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Contents

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Editorial Board Member of *World Journal of Transplantation*, Gerardo Cazzato, MD, PhD, IFCAP, Department of Emergency and Organ Transplantation, University of Bari "Aldo Moro", Bari 70124, Italy. gerardo.cazzato@uniba.it

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EDITORIAL

Is the near coming xenotransplantation era relieving us from needing to look for more non-living organ donors?

Fernando M Gonzalez, Francisca del Rocío Gonzalez

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Fernando M Gonzalez, Department of Nephrology, Faculty of Medicine, Universidad de Chile, Santiago 7500922, Chile

Francisca del Rocío Gonzalez, Web Intelligence Centre, Faculty of Physics and Mathematical Sciences, Universidad de Chile, Santiago 8370397, Chile

Corresponding author: Fernando M Gonzalez, MD, Full Professor, Department of Nephrology, Faculty of Medicine, Universidad de Chile, Av. Salvador 486, Providencia, Santiago 7500922, Chile. fgonzalf@uc.cl

Abstract

Despite organ transplantation being the most successful treatment for end-stage organ dysfunction, the number of annual solid organ transplantations is much lower than that required to satisfy the demand of patients on waiting lists. The explanation for this phenomenon is the relative scarcity of non-living organ donors due to several factors, such as: (1) Late arrival of patients with a neurocritical condition to an emergency service; (2) lack of detection of those patients as possible organ donors by health professionals dedicated to procurement or by clinicians at emergency and intensive care units, for instance; (3) late transfer of the patient to an intensive care unit to try to recover their health and to provide hemodynamic, ventilatory, and metabolic support; (4) lack of confirmation of the physiological status of the possible donor; (5) late or incorrect positive diagnosis of the subject's death, either due to brain or cardiac death; (6) difficulty in obtaining legal authorization, either by direct relatives or by the authority, for the extraction of organs; and (7) deficient retrieval surgery of the organs actually donated. The recent reports of relatively successful xenotransplants from genetically modified pigs open the possibility to fix this mismatch between supply and demand, but some technical (organ rejection and opportunistic infections), and economic issues, still remain before accepting a progressive replacement of the organ sources for transplantation. An approximate economic cost analysis suggests that the hypothetical acquisition cost of any genetically modified pig derived organ is high and would not even satisfy the solid organ demand of the wealthiest countries.

Key Words: Organ donation; Xenotransplantation; Procurement; Kidney transplantation; Costs

Core Tip: The recent promising xenotransplants derived from genetically modified pigs (heart and kidneys) will open a new discussion: to maintain and improve human non-living organ procurement or invest in the development of solid xenotransplant clinical services. Issues to be solved before reaching that point will be immunologic (preventing acute and chronic graft rejection), opportunistic infections from pigs (for example, porcine cytomegalovirus) and economic (how to finance and afford those technically complex organs for the population).

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INTRODUCTION

The recent promising xenotransplants derived from genetically modified pigs (heart and kidneys) will open a new discussion: To maintain and improve human non-living organ procurement or invest in the development of solid xenotransplant clinical services. Issues to be solved before reaching that point will be immunologic (preventing acute and chronic graft rejection), opportunistic infections from pigs (for example, porcine cytomegalovirus) and economic (how to finance and afford those technically complex organs for the population).

Solid organ transplantation has clearly improved medical performance in terms of the treatment of end-stage organ failure, as in the case of kidney, liver, or heart failure, among others. Consequently, it has improved the survival and quality of life of patients who suffer from those diseases[1]. Nevertheless, the main limitation in transplanting all patients in need is the availability of donors[2].

For many years it has been suggested that xenotransplantation might provide a solution to the imbalance between the demand and supply of organs for transplantation[3], but it has remained a theoretical option. The recent experiences of heart and kidney implants from genetically modified pigs, however, could mean that solving this imbalance may now be a real possibility and, therefore, it could mean that the activity of searching for and procuring organs, particularly from non-living donors, could decline[4-6].

However, this issue is still a subject of extensive technical considerations.

The prevalence of end-stage kidney, liver, or heart diseases increases as a country's population ages. Age-related chronic diseases appear along with this shift, and the medical treatments in use allow more patients to survive the acute phases of those diseases. As a consequence of this, as well as due to general improvement of road safety measures, potential organ donors no longer come from young subjects who die due to car accidents or trauma, but increasingly older adults and, often, with prevalent chronic diseases that reduce the functionality of the organs to be donated[7]. This could explain, in part, the asymmetries in organ donation rates in different countries, even when they are culturally similar, as occurs, for example, in those countries belonging to Latin America or those belonging to Western Europe[8].

If we analyze the figures of non-living donors in the world, we will see that there are marked differences between countries, ranging from 0.4 donors per million population (pmp) in the Dominican Republic or 4.4 pmp in Greece, to 38 pmp in the United States or Spain[8]. This implies that there are significant growth opportunities in the global procurement activity: Carrying out comparative studies of the realities of the procurement process between different countries and attempting to replicate the "best practices" of the leading countries could, as a conservative estimate, be enough to increase the global donation rate in America and Europe to 15-20 pmp, and could, thinking more ambitiously, be enough to even reach the leading countries[8].

The central question derived from the previous paragraph is why there are so many differences in countries' donation rates. In this regard, the procurement process (framed under a local legislation supportive towards organ donation) can be outlined as a series of stages that include: (1) Arrival of patients with a neurocritical condition (trauma or stroke, for example) to an emergency service; (2) Detection of that patient as a possible organ donor by health professionals dedicated to procurement (organ procurement organizations in the United States or procurement coordinators in Spain), or by clinicians at emergency and intensive care units, for instance; (3) Transfer of the patient to an intensive care unit to try to recover their health and to provide hemodynamic, ventilatory, and metabolic support (if there are critical beds available); (4) Confirmation of the physiological status of the possible donor and the organs to be donated — that is, the ruling out of pathological conditions that contraindicate the

subject as a potential donor (for example metastatic neoplastic disease, encephalitis due to transmissible viruses (rabies), and others); (5) Positive diagnosis of the subject's death, either due to brain or circulatory death; (6) Legal authorization, either by direct relatives or by the authority, for the retrieval of organs; and (7) Procurement surgery of the organs actually donated.

In any of these phases, effective donation is likely to be foiled. During the first year of the severe acute respiratory syndrome coronavirus 2 pandemic, in 2020, we witnessed a natural experiment in which it was possible to observe how the disease associated with the novel coronavirus disease 2019, reduced the arrival of patients with serious trauma or strokes to emergency services[9-11]; how hospitalizations in critical care units were reduced; and how the activity of local procurement units decreased, along with surgical retrieval activities and donation authorizations by family members[12]. These situations together explain why donation and transplant figures plummeted in several countries, including those in the United States and Spain[12,13].

If the failing stages of the process in each country could be improved, it would be feasible to increase their effective donation rates. For example, stage 1 could be improved with the implementation of rescue ambulance systems; stages 2 and 3 could be facilitated with the use of information technology [14]; stages 4 and 5 could benefit from the inclusion of trained professionals; and stage 6 could be improved by including experts in breaking bad news in the procurement team. These are general examples, but performing a careful benchmark analysis of the procurement stages in each country should provide even better improvement opportunities for each country, since the good initiatives observed in some countries could be adapted for other countries.

How much do the proposed improvements cost? Given that the main difficulty is setting up the procurement process and most of the countries have already carried out work to that end, the marginal cost should not be very high, since there would be no significant barriers to implementation of improvements from the economic point of view, and their cost could be easily apportioned by increasing organ implants and the savings that they imply for the health systems of each country.

On the other hand, we have the opportunity to use organs from animals with similarities to humans. Historically, at the beginning of the 20th century, xenotransplantation was conceived as the solution to replace failing organs[15]. However, all the experiences concluded that, although the surgical technique allowed the surgeons to successfully implant the organs, they irremediably did not function as a result of diffuse thrombosis in all the graft vessels. It was not until the second half of the same century when it was described that the cause of thrombosis was mediated by preformed antibodies in the recipients, against vascular antigens from the donor animal. This type of hyperacute rejection was impossible to overcome even with aggressive immunosuppression techniques in non-human models[16]. The second limitation was local thrombosis derived from immune aggression and an exaggerated activation of the complement system[17].

In fact, the cardiac graft implanted in January 2022 came from a transgenic pig with 10 genetic modifications: Three knock-outs of genes associated with cell membrane carbohydrates (galactose alpha-1,3-galactose, Sda blood group antigen and N-glycolylneuraminic acid), a knock-out for the growth hormone receptor, increased expression of CD-46 antigens and "decay accelerating factor" to mitigate the activation of the complement system, expression of thrombomodulin and protein C genes to reduce thrombogenicity, and finally, anti-inflammatory proteins CD-47 and heme-oxygenase-1[5]. The three kidneys implanted on similar dates somewhat later had similar genetic modifications, although in smaller numbers[4,6]. In all these cases, neither hyperacute rejection nor massive intraparenchymal thrombosis occurred, although elements of thrombotic microangiopathy were indeed observed. An additional element which requires cautious is the eventual transmission of infectious agents typical of pigs, such as the porcine-derived retrovirus, or the porcine cytomegalovirus, among others[4-6].

Despite these complications and the disastrous outcome of the recipient with the heart graft, these preliminary experiences are certainly auspicious and appropriate clinical studies will surely elucidate the real usefulness of xenotransplants from genetically modified pigs raised in highly controlled environments.

Assuming that this new xenotransplantation continues to develop favorably, one wonders how much each organ will cost and how many real patients it will benefit, with "real patients" being those who are not part of a clinical trial and who, therefore, must pay (themselves or their insurers) for the xenotransplantation and its associated pharmacological treatments.

One way to calculate the aforementioned cost could be using the economic benefit for society of transplantation with a traditional non-living donor as a reference, and based on these numbers, roughly estimate the value that each heart or kidney could have.

The cost per quality adjusted life year (QALY) of a heart transplant in someone who is on the waiting list receiving exclusive pharmacological therapy is close to US$97000, a figure that increases to US$226000 if the person waiting is connected to a left ventricular assist device[18]. If we consider that in the United States a figure of US$100000/QALY is considered acceptable for a heart transplant, this treatment would be economically viable only in the first group of patients and would therefore force transplant teams to enroll those who suffer from advanced heart failure early. For kidney transplantation, the cost per QALY is slightly less than US$50000[19,20].

Table 1 Organ procurement process and opportunities for improvement

Process	Improving opportunities
(1) Arrival of patients with a neurocritical condition to an emergency service	Implementation and improvement of rescue ambulance systems
(2) Identification as a possible organ donor by health professionals	Training health professionals, use of information technology
(3) Transfer to an intensive care unit to provide full support	Use of information technology, critical care bed selective dedication
(4) Confirmation of suitability to be a donor	Inclusion of trained health professionals
(5) Diagnosis of the subject's death, either due to brain or circulatory death	Availability of on-site neurologists and perfusionist specialists.
(6) Procurement surgery of the organs actually donated	Inclusion of experts in breaking bad news in the procurement team

The problem is, however, that the US$100000/QALY threshold is not necessarily valid for other countries. In fact, the willingness to pay of each country is correlated with its gross domestic product (GDP) per capita and, therefore, the cost-effectiveness analyses and the QALYs improved by a successful transplant should be adjusted for each country. By doing this, it becomes clear that the US$100000 for the United States does not compare fairly with the US$ < 10000 for Thailand or the US$20000-30000 for various South American and European countries which, in turn, also have lower GDP per capita[21].

The implications of the economic data presented are that the price to be paid for a desirable new good correlates with the expected benefit that good is estimated to provide. The price to be paid also correlates with the need for the return on investment demanded by the shareholders who own the companies that develop these improved goods. Finally, these two figures should be adjusted for the risk that such assets have to be successful in the market[22]. If we use the market price of onasemnogene abeparvovec-xioi for spinal muscular atrophy of €1.9 million as a reference, we may find that an independently calculated price would be close to €1.7 million[22]. The €200.000 (10% of €1.9 million) difference between both prices is, in the best of cases, an error in the calculation methodology or, in the worst scenario, an appropriation of "consumer surplus". The latter could imply that the price of an organ from a genetically modified pig would be close to the total QALY gained from the transplant (QALY/year multiplied by additional years of graft or host survival) plus a "consumer surplus" of 10%, which could be no less than US$500000 for a heart or US$250000 for a kidney (assuming that both grafts last only 5 years, which is a very conservative estimate) which, obviously, could be paid by very few people only from the wealthiest countries and certainly even the world strongest public health systems could not finance those transplants[21].

CONCLUSION

So, going back to our initial question: Is the near coming xenotransplantation era relieving us from having to look for more non-living organ donors? Our answer is "not at the moment"; even thinking that xenotransplants will have the same survival as allografts from human donors, their market prices will be prohibitive in many countries, forcing those countries to necessarily continue improving their actual procurement processes from non-living human donors (Table 1). Wealthy countries, however, are likely to be able to improve their transplant rates, at least in the short term, with organs from genetically modified pigs raised in highly controlled environments. Nevertheless, as the xenotransplantation technology and production processes improve, the prices will decrease allowing more consumers to afford a genetically modified xenograft. We did not include a discussion on allografts from living donors as besides the costs, it raises an ethical dilemma that was out of our scope.

