	-	-	2.7 (-2.9, 8.1)
	Death-censored graft survival	Pre	83.6 (81.5, 85.8)	81.6 (79.4, 83.9)	-	-	3.1 (1.2, 5)
		Post	90.1 (85.5, 94.9)	92 (87.9, 96.3)	-	-	0.4 (-5, 6.1)
D+ *vs* D- in R-	Patient survival	Pre	-	-	85.3 (82.3, 88.4)	73.5 (69.8, 77.4)	8 (5.2, 10.9)
		Post	-	-	89.1 (83.6, 94.9)	88.6 (81.6, 96.2)	-0.3 (-5.9, 6.1)
	Death-censored graft survival	Pre	-	-	86.9 (83.9, 89.9)	80.4 (76.8, 84.1)	7.4 (4.3, 10.5)
		Post	-	-	92.2 (87.8, 96.8)	93.8 (88.5, 99.4)	-2.3 (-7.4, 2.1)
R+ *vs* R- in D+	Patient survival	Pre	-	80.9 (77.3, 84.6)	-	76.7 (72.8, 80.7)	0.1 (-2.9, 3.1)
		Post	-	88.4 (84.3, 92.8)	-	85.1 (75.4, 96)	1.1 (-6.1, 7)
	Death-censored graft survival	Pre	-	79.4 (75.5, 83.5)	-	80.6 (76.9, 84.6)	1.2 (-2.5, 4.9)
		Post	-	93 (89.6, 96.5)	-	92.3 (86.2, 98.8)	0.7 (-5, 5.4)
R+ *vs* R- in D-	Patient survival	Pre	86.7 (85.8, 87.7)	-	88.7 (87.8, 89.6)	-	2.6 (1.9, 3.2)
		Post	88.1 (85.7, 90.5)	-	89.5 (87.3, 91.8)	-	-0.5 (-3.3, 2.2)
	Death-censored graft survival	Pre	84.2 (83.1, 85.3)	-	86.5 (85.5, 87.5)	-	3.5 (2.6, 4.4)
		Post	92.4 (90.6, 94.2)	-	92.1 (90.2, 94.1)	-	-0.2 (-2.4, 2)
D+R+ *vs* D-R-	Patient survival	Pre	-	85 (83.4, 86.5)	89 (87.7, 90.4)	-	5.3 (4.3, 6.4)
		Post	-	88.4 (85.5, 91.4)	91.8 (89.2, 94.4)	-	3.3 (0, 6.7)
	Death-censored graft survival	Pre	-	82.7 (81, 84.4)	87.8 (86.4, 89.2)	-	7.1 (5.7, 8.5)
		Post	-	93.3 (90.9, 95.8)	93.3 (90.9, 95.8)	-	1.7 (-1.4, 4.5)
D+R- *vs* D-R+	Patient survival	Pre	85.4 (82.1, 88.8)	-	-	75.6 (71.6, 79.7)	5.4 (2.6, 8.6)
		Post	88.7 (81.8, 96.3)	-	-	91.5 (85, 98.6)	3.2 (-5.9, 11.6)
	Death-censored graft survival	Pre	84.5 (81.1, 88.1)	-	-	81.1 (77.3, 85.1)	4.8 (1.4, 8.2)
		Post	94.4 (89.3, 99.7)	-	-	93.3 (87.4, 99.5)	2.5 (-3.6, 10)

D(-/+) R(-/+), hepatitis C virus (-) or (+) donors into hepatitis C virus (-) or (+) recipients. Pre: Pre-direct-acting antivirals era; Post: Post-direct-acting antivirals era.

appreciation of DAA effects in decreasing HCV+ kidney risks[12]. DGF was reduced in D+R- transplants, despite the longest CIT and higher HLA mismatch compared with other cohorts in both the pre- and post-DAA eras, which could be the result of lower DCD rates and other unmeasured donor factors. In the pre DAA-era, HCV+ in either the donor or recipient of HCV- kidneys was associated with poorer PS and DCGS, but donor HCV+ status impacted PS and DCGS moreso than did recipient HCV+ status. Additionally, donor plus recipient HCV+ (D+R+ *vs* D-R-) and donor infection in HCV- recipients (D+R- *vs* D-R-) displayed the largest absolute increase in mortality and DCGF. Importantly, the risks on PS and DCGS associated with HCV+ in donors and/or recipients were no longer statistically significant after the widespread adoption of DAA in 2015, except for a marginally significantly impaired PS in



