Characteristics and Outcomes of Patients Undergoing Combined Organ Transplantation (from the United Network for Organ Sharing)

Alexandros Briasoulis, MD, PhD*, Emmanuel Akintoye, MD, MPH, Toshiki Kuno, MD, PhD, and Paulino Alvarez, MD

Studies have shown that highly selected patients who underwent combined heart-kidney (HK) and heart-liver transplants (HLv) have short- and long-term outcomes comparable to those observed in primary heart transplantation (HT). Adults patients with stage D heart failure that underwent combined HK, HLv, and heart-lung (HL) were identified in the United Network for Organ Sharing registry from 1991 to 2016, with follow-up through March 2018. We conducted inverse probability of treatment weighting survival analysis of long-term survival stratified by type of combined organ transplant, accounting for donor, recipient, and operative characteristics. We identified 2,300 patients who underwent combined organ transplant (HK 1,257, HLv 212, HL 831). HL recipients were more likely white (77%), women (58%), with congenital heart disease (44.5%), and longer waiting list time (median 195 days). HK transplant increased significantly during the study period where as HL decreased significantly. Median survival was 12.2 years for HK (95% confidence intervals [CI] 10.8 to 12.8), 12 for HLv (95% CI 8.6 to 17.6) but significantly lower at 4.5 years for HL (95% CI 3.6 to 5.8). Combined HK and HLv transplantation rates are increasing and long-term survival is comparable to primary HT, unlike HL which is associated with decreasing trends and significantly lower survival. **(Am J Cardiol 2020;129:42−45)**

Patients with stage D Heart Failure (HF) and severe irreversible dysfunction of another organ are not candidates for isolated heart transplantation (HT). For highly selected patients, multiorgan transplantation (MT) is an option despite the complex medical and surgical aspects of this approach. MT rates have gradually increased since 1990[1] and in 2016 they comprised approximately 4% of all HT cases. The majority of MT is combined heart-kidney transplantation (HK) and it occurs more frequently in the setting of heart retransplantation, mainly due to calcineurin-inhibitor induced nephrotoxicity,[1] followed by heart-lung transplantation (HL) and heart-liver (HLv) transplantation. Interestingly, MT recipients exhibit lower rates of acute rejection and cardiac allograft vasculopathy, but higher rates of infectious complications compared with isolated HT recipients.[1] Despite the surgical complexity of MT, the current era outcomes of MT are comparable with these of isolated HT recipients. After taking into consideration the currently available evidence on MT, we sought to analyze a multicenter nationally representative dataset and further evaluate: (1) the characteristics of the most frequent MT recipients (HK, HL, and HLv), and (2) long-term outcomes after MT.

Methods

For the present analysis we utilized data from the United Network for Organ Sharing (UNOS) database registry. The UNOS registry follows longitudinally all prospective candidates listed for organ transplantation, documenting any change in status and date of any transplant. Also, it records additional clinical information at the time of transplant and continues to follow the recipients after transplantation. Available data in this registry include standard demographic, clinical, and laboratory information at the time of listing and transplantation, priority to receive an organ and long-term outcomes such as all-cause mortality. Among those patients included in this registry, we selected adult recipients of HK, HL, HLv transplantation from January 1991 to December 2016 with follow-up through March 2018. The main outcome was all-cause mortality after transplantation.

Patients were classified based on type of combined transplantation into HK, HL, and HLv. We compared baseline characteristics between the 3 groups using chi-square test for categorical variables and Kruskal-Wallis test for continuous variables. We then evaluated the association between combined transplantation status and all-cause mortality in separate analysis. The survival curves were estimated using the nonparametric Kaplan-Meier curve which is an acceptable estimator of the survival function. Using the Kaplan-Meier estimator, we were able to estimate the median survival without making assumption about the distribution of the data. To account to differences in baseline characteristics and potential confounding, we performed weighted Cox proportional−hazards regression models

Division of Cardiovascular Diseases, Section of Heart Failure and Transplant, University of Iowa Hospitals and Clinics, Iowa City, Iowa. Manuscript received April 6, 2020; revised manuscript received and accepted May 19, 2020.

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*Corresponding author: Tel: (319) 678-8418; fax: (319) 353-6343.
E-mail address: alexbriasoulis@gmail.com (A. Briasoulis).

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with inverse−probability−of−treatment weighting (teffect ipw order in STAT) for the treatment groups among patients with HK, HL, and HLv, that accounted for donor characteristics (age, gender, ethnicity, body mass index [BMI], history of cancer, cause of death), recipient characteristics (age, gender, ethnicity, previous cardiac surgery, indication for transplant, mechanical circulatory support at transplant, ventilator-dependent at transplant), donor-recipient gender mismatch, ischemic time, transplant center. When using this method, a weight is calculated for each subject that is equal to the inverse of the probability of receiving the treatment that was actually received. This approach was preferred over propensity-score matching to achieve the largest possible study sample.[2] The results are summarized as hazard ratios (HRs) and 95% confidence intervals (CIs). All analyses were performed using STATA 15 (StataCorp, College Statin, Texas) with level of significance set at 0.05.

