Journal of Cardiothoracic and Vascular Anesthesia ▮ (▮▮▮▮) ▮▮▮–▮▮▮

Contents lists available at ScienceDirect

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Original Article

Heart Transplantation in Patients ≥ 60 Years: Importance of Relative Pulmonary Hypertension and Right Ventricular Failure on Midterm Survival

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Objectives: To determine the impact of recipient age and perioperative risk factors on midterm survival after orthotopic heart transplantation (OHT). The authors hypothesized that perioperative variables are more important as predictors of mortality than is a recipient's age.
Design: Retrospective study.
Setting: Tertiary care university hospital.
Participants: The study comprised 126 consecutive adults who underwent OHT.
Interventions: After Institutional Review Board approval, the authors analyzed 126 consecutive adult patients who underwent OHT between January 2009 and December 2015 and followed-up with them up until June 2016. Patients were divided into the following 2 groups according to the recipient's age at the time of transplantation: older group (≥ 60 y old) and younger group (18 to 59 y).
Measurements and Main Results: Actuarial survival rates for all patients were 88.1%, 78.6%, and 72.2% at 30 days, 1 year, and after a median follow-up of 18.9 months (midterm survival) (1st quartile: 8.1; 3rd quartile: 37.4), respectively. In the unadjusted analysis, the older group demonstrated a significant increase in 1-year mortality ($p = 0.005$) and a trend toward worse midterm mortality ($p = 0.087$). Multivariable analysis was performed using Cox proportional hazards regression analysis. Independent risk factors related to midterm mortality after OHT were as follows: preoperative relative pulmonary hypertension using the mean arterial-to-mean pulmonary artery pressure ratio ≤ 3 (hazard ratio [HR] 5.39, 95% confidence interval [CI] 1.64-17.74, $p = 0.006$); cardiopulmonary bypass duration (per each 10-min increment) (HR 1.14, 95% CI 1.08-1.22, $p < 0.001$); and postoperative right ventricular dysfunction (HR 3.50, 95% CI 1.52-8.05, $p = 0.003$). Neither recipients ≥ 60 years old (HR 2.15, 95% CI 0.98-4.67, $p = 0.054$) nor donor/recipient body surface area ratio (HR 1.01, 95% CI 0.98-1.04, $p = 0.463$) was an independent risk factor for midterm mortality.
Conclusions: In patients undergoing heart transplantation, survival was related more to preoperative relative pulmonary hypertension, cardiopulmonary bypass duration, and postoperative right ventricular failure than to recipient age. Older patients should be selected for OHT carefully, taking into consideration preoperative factors other than age.

Key Words: heart transplantation; perioperative; elderly; pulmonary hypertension; survival

DESPITE ADVANCES in medical and surgical therapies, including mechanical circulatory support, heart transplantation continues to be the gold standard treatment of end-stage heart

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http://dx.doi.org/10.1053/j.jvca.2017.09.017
1053-0770/

failure. With increased life expectancy and improved heart failure care, currently there are older potential candidates for cardiac transplantation, and health centers are accepting higher-risk patients.[1] The International Society of Heart and Lung Transplantation (ISHLT) has reported that the percentage of heart transplantation patients older than 60 years has increased steadily over the last decades,[2] which is in agreement with records from the United Network for Organ Sharing (UNOS).[3] Due to limited organ availability and concerns for increased mortality, advanced age traditionally had been considered a relative contraindication for transplantation. Studies evaluating heart transplantation in older patients have yielded mixed results, with some series showing no differences in survival rates[4–20] and others reporting worse outcome among elderly patients.[3,21–28]

The issue of whether older patients should be considered equally for orthotopic heart transplantation (OHT) still is a matter of great debate. The upper age limit remains poorly defined, due in part to the high demand for transplantations and the critical shortage of donors. The ISHLT recommends that older recipients should be selected more carefully than standard candidates[29] because survival risk factors are not only a matter of age, per se. Many other risk factors have to be considered beyond chronologic age, including perioperative hazards.

This study was designed to evaluate the effects of recipient age and perioperative variables on midterm survival after OHT. The extent to which recipient age is an independent predictor of mortality when considering other perioperative variables such as the mean arterial pressure to mean pulmonary artery pressure ratio (MAP/MPAP) (relative pulmonary hypertension [PH]) and right ventricular (RV) failure is unknown. The authors hypothesized that perioperative variables are more important as predictors of mortality than is age.