DOI: 10.5500/wjt.v13.i2.44

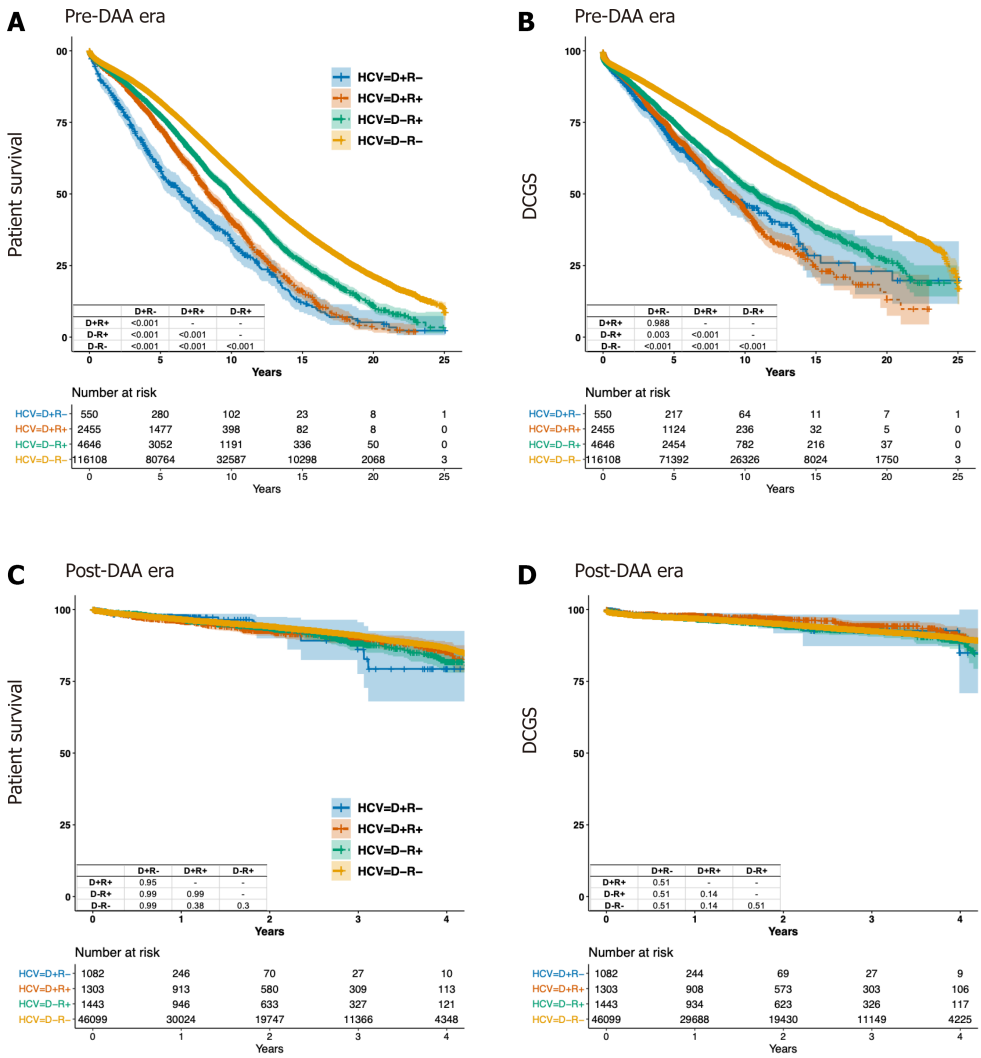
Figure 2 Yearly distribution of the kidney transplantation stratified by hepatitis C virus status in donor and/or recipient. Numbers of kidney transplants performed each year from January 1994 and March 2019 were plotted and stratified into four groups according to hepatitis C virus infection in the donor or recipient: D-R-, D+R-, D-R+, and D+R+.