Results

We identified a total of 51,231 patients who underwent HT, 1,552 who underwent heart re-transplantation and 2,300 adults (HK 1,257, HL 831, HLv 212, 2.28%, 1.51%, 0.38% of all heart transplants respectively) who underwent MT from 1991 to 2016. The patient characteristics are presented in Table 1. HL patients were younger (39.3 vs 52.6 vs 48.6 for HL, HK, HLv respectively, p <0.001), more frequently women (58% vs 21.9% vs 27.8% for HL, HK, HLv respectively, p <0.001) and white (77% vs 59.4% vs 68.8% for HL, HK, HLv, respectively, p <0.001), more likely to receive organs from a female donor (49.5% vs 29% vs 25.4% respectively, p <0.001), and with longer median time from listing to transplantation (195 vs 97 vs 123 days, for HL, HK, HLv, respectively, p <0.001). HK patients were more frequently African-American (27.9% vs 9.9% vs 27.8% for HK, HL, HLv, respectively, p <0.001) with higher rates of diabetes mellitus (38.3%, vs 7% vs 13%, for HK, HL, HLv, respectively, p <0.001). The indications for each type of MT differed; congenital heart disease (CHD) was the most common indication for HL in 44.5% of cases, restrictive cardiomyopathy (32%), dilated cardiomyopathy (31.6%) and CHD were the most frequent indications for HLv, whereas dilated cardiomyopathy (70.1%) and heart retransplantation (14.5%) were the main indications for HK cases. Significantly more patients with HK underwent heart retransplantation (14.5% vs 0.6% vs 0.47% for HLv, p <0.001).

During the study period the rates of HK and HLv transplantation increased significantly whereas the HL rates decreased significantly. Particularly HK transplantation cases per year more than doubled since 2010 (Figure 1). One-year survival was significantly higher in HLv and HK compared with HL transplantation (87% vs 86% vs 70%, p <0.001). As shown in Figure 2, the median survival was 12.2 years for HK (95% CI 10.8 to 12.8), 12 for HLv (95% CI 8.6 to 17.6) but significantly lower at 4.5 years for HL (95% CI 3.6 to 5.8; p <0.001). During the same period the median survival for isolated first-time HT was 11.2 years (95% CI 11.1 to 11.4 years) and for heart retransplantation was significantly lower (8.7 years, 95% CI 7.9 to 9.5 years, p <0.001). In a subgroup analysis of patients transplanted in the last 10 years of available data in this database (2006 to 2016), the 5-year survival was 78% for HK, 82% HLv, 52% for HL, and 77% for isolated first-time HT (p <0.001, Figure 3). The median survival was significantly higher with isolated first-time HT compared with all MT together

Table 1
Baseline characteristics of patients undergoing multiorgan transplantation

	Lung	Kidney	Liver
No. of transplants	831	1,257	212
Donor characteristics			
Donor age, mean (SD)	28.9 (12.9)	31.3 (11.8)	30.7 (11.6)
Female donor	49.5%	29.0%	25.4%
Donor ethnicity			
White	68.1%	64.7%	61.7%
Black	11.1%	14.0%	16.0%
Hispanic	16.2%	18.5%	18.4%
Asian	3.0%	1.5%	2.8%
Recipient characteristics			
Recipient age, mean (SD)(years)	39.3 (11.4)	52.6 (11.7)	48.3 (13.0)
Female recipient	58.0%	21.9%	27.8%
Recipient ethnicity			
White	77.0%	59.4%	68.8%
Black	9.9%	27.9%	18.8%
Hispanic	7.7%	7.9%	9.4%
Asian	3.8%	3.5%	1.4%
Diabetes mellitus	7.0%	38.3%	13.0%
Body mass index (kg/m2) (SD)	23.0 (4.5)	26.2 (5.0)	25.3 (4.6)
Primary diagnosis			
Dilated cardiomyopathy*	4.4%	70.1%	31.6%
Restrictive cardiomyopathy	1.5%	3.1%	32.0%
Congenital heart disease	44.5%	1.6%	19.3%
Re-transplant	0.60%	14.5%	0.47%
Median time from listing to transplant (days)	195.0 (59-502)	97 (38-253)	123 (48-304)

* In this database, dilated cardiomyopathy includes cases of idiopathic, chemotherapy-induced, peri-partum, alcoholic, viral (myocarditis), familial and ischemic cardiomyopathies, distinct from restrictive, valvular, arrhythmogenic right ventricular cardiomyopathies, congenital heart disease and other types of cardiomyopathy.