Methods

Patient Population

After obtaining Institutional Review Board approval, the authors retrospectively studied all consecutive adult patients who underwent OHT between January 2009 and December 2015 at a tertiary care university hospital and followed-up with them until June 2016. Follow-up was accomplished for all patients. Patients included in the analysis had undergone OHT and were 18 years or older. Multiple organ transplantation recipients were excluded. Patients were divided into the following 2 groups according to recipient age at the time of transplantation: older group (≥ 60 y) and younger group (18 to 59 y). The recipient listing criteria were the same for all patients. The authors' program does not use an alternative list for older or so-called "marginal" donor hearts.

Data Collection

Medical records were reviewed to collect preoperative data, which included donor and recipient age, sex, height, and weight. Body surface area and body mass index were calculated using standard formulae. Anthropometric measurements of donors and recipients were correlated. History or presence of chronic renal and liver failure, diabetes mellitus, hypothyroidism, and malnutrition status (obesity and cachexia) were documented. Other relevant information, including systemic hypertension, dyslipidemia, history of stroke, anticoagulant therapy, prior cardiac surgery, or retransplantation also were recorded. Data on priority status in the recipient's waiting list (elective, urgent, or emergency) at transplantation; donor heart ischemia time; and cardiopulmonary bypass (CPB) time also were collected. Intensive care unit and hospital stay, post-transplantation echocardiographic assessment, OHT-associated complications, and mortality also were registered.

Perioperative Hemodynamic Parameters

A thermodilution pulmonary artery catheter (Edwards Lifesciences, Irvine, CA) was inserted, and a complete hemodynamic profile was obtained as part of the pretransplantation evaluation. Measured variables included systolic, diastolic, and mean pulmonary arterial pressures. The pulmonary vascular resistance was calculated as Wood units using standard formulae. Relative PH is defined by a ratio that relates MAP/MPAP. The MAP/MPAP ratio was calculated for every patient. MAP/MPAP ≤ 3 was considered as being abnormal.[30] PH secondary to left heart disease was defined as MPAP > 25 mmHg in the presence of elevated pulmonary capillary wedge pressure (> 15 mmHg) or left ventricular end-diastolic pressure (> 18 mmHg).[31] Left ventricular ejection fraction and RV function were evaluated using perioperative echocardiography. RV dysfunction was defined as tricuspid annular plane systolic excursion < 17 mm, RV fractional area change $< 35\%$, severely dilated right ventricle (RV size equal or even exceeding left ventricular dimensions), significant tricuspid regurgitation, and hypokinesia of the RV free wall.[32] Additional data such as perioperative need for a ventricular assist device and intra-aortic balloon pump also were recorded.

Statistics

Student t test or Mann-Whitney U test was used for continuous variables and Pearson chi-square or Fisher exact test for categorical variables in order to compare data from older versus younger patients. Multivariable analysis was performed using Cox proportional hazards regression analysis. Significant univariate variables and clinically relevant variables were incorporated into the multivariate models in a stepwise fashion to predict midterm mortality after OHT and to compute the hazard ratio with 95% confidence interval. Alternative models were analyzed and compared with the likelihood ratio test and Akaike information criteria values. Both criteria were used to select the best model. Unless otherwise stated, p values < 0.05 were considered to be statistically significant, and the results are expressed as mean $\pm$ standard deviation and median (interquartile range) according

Please cite this article as: Bianco JC, et al. (2017), http://dx.doi.org/10.1053/j.jvca.2017.09.017

to their distribution or as number of patients (percentages) for categorical variables. Statistical analyses were performed with Stata, Version 14.1 (Stata Corp., College Station, TX).

Results

During the study period, 133 patients underwent OHT. Patients who underwent simultaneous heart and kidney transplantation (n = 6) or heart-lung transplantation (n = 1) were excluded. A total of 126 patients met the inclusion criteria. Among the included patients, 30 (23.8%) were ≥ 60 years old (range 60-72 y). Median recipient age was 52 (interquartile range 44-59) years. Preoperative recipient characteristics are shown in Table 1. The underlying primary diagnosis of heart failure was different according to age in the heart transplantation recipients (Fig 1). Table 2 depicts donor features.