D+R+ *vs* D-R-, which possessed the largest risk difference in the pre-DAA era.

The presumed risks of viral transmission in HCV+ transplants made these transplants scarce in the pre-DAA era (< 50 annually D+R-)[13-15]. DAAs encouraged broader acceptance of HCV+ candidates and more aggressive utilization of HCV+ kidneys. Two pilot trials in 2017 and 2018 of HCV+ kidney transplants into HCV- recipients found that, despite inevitable HCV transmission, subsequent DAA therapy provided HCV cure in a cost-effective approach that also resulted in well-functioning allografts [16,17]. Similarly, our observational study shows equivalent outcomes between D+R- and D-R- cohorts in the DAA era.

Many studies evaluated the effect of donor HCV+ on KT outcomes prior to the introduction of DAA [13-15], with HCV+ KT improving survival among all patients when compared to staying waitlisted and not receiving a kidney[2]. A single-center analysis summarizing 1990-2007 data compared long-term D+R+ outcomes to D-R+, showing that HCV+ donor status in HCV+ recipients did not significantly influence mortality, graft failure, or liver disease[14]. However, 1995-2008 national registry data showed D+R+ patients had a 2.6-fold higher hazard of joining the liver wait-list ($P < 0.001$). Nonetheless, the absolute risk difference in subsequently listing for liver transplant was < 2% between recipients of HCV+ and HCV- kidneys[15]. A recent study using 2005-2017 data reported that among HCV+ recipients, receiving an HCV+ kidney was associated with 19% higher mortality (aHR, $_{1.07}1.19_{1.32}$), an effect that disappeared in the DAA era[5]. Our study evaluated the HCV effect of donor separately in HCV+ recipients and HCV- recipients and found similar trends of donor HCV associated PS and DCGS impairment in both recipients groups. with both mortality and DCGF absolute risk differences being larger in HCV- than HCV+ recipients (Table 4).

Two meta-analyses have evaluated the effect of recipient HCV+ status on KT outcomes[18,19], finding HCV+ correlated with increased mortality (aHR: $_{1.49}1.85_{2.31}$, $_{1.33}1.69_{1.97}$) and graft failure (aHR: $_{1.46}1.76_{2.11}$, $_{1.22}1.56_{2.00}$). However, neither distinguished donor HCV status. Our study found that the effect of recipients' HCV+ status was dramatically modified by the donor's HCV status—recipient's HCV+ only impaired transplant outcomes when receiving an HCV-, but not HCV+, kidney. This finding parallels