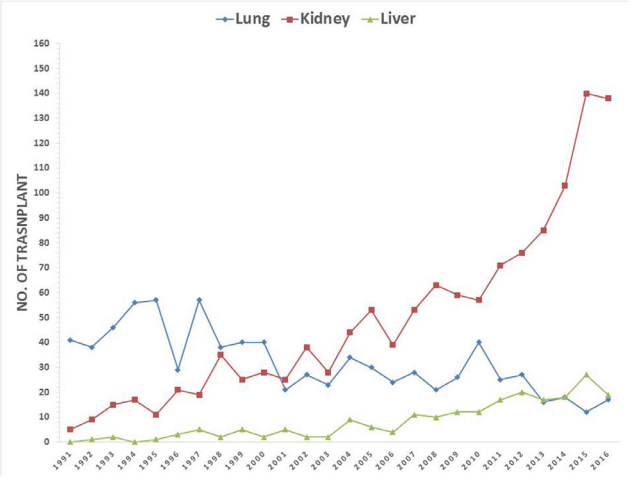

Figure 1. Trends in multiorgan transplantation.

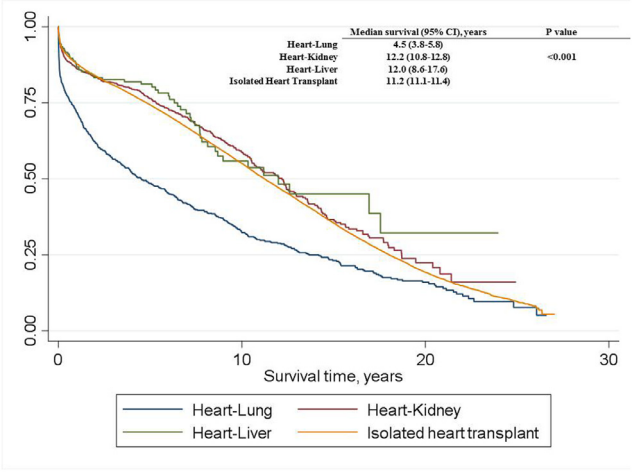

Figure 2. Differences in survival among different combined transplantation types and isolated heart transplantation with the use of inverse-probability weighted estimator that accounts for donor and recipients characteristics.

(11.2 years vs 9.5 years, p <0.001). However, when HL transplantation was excluded, median survival was not significantly different between isolated first-time HT and HK or HLv transplantation (11.2 years vs 12 years, p = 0.77). The top 3 causes of death for HLv transplantation were infections (15.9%), pulmonary complications (11.1%) and multiorgan failure (9.5%), Infections (19.7%), malignancies and cardiovascular events (9.4%) were the main causes of death for HK recipients, whereas pulmonary complications (17.7%), infections (17.4%) and cardiovascular events (7.4%) were the main causes of death for HL recipients.

With regards to complication rates, overall rejection rates were significantly lower in HLv compared with HK and HL patients at one year post-transplantation (3.6% vs 11.5% vs 41% respectively, p <0.001). Similarly, primary graft failure was significantly lower in HLv recipients compared with HK and HL (1.4% vs 4.7% vs 12.8%, p <0.001).

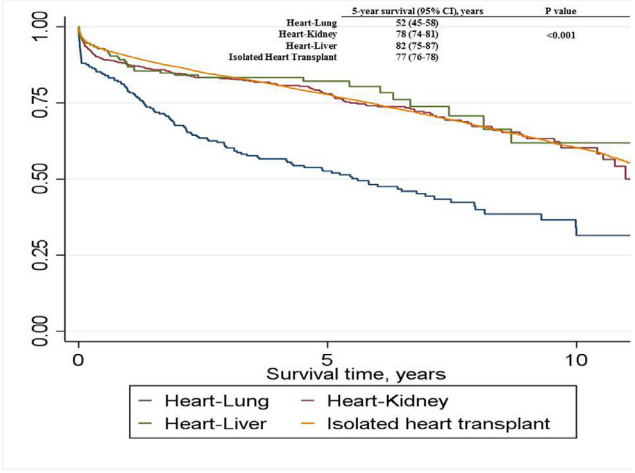

Figure 3. Differences in survival among different combined transplantation types and isolated heart transplantation from 2006 to 2016.

Discussion

The salient findings of this analysis of combined organ HT from 1991 to 2016 from a nationally representative multicenter database, can be summarized as follows: (1) HK patients were more likely older, African-American, diabetic males with higher rates of heart re-transplantation, (2) HL patients were more likely younger women with CHD, (3) HK and HLv transplantation rates increased significantly whereas HL transplantation rates decreased during the study period, (4) median survival of HK and HLv transplantation are significantly higher than HL and comparable (numerically higher) with isolated fist-time HT, and (5) rejection rates and primary graft failure were the lowest among HLv and the highest among HL recipients.