FOOTNOTES

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REFERENCES

1 **Black CK**, Termanini KM, Aguirre O, Hawksworth JS, Sosin M. Solid organ transplantation in the 21st century. *Ann Transl Med* 2018; **6**: 409 [PMID: 30498736 DOI: 10.21037/atm.2018.09.68]
2 **Lewis A**, Koukoura A, Tsianos GI, Gargavanis AA, Nielsen AA, Vassiliadis E. Organ donation in the US and Europe: The supply *vs* demand imbalance. *Transplant Rev (Orlando)* 2021; **35**: 100585 [PMID: 33071161 DOI: 10.1016/j.trre.2020.100585]
3 **Ekser B**, Ezzelarab M, Hara H, van der Windt DJ, Wijkstrom M, Bottino R, Trucco M, Cooper DK. Clinical xenotransplantation: the next medical revolution? *Lancet* 2012; **379**: 672-683 [PMID: 22019026 DOI: 10.1016/S0140-6736(11)61091-X]
4 **Porrett PM**, Orandi BJ, Kumar V, Houp J, Anderson D, Cozette Killian A, Hauptfeld-Dolejsek V, Martin DE, Macedon S, Budd N, Stegner KL, Dandro A, Kokkinaki M, Kuravi KV, Reed RD, Fatima H, Killian JT Jr, Baker G, Perry J, Wright ED, Cheung MD, Erman EN, Kraebber K, Gamblin T, Guy L, George JF, Ayares D, Locke JE. First clinical-grade porcine kidney xenotransplant using a human decedent model. *Am J Transplant* 2022; **22**: 1037-1053 [PMID: 35049121 DOI: 10.1111/ajt.16930]
5 **Griffith BP**, Goerlich CE, Singh AK, Rothblatt M, Lau CL, Shah A, Lorber M, Grazioli A, Saharia KK, Hong SN, Joseph SM, Ayares D, Mohiuddin MM. Genetically Modified Porcine-to-Human Cardiac Xenotransplantation. *N Engl J Med* 2022; **387**: 35-44 [PMID: 35731912 DOI: 10.1056/NEJMoa2201422]
6 **Montgomery RA**, Stern JM, Lonze BE, Tatapudi VS, Mangiola M, Wu M, Weldon E, Lawson N, Deterville C, Dieter RA, Sullivan B, Boulton G, Parent B, Piper G, Sommer P, Cawthon S, Duggan E, Ayares D, Dandro A, Fazio-Kroll A, Kokkinaki M, Burdorf L, Lorber M, Boeke JD, Pass H, Keating B, Griesemer A, Ali NM, Mehta SA, Stewart ZA. Results of Two Cases of Pig-to-Human Kidney Xenotransplantation. *N Engl J Med* 2022; **386**: 1889-1898 [PMID: 35584156 DOI: 10.1056/NEJMoa2120238]
7 **Hassanain M**, Simoneau E, Doi SA, Aljiffry M, Aloraini A, Madkhali A, Metrakos P. Trends in brain-dead organ donor characteristics: a 13-year analysis. *Can J Surg* 2016; **59**: 154-160 [PMID: 26999472 DOI: 10.1503/cjs.007415]
8 **IRODaT**. International Registry on Organ Donation and Transplantation. [cited 1 Apr 2018]. In: IRODaT [Internet]. Available from: http://irodat.org//img/database/pdf/Irodat%20December_final%202020.pdf
9 **Zhao J**, Li H, Kung D, Fisher M, Shen Y, Liu R. Impact of the COVID-19 Epidemic on Stroke Care and Potential Solutions. *Stroke* 2020; **51**: 1996-2001 [PMID: 32432997 DOI: 10.1161/STROKEAHA.120.030225]
10 **Staunton P**, Gibbons JP, Keogh P, Curtin P, Cashman JP, O'Byrne JM. Regional trauma patterns during the COVID-19 pandemic. *Surgeon* 2021; **19**: e49-e52 [PMID: 32893129 DOI: 10.1016/j.surge.2020.08.003]
11 **Bres Bullrich M**, Fridman S, Mandzia JL, Mai LM, Khaw A, Vargas Gonzalez JC, Bagur R, Sposato LA. COVID-19: Stroke Admissions, Emergency Department Visits, and Prevention Clinic Referrals. *Can J Neurol Sci* 2020; **47**: 693-696 [PMID: 32450927 DOI: 10.1017/cjn.2020.101]
12 **Ahmed O**, Brockmeier D, Lee K, Chapman WC, Doyle MBM. Organ donation during the COVID-19 pandemic. *Am J Transplant* 2020; **20**: 3081-3088 [PMID: 32659028 DOI: 10.1111/ajt.16199]
13 **Domínguez-Gil B**, Coll E, Fernández-Ruiz M, Corral E, Del Río F, Zaragoza R, Rubio JJ, Hernández D. COVID-19 in Spain: Transplantation in the midst of the pandemic. *Am J Transplant* 2020; **20**: 2593-2598 [PMID: 32359194 DOI: 10.1111/ajt.15983]
14 **González F**, Vera F, González F, Velásquez JD. Kefuri: A novel technological tool for increasing organ donation in Chile. *IEEE* 2020; 470-475 [DOI: 10.1109/WIIAT50758.2020.00070]
15 **Schlich T**, Lutters B. Historical perspectives on xenotransplantation. *Lancet* 2022; **399**: 1220-1221 [PMID: 35339217 DOI: 10.1016/S0140-6736(22)00529-3]
16 **Lin SS**, Weidner BC, Byrne GW, Diamond LE, Lawson JH, Hoopes CW, Daniels LJ, Daggett CW, Parker W, Harland RC, Davis RD, Bollinger RR, Logan JS, Platt JL. The role of antibodies in acute vascular rejection of pig-to-baboon cardiac transplants. *J Clin Invest* 1998; **101**: 1745-1756 [PMID: 9541506 DOI: 10.1172/JCI2134]
17 **Cooper DKC**, Hara H, Iwase H, Yamamoto T, Wang ZY, Jagdale A, Bikhet MH, Nguyen HQ, Foote JB, Paris WD, Ayares D, Kumar V, Anderson DJ, Locke JE, Eckhoff DE. Pig kidney xenotransplantation: Progress toward clinical trials. *Clin Transplant* 2021; **35**: e14139 [PMID: 33131148 DOI: 10.1111/ctr.14139]
18 **Long EF**, Swain GW, Mangi AA. Comparative survival and cost-effectiveness of advanced therapies for end-stage heart failure. *Circ Heart Fail* 2014; **7**: 470-478 [PMID: 24563450 DOI: 10.1161/CIRCHEARTFAILURE.113.000807]
19 **Yang F**, Liao M, Wang P, Yang Z, Liu Y. The Cost-Effectiveness of Kidney Replacement Therapy Modalities: A Systematic Review of Full Economic Evaluations. *Appl Health Econ Health Policy* 2021; **19**: 163-180 [PMID: 33047212 DOI: 10.1007/s40258-020-00614-4]
20 **Yang F**, Liao M, Wang P, Liu Y. Cost-effectiveness analysis of renal replacement therapy strategies in Guangzhou city, southern China. *BMJ Open* 2021; **11**: e039653 [PMID: 33550227 DOI: 10.1136/bmjopen-2020-039653]
21 **Cameron D**, Ubels J, Norström F. On what basis are medical cost-effectiveness thresholds set? *Glob Health Action* 2018; **11**: 1447828 [PMID: 29564962 DOI: 10.1080/16549716.2018.1447828]

22 **Nuijten M**. Pricing Zolgensma - the world's most expensive drug. *J Mark Access Health Policy* 2022; **10**: 2022353 [PMID: 34992762 DOI: 10.1080/20016689.2021.2022353]

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MINIREVIEWS

Review of heart transplantation from hepatitis C-positive donors

Palak Patel, Nirav Patel, Fahad Ahmed, Jason Gluck

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Palak Patel, Department of Cardiology, West Roxbury VA Center, West Roxbury, MA 02132, United States

Nirav Patel, Department of Cardiology, University of Connecticut, Harford Hospital, Hartford, CT 06102, United States

Nirav Patel, Department of Cardiology, University of California, CA 90065, United States

Fahad Ahmed, Department of Internal Medicine, Hartford Hospital, Hartford, CT 06106, United States

Jason Gluck, Advanced Heart Failure, Hartford Hospital, Hartford, CT 06102, United States

Corresponding author: Jason Gluck, DO, FACC, Attending Doctor, Chief Physician, Advanced Heart Failure, Hartford Hospital, 85 Seymour Street, Hartford, CT 06102, United States. jason.gluck@hhchealth.org

Abstract

Significant scarcity of a donor pool exists for heart transplantation (HT) as the prevalence of patients with end-stage refractory heart failure is increasing exceptionally. With the discovery of effective direct-acting antiviral and favorable short-term outcomes following HT, the hearts from hepatitis C virus (HCV) patient are being utilized to increase the donor pool. Short-term outcomes with regards to graft function, coronary artery vasculopathy, and kidney and liver disease is comparable in HCV-negative recipients undergoing HT from HCV-positive donors compared to HCV-negative donors. A significant high incidence of donor-derived HCV transmission was observed with great success of achieving sustained viral response with the use of direct-acting antivirals. By accepting HCV-positive organs, the donor pool has expanded with younger donors, a shorter waitlist time, and a reduction in waitlist mortality. However, the long-term outcomes and impact of specific HCV genotypes remains to be seen. We reviewed the current literature on HT from HCV-positive donors.

Key Words: Heart transplant; Hepatitis C-positive donors; Direct-acting antiviral; Coronary allograft vasculopathy; Allograft rejection

Core Tip: Given the favorable preliminary data and ongoing opioid epidemic, the utilization of hepatitis C virus-positive hearts is on the rise, which is aiding in the closure of the gap between heart transplantation candidates and donors. Additionally, with future studies evaluating long-term outcomes and standardization of direct-acting antiviral therapy, more transplant centers will accept hepatitis C virus-positive organs.

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INTRODUCTION

Heart failure (HF) prevalence is increasing, with 6.2 million adults diagnosed from 2013 to 2016 compared to 5.7 million from 2009 to 2013. The prevalence is estimated to increase to more than 8 million by 2030[1,2]. In 10%-15% of patients, end-stage refractory HF will develop requiring advanced therapies including orthotopic heart transplantation (OHT) or durable mechanical support therapies[2,3]. There is a substantial mismatch between donors and recipients as there is an increasing prevalence of HF over the years with a constant rate of OHTs performed. During 2018, 268 patients died while waiting for OHT with 3883 patients being added to the transplant list and 3440 OHTs performed[4]. Expanding the donor pool with utilization of organs from hepatitis C virus (HCV)-positive individuals is an opportunity to close this gap.

Historically, HCV-positive donors were not considered due to high risk of HCV transmission, ineffective and unsafe HCV treatments, and overall inferior survival following heart transplantation (HT)[5,6]. With the discovery of direct-acting antivirals (DAAs), the donor pool has expanded with the addition of HCV-positive donors due to great success of treating HCV, limited interaction with immunosuppression, and optimal short-term outcomes following HT. Data of long-term outcomes are scarce, and there is a wide variation with the use of different DAA agents and optimal initiation among the studies. Therefore, we reviewed the current literature of HT from HCV-positive donors in HCV-negative recipients and discussed the epidemiology, outcomes of HT in the pre- and post-DAA era, complications, and potential barriers for more widespread utilization of HCV-positive donors.

MATERIALS AND METHODS

We searched the terms "heart transplant," "organ transplant," "transplant," and "hepatitis C" in various combinations in Medline through November 2021.

DONOR HCV STATUS CLASSIFICATION

HCV infection in donors can be classified using two serological markers: HCV antibodies (Ab), which typically present after 6-8 wk of exposure to HCV[7]; and nucleic acid testing (NAT), which is present during an active infection occurring after 3-4 d of exposure to HCV[8,9].

HCV Ab-positive NAT-negative

Donors that are HCV Ab-positive and NAT-negative have spontaneously cleared the virus or were treated with antiretrovirals. There is low to no risk of transmission of the virus to the HT recipient[10,11].

HCV Ab-positive NAT-positive

Donors that are HCV Ab-positive and NAT-positive have an ongoing infection or chronic active hepatitis. There is a high risk of HCV transmission to the HT recipient.

HCV Ab-negative NAT-positive

Donors that are HCV Ab-negative and NAT-positive have an acute HCV infection without adequate time for Ab production against HCV. There is a high risk of transmission in solid organ transplant recipients.

HCV Ab-negative NAT-negative

Donors that are HCV Ab-negative and NAT-negative are in the eclipse period (within a week) of acquisition of HCV when NAT is not detectable with negative HCV Ab. This serological classification typically includes high-risk donors and intravenous drug users (IVDU). The potential of such donors is 32.4 per 10000 in the United States[12].

EPIDEMIOLOGY AND HCV-POSITIVE DONOR POOL

HCV, a single-stranded RNA virus, is the most frequent blood-borne infection common among IVDUs [13,14]. The World Health Organization reports that the HCV worldwide prevalence is 71 million with an annual incidence of 50300 in 2018 in the United States and a 3-fold increase from 2009 to 2018 with a rate of 0.3 to 1.2 per 100000 population[15].

The prevalence of HCV infection among IVDUs increased from 28% in 2008 to 40% in 2015 in North America[14,16], and it is estimated to increase by 43% by 2030[17]. The pool of HCV-positive donors is increasing by 10-fold due to the current opioid epidemic in the United States and to the increase in deaths related to overdose since 2000, which is on the rise from 15.1% in 2010 to 26.1% in 2018[18]. In 2020, 81230 deaths due to opioid overdose increased by 38.4% over a 12-mo period from June 2019 to May 2020. These younger victims without significant comorbidities are a potential for prolonged organ survival following HT[19,20]. The United Network of Organ Sharing reported HT from HCV-positive donors is on the rise from 247 to 362 HT from HCV-positive donors from 2018 to 2019. A single center reported doubling their transplant volume by utilizing HCV-positive hearts from 130 to 260 from 2013 to 2018, with a reduced mean waiting period of 4 d[21]. Nationwide utilization of HCV-positive donors can increase the number of HTs resulting in reduction in the waiting period and closing the gap between donors and recipients.

HCV-POSITIVE TRANSPLANT IN THE PRE-DAA ERA

Limited data are available on HT from HCV-positive donors in the pre-DAA era (Table 1)[5,22-31]. Studies reported a high transmission rate of HCV with an inferior survival rate of 70% at 1 year compared to 89% in controls[5] and a 10-year survival rate of 25% in the HCV-positive group *vs* 53% in controls[31] due to a higher incidence of cardiac allograft rejections, cardiac allograft vasculopathy, progression to chronic HCV infection, and liver disease[5]. Haji *et al*[30] reported HCV seropositivity as an independent risk factor for overall mortality by 2.8-fold and increased incidence of cardiac allograft vasculopathy by 3-fold. Historically, interferon-based therapy was being utilized for HCV infection, which demonstrated poor tolerability and a risk of interaction with immunosuppressants[32]. Due to these complications and decreased overall survival, the use of HCV-positive donors diminished until recent years following the discovery of DAAs.