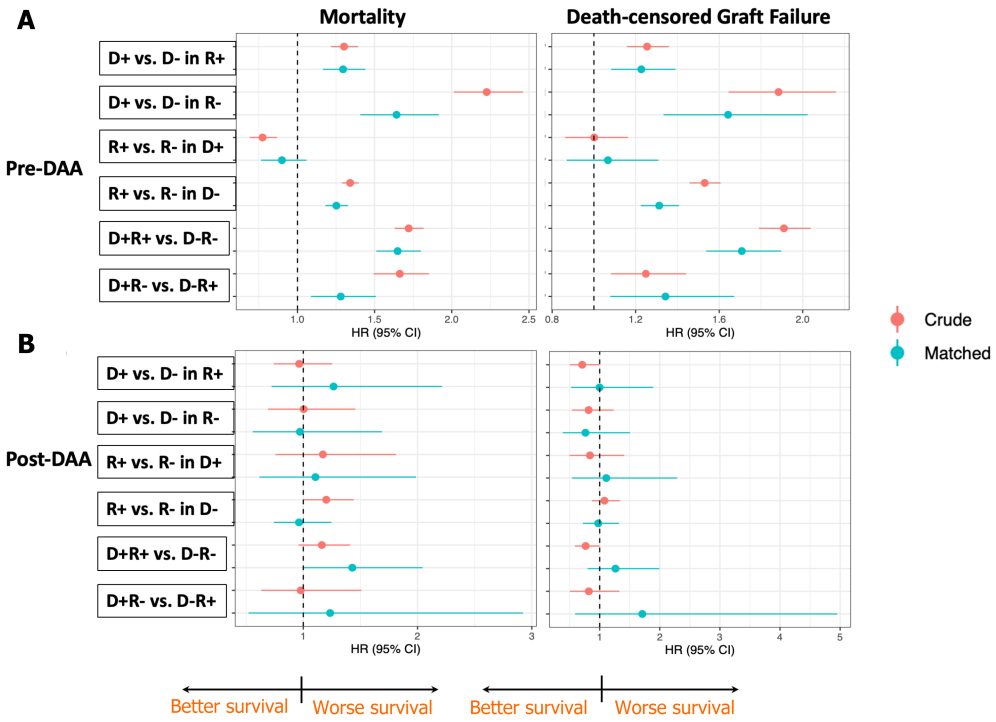


DOI: 10.5500/wjt.v13.i2.44 **Copyright** ©The Author(s) 2023.

Figure 3 Crude patient survival and death-censored graft survival among four cohorts in the pre- and post-direct-acting antivirals eras. Survival was presented in Kaplan-Meier curves and analyzed by log-rank tests. Multiple comparison was adjusted by Bonferroni correction. A: Crude patient survival in the pre-direct-acting antivirals (DAA) era; B: Crude death-censored graft survival (DCGS) in the pre-DAA era; C: Crude patient survival in the post-DAA era; D: crude DCGS in the post-DAA era. DAA: Direct-acting antivirals; HCV: Hepatitis C virus; DCGS: Death-censored graft survival.

our previous study analyzing outcomes of transplanting the same donor's pair of kidneys to one HCV+ and to one HCV- recipient[20].

There are several limitations to our study. First, most D+R- patients received transplants in the DAA era with relatively short follow up. Dividing the dataset into pre- and DAA eras resulted in smaller sample sizes. Second, PSM use to eliminate confounders between comparator groups could be biased by unmeasured potential confounders, including HCV genotype, viral load, infection duration and severity, graft rejection, and immunosuppression intensity, none of which is found in the used registry data. Third, we lack viremia data—while most viremic patients are antibody positive, a small portion of antibody positive patients are aviremic. We defined HCV+ by antibody status prior to 2015, and by antibody and NAT results since 2015. Antibody positive aviremic donors or recipients were included as HCV+ in both eras' analyses, and a miniscule fraction of viremic patients who are antibody negative would have been included in the HCV- cohort in the pre-DAA analysis. Including these patients would yield worse outcomes in the uninfected population, underestimating the difference observed between infected and uninfected groups. Fourth, the registry data does not verify DAA treatment. Fifth, we used a pair matching method to estimate the "average treatment effect in the treated." Some exposed subjects were excluded from the matched sample because of no available unexposed subjects within the specified caliper distance of the exposed subjects. There might be potential bias generated when unmatched exposed subjects differ systematically from the matched exposed subjects[21]. Other statistical methods, including full matching or inverse probability weighting, with the aim to include all the samples in both groups in comparison could also result in biased estimation due to increased heterogenicity within each group. Lastly, we used single imputation for variables with missingness over 1 percent. Limited impact was found on the magnitude of the hazard ratio or the significance of the



DOI: 10.5500/wjt.v13.i2.44 **Copyright** ©The Author(s) 2023.

Figure 4 Relative risk of mortality and death-censored graft failure in six pair-wised comparison in the pre- and post-direct-acting antivirals eras. Four groups of patients classified by hepatitis C virus infection in the donor or recipient: D-R-, D+R-, D-R+, and D+R+, were compared pair-wisely before and after propensity score matching. Hazard ratio were presented in the forest plot with dot represented the HR and line represented the 95% confidence interval. D+ *vs* D- in R+ represented the relative risk of mortality or death-censored graft failure (DCGF) in D+R+ patients as compared with D-R+ patients. Similar interpretation in the other five pairs of comparison. The dashed line represented HR = 1. Dots located in the right of the dashed line means higher mortality or DCGF (worse survival) compared to the reference group. A: Relative risk in the pre-direct-acting antivirals (DAA) era; B: Relative risk in the post-DAA era. DAA: Direct-acting antivirals.

findings of DCGS and patient survival, with multiple imputation method.