Table 1
Preoperative Recipient Data

Variables	Total Population	< 60 y	≥ 60 y	p Value
	n = 126	n = 96	n = 30	
Demographic data				
Age,* y	52 (44-59)	49 (40-55)	64 (62-65)	< 0.001
Sex, females	35 (27.8%)	27 (21.4%)	8 (6.4%)	0.876
Weight,† kg	71.5 (14)	71.6 (13.8)	71.2 (14.7)	0.878
Height,† m	1.68 (0.09)	1.68 (0.08)	1.67 (0.11)	0.654
BMI,* kg/m^2	24 (22-28)	24 (22-27)	24 (22-28)	0.904
BSA,† m^2	1.80 (0.20)	1.81 (0.20)	1.80 (0.22)	0.763
Comorbidities				
Hypertension	47 (37.3%)	26 (27.1%)	21 (70%)	< 0.001
Diabetes mellitus	16 (12.7%)	8 (8.3%)	8 (26.7%)	0.008
Dyslipidemia	41 (32.5%)	25 (26%)	16 (53.3%)	0.005
Chronic renal failure	25 (19.8%)	15 (15.6%)	10 (33.3%)	0.034
Liver failure	5 (4%)	4 (4.2%)	1 (3.3%)	0.838
Hypothyroidism	27 (21.4%)	19 (19.8%)	8 (26.7%)	0.423
Stroke	6 (4.8%)	5 (5.2%)	1 (3.3%)	0.674
Ventricular arrythmias	35 (27.8%)	23 (24%)	12 (40%)	0.087
Anticoagulated patient	40 (31.8%)	31 (32.3%)	9 (30%)	0.814
Smoking	53 (42.1%)	35 (36.5%)	18 (60%)	0.023
Obesity	16 (12.7%)	12 (12.5%)	4 (13.3%)	0.905
Cachexia	7 (5.6%)	5 (5.2%)	2 (6.7%)	0.671
Laboratory				
Serum creatinine,* mg/dL	1.1 (0.9-1.4)	1.0 (0.9-1.3)	1.3 (1.1-1.4)	0.018
Creatinine clearence,* mL/min	64 (52-83)	70 (55-86)	56 (46-69)	0.002
PH-LHD	87 (69%)	66 (68.8%)	21 (70%)	0.897
Redo surgery	29 (23.0%)	21 (21.9%)	8 (26.7%)	0.586
Waiting list priority				
Elective	22 (17.5%)	15 (15.6%)	7 (23.3%)	0.332
Urgent	71 (56.4%)	53 (55.2%)	18 (60%)	0.644
Emergency	33 (26.2%)	28 (29.2%)	5 (16.7%)	0.174

NOTE. Variables are presented as number of patients (percent).
Abbreviations: BMI, body mass index; BSA, body surface area; PH-LHD, pulmonary hypertension secondary to left heart disease.
*Provided variables correspond to median values (interquartile ranges) because their distribution was asymmetric.
†Variables are expressed as mean (standard deviation).

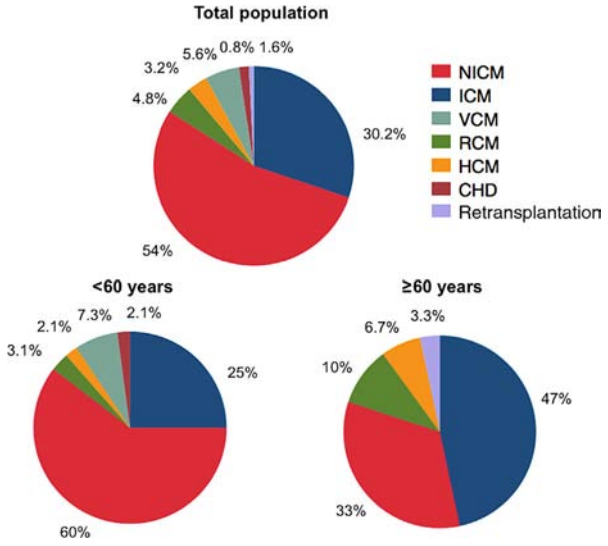

Fig 1. Underlying diagnosis of heart failure leading to heart transplantation in the total population and divided by age. CHD, congenital heart disease; HCM, hypertrophic cardiomyopathy; ICM, ischemic cardiomyopathy; NICM, non-ischemic cardiomyopathy; RCM, restrictive cardiomyopathy;VCM, valvular cardiomyopathy.

A complete preoperative hemodynamic profile of the recipients and main intraoperative and postoperative characteristics and events are shown in Tables 3 and 4, respectively.