HCV-POSITIVE TRANSPLANT IN THE POST-DAA ERA

In 2011, DAAs were introduced demonstrating high efficacy in eradicating HCV and achieving remission[33]. In 2013, the combination of sofosbuvir and simeprevir achieved 92% sustained virologic response (SVR) at 12 wk after completion of the antiretroviral regimen without the addition of historical medications such as interferon and ribavirin[34]. In 2014, a four-drug combination was approved for acute HCV infection with ombitasvir, paritaprevir, ritonavir, and dasabuvir, which achieved 100% SVR [35]. These DAAs used in post-transplant recipients achieved comparable SVR to non-transplanted patients[11,33,36-38]. The overall survival in HCV-negative recipients receiving hearts from HCV-positive donors is comparable to HCV-negative donors (Table 2)[10,11,21,33,36,37,39-52].

POTENTIAL COMPLICATIONS OF HT IN HCV-NEGATIVE RECIPIENT FROM HCV-POSITIVE DONOR

HCV contraction

HCV contraction is 82% to 100% from HCV NAT-positive donors. Schlendorf *et al*[11] demonstrated 95.7% of donor-derived HCV from HCV NAT-positive donors, and the risk of acquiring HCV from HCV Ab-positive and NAT-negative donors is low. One study demonstrated no viremia up to 1 year in 10 HCV-negative recipients receiving hearts from NAT-negative donors[11]. The risk of developing HCV is variable across all the studies, but it appears to be reduced with the use of HCV NAT-negative

Table 1 Heart transplantation from hepatitis C virus-positive donors in the pre-direct-acting antivirals era

Ref.	Study type	Study group	Outcome
Pereira *et al*[22], 1991	Retrospective, observational	6 HCV-negative recipients underwent HT from HCV Ab-positive donors	50% of recipients acquired HCV infection and higher incidence of liver disease was noted
Hayashi *et al*[23], 1994	Case Report	46-yr-old male with end- stage cardiomyopathy receiving HT from HCV Ab-positive donor	Fulminant liver failure and patient died in less than 2 yr
Lim *et al*[24], 1994	Case Report	51-yr-old male undergoing HT from HCV Ab-positive donor	Fulminant hepatitis, which was treated successfully with interferon-based therapy; Died due to pulmonary aspergillosis
Zein *et al*[25], 1995	Observational	1 HCV-negative recipient underwent HT from HCV Ab-positive donors	Cholestatic liver disease and liver failure-related mortality
Pfau *et al*[26], 2000	Retrospective	5 recipients without HCV infection underwent HT with HCV Ab-positive donors	1 out of 5 recipients became HCV Ab-positive; Elevated liver enzymes were noted and normalized by 12 mo
Marelli *et al*[27], 2002	Retrospective	20 recipients (10 were status I and 10 were status II) without HCV infection underwent HT from HCV NAT-positive donors	Overall survival was 90% in status I and 80% in status II group; Higher incidence of rejection and CAV were noted
File *et al*[5], 2003	Retrospective	10 recipients without HCV infection underwent HT from HCV-positive and NAT-positive	All recipients became HCV NAT-positive, 6 out of 9 recipients developed hepatitis and severe liver injury occurring in 2 patients; Inferior survival of 70% was noted
Gudmundsson *et al*[28], 2003	Retrospective	7 recipients without HCV infection underwent HT from HCV Ab-positive donors	Overall 5-yr survival was 71.4%; 3 developed chronic active hepatitis, 1 died from liver failure
Wang *et al*[29], 2004	Retrospective	4 recipients without HCV infection underwent HT with HCV Ab-positive donors	1 recipient became HCV Ab-positive without clinical hepatitis
Haji *et al*[30], 2004	Retrospective	34 recipients without HCV infection underwent HT from HCV Ab-positive donors and evaluated overall mortality and CAV	75% of recipients became HCV seropositive; Higher mortality by 2.8-fold and accelerated CAV by 3.0-fold was noted compared to the control group
Gasink *et al*[31], 2006	Retrospective, registry-based, cohort	261 recipients without HCV infection underwent HT with HCV Ab-positive donor	Overall inferior 1-yr, 5-yr, and 10-yr survival compared to control; Higher incidence of liver disease and CAV were noted

Ab: Antibodies; CAV: Cardiac allograft vasculopathy; HT: Heart transplant; HCV: Hepatitis C Virus; NAT: Nucleic acid test.

donors compared to HCV NAT-positive donors. All patients with donor-derived HCV achieved SVR across all studies with DAA treatment.

Cardiac allograft rejection

Transplant allograft rejection, either cellular or antibody-mediated, is associated with poor allograft survival and increased mortality[53]. In the pre-DAA era, the studies demonstrated an increased rate of allograft rejection in HT recipients from HCV-positive donors, and the risk was directly associated with viremia post-HT[5,27,54]. Two potential pathways are linked with allograft rejection from HCV infection. The first is the activation of lymphocytes, predominately T cells, through direct and indirect pathways affecting the endothelium, and the second is direct allograft injury is mediated by upregulation of interferon-alpha and apoptotic and proliferative genes[55].

The incidence of allograft rejection was 58% in 12 HCV-negative recipients undergoing HT from HCV NAT-positive donors compared to 30% in 13 HCV NAT-negative donors with a mean follow-up of 147 d[56]. Another study demonstrated allograft rejection of 12% and 3% in HCV-negative recipients from HCV Ab-positive NAT-positive compared to HCV Ab-positive NAT-negative donors at 180 d follow-up, respectively. The time to first event of rejection was earlier in recipients with NAT-positive compared to NAT-negative donors demonstrating viremia directly played a role in acute allograft rejection[54]. Schlendorf *et al*[42] reported two events of acute cellular rejection requiring treatment in recipients who became viremic at a mean of 4 d, and the initiation of DAAs was delayed as they were introduced on an outpatient basis at a mean of 33 d. Therefore, early detection and aggressive implementation of DAAs are required to decrease the incidence of allograft rejection. Overall short-term survival in the current era is similar, but the long-term risk of allograft rejection remains to be seen.

Cardiac allograft vasculopathy

Cardiac allograft vasculopathy (CAV) is the major cause of morbidity and mortality following HT with an incidence of 8% at 1-year and 50% at 10-year[57], and the risk of CAV is increased by 3-fold in donor-derived HCV recipients[30]. The pathophysiology of CAV is not completely understood but presumed to be immune-mediated endothelial injuries observed with elevated intracellular adhesion molecule-1 in HCV-infected patients[58]. The risk was observed to be further increased with B cell cross-reactivity in

Table 2 Heart transplantation from hepatitis C virus-positive donors in the post-direct-acting antivirals era

Ref.	Study type	Study group	Outcome
Gottlieb *et al* [33], 2017	Case report	1 recipient without HCV infection underwent HT with HCV NAT-positive donor; treated with sofosbuvir/velpatasvir for 12 wk	A recipient acquired HCV infection on day 9, and it was cured at 12 wk
Jawad *et al* [39], 2018	Case report	1 recipient without HCV infection underwent HT with HCV-positive donor; in 2014, after approval of DAA, the patient was treated with sofosbuvir and daclatasvir for 8 mo	Patient acquired HCV infection in 2010 without any clinical sequelae and with treatment of DAA in 2014 it was eradicated; Progressive CAV was noted
Moayedi *et al* [40], 2018	Single center, single arm	2 recipients without HCV infection underwent HT with HCV NAT-positive donors	Low cost of HCV treatment compared to alternative treatment with mechanical cardiac support; Potential for 300-500 more HT annually noted
Moayedi *et al* [41], 2018	Retrospective, registry-based	From 2013 to 2017, 64 (5%) underwent HT from HCV-positive donors; Total of 1305 HCV-positive donors were recovered during this time period	Comparable survival was noted in recipients of HCV-positive donors to HCV-negative donors
Patel *et al*[10], 2018	Single center, single arm case series	14 HCV-negative recipients underwent HT in 2017 from HCV Ab-positive and NAT-negative donors	None developed HCV infection
Schlendorf *et al*[42], 2018	Single center, single arm prospective observational case series	13 HCV-negative (1 was treated) recipients underwent HT from HCV-positive donors and treated with DAA	69% of these recipients acquired HCV, and all of them achieved SVR following therapy with DAA except 1 who died due to pulmonary embolism
McLean *et al* [36], 2019	Single arm, single centered, prospective case series	10 HCV-negative recipients underwent HT with HCV NAT-positive donors, treated with elbasvir/grazoprevir after viral detection	Overall 9/10 recipients achieve SVR following DAA; 1 recipient died due to Ab cross-match leading to rejection, graft failure, and multiorgan failure
Woolley *et al* [43], 2019	Non-randomized, single center, prospective trial	8 HCV-negative recipients underwent HT from HCV NAT-positive donors; Treated with sofosbuvir-velpatasvir for 4 wk; Overall survival was compared to 12 recipients undergoing HT from HCV-negative donors	100% SVR was noted; Comparable survival rate at 12 mo in both groups
Frager *et al* [44], 2019	Single arm, single center, prospective trial	6 HCV-negative recipients underwent HT from HCV NAT-positive donors; multiple regimens of DAA were implemented	4 achieved SVR; 5 with 1R-2R rejection and 2 with stable chronic kidney disease; Decreased time on the waiting list noted
Schlendrof *et al*[11], 2019	Single arm, single center, prospective observational case series with a 1-year follow-up	80 HCV-negative recipients underwent HT from HCV Ab-positive and/or NAT-negative donors; Multiple DAA regimens utilized	95.7% of recipients acquired HCV infection from donors with HCV NAT-positive; DAA SVR was achieved in all recipients; No recipients acquired donor-derived HCV from NAT-negative recipients; Comparable 1-yr survival of 90.7% in both groups, and median wait time of 4 d was noted
Reyentovich *et al*[37], 2019	Non-randomized, single center, prospective observational case series	12 HCV-negative recipients underwent HT with HCV NAT-positive donors treated with glecaprevir/pibrentasvir for 8 wk compared to 13 controls undergoing HT from HCV-negative donors	Equivalent survival rate in both groups; Mean waiting period of 62 d noted
Aslam *et al* [45], 2019	Retrospective, single center, observational	21 HCV-negative recipients underwent HT with HCV Ab-positive and NAT-negative or positive donors	All recipients of NAT-positive donors acquired HCV infection; With DAA treatment 100% SVR was achieved; All recipients (2/2) were Ab-positive but NAT-negative and did not acquire HCV infection
Morris *et al* [46], 2019	Single center, retrospective	25 HCV-negative recipients underwent HT from HCV Ab-positive and NAT-positive (n = 23) or negative (n = 2) donors; DAA regimen was implemented, and outcomes were compared to 37 recipients undergoing HT from HCV- negative donors	22 of 23 recipients received hearts from HCV viremia acquired HCV infection; No difference in overall survival, rejection, hospitalization, and CAV between 2 groups; Delay in HCV treatment was due to insurance coverage
Lebeis *et al* [47], 2019	Single center, retrospective	23 HCV-negative recipients underwent HT with HCV-positive donors compared to control group receiving hearts from HCV donors	Recipients receiving preemptive treatment with DAA had preserved early allograft function receiving hearts from HCV-positive donors
Gaj *et al*[48], 2019	Single center, retrospective	Baseline characteristics were assessed in 111 HT; 23 of these organs came from HCV-positive donors	20% of recipients underwent HT from HCV-positive donors, and the donors were younger with a mean of 37 compared to 40 yr old; Short-term outcomes were similar in both groups
Kilic *et al*[21], 2020	Multicenter, retrospective, registry-based	Of 7889 HT, 343 HCV-negative recipients received hearts from HCV-positive donors	1-yr survival rate was indifferent between 2 groups; From 2016-2018, 28% of transplant centers utilized HCV-positive donors
Zhu *et al*[49], 2020	Single center, retrospective	10 HCV-negative recipients underwent HT from HCV-positive donors between 1997-2019	1-yr survival was 80%; 4 recipients acquired donor-derived HCV, and 3 of them demonstrated cure with DAA treatment

McMaster *et al* [50], 2020	Single center, retrospective	12 HCV-negative recipients underwent combined heart and kidney transplant from HCV Ab-positive and 10/12 were NAT-positive donors and were compared to 27 HCV-negative donors	A shorter median waitlist time for HCV-positive organs; Both groups had similar perioperative cardiac and renal function; Creatinine was higher in HCV-positive recipients at 3 mo compared to the control group, but at 1-yr it was similar in both groups; 80% of recipients acquired donor-derived HCV infection, and with DAA treatment 100% SVR was noted
Zalawadiya *et al*[51], 2020	Single center, retrospective	45 HCV-negative recipients underwent HT between 2016-2018 from HCV Ab-positive and NAT-positive donors; Renal function was assessed following transplantation	Data from 23 recipients were available at 12 wk and 18 recipients at 1 yr; No significant change in renal function up to 1-yr was noted
Reyentovich e *et al*[52], 2020	Single center prospective observational	22 HCV-negative recipients underwent HT between 2018-2019 from HCV NAT-positive donors; Data were compared to 28 HCV NAT-negative recipients	All recipients acquired donor-derived HCV; 20 recipients achieved 100% SVR following DAA therapy; Comparable outcomes with Ab-mediated rejection in both groups

Ab: Antibodies; CAV: Cardiac allograft vasculopathy; DAA: Direct acting antiretroviral; HT: Heart transplant; HCV: Hepatitis C Virus; NAT: Nucleic acid test; SVR: Systemic viral response.

HCV-positive heart recipients[30]. CAV has been associated with increased alloimmune response[59,60]. CAV directly affects the longevity of the graft, but treatment with DAAs rapidly clears viremia, and studies have demonstrated no statistically significant risk of CAV at 1 year following HT from HCV-positive donors[11,59]. Zalawadiya *et al*[61] reviewed intracoronary ultrasound of 54 HCV-negative recipients from HCV-positive hearts treated with ledipasvir and sofosbuvir for 12 or 24 wk following HT and up to 1-year follow-up. They found no significant difference in CAV compared to the control group. Schlendrof *et al*[11] also showed that 29 recipients receiving hearts from HCV-positive donors had no statistically significant incidence of CAV compared to HCV-negative donors. All current studies are single centered and small sample size with short-term follow-up of 1 year. However, compared to the pre-DAA era, the evidence shows that there is a decreased reduction in the incidence of CAV secondary to rapid and effective clearance of HCV with DAA-based therapy. Long-term risk of CAV and its impact on graft survival remains to be explored.