Combined HK transplantation is indicated for patients with combined stage D HF and end-stage renal disease and since the first report of HK transplantation from a single donor in 1978,[3] the rates of this type of combined transplantation are increasing out of proportion to isolated first-time HT.[4] Impaired renal function before HT is frequent among stage D HF patients and can worsen after HT due to long-term calcineurin inhibitor nephrotoxicity. Renal transplantation is indicated and can be performed simultaneously with HT or as a later procedure to treat advanced kidney disease after HT. Isolated HT recipients with estimated GFR less than 30 ml/minute have worse survival than HK recipients.[4] Evidence from retrospective observational studies suggests similar long-term survival between HK and isolated HT with lower rates of acute rejection and allograft vasculopathy.[5,6] A previous analysis of simultaneous HK versus renal transplantation after previous HT[7] showed similar overall survival but inferior allograft kidney survival among previous HT recipients. Our data confirm the excellent outcomes of HK transplantation and preemptive HK transplantation may be the preferred approach instead of delayed renal transplantation after HT. Also, our analysis confirmed previous observations of similar long-term survival between HLv and isolated HT. The rates of HLv transplantation have increased but remain low, approximately 20 to 30 cases per year, and they are performed in specialized centers with the main indication being familial transthyretin amyloidosis.[8,9] Interestingly, HLv recipients have lower rates of rejection despite reduced levels of immunosuppression compared with isolated HT, with approximately 28% of cases treated with single agent immunosuppressive regimens in long-term follow-up.[8] This finding of excellent long-term graft and overall survival with low rejection and cardiac allograft vasculopathy rates see in this analysis but also in previous reports is mechanistically explained by the protective role of allografts to other transplanted organs from rejection.[10] Early preclinical studies suggested a protective role of liver from hyperacute rejection even in the presence of positive crossmatch[11] and the concept of "immunoprotection" of liver allograft to other organs transplanted simultaneously was also observed in cases of HK transplantation.[12] A previous UNOS registry analysis suggested that heart and kidney allografts may also be highly protective of another organ transplanted either simultaneously or subsequently.[13] However, it's important to note here that HK recipients are maintained on higher intensity immunosuppression that HT or HLv recipients. In the case

HLv transplantations, the immunomodulatory effects may be based on the liver's ability to reduce the levels of donor specific lymphocytotoxic alloantibodies.[14,15] whereas heart and kidney may not have this capacity. Another possible mechanism for decreased rejection rates among MT recipients is the large burden of foreign tissue leading to diminished immune response within the recipient.

Unlike HK and HLv, HL transplantation rates are decreasing as isolated lung or HT are preferred to the combined procedure. Several disadvantages including longer waiting ischemic times, higher risk of primary cardiac and lung allograft failure, bleeding risk especially in patients with complex CHD, and phrenic nerve dysfunction increase morbidity and mortality after HL compared with isolated organ transplantation. Despite these concerns the rates of acute rejection and cardiac allograft vasculopathy remain lower among HL recipients than isolated HT recipients.[16]

Despite equivalent long-term outcomes of most MT transplantations with isolated HT, combined transplantation occurs in less than 5% of HT recipients. Most of MT are HK procedures and take place in North America.[1] Potential barriers to MT include the shortage of multiple organs of good quality from the same donor, but also the complexity and the technical expertise which is available in a limited number of transplant centers. Since MT has comparable long-term outcomes with isolated HT and potentially confers protection against rejection, any barriers to these procedures from suitable single donors should be eliminated.

The findings of our study should be interpreted in the context of certain limitations, including the retrospective analysis design of a registry database, the quality of the source data, and the differences in practices followed in the participating centers. Post-transplant immunosuppression regimens were different among combined transplant recipients and they may impact outcomes. Although, data on immunosuppression are available in UNOS, heterogeneity in practices from center to center and lack of drug levels are the main reasons we did not include these in the analysis. In conclusion, Combined HK and HLv transplantation rates are increasing and long-term survival is comparable to primary HT, unlike HL which is associated with decreasing trends and significantly lower survival.

Credit Statement

Alexandros Briasoulis→conceived idea, wrote and revised the manuscript, participated in analysis.

Emmanuel Akintoye MD MPH→ performed analysis, revised manuscript.

Toshiki Kuno MD PhD→ participated in analysis and preparation of the first draft.

Paulino Alvarez MD→supervised and reviewed the final drafts.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Disclosures

The authors have no conflicts of interest to disclose.

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