The survival rates for all patients were 88.1%, 78.6%, and 72.2% at 30 days, 1 year, and after a median follow-up of 18.9 months (midterm survival) (1st quartile: 8.1; 3rd quartile: 37.4), respectively (Fig 2).

In the unadjusted analysis, the older group demonstrated a significant increase in 1-year mortality (p = 0.005) and a trend toward a worse midterm mortality (p = 0.087) (Table 5). Using multivariate Cox proportional hazard regression analysis, the independent risk factors related to midterm mortality after OHT were preoperative relative PH (MAP/MPAP ≤ 3), CPB duration, and postoperative RV dysfunction. Neither recipients ≥ 60 years old nor the donor/recipient body surface area ratio was an independent risk factor for midterm mortality (Table 6).

Discussion

Pulmonary hypertension is an important risk factor for increased morbidity and mortality in heart transplantation.[33] In patients undergoing heart transplantation, absolute values for systolic pulmonary arterial pressure > 50 mmHg[34] and MPAP > 35 mmHg[35] have been used as predictors of outcome. In this study's patient population, relative PH was superior to any other hemodynamic variable in predicting survival.

The importance of relative PH already has been shown in several studies. In a study by Robitaille et al of 1,439 patients

Table 2
Donor Characteristics

Variables	Total Population	< 60 y	≥ 60 y	p Value
	n = 126	n = 96	n = 30	
Demographic data				
Age,* y	27 (20-41)	27 (20-43)	27 (19-34)	0.647
≥ 50 y	10 (7.9%)	8 (8.3%)	2 (6.7%)	0.768
Sex, females	37 (29.4%)	30 (31.3%)	7 (23.3%)	0.406
D/R sex mismatch	16 (12.7%)	11 (11.5%)	5 (16.7%)	0.531
Height,† m	1.69 (0.8)	1.69 (0.08)	1.70 (0.08)	0.525
Weight,* kg	70 (68-80)	70 (68-80)	75 (70-80)	0.761
BMI,* kg/m^2	25 (23-28)	26 (23-28)	25 (23-28)	0.748
BSA,† m^2	1.85 (0.16)	1.84 (0.15)	1.86 (0.17)	0.685
D/R anthropometry				
D/R weight, %*	106 (92-117)	105 (92-116)	106 (100-117)	0.555
D/R height, %*	101 (96-105)	100 (96-104)	103 (95-106)	0.465
D/R BMI, %*	102 (92-118)	102 (93-116)	104 (88-121)	0.945
D/R BSA, %*	102 (95-110)	101 (95-110)	104 (98-110)	0.464
Cause of death				0.230
Trauma	67 (53.2%)	51 (53.1%)	16 (53.3%)	
Cerebrovascular accident	44 (34.9%)	36 (37.5%)	8 (26.6%)	
Others	15 (11.9%)	9 (9.4%)	6 (20%)	
Laboratory				
Hematocrit,† %	31.9 (7.2)	32.1 (7)	31.4 (7.9)	0.645
Glycemia,* mg/dL	132 (108-175)	135 (111-183)	122 (94-149)	0.062
Serum creatinine,* mg/dL	0.84 (0.6-1.1)	0.84 (0.6-1.1)	0.84 (0.6-1)	0.785
AST,* IU/L	38 (25-61)	40 (27-67)	33 (20-46)	0.060
ALT,* IU/L	26 (16-41)	26 (16-44)	25 (14-32)	0.140
Total bilirubin,* mg/dL	0.6 (0.4-1)	0.6 (0.4-1)	0.5 (0.4-0.9)	0.364
ALP,* IU/L	99 (60-158)	97 (59-157)	125 (73-165)	0.666
Addiction				
Drug abuse	6 (4.8%)	4 (4.2%)	2 (6.7%)	0.629
Alcohol abuse	6 (4.8%)	4 (4.2%)	2 (6.7%)	0.629

Abbreviations: ALP, alkaline phosphatase; ALT, aspartate aminotransferase; AST, aspartate transaminase; BMI, body mass index; BSA, body surface area; D/R, donor/recipient ratio.

NOTE. Variables are presented as number of patients (percent).

*Provided variables correspond to median (interquartile range).

†Variables are expressed as mean (standard deviation) because their distribution was normal.