Liver disease

A higher incidence of liver disease was noted in the pre-DAA era attributing to increased mortality in HCV-positive recipients[31]. HCV is a known cause of progressive liver disease leading to liver cirrhosis and risk of hepatocellular carcinoma (HCC)[62]. Early eradication of HCV reverses the liver damage that is caused by inflammation from HCV and decreases the incidence of downstream effects. Untreated HCV in transplant patients resulted in fulminant liver failure, cholestatic liver disease, and chronic hepatitis[23-25].

Pre-DAA recipients receiving hearts from HCV-positive donors had higher liver-related mortality with a hazard ratio of 5.9[63]. In immunocompromised hosts, the progression to advanced liver disease and cirrhosis was accelerated by a median of 2 years to 10 years compared to 30 years in immunocompetent individuals[64], and the recipients receiving an anti-lymphocyte preparation peritransplant had a higher risk of liver disease[22].

HCV has 6 different genotypes, with 1 to 4 being the most the common worldwide[65,66]. Genotype 1b and 3b are associated with a higher rate of liver disease compared to other genotypes[67,68]. Genotype 2 carriers have an improved overall HCC survival, and other genotypes can lead to progressive liver disease and HCC[69]. Both antiviral therapies, including interferon and DAAs, reduce the risk of HCC following achievement of SVR[70], but DAAs are more tolerable and efficacious compared to interferon[71]. All HCV genotypes can be responsive with various combinations of DAA treatment. However, relapse of HCV has been observed after DAA treatment[72,73].

DAA in HT recipients

No data are available on the optimal initiation for DAA-therapies following HT. However, recent studies report an increased risk of rejection with delayed treatment[54]. Empirical initiation of DAAs have decreased the viral load and shown the rapid clearance of HCV in 10 d[74]. Hence, early initiation of DAAs post-transplant while in the hospital should be highly encouraged[11,75]. Fluctuating kidney function following HT limits the use of DAAs as some agents like sofosbuvir may adversely affect kidney function, but DAAs have been used successfully in renal transplant recipients with no impact on renal function[51].

DAAs are well tolerated with no major adverse effects, and recipients typically suffer from self-limiting constitutional symptoms like headaches, fatigue, or insomnia[75]. Overall cost of a 12-wk course of DAAs are expensive, ranging from $80000 to $100000, but recently the cost has been reduced to as low as $30000 in 2020[33,40,49]. This is far less compared to the cost of a mechanical cardiac support device with an average cost of hospitalization of $726000 and a yearly cost ranging from $30000 to $80000 for follow-up and maintenance[32,76]. The burden of caring for durable mechanical support

by the patient and their families should also be noted.

Overall survival

In the pre-DAA era, the overall mortality was increased by 2-fold in recipients receiving hearts from HCV-positive donors[5,6]. With the effective treatment against HCV with DAAs, the 1-year survival rate is 90.4% in HCV-positive recipients similar to HCV-negative recipients[37,48,61]. However, there is a scarcity of available data beyond 1 year. Larger studies are currently ongoing for evaluating long-term outcomes[11,37]. The average waiting period for HT is reduced and thereby decreasing waiting list mortality[11,37]. Data on multiorgan transplants are limited. McMaster *et al*[50] demonstrated equivalent survival rates in combined heart and kidney transplants with preservation of renal function[48-50].

Future of HCV-positive donor utilization

The studies have demonstrated comparable 1-year outcomes following HT from HCV-positive donors compared to HCV-negative donors with a potential for younger donors[47]. Generally, the recipients have an uncomplicated course following HT with rapid clearance of viremia with the use of DAAs with minimal interactions with immunosuppressants and few side effects[77,78]. One-year outcomes of HT recipients from HCV-positive donors are encouraging, but further studies are needed to evaluate the risk of allograft rejection, development of CAV, long-term sequela of liver disease and potential HCC risk, HCV genotype-specific effects, and recurrence of HCV and its impact on morbidity and mortality beyond the 1st year. In 2020, only 28% of the transplant centers were utilizing HCV-positive hearts[21], but with more experience and reassuring long-term outcomes, more transplant centers will begin accept HCV-positive organs.

CONCLUSION

As the IVDUs and opioid epidemic is on the rise in the United States, the donor pool, including HCV-positive hearts is going to increase in the coming years. With highly effective DAA therapy and comparable short-term outcomes following HT, it is reasonable to utilize these organs to meet the increasing prevalence of end-stage refractory HF patients. However, a multidisciplinary team approach and close monitoring of these recipients are needed with close observation for long-term sequelae.

FOOTNOTES

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Country/Territory of origin: United States

ORCID number: Palak Patel 0000-0001-7136-7633; Nirav Patel 0000-0001-7797-7248; Jason Gluck 0000-0002-9123-830X.

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REFERENCES

1 **Virani SS**, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Chang AR, Cheng S, Delling FN, Djousse L, Elkind MSV, Ferguson JF, Fornage M, Khan SS, Kissela BM, Knutson KL, Kwan TW, Lackland DT, Lewis TT, Lichtman JH, Longenecker CT, Loop MS, Lutsey PL, Martin SS, Matsushita K, Moran AE, Mussolino ME, Perak AM, Rosamond WD, Roth GA, Sampson UKA, Satou GM, Schroeder EB, Shah SH, Shay CM, Spartano NL, Stokes A, Tirschwell DL, VanWagner LB, Tsao CW; American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics-2020 Update: A Report From the American Heart Association. *Circulation* 2020; **141**: e139-e596 [PMID: 31992061 DOI:

10.1161/CIR.0000000000000757]
2 **Heidenreich PA**, Albert NM, Allen LA, Bluemke DA, Butler J, Fonarow GC, Ikonomidis JS, Khavjou O, Konstam MA, Maddox TM, Nichol G, Pham M, Piña IL, Trogdon JG; American Heart Association Advocacy Coordinating Committee; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiovascular Radiology and Intervention; Council on Clinical Cardiology; Council on Epidemiology and Prevention; Stroke Council. Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. *Circ Heart Fail* 2013; **6**: 606-619 [PMID: 23616602 DOI: 10.1161/HHF.0b013e318291329a]
3 **Yancy CW**, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Colvin MM, Drazner MH, Filippatos GS, Fonarow GC, Givertz MM, Hollenberg SM, Lindenfeld J, Masoudi FA, McBride PE, Peterson PN, Stevenson LW, Westlake C. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *J Card Fail* 2017; **23**: 628-651 [PMID: 28461259 DOI: 10.1016/j.cardfail.2017.04.014]
4 **Colvin M**, Smith JM, Hadley N, Skeans MA, Uccellini K, Goff R, Foutz J, Israni AK, Snyder JJ, Kasiske BL. OPTN/SRTR 2018 Annual Data Report: Heart. *Am J Transplant* 2020; **20** Suppl s1: 340-426 [PMID: 31898418 DOI: 10.1111/ajt.15676]
5 **File E**, Mehra M, Nair S, Dumas-Hicks D, Perrillo R. Allograft transmission of hepatitis C virus infection from infected donors in cardiac transplantation. *Transplantation* 2003; **76**: 1096-1100 [PMID: 14557759 DOI: 10.1097/01.TP.0000088663.76640.C9]
6 **Pol S**, Lagaye S. The remarkable history of the hepatitis C virus. *Genes Immun* 2019; **20**: 436-446 [PMID: 31019253 DOI: 10.1038/s41435-019-0066-z]
7 **Gupta E**, Bajpai M, Choudhary A. Hepatitis C virus: Screening, diagnosis, and interpretation of laboratory assays. *Asian J Transfus Sci* 2014; **8**: 19-25 [PMID: 24678168 DOI: 10.4103/0973-6247.126683]
8 **Vanhommerig JW**, Thomas XV, van der Meer JT, Geskus RB, Bruisten SM, Molenkamp R, Prins M, Schinkel J; MOSAIC (MSM Observational Study for Acute Infection with hepatitis C) Study Group. Hepatitis C virus (HCV) antibody dynamics following acute HCV infection and reinfection among HIV-infected men who have sex with men. *Clin Infect Dis* 2014; **59**: 1678-1685 [PMID: 25186590 DOI: 10.1093/cid/ciu695]
9 **Humar A**, Morris M, Blumberg E, Freeman R, Preiksaitis J, Kiberd B, Schweitzer E, Ganz S, Caliendo A, Orlowski JP, Wilson B, Kotton C, Michaels M, Kleinman S, Geier S, Murphy B, Green M, Levi M, Knoll G, Segev DL, Brubaker S, Hasz R, Lebovitz DJ, Mulligan D, O'Connor K, Pruett T, Mozes M, Lee I, Delmonico F, Fischer S. Nucleic acid testing (NAT) of organ donors: is the 'best' test the right test? *Am J Transplant* 2010; **10**: 889-899 [PMID: 20121734 DOI: 10.1111/j.1600-6143.2009.02992.x]
10 **Patel SR**, Madan S, Saeed O, Sims DB, Shin JJ, Nucci C, Borukhov E, Goldstein DY, Jakobleff W, Forest S, Vukelic S, Murthy S, Reinus J, Puius Y, Goldstein DJ, Jorde UP. Cardiac transplantation from non-viremic hepatitis C donors. *J Heart Lung Transplant* 2018; **37**: 1254-1260 [PMID: 30126825 DOI: 10.1016/j.healun.2018.06.012]
11 **Schlendorf KH**, Zalawadiya S, Shah AS, Perri R, Wigger M, Brinkley DM, Danter MR, Menachem JN, Punnoose LR, Balsara K, Sacks SB, Ooi H, Awad JA, Sandhaus E, Schwartz C, O'Dell H, Carver AB, Edmonds CL, Ruzevich-Scholl S, Lindenfeld J. Expanding Heart Transplant in the Era of Direct-Acting Antiviral Therapy for Hepatitis C. *JAMA Cardiol* 2020; **5**: 167-174 [PMID: 31851352 DOI: 10.1001/jamacardio.2019.4748]
12 **Kucirka LM**, Sarathy H, Govindan P, Wolf JH, Ellison TA, Hart LJ, Montgomery RA, Ros RL, Segev DL. Risk of window period hepatitis-C infection in high infectious risk donors: systematic review and meta-analysis. *Am J Transplant* 2011; **11**: 1188-1200 [PMID: 21401874 DOI: 10.1111/j.1600-6143.2011.03460.x]
13 **White EF**, Garfein RS, Brouwer KC, Lozada R, Ramos R, Firestone-Cruz M, Pérez SG, Magis-Rodríguez C, Conde-Glez CJ, Strathdee SA. Prevalence of hepatitis C virus and HIV infection among injection drug users in two Mexican cities bordering the U.S. *Salud Publica Mex* 2007; **49**: 165-172 [PMID: 17589770 DOI: 10.1590/s0036-36342007000300001]
14 **Hagan H**, Des Jarlais DC. HIV and HCV infection among injecting drug users. *Mt Sinai J Med* 2000; **67**: 423-428 [PMID: 11064493]
15 **Ryerson AB**, Schillie S, Barker LK, Kupronis BA, Wester C. Vital Signs: Newly Reported Acute and Chronic Hepatitis C Cases - United States, 2009-2018. *MMWR Morb Mortal Wkly Rep* 2020; **69**: 399-404 [PMID: 32271725 DOI: 10.15585/mmwr.mm6914a2]
16 **Grebely J**, Larney S, Peacock A, Colledge S, Leung J, Hickman M, Vickerman P, Blach S, Cunningham EB, Dumchev K, Lynskey M, Stone J, Trickey A, Razavi H, Mattick RP, Farrell M, Dore GJ, Degenhardt L. Global, regional, and country-level estimates of hepatitis C infection among people who have recently injected drugs. *Addiction* 2019; **114**: 150-166 [PMID: 30035835 DOI: 10.1111/add.14393]
17 **Trickey A**, Fraser H, Lim AG, Peacock A, Colledge S, Walker JG, Leung J, Grebely J, Larney S, Martin NK, Hickman M, Degenhardt L, May MT, Vickerman P. The contribution of injection drug use to hepatitis C virus transmission globally, regionally, and at country level: a modelling study. *Lancet Gastroenterol Hepatol* 2019; **4**: 435-444 [PMID: 30981685 DOI: 10.1016/S2468-1253(19)30085-8]
18 **Samji H**, Yu A, Wong S, Wilton J, Binka M, Alvarez M, Bartlett S, Pearce M, Adu P, Jeong D, Clementi E, Butt Z, Buxton J, Gilbert M, Krajden M, Janjua NZ. Drug-related deaths in a population-level cohort of people living with and without hepatitis C virus in British Columbia, Canada. *Int J Drug Policy* 2020; **86**: 102989 [PMID: 33091735 DOI: 10.1016/j.drugpo.2020.102989]
19 **Phillips KG**, Ranganath NK, Malas J, Lonze BE, Gidea CG, Smith DE, Kon ZN, Reyentovich A, Moazami N. Impact of the Opioid Epidemic on Heart Transplantation: Donor Characteristics and Organ Discard. *Ann Thorac Surg* 2019; **108**: 1133-1139 [PMID: 31178157 DOI: 10.1016/j.athoracsur.2019.03.076]
20 HAN Archive - 00438. 2021. Available from: https://emergency.cdc.gov/han/2020/han00438.asp
21 **Kilic A**, Hickey G, Mathier M, Sultan I, Gleason TG, Horn E, Keebler ME. Outcomes of Adult Heart Transplantation Using Hepatitis C-Positive Donors. *J Am Heart Assoc* 2020; **9**: e014495 [PMID: 31910781 DOI: 10.1161/JAHA.119.014495]
22 **Pereira BJ**, Milford EL, Kirkman RL, Levey AS. Transmission of hepatitis C virus by organ transplantation. *N Engl J Med*

