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**Review of heart transplantation from hepatitis C-positive donors**

Patel P *et al*. Heart transplantation from hepatitis C-positive donors

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**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

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**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.

**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 infectionwith 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 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 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.

**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? A consensus conference report. *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**, McGreger 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 207-8 [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, 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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**Table 1 Heart transplantation from hepatitis C virus-positive donors in the pre-direct-acting antivirals era**

|  |  |  |  |
| --- | --- | --- | --- |
| **Study** | **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.

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

|  |  |  |  |
| --- | --- | --- | --- |
| **Study** | **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.