Table 3
Preoperative Recipient Hemodynamic Variables

Variables	Total Population	< 60 y	≥ 60 y	p Value
	n = 126	n = 96	n = 30	
SAP,* mmHg	104 (96-112)	103 (96-110)	107 (95-114)	0.364
DAP,† mmHg	65.6 (12.5)	64.9 (12.6)	67.7 (12.1)	0.296
MAP,* mmHg	75 (67-83)	75 (67-81)	78 (69-85)	0.232
CI,* L/min/m^2	2.1 (1.7-2.6)	2.1 (1.7-2.5)	2.4 (1.9-2.8)	0.040
CVP,* mmHg	11.5 (7-15)	11 (7-15)	12 (9-17)	0.336
SPAP,* mmHg	50 (35-60)	48 (35-58)	54 (38-60)	0.276
DPAP,† mmHg	25.3 (8.6)	25.2 (8.8)	25.7 (8.1)	0.086
MPAP,* mmHg	34 (24-40)	33 (23-40)	36 (25-40)	0.461
Wedge,† mmHg	20.5 (7.8)	20.3 (8.2)	21.0 (6.8)	0.709
PVR,* Wood units	2.9 (2-4.2)	3.1 (2.1-4.3)	2.4 (1.9-4)	0.227
SVRI,* dynes/s/cm^5/m^2	716 (520-975)	738 (520-979)	675 (511-819)	0.206
PVRI,* dynes/s/cm^5/m^2	123 (80-192)	138 (90-199)	100 (78-172)	0.213
MAP/MPAP, ≤ 3	89 (70.6%)	68 (70.8%)	21 (70%)	0.930

Abbreviations: CI, cardiac index; CVP, central venous pressure; DAP, diastolic arterial pressure; DPAP, diastolic pulmonary arterial pressure; MAP, mean arterial pressure; MPAP, mean pulmonary arterial pressure; PVR, pulmonary vascular resistance; PVRI, pulmonary vascular resistance index; SAP, systolic arterial pressure; SPAP, systolic pulmonary arterial pressure; SVRI, systemic vascular resistance index.

NOTE. Variables are presented as number of patients (percent).

*Variables correspond to median values (interquartile range) because their distribution was skewed.

†Variables are expressed as mean ± standard deviation.

undergoing cardiac surgery, the MAP/MPAP ratio was identified as the best predictor of hemodynamic complications, which included the use of intra-aortic balloon pump, need for vasopressor drugs > 24 hours after surgery, resuscitated cardiac arrest, or death.[36] Carricart et al showed that the MAP/MPAP ratio was superior to hepatic venous flow as an independent predictor of difficult separation from CPB.[37] However, in those studies, patients were followed-up only during their hospital stay. In a study of patients who underwent aortic valve replacement with a 5-year follow-up, the authors were able to demonstrate that the prognostic value of the MAP/MPAP ratio remains valid up to 5 years after surgery.[38] Finally, Haddad et al observed in 85 patients with PH that the best predictor of septal curvature also was related to relative pulmonary artery presssure.[39] Nevertheless, MAP/MPAP has never been used as a survival risk factor in heart transplantation. PH commonly is present in end-stage heart failure. Quantifying PH as a ratio of systemic and pulmonary arterial pressures has the advantage of taking into consideration the close relationship of the 2 circulatory systems and the impact of PH on systemic pressures. This notion of relative PH has been used in congenital heart disease for stratification of the severity of PH.[40] Relative PH is relevant in patients undergoing general anesthesia or sedation, in which the reduction of MAP and MPAP often is noticed. Despite the absolute value reduction, the MAP/MPAP ratio remains unchanged. For the same elevated pulmonary artery pressure, patients with lower systemic arterial pressure present a more severe relative PH.

The presence of relative PH also could explain to some extent recipients' chronic renal failure. As PH increases the right atrial pressure or central venous pressure, it also can increase the risk of cardiorenal syndrome through venous congestion. A recent study by Iida et al in patients with heart failure showed that the best predictor of 1-year survival or rehospitalization was determined by the degree of renal venous congestion measured using Doppler.[41] In the present study, patients with preoperative creatinine clearance ≤ 30 mL/min demonstrated a more severe relative PH compared with those without renal failure (MAP/MPAP ratio 3.27 [0.36] *v* 2.15 [1.11], p = 0.026). In addition, PH predisposes patients to right heart failure. The latter is a well-known risk factor for increased mortality in OHT.[42] In the present study, the authors