1991; **325**: 454-460 [PMID: 1649402 DOI: 10.1056/NEJM199108153250702]
23 **Hayashi PH**, Fernando L, Schuch DR, Koldinger R, Kelly PB, Ingram M, DeFelice R, Marriott SE, Holland PV, Zeldis JB. Seronegative hepatitis C virus liver failure following transplantation of a cadaveric heart. *West J Med* 1994; **160**: 368-371 [PMID: 8023494]
24 **Lim HL**, Lau GK, Davis GL, Dolson DJ, Lau JY. Cholestatic hepatitis leading to hepatic failure in a patient with organ-transmitted hepatitis C virus infection. *Gastroenterology* 1994; **106**: 248-251 [PMID: 8276189 DOI: 10.1016/s0016-5085(94)95829-7]
25 **Zein NN**, McGregor CG, Wendt NK, Schwab K, Mitchell PS, Persing DH, Rakela J. Prevalence and outcome of hepatitis C infection among heart transplant recipients. *J Heart Lung Transplant* 1995; **14**: 865-869 [PMID: 8800721]
26 **Pfau PR**, Rho R, DeNofrio D, Loh E, Blumberg EA, Acker MA, Lucey MR. Hepatitis C transmission and infection by orthotopic heart transplantation. *J Heart Lung Transplant* 2000; **19**: 350-354 [PMID: 10775815 DOI: 10.1016/s1053-2498(00)00062-0]
27 **Marelli D**, Bresson J, Laks H, Kubak B, Fonarow G, Tsai FC, Tran J, Weston SR, Kobashigawa J. Hepatitis C-positive donors in heart transplantation. *Am J Transplant* 2002; **2**: 443-447 [PMID: 12123210 DOI: 10.1034/j.1600-6143.2002.20508.x]
28 **Gudmundsson GS**, Malinowska K, Robinson JA, Pisani BA, Mendez JC, Foy BK, Mullen GM. Five-year follow-up of hepatitis C-naïve heart transplant recipients who received hepatitis C-positive donor hearts. *Transplant Proc* 2003; **35**: 1536-1538 [PMID: 12826214 DOI: 10.1016/s0041-1345(03)00368-3]
29 **Wang SS**, Chou NK, Ko WJ, Yu HY, Chen YS, Hsu RB, Huang SC, Chi NH, Tsao CI, Lai MY, Liau CS, Lee YT. Heart transplantation using donors positive for hepatitis. *Transplant Proc* 2004; **36**: 2371-2373 [PMID: 15561252 DOI: 10.1016/j.transproceed.2004.08.112]
30 **Haji SA**, Starling RC, Avery RK, Mawhorter S, Tuzcu EM, Schoenhagen P, Cook DJ, Ratliff NB, McCarthy PM, Young JB, Yamani MH. Donor hepatitis-C seropositivity is an independent risk factor for the development of accelerated coronary vasculopathy and predicts outcome after cardiac transplantation. *J Heart Lung Transplant* 2004; **23**: 277-283 [PMID: 15019636 DOI: 10.1016/S1053-2498(03)00148-7]
31 **Gasink LB**, Blumberg EA, Localio AR, Desai SS, Israni AK, Lautenbach E. Hepatitis C virus seropositivity in organ donors and survival in heart transplant recipients. *JAMA* 2006; **296**: 1843-1850 [PMID: 17047214 DOI: 10.1001/jama.296.15.1843]
32 **Levitsky J**, Doucette K; AST Infectious Diseases Community of Practice. Viral hepatitis in solid organ transplantation. *Am J Transplant* 2013; **13** Suppl 4: 147-168 [PMID: 23465008 DOI: 10.1111/ajt.12108]
33 **Gottlieb RL**, Sam T, Wada SY, Trotter JF, Asrani SK, Lima B, Joseph SM, Gonzalez-Stawinski GV, Hall SA. Rational Heart Transplant From a Hepatitis C Donor: New Antiviral Weapons Conquer the Trojan Horse. *J Card Fail* 2017; **23**: 765-767 [PMID: 28801074 DOI: 10.1016/j.cardfail.2017.08.448]
34 **Lawitz E**, Matusow G, DeJesus E, Yoshida EM, Felizarta F, Ghalib R, Godofsky E, Herring RW, Poleynard G, Sheikh A, Tobias H, Kugelmas M, Kalmeijer R, Peeters M, Lenz O, Fevery B, De La Rosa G, Scott J, Sinha R, Witek J. Simeprevir plus sofosbuvir in patients with chronic hepatitis C virus genotype 1 infection and cirrhosis: A phase 3 study (OPTIMIST-2). *Hepatology* 2016; **64**: 360-369 [PMID: 26704148 DOI: 10.1002/hep.28422]
35 **Sperl J**, Kreidlova M, Merta D, Chmelova K, Senkerikova R, Frankova S. Paritaprevir/Ritonavir/Ombitasvir Plus Dasabuvir Regimen in the Treatment of Genotype 1 Chronic Hepatitis C Infection in Patients with Severe Renal Impairment and End-Stage Renal Disease: a Real-Life Cohort. *Kidney Blood Press Res* 2018; **43**: 594-605 [PMID: 29669332 DOI: 10.1159/000488965]
36 **McLean RC**, Reese PP, Acker M, Atluri P, Bermudez C, Goldberg LR, Abt PL, Blumberg EA, Van Deerlin VM, Reddy KR, Bloom RD, Hasz R, Suplee L, Sicilia A, Woodards A, Zahid MN, Bar KJ, Porrett P, Levine MH, Hornsby N, Gentile C, Smith J, Goldberg DS. Transplanting hepatitis C virus-infected hearts into uninfected recipients: A single-arm trial. *Am J Transplant* 2019; **19**: 2533-2542 [PMID: 30768838 DOI: 10.1111/ajt.15311]
37 **Reyentovich A**, Gidea C, Smith D, Lonze B, Pavone J, Katz S, Pan S, Rao S, Saraon T, Moazami N. Clinical Experience with Heart Transplantation from Hepatitis C Positive Donors. *J Heart Lung Transplant* 2019; **38**: S48 [DOI: 10.1016/j.healun.2019.01.104]
38 **Chhatwal J**, Samur S, Bethea ED, Ayer T, Kanwal F, Hur C, Roberts MS, Terrault N, Chung RT. Transplanting hepatitis C virus-positive livers into hepatitis C virus-negative patients with preemptive antiviral treatment: A modeling study. *Hepatology* 2018; **67**: 2085-2095 [PMID: 29222916 DOI: 10.1002/hep.29723]
39 **Jawad K**, Feder S, Barten M, Garbade J. Curative therapy of a hepatitis C infection due to an infected heart donor: 5-year outcomes after heart transplantation. *Eur J Cardiothorac Surg* 2018; **54**: 400-401 [PMID: 29514173 DOI: 10.1093/ejcts/ezy051]
40 **Moayedi Y**, Gulamhusein AF, Ross HJ, Teuteberg JJ, Khush KK. Accepting hepatitis C virus-infected donor hearts for transplantation: Multistep consent, unrealized opportunity, and the Stanford experience. *Clin Transplant* 2018; **32**: e13308 [PMID: 29869354 DOI: 10.1111/ctr.13308]
41 **Moayedi Y**, Fan CPS, Gulamhusein AF, Manlhiot C, Ross HJ, Teuteberg JJ, Khush KK. Current Use of Hearts From Hepatitis C Viremic Donors. *Circ Heart Fail* 2018; **11**: e005276 [PMID: 30562093 DOI: 10.1161/CIRCHEARTFAILURE.118.005276]
42 **Schlendorf KH**, Zalawadiya S, Shah AS, Wigger M, Chung CY, Smith S, Danter M, Choi CW, Keebler ME, Brinkley DM, Sacks SB, Ooi H, Perri R, Awad JA, Lewis S, Hayes R, O'Dell H, Darragh C, Carver A, Edmonds C, Ruzevich-Scholl S, Lindenfeld J. Early outcomes using hepatitis C-positive donors for cardiac transplantation in the era of effective direct-acting anti-viral therapies. *J Heart Lung Transplant* 2018; **37**: 763-769 [PMID: 29530322 DOI: 10.1016/j.healun.2018.01.1293]
43 **Woolley AE**, Singh SK, Goldberg HJ, Mallidi HR, Givertz MM, Mehra MR, Coppolino A, Kusztos AE, Johnson ME, Chen K, Haddad EA, Fanikos J, Harrington DP, Camp PC, Baden LR; DONATE HCV Trial Team. Heart and Lung Transplants from HCV-Infected Donors to Uninfected Recipients. *N Engl J Med* 2019; **380**: 1606-1617 [PMID: 30946553 DOI: 10.1056/NEJMoa1812406]

44 **Frager SZ**, Dhand A, Gass A, Levine A, Spielvogel D, Nog R, Wolf DC, Bodin RI. Heart Transplantation for Hepatitis C Virus Non-Viremic Recipients From Hepatitis C Virus Viremic Donors. *Cardiol Rev* 2019; **27**: 179-181 [PMID: 31180937 DOI: 10.1097/CRD.0000000000000255]

45 **Aslam S**, Yumul I, Mariski M, Pretorius V, Adler E. Outcomes of heart transplantation from hepatitis C virus-positive donors. *J Heart Lung Transplant* 2019; **38**: 1259-1267 [PMID: 31521479 DOI: 10.1016/j.healun.2019.08.019]

46 **Morris KL**, Adlam JP, Padanilam M, Patel A, Garcia-Cortes R, Chaudhry SP, Seasor E, Tompkins S, Hoefer C, Zanotti G, Walsh MN, Salerno C, Bochan M, Ravichandran A. Hepatitis C donor viremic cardiac transplantation: A practical approach. *Clin Transplant* 2020; **34**: e13764 [PMID: 31830339 DOI: 10.1111/ctr.13764]

47 **Lebeis TA**, Afari ME, Bethea ED, Gaj K, Gustafson JL, Turvey K, Coglianese E, Thomas SS, Newton-Cheh C, Ibrahim N, Carlson WD, Ho JE, Nayor M, Steiner JK, Spahillari A, Villavicencio-Theoduloz MA, D'Alessandro DA, Soydara C, Lever N, Chung RT, Lewis GD. Evaluation of Early Allograft Function in Donor HCV-Positive to Recipient HCV-Negative Cardiac Transplantation Managed with Preemptive Direct Acting Antiviral Therapy. *J Heart Lung Transplant* 2019; **38**: S275-S276 [DOI: 10.1016/j.healun.2019.01.687]

48 **Gaj KJ**, D'Alessandro DA, Bethea ED, Gustafson JL, Villavicencio-Theoduloz MA, Chung RT, Lewis GD. Acceptance of HCV-Positive Donor Hearts Improves Organ Acceptance Selectivity: Single Center Experience. *J Heart Lung Transplant* 2019; **38**: S49-S50 [DOI: 10.1016/j.healun.2019.01.108]

49 **Zhu Y**, Shudo Y, Lee R, Woo YJ. Heart Transplant Using Hepatitis C-Seropositive and Viremic Organs in Seronegative Recipients. *Ann Transplant* 2020; **25**: e922723 [PMID: 32527989 DOI: 10.12659/AOT.922723]

50 **McMaster WG Jr**, Rahaman ZM, Shipe ME, Quintana EN, Sandhaus EM, Smith SS, Crockett JE, Forbes RC, Schlendorf KH, Shah AS. Early Outcomes of Multivisceral Transplant Using Hepatitis C-Positive Donors. *Ann Thorac Surg* 2021; **112**: 511-518 [PMID: 33121968 DOI: 10.1016/j.athoracsur.2020.08.044]

51 **Zalawadiya SK**, Lindenfeld J, Shah A, Wigger M, Danter M, Brinkley DM, Menachem J, Punnoose L, Balsara K, Brown Sacks S, Ooi H, Perri R, Awad J, Smith S, Fowler R, O'Dell H, Darragh C, Ruzevich-Scholl S, Schlendorf K. Trends in Renal Function Among Heart Transplant Recipients of Donor-Derived Hepatitis C Virus. *ASAIO J* 2020; **66**: 553-558 [PMID: 31425256 DOI: 10.1097/MAT.0000000000001034]

52 **Reyentovich A**, Gidea CG, Smith D, Lonze B, Kon Z, Fargnoli A, Pavone J, Rao S, Saraon T, Lewis T, Qian Y, Jacobson I, Moazami N. Outcomes of the Treatment with Glecaprevir/Pibrentasvir following heart transplantation utilizing hepatitis C viremic donors. *Clin Transplant* 2020; **34**: e13989 [PMID: 32441413 DOI: 10.1111/ctr.13989]

53 **Rodriguez Cetina Biefer H**, Sündermann SH, Emmert MY, Enseleit F, Seifert B, Ruschitzka F, Jacobs S, Lachat ML, Falk V, Wilhelm MJ. Surviving 20 years after heart transplantation: a success story. *Ann Thorac Surg* 2014; **97**: 499-504 [PMID: 24140213 DOI: 10.1016/j.athoracsur.2013.08.040]

54 **Gidea CG**, Narula N, Reyentovich A, Fargnoli A, Smith D, Pavone J, Lewis T, Karpe H, Stachel M, Rao S, Moreira A, Saraon T, Raimann J, Kon Z, Moazami N. Increased early acute cellular rejection events in hepatitis C-positive heart transplantation. *J Heart Lung Transplant* 2020; **39**: 1199-1207 [PMID: 32739334 DOI: 10.1016/j.healun.2020.06.022]

55 **Burton JR Jr**, Rosen HR. Acute rejection in HCV-infected liver transplant recipients: The great conundrum. *Liver Transpl* 2006; **12**: S38-S47 [PMID: 17051562 DOI: 10.1002/lt.20944]

56 **Gidea CG**, Narula N, Reyentovich A, Smith D, Pavone J, Katz S, Pan S, Rao S, Saraon T, Moazami N. The Impact of HCV Viremia in Heart Transplant Recipients from Donors with HCV Infection on Acute and Humoral Cellular Rejection. *J Heart Lung Transplant* 2019; **38**: S66 [DOI: 10.1016/j.healun.2019.01.149]

57 **Lund LH**, Edwards LB, Kucheryavaya AY, Benden C, Christie JD, Dipchand AI, Dobbels F, Goldfarb SB, Levvey BJ, Meiser B, Yusen RD, Stehlik J; International Society of Heart and Lung Transplantation. The registry of the International Society for Heart and Lung Transplantation: thirty-first official adult heart transplant report--2014; focus theme: retransplantation. *J Heart Lung Transplant* 2014; **33**: 996-1008 [PMID: 25242124 DOI: 10.1016/j.healun.2014.08.003]

58 **Yang SS**, Tsai G, Wu CH, Chen DS. Circulating soluble intercellular adhesion molecule-1 in type C viral hepatitis. *Hepatogastroenterology* 1996; **43**: 575-581 [PMID: 8799398]