CONCLUSION

In conclusion, although HCV+ in either KT donors or recipients negatively impacted PS and DCGS pre-DAA, neither donor nor recipient HCV+ appears to portend worse outcomes in the DAA era, supporting increased utilization of HCV+ kidneys as the standard of care. Given comparable outcomes across all four patient cohorts in the DAA era, a new allocation algorithm, eliminating HCV+ kidneys' negative influence on the KDRI, is urgently needed to improve utilization and allocation of this under-utilized resource.

ARTICLE HIGHLIGHTS

Research background

While Hepatitis C virus infection (HCV+) kidneys have traditionally been discarded rather than transplanted into HCV- recipients, the introduction of direct-acting antivirals (DAAs) in 2013 revolutionized HCV treatment by consistently achieving sustained virologic responses, opening the door for transplantation of HCV+ organs.

Research motivation

As HCV+ rates in kidney donors and transplant recipients rise, the introduction of DAA may effect transplant outcomes.

Research objectives

To analyze the effects of HCV+ in donors, recipients, or both, on deceased-donor (DD) kidney

transplantation (KT) outcomes, and the impact of DAAs on those effects.

Research methods

The Organ Procurement and Transplantation Network data of adult first solitary DD-KT recipients 1994-2019 were allocated into four groups by donor and recipient HCV+ status. We performed patient survival (PS) and death-censored graft survival (DCGS) pairwise comparisons after propensity score matching to assess the effects of HCV+ in donors and/or recipients, stratifying our study by DAA era to evaluate potential effect modification.

Research results

Pre-DAA, for HCV+ recipients, receiving an HCV+ kidney was associated with 1.28-fold higher mortality (HR $_{1.15}1.28_{1.42}$) and 1.22-fold higher death-censored graft failure (HR $_{1.08}1.22_{1.39}$) compared to receiving an HCV- kidney and the absolute risk difference was 3.3% (95%CI: 1.8%-4.7%) for PS and 3.1% (95%CI: 1.2%-5%) for DCGS at 3 years. The HCV dual-infection (donor plus recipient) group had worse PS (0.56-fold) and DCGS (0.71-fold) than the dual-uninfected. Donor HCV+ derived worse post-transplant outcomes than recipient HCV+ (PS 0.36-fold, DCGS 0.34-fold). In the DAA era, the risk associated with HCV+ in donors and/or recipients was no longer statistically significant, except for impaired PS in the dual-infected *vs* dual-uninfected (0.43-fold).

Research conclusions

Prior to DAA introduction, donor HCV+ negatively influenced kidney transplant outcomes in all recipients, while recipient infection only relatively impaired outcomes for uninfected donors. These adverse effects disappeared with the introduction of DAA.

Research perspectives

Given comparable outcomes across all four patient cohorts in the DAA era, a new allocation algorithm, eliminating HCV+ kidneys' negative influence on the KDRI, is urgently needed to improve utilization and allocation of this under-utilized resource.

FOOTNOTES

Author contributions: Yuan Q and Elias N contributed to study conception and design; Acquisition of data: Elias N contributed to analysis and interpretation of data; Yuan Q, Hong S, Leya G, Roth E, Tsoulfas G, Williams WW and Elias N contributed to analysis and interpretation of data; Yuan Q, Hong S, Leya G, Roth E, Tsoulfas G, Williams WW and Elias N contributed to drafting of manuscript; all authors have read and approve the final manuscript.

Institutional review board statement: The above referenced project does not meet the criteria for human subject research as defined by Mass General Brigham Human Research Office policies and Health and Human Services regulations set forth in 45 CFR 46. Based on the information you provided this activity is not human subjects research because it does not involve human subjects. The project does not require IRB approval.

Conflict-of-interest statement: The authors have no conflicts of interest to declare.