Table 4
Intraoperative and Postoperative Recipient Features

Variables	Total Population	< 60 y	≥ 60 y	p Value
	n = 126	n = 96	n = 30	
Intraoperative				
CPB duration,* min	111 (98-129)	111 (100-130)	112 (96-127)	0.843
Allograft ischemic time,* min	183 (139-229)	179 (135-228)	189 153-240	0.376
Return to CPB	5 (4%)	3 (3.1%)	2 (6.7%)	0.592
> 2 inotropes	25 (19.8%)	18 (18.8%)	7 (23.3%)	0.583
Mechanical circulatory assistance				
IABP	23 (18.3%)	18 (18.8%)	5 (16.7%)	0.797
VAD	5 (4%)	5 (5.2%)	0 (0%)	0.337
Transfusion				
PRBC,* U	2 (0-4)	2 (0-4)	3 (2-4)	0.219
FFP,* U	3 (0-4)	2 (0-4)	3 (2-6)	0.067
Platelets,* U	0 (0-8)	0 (0-7)	6 (0-10)	0.035
Cryoprecipitates,* U	0 (0-0)	0 (0-0)	0 (0-0)	0.940
> 10 U transfused	55 (43.7%)	37 (38.5%)	18 (60%)	0.039
Postoperative				
Complications				
Bleeding,* mL	370 (220-690)	340 (210-720)	410 (260-620)	0.407
Liver failure	14 (11.1%)	8 (8.3%)	6 (20%)	0.097
Renal failure	62 (49.2%)	42 (43.8%)	20 (66.7%)	0.028
Hemodialysis	23 (18.3%)	13 (13.5%)	10 (33.3%)	0.014
Infections	23 (18.3%)	17 (17.7%)	6 (20%)	0.777
Sepsis	12 (9.5%)	9 (9.4%)	3 (10%)	0.919
Primary graft dysfunction	26 (20.6%)	18 (18.8%)	8 (26.7%)	0.350
TEE				
RV dysfunction	15 (11.9%)	12 (12.5%)	3 (10%)	0.712
LVEF,* %	60 (58-65)	60 (58-65)	60 (55-66)	0.772
MR moderate/severe	7 (5.6%)	5 (5.2%)	2 (6.7%)	0.675

Abbreviations: CPB, cardiopulmonary bypass; FFP, fresh frozen plasma; IABP, intra-aortic balloon pump; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; PRBC, packed red blood cells; RV, right ventricle; TEE, transesophageal echocardiography; VAD, ventricular assist device.
NOTE. Variables are presented as number of patients (percent).
*Variables are given as median (interquartile range) because their distribution was asymmetric.

show, using multivariable analysis, that the risk of death is 3.5 times greater in recipients experiencing postoperative RV failure after heart transplantation.

The ability of the right ventricle to adapt to the progressive increased PH in advanced heart failure is the main determinant of a patient's survival.[43] The donor's heart implanted in a recipient with increased pulmonary vascular resistance could result in an acute RV dysfunction attributed mainly to failure of the donor right ventricle to adapt to the sudden increase in afterload. A decrease in RV stroke volume leads to underfilling of the left ventricle. Filling of the left ventricle also is impaired due to the development of leftward ventricular septal

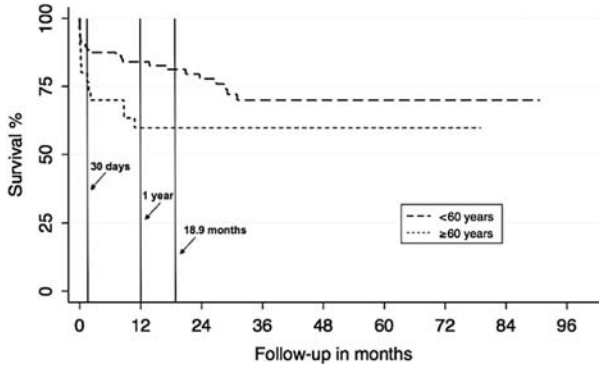

Fig 2. Kaplan-Meier survival curve in recipients who underwent orthotopic heart transplantation, according to age at time of transplantation.