59 **Rose EA**, Smith CR, Petrossian GA, Barr ML, Reemtsma K. Humoral immune responses after cardiac transplantation: correlation with fatal rejection and graft atherosclerosis. *Surgery* 1989; **106**: 203-7; discussion 207 [PMID: 2669195]

60 **Hosenpud JD**, Everett JP, Morris TE, Mauck KA, Shipley GD, Wagner CR. Cardiac allograft vasculopathy. Association with cell-mediated but not humoral alloimmunity to donor-specific vascular endothelium. *Circulation* 1995; **92**: 205-211 [PMID: 7600652 DOI: 10.1161/01.cir.92.2.205]

61 **Zalawadiya S**, Lindenfeld J, Haddad E, Shah A, Wigger M, Negrotto S, Danter M, Brinkley D, Menachem J, Punnoose L, Brown Sacks S, Ooi H, Balsara K, Perri R, Awad J, Smith S, Fowler R, O'Dell H, Darragh C, Ruzevich-Scholl S, Schlendorf K. Intracoronary Intimal Thickness in Transplant Recipients of Hepatitis C-Positive Donor Hearts. *J Heart Lung Transplant* 2019; **38**: S281 [DOI: 10.1016/j.healun.2019.01.703]

62 **de Oliveria Andrade LJ**, D'Oliveira A, Melo RC, De Souza EC, Costa Silva CA, Paraná R. Association between hepatitis C and hepatocellular carcinoma. *J Glob Infect Dis* 2009; **1**: 33-37 [PMID: 20300384 DOI: 10.4103/0974-777X.52979]

63 **Piselli P**, Serraino D, Fusco M, Girardi E, Pirozzi A, Toffolutti F, Cimaglia C, Taborelli M; Collaborating Study Group. Hepatitis C virus infection and risk of liver-related and non-liver-related deaths: a population-based cohort study in Naples, southern Italy. *BMC Infect Dis* 2021; **21**: 667 [PMID: 34238231 DOI: 10.1186/s12879-021-06336-9]

64 **Zignego AL**, Giannini C, Gragnani L, Piluso A, Fognani E. Hepatitis C virus infection in the immunocompromised host: a complex scenario with variable clinical impact. *J Transl Med* 2012; **10**: 158 [PMID: 22863056 DOI: 10.1186/1479-5876-10-158]

65 **Messina JP**, Humphreys I, Flaxman A, Brown A, Cooke GS, Pybus OG, Barnes E. Global distribution and prevalence of hepatitis C virus genotypes. *Hepatology* 2015; **61**: 77-87 [PMID: 25069599 DOI: 10.1002/hep.27259]

66 **Zein NN**. Clinical significance of hepatitis C virus genotypes. *Clin Microbiol Rev* 2000; **13**: 223-235 [PMID: 10755999 DOI: 10.1128/CMR.13.2.223]

67 **Wu N**, Rao HY, Yang WB, Gao ZL, Yang RF, Fei R, Gao YH, Jin Q, Wei L. Impact of hepatitis C virus genotype 3 on liver disease progression in a Chinese national cohort. *Chin Med J (Engl)* 2020; **133**: 253-261 [PMID: 31934936 DOI: 10.1097/CM9.0000000000000629]

68 **Osella AR**, Misciagna G, Guerra V, Elba S, Buongiorno G, Cavallini A, Di Leo A, Sonzogni L, Mondelli MU, Silini EM. Hepatitis C virus genotypes and risk of cirrhosis in southern Italy. *Clin Infect Dis* 2001; **33**: 70-75 [PMID: 11389497 DOI: 10.1086/320887]

69 **Mangia A**, Cascavilla I, Lezzi G, Spirito F, Maertens G, Parlatore L, Saracco G, Rizzetto M, Andriulli A. HCV genotypes in patients with liver disease of different stages and severity. *J Hepatol* 1997; **26**: 1173-1178 [PMID: 9210601 DOI: 10.1016/s0168-8278(97)80449-7]

70 **Su F**, Ioannou GN. Hepatocellular Carcinoma Risk After Direct-Acting Antiviral Therapy. *Clin Liver Dis (Hoboken)* 2019; **13**: 6-12 [PMID: 31168359 DOI: 10.1002/cld.781]

71 **Kohli A**, Shaffer A, Sherman A, Kottilil S. Treatment of hepatitis C: a systematic review. *JAMA* 2014; **312**: 631-640 [PMID: 25117132 DOI: 10.1001/jama.2014.7085]

72 **Kurokawa K**, Ohki T, Kato J, Fukumura Y, Imai M, Shibata C, Arai J, Kondo M, Takagi K, Kojima K, Seki M, Mori M, Toda N, Tagawa K. Hepatitis C virus relapse after successful treatment with direct-acting antivirals, followed by sarcomatous changes in hepatocellular carcinoma: a case report. *J Med Case Rep* 2020; **14**: 62 [PMID: 32456712 DOI: 10.1186/s13256-020-02392-y]

73 **Bernhard B**, Stickel F. Successful fourth line treatment of a relapse patient with chronic hepatitis C virus infection genotype 3a using sofosbuvir, glecaprevir/pibrentasvir, and ribavirin: a case report. *Z Gastroenterol* 2020; **58**: 451-455 [PMID: 32392606 DOI: 10.1055/a-1131-8058]

74 **Smith DE**, Chen S, Fargnoli A, Lewis T, Galloway AC, Kon ZN, Moazami N. Impact of Early Initiation of Direct-Acting Antiviral Therapy in Thoracic Organ Transplantation From Hepatitis C Virus Positive Donors. *Semin Thorac Cardiovasc Surg* 2021; **33**: 407-415 [PMID: 32621962 DOI: 10.1053/j.semtcvs.2020.06.045]

75 **Liu CH**, Chen YS, Wang SS, Liu CJ, Su TH, Yang HC, Hong CM, Chen PJ, Chen DS, Kao JH. Sofosbuvir-based Interferon-Free Direct Acting Antiviral Regimens for Heart Transplant Recipients With Chronic Hepatitis C Virus Infection. *Clin Infect Dis* 2018; **66**: 289-292 [PMID: 29020359 DOI: 10.1093/cid/cix787]

76 **Baras Shreibati J**, Goldhaber-Fiebert JD, Banerjee D, Owens DK, Hlatky MA. Cost-Effectiveness of Left Ventricular Assist Devices in Ambulatory Patients With Advanced Heart Failure. *JACC Heart Fail* 2017; **5**: 110-119 [PMID: 28017351 DOI: 10.1016/j.jchf.2016.09.008]

77 **Lewis GD**, Bethea ED, Gaj K, Gustafson J, Dugal A, Turvey K, Coglianese E, Thomas SS, Newton-Cheh C, Ibrahim NE, Carlson WD, Shah RV, Ho JE, Nayor M, Steiner JK, Afari ME, Lebeis T, Madsen JC, Villavicencio-Theoduloz MA, Chung RT, D'Alessandro DA. Preemptive Pan-Genotypic Direct Acting Antiviral Therapy in Donor HCV-Positive to Recipient HCV-Negative Cardiac Transplantation Produces Viral Clearance and is Associated with Favorable Outcomes. *J Heart Lung Transplant* 2019; **38**: S65 [DOI: 10.1016/j.healun.2019.01.146]

78 **Gidea CG**, Reyentovich A, Smith D, Pavone J, Katz S, Pan S, Rao S, Saraon T, Moazami N. Magnitude of Recipient Viremia after Heart Transplantation from HCV Viremic Donors and Time to Clearance with Therapy. *J Heart Lung Transplant* 2019; **38**: S65-S66 [DOI: 10.1016/j.healun.2019.01.147]

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Current practice of live donor nephrectomy in Turkey

Bakytbek Mankiev, Sanem Guler Cimen, Ismail Oskay Kaya, Sertac Cimen, Asir Eraslan

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Bakytbek Mankiev, Sanem Guler Cimen, Department of General Surgery, Sağlık Bilimleri Üniversitesi, Ankara 65100, Turkey

Ismail Oskay Kaya, Departments of Surgery, University of Health Sciences, Diskapi Yildirim Beyazit Training and Research Hospital, Ankara 65100, Turkey

Sertac Cimen, Department of Urology, Saglık Bilimleri Universitesi, Ankara 65100, Turkey

Asir Eraslan, Department of Urology, Somalia Turkish Training and Research Hospital, Mogadishu 23451, Somalia

Corresponding author: Sanem Guler Cimen, Doctor, FEBS, Adjunct Associate Professor, Department of General Surgery, Sağlık Bilimleri Üniversitesi, Altindag, Ankara 65100, Turkey. sanem.cimen@sbu.edu.tr

Abstract

BACKGROUND

Over the last few years, the deceased donor organ donation rate was declined or remained stable, whereas the live donor organ donation rate has increased to compensate for the demand. Minimally invasive techniques for live donor nephrectomy (LDN) have also improved the live donor kidney donation rates. This increase has led to an interest in the surgical procedures used for LDN.

AIM

To evaluate the LDN techniques performed in Turkey, the structure of surgical teams, and the training received. Additionally, the number of kidney transplantations at different centers, the surgeon experience level, differences in surgical approach during donor surgeries, and outcomes were assessed.

METHODS

A questionnaire was sent to the Turkish Ministry of Health-accredited transplant centers. It inquired of the number of LDN surgeries, surgical techniques, complications, optimization protocols, the experience of surgeons, and the training. Descriptive statistics were outlined as follows: Discrete numeric variables were expressed as medians (minimum-maximum), while categorical variables were shown as numbers and percentages. As a result of the goodness-of-fit tests, if the significance of the differences between the groups in discrete numerical variables for which the parametric test statistical assumptions were not met, data were analyzed with the Mann Whitney *U* test and the χ^2 test.

RESULTS

The questionnaire was sent to 72 transplant centers, all of which replied. Five centers that reported not performing LDN procedures were excluded. Responses from the remaining 67 centers were analyzed. In 2019, the median number of kidney transplants performed was 45, and the median number of kidney transplants from living donors was 28 (1-238). Eleven (16.5%) centers performed 5-10, while 34 (50.7%) centers performed more than 100 live donor kidney transplants in 2019. While 19 (28.4%) centers performed the LDN procedures using the open technique, 48 (71.6%) centers implemented minimally invasive techniques. Among the centers preferring minimally invasive techniques for LDN, eight (16.6%) used more than one surgical technique. The most and the least common surgical techniques were transperitoneal laparoscopic (43 centers, 89.6%) and single port laparoscopic LDN (1 center, 2.1%) techniques, respectively. A positive association was found between the performance of minimally invasive techniques and the case volume of a transplant center, both in the total number and live donor kidney transplants (15 *vs* 55, $P = 0.001$ and 9 *vs* 42, $P \leq 0001$ respectively). The most frequently reported complication was postoperative atelectasis ($n = 33$, 49.2%). There was no difference between the techniques concerning complications except for the chyle leak.

CONCLUSION

Turkish transplant centers performed LDN surgeries successfully through various techniques. Centers implementing minimally invasive techniques had a relatively higher number of live donor kidney transplants in 2019.

Key Words: Kidney donation; Live donor nephrectomy; Laparoscopic donor nephrectomy; Donor complications; Minimally invasive techniques; Donation rate

Core Tip: This study showed that centers using minimally invasive techniques had a relatively higher number of live donor kidney transplants in 2019. It also demonstrated that Turkish transplant teams performed live donor nephrectomy surgeries successfully through various techniques by considering that donor safety and center experience were the essential determinants when selecting the optimal approach for each donor.

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INTRODUCTION

Over the last few years, deceased donor organ donations have decreased[1]. In 2019, the overall organ donation rate was 46.5 per million population in Turkey[2]. This figure demonstrated a decline from the preceding years. However, this decline was less remarkable than in other European countries since live organ donation was promoted to compensate for demand. In line with this, countries like Turkey reported a rise in the number of living donor kidney transplantations during the pandemic. In 2019 according to the Turkish Ministry of Health data, 3963 kidney transplantations were performed in Turkey[2]. Among these patients, 3548 were transplanted from live donors. This increased living donor rate stimulated interest in Turkey's surgical techniques and live donor nephrectomy (LDN) practices.

The introduction of laparoscopic donor nephrectomy was by Ratner *et al*[3]. Various minimally invasive techniques have been described and performed for live kidney donation. These include hand-assisted laparoscopic, retroperitoneoscopic, single port, natural orifice, and robotic nephrectomy techniques[4]. Meanwhile, the open donor nephrectomy technique remained a gold standard for patients with variant anatomies and previous abdominal surgeries. Studies conducted in Europe and the United States showed that minimally invasive donor nephrectomy improved the live kidney donation rates[5,6]. Due to shorter recovery time, less post-surgical pain, and better cosmetic results, live kidney donors preferred minimally invasive techniques. Therefore, many transplant centers implemented these techniques with considerable success.

Despite the high number of live donor kidney transplantations in Turkey, the surgical techniques for LDN have not been widely studied. This study evaluates the LDN techniques performed in Turkey, the structure of surgical teams, and the training received. Additionally, the number of kidney transplant-

ations at different centers, the surgeon experience level, differences in surgical approach during donor surgeries, and outcomes were assessed.

MATERIALS AND METHODS

This study was conducted by the University of Health Sciences, Diskapi Training and Research Hospital, Department of Surgery after approval from the institutional ethical review committee (83/06). A previously used questionnaire to screen kidney transplant centers in Europe was modified for Turkish transplant centers and used for study purposes[7]. The questionnaire was prepared using online survey software (SurveyMonkey®, California, United States). It was sent *via* e-mail to the transplant surgeon, nephrologist, or urologist working in the transplant centers registered with the Turkish Ministry of Health. The e-mail addresses were retrieved from the Turkish Ministry of Health database and several national transplant society websites.

In May 2020, the first round of questionnaires was sent out, while the second round was sent in September 2020. Data collection was closed after the last questionnaire was received on December 2, 2020. The questionnaire consisted of questions regarding the number of living donor nephrectomies performed in 2019, surgical techniques used, the experience of primary surgeons, and the training they had received. Data regarding average blood loss, donor warm ischemia time (DWIT), surgical complications, preferred nephrectomy side, and kidney extraction site were also interrogated. All donors included in the study were live and related to the recipient.