Data sharing statement: The data sources for this study are publicly available from the OPTN web site: http://optn.transplant.hrsa.gov.

Country/Territory of origin: United States

ORCID number: Gregory Leya 0000-0002-2691-8659; Georgios Tsoulfas 0000-0001-5043-7962; Nahel Elias 0000-0001-6466-7347.

S-Editor: Chang KL
L-Editor: A
P-Editor: Chang KL

REFERENCES

1 **Morales JM**, Fabrizi F. Hepatitis C and its impact on renal transplantation. *Nat Rev Nephrol* 2015; **11**: 172-182 [PMID: 25643666 DOI: 10.1038/nrneph.2015.5]

2 **Abbott KC**, Lentine KL, Bucci JR, Agodoa LY, Peters TG, Schnitzler MA. The impact of transplantation with deceased donor hepatitis c-positive kidneys on survival in wait-listed long-term dialysis patients. *Am J Transplant* 2004; **4**: 2032-2037 [PMID: 15575906 DOI: 10.1046/j.1600-6143.2004.00606.x]

3 **Durand CM**, Bowring MG, Thomas AG, Kucirka LM, Massie AB, Cameron A, Desai NM, Sulkowski M, Segev DL. The Drug Overdose Epidemic and Deceased-Donor Transplantation in the United States: A National Registry Study. *Ann Intern Med* 2018; **168**: 702-711 [PMID: 29710288 DOI: 10.7326/M17-2451]

4 **Mandal AK**, Kraus ES, Samaniego M, Rai R, Humphreys SL, Ratner LE, Maley WR, Burdick JF. Shorter waiting times for hepatitis C virus seropositive recipients of cadaveric renal allografts from hepatitis C virus seropositive donors. *Clin Transplant* 2000; **14**: 391-396 [PMID: 10946777 DOI: 10.1034/j.1399-0012.2000.14040602.x]

5 **Bowring MG**, Kucirka LM, Massie AB, Ishaque T, Bae S, Shaffer AA, Garonzik Wang J, Sulkowski M, Desai N, Segev DL, Durand CM. Changes in Utilization and Discard of HCV Antibody-Positive Deceased Donor Kidneys in the Era of Direct-Acting Antiviral Therapy. *Transplantation* 2018; **102**: 2088-2095 [PMID: 29912046 DOI: 10.1097/TP.0000000000002323]

6 **Geddawy A**, Ibrahim YF, Elbahie NM, Ibrahim MA. Direct Acting Anti-hepatitis C Virus Drugs: Clinical Pharmacology and Future Direction. *J Transl Int Med* 2017; **5**: 8-17 [PMID: 28680834 DOI: 10.1515/jtim-2017-0007]

7 **AASLD/IDSA HCV Guidance**. Recommendations for Testing, Managing, and Treating Hepatitis C. *Clinical Liver Disease* 2018; **12**: 117-117 [DOI: 10.1002/cld.791]

8 **Welzel TM**, Zeuzem S. Mixing and matching drugs: what makes sense? *Clin Liver Dis* 2011; **15**: 657-664 [PMID: 21867943 DOI: 10.1016/j.cld.2011.05.012]

9 **Rao PS**, Schaubel DE, Guidinger MK, Andreoni KA, Wolfe RA, Merion RM, Port FK, Sung RS. A comprehensive risk quantification score for deceased donor kidneys: the kidney donor risk index. *Transplantation* 2009; **88**: 231-236 [PMID: 19623019 DOI: 10.1097/TP.0b013e3181ac620b]

10 **Snyder JJ**, Salkowski N, Kim SJ, Zaun D, Xiong H, Israni AK, Kasiske BL. Developing Statistical Models to Assess Transplant Outcomes Using National Registries: The Process in the United States. *Transplantation* 2016; **100**: 288-294 [PMID: 26814440 DOI: 10.1097/TP.0000000000000891]

11 **Austin PC**. Absolute risk reductions and numbers needed to treat can be obtained from adjusted survival models for time-to-event outcomes. *J Clin Epidemiol* 2010; **63**: 46-55 [PMID: 19595575 DOI: 10.1016/j.jclinepi.2009.03.012]

12 **Sise ME**, Wojciechowski D, Chute DF, Gustafson J, Chung RT, Williams WW, Elias N. Process of selecting and educating HCV-uninfected kidney waiting-list candidates for HCV-infected kidney transplantation. *Artif Organs* 2019; **43**: 913-920 [PMID: 31001828 DOI: 10.1111/aor.13473]

13 **Bucci JR**, Matsumoto CS, Swanson SJ, Agodoa LY, Holtzmuller KC, Peters TG, Abbott KC. Donor hepatitis C seropositivity: clinical correlates and effect on early graft and patient survival in adult cadaveric kidney transplantation. *J Am Soc Nephrol* 2002; **13**: 2974-2982 [PMID: 12444217 DOI: 10.1097/01.asn.0000034944.90425.75]

14 **Morales JM**, Campistol JM, Domínguez-Gil B, Andrés A, Esforzado N, Oppenheimer F, Castellano G, Fuertes A, Bruguera M, Praga M. Long-term experience with kidney transplantation from hepatitis C-positive donors into hepatitis C-positive recipients. *Am J Transplant* 2010; **10**: 2453-2462 [PMID: 20977636 DOI: 10.1111/j.1600-6143.2010.03280.x]

15 **Kucirka LM**, Peters TG, Segev DL. Impact of donor hepatitis C virus infection status on death and need for liver transplant in hepatitis C virus-positive kidney transplant recipients. *Am J Kidney Dis* 2012; **60**: 112-120 [PMID: 22560841 DOI: 10.1053/j.ajkd.2012.03.015]

16 **Durand CM**, Bowring MG, Brown DM, Chattergoon MA, Massaccesi G, Bair N, Wesson R, Reyad A, Naqvi FF, Ostrander D, Sugarman J, Segev DL, Sulkowski M, Desai NM. Direct-Acting Antiviral Prophylaxis in Kidney Transplantation From Hepatitis C Virus-Infected Donors to Noninfected Recipients: An Open-Label Nonrandomized Trial. *Ann Intern Med* 2018; **168**: 533-540 [PMID: 29507971 DOI: 10.7326/M17-2871]

17 **Goldberg DS**, Abt PL, Blumberg EA, Van Deerlin VM, Levine M, Reddy KR, Bloom RD, Nazarian SM, Sawinski D, Porrett P, Naji A, Hasz R, Suplee L, Trofe-Clark J, Sicilia A, McCauley M, Farooqi M, Gentile C, Smith J, Reese PP. Trial of Transplantation of HCV-Infected Kidneys into Uninfected Recipients. *N Engl J Med* 2017; **376**: 2394-2395 [PMID: 28459186 DOI: 10.1056/NEJMc1705221]

18 **Fabrizi F**, Martin P, Dixit V, Messa P. Meta-analysis of observational studies: hepatitis C and survival after renal transplant. *J Viral Hepat* 2014; **21**: 314-324 [PMID: 24716634 DOI: 10.1111/jvh.12148]

19 **Rostami Z**, Nourbala MH, Alavian SM, Bieraghdar F, Jahani Y, Einollahi B. The impact of Hepatitis C virus infection on kidney transplantation outcomes: A systematic review of 18 observational studies: The impact of HCV on renal transplantation. *Hepat Mon* 2011; **11**: 247-254 [PMID: 22087151]

20 **Yuan Q**, Hong S, Perez-Ortiz A, Roth E, Chang DC, Madsen JC, Elias N. Effect of Recipient Hepatitis C Status on Outcomes of Deceased Donor Kidney Transplantation. *J Am Coll Surg* 2020; **230**: 853-861.e3 [PMID: 32035979 DOI: 10.1016/j.jamcollsurg.2019.12.039]

21 **Austin PC**. The use of propensity score methods with survival or time-to-event outcomes: reporting measures of effect similar to those used in randomized experiments. *Stat Med* 2014; **33**: 1242-1258 [PMID: 24122911 DOI: 10.1002/sim.5984]

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