Statistical analysis

Data analysis was performed using IBM SPSS (Statistical Package for Social Sciences) Statistics 17.0 (IBM Corporation, Armonk, NY, United States) software. The Shapiro-Wilk test was used to determine whether the distribution of discrete numerical variables was close to normal. Descriptive statistics were outlined as follows: Discrete numeric variables were expressed as medians (minimum-maximum); and categorical variables were shown as numbers and percentages. As a result of the goodness-of-fit tests, if the significance of the differences between the groups in terms of discrete numerical variables for which the parametric test statistical assumptions were not met, data were analyzed with the Mann-Whitney *U* test. In the 2 × 2 cross-tabs, if the expected frequency was below 5 in at least one-quarter of the cells, the categorical data were evaluated by Fisher's exact probability test. The χ^2 test with continuity correction was used when the expected frequency was between 5-25. If no more than one-fifth of the cells had expected values equal to or less than 5, the categorical data were evaluated using the Fisher-Freeman Halton test. For $P < 0.05$, the results were considered statistically significant.

RESULTS

The questionnaire was sent to 72 kidney transplant centers, all of which replied. Five centers that reported not performing live donor kidney transplants were excluded. The responses from the remaining 67 centers were analyzed. In 2019, the median number of kidney transplants performed was 45 (1-484), and the median number of kidney transplants from living donors was 28 (1-238) (Table 1). Eleven centers (16.5%) reported performing 5-10, whereas 34 (50.7%) reported performing more than 100 live donor kidney transplants during 2019. Nineteen (28.4%) centers performed LDN using the open technique and 48 (71.6%) using minimally invasive techniques.

Composition and training of the surgical team

LDNs were carried out by a transplant surgeon in 27 centers (40.3%), by a general surgeon in 24 centers (35.8%), and by a urologist in 16 centers (23.9%) (Table 1). The surgical experience was 5 or more years in 42 centers (62.7%), whereas 12 centers (17.9%) were newly established with 1-3 years of experience in donor nephrectomies. In addition, the technique for LDN was adopted through fellowship training in 28 centers (41.8%), surgical residency training in 22 centers (32.8%), workshops and courses in 14 centers (20.9%), and other routes in 13 centers (19.4%). Fifty-seven centers (85.1%) reported having a second surgeon as a backup. Only 10 centers (14.9%) did not have a backup surgeon. The average blood loss ranged between 0-100 mL during LDN in 52 centers (77.6%). Ten centers (14.9%) reported an average of 100-200 mL blood loss. Sixty-one centers (91%) reported a DWIT of 1-5 min, while DWIT was 5-10 min in 4 centers (0.6%) and 10-15 min in 2 centers (0.3%). Forty-nine centers (73.1%) recorded surgeries for optimization. Technical troubleshooting protocol was in place in 61 centers (91%).

Minimally invasive techniques

Among the 48 centers preferring minimally invasive techniques for LDN, 8 (16.6%) implemented more than one surgical technique. The surgical techniques and number of centers using these methods are displayed in Figure 1. As can be seen in this figure, transperitoneal laparoscopic donor nephrectomy

Table 1 Transplant center characteristics, composition, and training of the surgical team

Characteristics	Values
Number of kidney transplants performed in 2019	45 (1-484)
Number of kidney transplants from living donors in 2019	28 (1-238)
Number of donor nephrectomies performed in 2019 percenter	
5-10	11 (16.5%)
11-25	6 (9.0%)
26-50	9 (13.4%)
51-100	7 (10.4%)
> 100	34 (50.7%)
Primary surgeon	
General surgeon	24 (35.8%)
Urologist	16 (23.9%)
Transplant surgeon	27 (40.3%)
Live donor nephrectomy technique	
Open donor nephrectomy	19 (28.4%)
Minimally invasive techniques	48 (71.6%)
Number of years using the preferred technique	
1-3 yr	12 (17.9%)
3-5 yr	13 (19.4%)
> 5 yr	42 (62.7%)
Type of training received by the surgeon	
Fellowship training	28 (41.8%)
Residency training	22 (32.8%)
Surgical courses	14 (20.9%)
Other	13 (19.4%)

was the most commonly performed technique, while single port laparoscopic donor nephrectomy was the least common technique.

The left donor nephrectomy was favored in 26 transplant centers (54.3%). The conversion rate was below 1% in 58 centers (86.5%). Eight centers (11.9%) reported a conversion rate between 1%-3%, and only 1 center (1.5%) reported a conversion rate of 3%-5%. The most frequent reason for conversion was venous bleeding (n = 10, 20.8%). Other reasons were abdominal adhesions (n = 8, 16.7%), technical problems related to gadgets and devices (n = 7, 14.6%), arterial bleeding (n = 5, 10.4%), adjacent organ injury (n = 1, 2.1%), and miscellaneous (n = 1, 2.1%).

Thirty-four surgeons (50.7%) stated having performed more than 100 donor nephrectomies as the primary surgeon with the accustomed technique in 2019 (Table 1). On the other hand, 11 surgeons (16.5%) reported performing 5-10 donor nephrectomies as the primary surgeon. There was a positive association between the performance of minimally invasive techniques and the case volume of a transplant center regarding both the total number of transplants and live donor kidney transplants (15 *vs* 55, P = 0.001 and 9 *vs* 42, $P \leq 0.001$ respectively) (Figure 2).

Variations in the minimally invasive techniques

Nine centers (18.8%) reported using hand assistance, whereas 39 centers (81.2%) did not. While 41 centers (85.4%) reported using vascular staplers for division of the renal pedicle, 6 centers (12.5%) used self-locking surgical clips, and 1 center (2.1%) titanium clips. Modification of the surgical technique due to anatomical variations or body mass index of the donor was not preferred in 56.7% and 68.7% of the centers, respectively. Pfannenstiel incision was the most preferred extraction site for the kidney (n = 30, 62.5%). It was followed by the paramedian (n = 9, 18.7%), midline (n = 7, 14.6%), and modified incisions (n = 2, 4.2%).

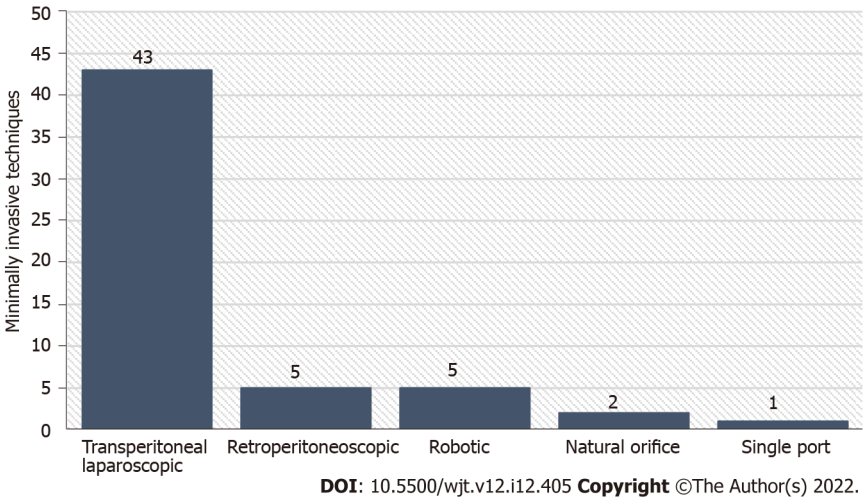

Figure 1 Distribution of minimally invasive techniques for donor nephrectomy.

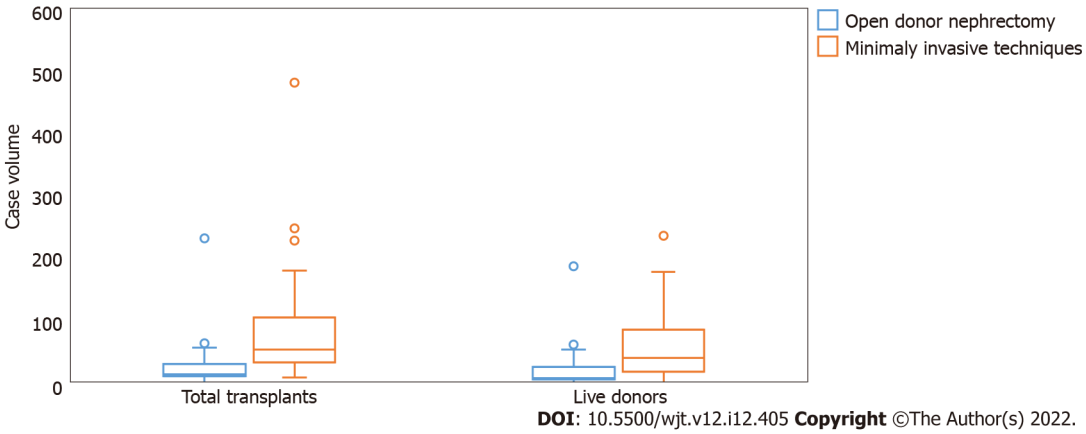

Figure 2 Association of minimally invasive technique usage and case volume.

Complications of donor nephrectomy surgeries

The most frequently reported complication was postoperative atelectasis (n = 33, 49.2%), while the second most frequent complication was bleeding requiring blood transfusion (n = 25, 37.3%) (Figure 3). Wound infection, hernia, and chyle leak were also reported (n = 22, 33.8%). Thirty-nine centers (81.2%) reported an incisional hernia rate of 1%-5%, while 6 centers (12.5%) reported a rate of 5%-10%, and 3 centers (6.3%) reported 10%-20%. Surgical site fluid collections, ileus, deep venous thrombosis, pneumonia, and urinary retention were also reported. Graft loss due to inadvertent intraoperative damage was encountered in two transplant centers (2.9%) (Figure 3). The rates of these declared complications did not differ among the centers using open and minimally invasive techniques except for the chyle leak (Table 2). Chyle leak was reported significantly more frequently by centers using the minimally invasive techniques (P = 0.006).

DISCUSSION

Persistent organ shortage has led to increased interest in live organ donation. As a result, the number of live kidney transplantations is increasing annually. It was previously reported that minimally invasive techniques for LDN might increase the number of donations. Nonetheless, the critical principle in live organ donation is the safety of the donor[8]. Therefore, donor safety should always be the greatest determinant when deciding on the LDN technique[9]. This study presented a cross-sectional view of the techniques of LDN, transplant team composition, training, and the list of the complications encountered at Turkish kidney transplant centers.

Our findings were similar to those of Klop *et al*[10]. They reported that 59 of the transplant centers in Europe performed minimally invasive techniques for LDN[10]. In their survey, 48 European transplant

Table 2 Rates of declared postoperative complications

	Centers performing open donor nephrectomy, *n* = 19%	Centers performing minimally invasive techniques, *n* = 48%	*P* value
Bleeding	7 (36.8%)	18 (37.5%)	> 0.999
Chyle leak	1 (5.3%)	21 (43.8%)	0.006
Surgical site fluid collection	5 (26.3%)	14 (29.2%)	> 0.999
Urinary retention	0 (0.0%)	2 (4.2%)	> 0.999
Atelectasis	11 (57.9%)	22 (45.8%)	0.536
Pneumonia	0 (0.0%)	2 (4.2%)	> 0.999
Deep vein thrombosis	3 (15.8%)	1 (2.1%)	0.066
Ileus	0 (0.0%)	6 (12.5%)	0.173
Hernia	5 (26.3%)	17 (35.4%)	0.670
Graft loss	1 (5.3%)	1 (2.1%)	0.490
Wound infection	7 (36.8%)	15 (31.3%)	0.880

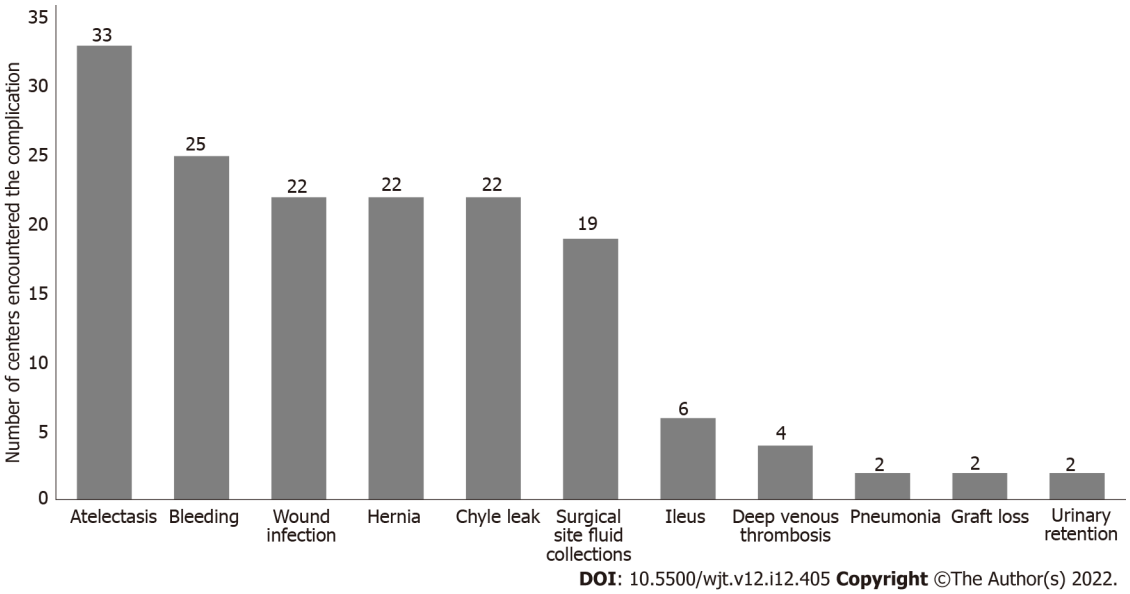

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Figure 3 Complications of donor nephrectomy surgeries.

centers used the laparoscopic approach, and 9 centers used the retroperitoneoscopic approach. In our study, 48 centers reported performing minimally invasive techniques. Among those, 43 used the laparoscopic approach, and 5 used retroperitoneoscopic methods. In line with the American and European centers, robotic surgery is also used for LDN in Turkey[11,12]. Five transplant centers in our study reported implementing robotic-assisted techniques. In 2009, only two centers in Europe used robotic-assisted techniques. However, this number increased gradually, with several case series being published in the literature[13-16].

In our survey, 19 centers reported using the open technique for donor nephrectomy. This result was in accordance with the findings of the European survey, which reported that 37 centers performed open donor nephrectomies[10]. This similarity indicates the international trend for minimally invasive techniques. As per the literature, the total number of kidney transplants and live donor kidney transplants is in line with the increased use of minimally invasive donor nephrectomy techniques in Turkish transplant centers[4,7,10].

A comparison of the centers regarding case volumes revealed a significant variation among centers in this regard. Thirty-four centers performed more than 100 live donor kidney transplants in 2019. These centers represented 50.7% of the transplant centers enrolled in our study. While these centers performed more than 3400 kidney transplants, the remaining 33 centers performed approximately 200 live donor kidney transplants in total. This disproportionate distribution can be explained by the higher number of

live donations in highly populous cities of Turkey, such as Istanbul and Ankara. On the other hand, in Europe, as of 2009, only four centers were performing more than 100 live donor kidney transplants per year, while 30 centers were performing fewer than 100 live donor kidney transplants[10].

The spectrum of postoperative complications did not differ between the centers performing minimally invasive donor nephrectomy and those performing open donor nephrectomy. Among all complications, only chyle leak was more frequently encountered in the centers using minimally invasive techniques. Two centers reported graft loss due to intraoperative damage of the graft: One from a center using open donor nephrectomy and the other from a minimally invasive center. In our study, the relationship between the caseload of the transplant center and the complication of graft loss could not be analyzed due to the small numbers.

The team setup and staff training in Turkish transplant centers demonstrate similar results with the other transplant centers in the United States and Europe, where 41.8% of the staff have received fellowship training for organ transplantation[17,18]. Our findings revealed that most (*i.e.*, 40.3) of the LDN procedures were performed by transplant surgeons in Turkish transplant centers. A scientific committee that consists of experienced transplant surgeons, nephrologists, transplant coordinators, and hepatologists evaluates the surgical trainee in terms of scientific and surgical qualifications for transplant proficiency. If the requirements are satisfied, then a certificate is given to the surgeon as a transplant surgeon. This certificate grants the surgeon to lead a transplant surgical team and perform transplants in his/her hospital.

The average blood loss ranged between 0-100 mL in 77.6% of the transplant centers in Turkey. The amount of blood loss and DWIT were compatible with the literature[19-22]. Technical troubleshooting protocol was in place and intraoperative video recording was routinely performed in the majority of the transplant centers in Turkey.

Eight centers in our study reported using more than one surgical technique. As a matter of course, performing LDN with more than one surgical technique provides advantages. These advantages are selecting the best technique for the donor and the ability to adapt the preferred technique to the donor anatomy, body mass index, surgical history, and abdominal adhesions. As an additional advantage, it can reduce the risk of conversion to open surgery. For example, in cases of venous bleeding, which was reported as the most common cause of conversion in our study, the surgeon can complete the surgery with a hand-assisted technique by placing an additional hand port.

To our knowledge, this is the first study evaluating donor nephrectomy techniques in Turkey. All transplant centers performing LDN responded to the survey and were included in our analysis. However, this study has some limitations which need to be considered while evaluating its findings. First, it is a survey study, and the reliability of the data depends on the accuracy of the answers and the honesty of the responders. Second, our findings could have been affected by a recall bias. However, this study provides an overview of the centers performing LDN in Turkey despite these limitations. The results of this study and future similar studies may act as instruments revealing any weaknesses that may need improvement.

CONCLUSION

Turkey is one of the leading countries for live organ donation. In this article we explored the transplant climate in Turkey *via* a detailed survey sent to transplant program directors. The questionnaire was sent to 72 kidney transplant centers, all of which replied. In 2019, the median number of kidney transplants performed was 45 (1-484), and the median number of kidney transplants from living donors was 28 (1-23). Among the 48 centers preferring minimally invasive techniques for LDN, 8 (16.6%) implemented more than one surgical technique. Transperitoneal laparoscopic donor nephrectomy was the most commonly performed technique, while single port laparoscopic donor nephrectomy was the least common technique. There was a positive association between the performance of minimally invasive techniques and the case volume of a transplant center regarding both the total number of transplants and live donor kidney transplants. To our knowledge, this is the first study evaluating donor nephrectomy techniques in Turkey. Therefore, this study represents the national transplant environment in Turkey.

ARTICLE HIGHLIGHTS

Research background

Minimally invasive surgical techniques for live donor nephrectomy (LDN) are varied. These techniques include hand-assisted laparoscopic, retroperitoneoscopic, single port, natural orifice, and robotic nephrectomy techniques. Turkey has a high number of live kidney donors. The reports regarding LDN in Turkey are missing. In this study, we demonstrated the center volume, preferred techniques for LDN, complications, team setup, and training of transplant teams.

Research motivation
In 2019 according to the Turkish Ministry of Health data, 3963 kidney transplantations were performed in Turkey. Among these patients, 3548 were transplanted from live donors. This increased living donor rate stimulated interest in various surgical techniques applied in Turkey and LDN practice.

Research objectives
To gain insight into the practices of LDNs in Turkish transplant centers.

Research methods
A questionnaire was sent to the Turkish Ministry of Health-accredited transplant centers. It inquired of the number of LDN surgeries, surgical techniques, complications, optimization protocols, the experience of surgeons, and the training. Descriptive statistics were outlined as follows: Discrete numeric variables were expressed as medians (minimum-maximum), while categorical variables were shown as numbers and percentages. As a result of the goodness-of-fit tests, if the significance of the differences between the groups in discrete numerical variables for which the parametric test statistical assumptions were not met, data were analyzed with the Mann Whitney U test and the χ^2 test.

Research results
The questionnaire was sent to registered transplant centers in Turkey. All 72 centers replied. In 2019, the median number of kidney transplants performed was 45 per center, and the median number of kidney transplants from living donors was 28. There was a wide range between the centers in terms of transplant numbers (1-238 transplant per year). The open technique was preferred by 19 centers (28.4%). The minimally invasive LDN was performed by 48 centers (71.6%). Among the centers, 8 (16.6%) used more than one surgical technique. A positive correlation between the performance of minimally invasive LDN and the case volume of a transplant center, both in the total number of transplants and live donor kidney transplants, existed (15 *vs* 55, $P = 0.001$ and 9 *vs* 42, $P \leq 0.001$ respectively). The most frequently reported complication was postoperative atelectasis ($n = 33$, 49.2%).

Research conclusions
The analysis of the questionnaire answers revealed that Turkish transplant centers successfully performed LDN operations using various techniques. A relatively higher numbers of living donor kidney transplants were performed in 2019 at centers using minimally invasive techniques.

Research perspectives
The data regarding the annual kidney transplant numbers, complication rates, and center successes should be released by the Ministry of Health in Turkey. This would allow the control and improvement of the transplant centers when necessary. Despite this, the current status of Turkish transplant centers, as observed in the results of this study, is comparable to transplant centers in Europe and the United States.

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FOOTNOTES

Author contributions: Mankiev B and Cimen SG designed the research; Cimen S and Kaya IO performed the research; Eraslan A collected data; Cimen S analyzed data; Cimen SG wrote the paper.

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Informed consent statement: The participants were informed about the questionnaire *via* e-mail, and after an online consent process the Survey Monkey questionnaire link was shared.

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ORCID number: Bakytbek Mankiev 0000-0002-4995-1128; Sanem Guler Cimen 0000-0002-5266-9529; Ismail Oskay Kaya 0000-0002-1864-896X; Sertac Cimen 0000-0002-0252-8840; Asir Eraslan 0000-0002-2204-1327.

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REFERENCES

1 **Caliskan G**, Sayan A, Kilic I, Haki C, Kelebek Girgin N. Has the COVID-19 Pandemic Affected Brain Death Notifications and Organ Donation Time? *Exp Clin Transplant* 2021 [PMID: 34387157 DOI: 10.6002/ect.2021.0090]
2 **Böbrek Sağlığı Hakkında**. Güncel Organ Bağış Ve Nakil İstatistikleri. [cited 16 July 2022]. Available from: https://www.tbv.com.tr/bobrek-sagligi/guncel-organ-bagis-ve-nakil-i-statistikleri/
3 **Ratner LE**, Ciseck LJ, Moore RG, Cigarroa FG, Kaufman HS, Kavoussi LR. Laparoscopic live donor nephrectomy. *Transplantation* 1995; **60**: 1047-1049 [PMID: 7491680]
4 **Dols LF**, Kok NF, Ijzermans JN. Live donor nephrectomy: a review of evidence for surgical techniques. *Transpl Int* 2010; **23**: 121-130 [PMID: 20003169 DOI: 10.1111/j.1432-2277.2009.01027.x]
5 **Mjøen G**, Holdaas H, Pfeffer P, Line PD, Øyen O. Minimally invasive living donor nephrectomy - introduction of hand-assistance. *Transpl Int* 2010; **23**: 1008-1014 [PMID: 20412538 DOI: 10.1111/j.1432-2277.2010.01087.x]
6 **Schweitzer EJ**, Wilson J, Jacobs S, Machan CH, Philosophe B, Farney A, Colonna J, Jarrell BE, Bartlett ST. Increased rates of donation with laparoscopic donor nephrectomy. *Ann Surg* 2000; **232**: 392-400 [PMID: 10973389 DOI: 10.1097/00000658-200009000-00011]
7 **Kok NF**, Weimar W, Alwayn IP, Ijzermans JN. The current practice of live donor nephrectomy in Europe. *Transplantation* 2006; **82**: 892-897 [PMID: 17038903 DOI: 10.1097/01.tp.0000235511.19629.0d]
8 **Kortram K**, Lafranca JA, IJzermans JN, Dor FJ. The need for a standardized informed consent procedure in live donor nephrectomy: a systematic review. *Transplantation* 2014; **98**: 1134-1143 [PMID: 25436923 DOI: 10.1097/TP.0000000000000518]
9 **Merlin TL**, Scott DF, Rao MM, Wall DR, Francis DM, Bridgewater FH, Maddern GJ. The safety and efficacy of laparoscopic live donor nephrectomy: a systematic review. *Transplantation* 2000; **70**: 1659-1666 [PMID: 11152094 DOI: 10.1097/00007890-200012270-00001]
10 **Klop KW**, Dols LF, Kok NF, Weimar W, Ijzermans JN. Attitudes among surgeons towards live-donor nephrectomy: a European update. *Transplantation* 2012; **94**: 263-268 [PMID: 22790449 DOI: 10.1097/TP.0b013e3182577501]
11 **Serni S**, Pecoraro A, Sessa F, Gemma L, Greco I, Barzaghi P, Grosso AA, Corti F, Mormile N, Spatafora P, Caroassai S, Berni A, Gacci M, Giancane S, Tuccio A, Sebastianelli A, Li Marzi V, Vignolini G, Campi R. Robot-Assisted Laparoscopic Living Donor Nephrectomy: The University of Florence Technique. *Front Surg* 2020; **7**: 588215 [PMID: 33521044 DOI: 10.3389/fsurg.2020.588215]

12 **Geffner S**, Klaassen Z, Tichauer M, Chamberlain RS, Paragi PR. Robotic-assisted laparoscopic donor nephrectomies: early experience and review of the literature. *J Robot Surg* 2011; **5**: 115-120 [PMID: 27637537 DOI: 10.1007/s11701-011-0245-z]

13 **Janki S**, Klop KWJ, Hagen SM, Terkivatan T, Betjes MGH, Tran TCK, Ijzermans JNM. Robotic surgery rapidly and successfully implemented in a high volume laparoscopic center on living kidney donation. *Int J Med Robot* 2017; **13** [PMID: 26987773 DOI: 10.1002/rcs.1743]

14 **Giffen ZC**, Cairl N, Ortiz J, Sindhwani P, Ekwenna O. Robotic-assisted Donor Nephrectomy: As Safe as Laparoscopic Donor Nephrectomy. *Surg Technol Int* 2020; **37**: 171-174 [PMID: 32520390]

15 **LaMattina JC**, Alvarez-Casas J, Lu I, Powell JM, Sultan S, Phelan MW, Barth RN. Robotic-assisted single-port donor nephrectomy using the da Vinci single-site platform. *J Surg Res* 2018; **222**: 34-38 [PMID: 29273373 DOI: 10.1016/j.jss.2017.09.049]

16 **Cohen AJ**, Williams DS, Bohorquez H, Bruce DS, Carmody IC, Reichman T, Loss GE Jr. Robotic-assisted laparoscopic donor nephrectomy: decreasing length of stay. *Ochsner J* 2015; **15**: 19-24 [PMID: 25829876]

17 **Özdemir-van Brunschot DM**, Warlé MC, van der Jagt MF, Grutters JP, van Horne SB, Kloke HJ, van der Vliet JA, Langenhuijsen JF, d'Ancona FC. Surgical team composition has a major impact on effectiveness and costs in laparoscopic donor nephrectomy. *World J Urol* 2015; **33**: 733-741 [PMID: 25362559 DOI: 10.1007/s00345-014-1428-9]

18 **Raque J**, Billeter AT, Lucich E, Marvin MM, Sutton E. Training techniques in laparoscopic donor nephrectomy: a systematic review. *Clin Transplant* 2015; **29**: 893-903 [PMID: 26179472 DOI: 10.1111/ctr.12592]

19 **Gimenez E**, Leeser DB, Wysock JS, Charlton M, Kapur S, Del Pizzo JJ. Laparoendoscopic single site live donor nephrectomy: initial experience. *J Urol* 2010; **184**: 2049-2053 [PMID: 20850822 DOI: 10.1016/j.juro.2010.06.138]

20 **Friedman AL**, Peters TG, Jones KW, Boulware LE, Ratner LE. Fatal and nonfatal hemorrhagic complications of living kidney donation. *Ann Surg* 2006; **243**: 126-130 [PMID: 16371747 DOI: 10.1097/01.sla.0000193841.43474.ec]

21 **Biancofiore G**, Amorose G, Lugli D, Bindi L, Esposito M, Fossati N, Meacci L, Pasquini C, Pieri M, Boggi U, Pietrabissa A, Mosca F. Perioperative management for laparoscopic kidney donation. *Minerva Anestesiol* 2003; **69**: 681-686, 686 [PMID: 14564238]

22 **Mateo R**, Henderson R, Jabbour N, Gagandeep S, Goldsberry A, Sher L, Qazi Y, Selby RR, Genyk Y. Living related donor nephrectomy in transfusion refusing donors. *Transpl Int* 2007; **20**: 490-496 [PMID: 17313445 DOI: 10.1111/j.1432-2277.2007.00464.x]

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