Table 5
Recipient Outcomes

Variables	Total Population	< 60 y	≥ 60 y	p Value
	n = 126	n = 96	n = 30	
Length of hospital stay,* d	26 (16-40)	27 (17-44)	21 (14-37)	0.239
Follow-up,* mo	18.9 (8.1-37.4)	20.2 (8.3-40)	14.2 (1.8-28.1)	0.090
30-d mortality	15 (11.9%)	9 (9.4%)	6 (20%)	0.192
1-y mortality	27 (21.4%)	15 (15.6%)	12 (40%)	0.005
Total mortality	35 (27.8%)	23 (24%)	12 (40%)	0.087

NOTE. Variables are presented as number of patients (percent).
*Variables are given as median (interquartile range) because their distribution was asymmetric.

Table 6
Multivariate Cox Proportional Hazard Regression Analysis

Variables	Hazard Ratio	95% CI	p Value
Age ≥ 60 y	2.15	0.98-4.67	0.054
MAP/MPAP ≤ 3	5.39	1.64-17.74	0.006
Postoperative RV dysfunction	3.50	1.52-8.05	0.003
CPB duration, increase by 10 min	1.14	1.08-1.22	< 0.001
D/R BSA, %	1.01	0.98-1.04	0.463

Abbreviation: CI, confidence interval; CPB, cardiopulmonary bypass; D/R BSA, donor-to-recipient body surface area ratio; MAP/MPAP, mean arterial pressure/mean pulmonary arterial pressure; RV, right ventricle.

bowing. This, together with systolic/diastolic RV dysfunction, contributes to the marked decline in cardiac output seen in severe PH.[44]

CPB has been related to perioperative mortality in heart transplantation.[45] The detrimental effect of CPB has been associated with the inflammatory response,[46] presence of particulates or gaseous microemboli and foreign material in the CPB circuit,[47] and hyperthermia after fast rewarming during the final period of CPB. Furthermore, CPB activates the coagulation cascade and the fibrinolytic system,[48] which in addition to hemodilution and hypothermia during extracorporeal circulation, results in an increase of perioperative bleeding, redo surgeries, and need for transfusions.[49] Likewise, reinfusion of cardiotomy suction blood and hyperglycemia could play a role in the detrimental effect of CPB during cardiac surgery.[50]

Thus, it is reasonable that the longer the CPB time, the worse the outcome after OHT. Furthermore, CPB prolongation usually indicates surgical difficulties or difficult separation from CPB due to hemodynamic instability, mainly left or RV allograft dysfunction. These complications can prompt a return to CPB, the addition of inotropic or vasoactive drugs, or the need for implantation of mechanical assist devices.[51]

From ISHLT reports, it is clear that the number of OHT procedures is increasing in the elderly, and it is expected that the demand for OHT in this population will continue to increase.[2] In addition, the advent of ventricular assist devices as a destination therapy for end-stage heart failure makes the determination of the optimal therapeutic option for patients 60 years and older with advanced congestive heart failure a major challenge. Because there is an increasing number of older patients with many comorbidities who are candidates for heart transplantation, with a shortage of organs, some centers use formal or informal "alternative lists," accepting higher-risk and older donors.[52,53]

The most important studies that compare young and elderly recipients considering age as predictor of outcome in OHT are summarized in Table 7. Several studies point out age as an independent predictor of survival,[3,21–28] but others do not confirm this.[4–20] In 4 studies in which older age correlated with survival, data were extracted from the UNOS database, with different portions of the same population overlapping in different studies.[3,23,25,26] A recent study that used the UNOS registry showed that 5-year survival was lower in recipients older than 60 years, but this could not be proven in patients older than 70 years in the multivariate analysis.[3] Large registries have shown decreased survival in older patients because these recipients seem to receive hearts from suboptimal donors, including older donors with a high prevalence of diabetes and infections, as evidenced by an analysis of the UNOS database.[3] Few studies have included perioperative hemodynamic data. The scarce hemodynamic data collected mostly were evaluated only in univariate analyses.[6,9,13,18,19,25] To the authors' knowledge, none of the studies included RV failure and relative PH in addition to age in the multivariate analysis of survival. The inclusion of these variables, which were strong predictors of survival in the present study, could have influenced the results of some other investigations.

Several studies, including the present one, have shown that in older recipients (≥ 60, 65, or 70 y) age was not a predictive factor of mortality.[4–7,9–20] Older recipients are not at greater risk because of their chronologic age, per se. As shown in the present study, a patient's comorbidities are the main risk factor for survival. Nowadays, patients are reaching older ages in better health condition. Therefore, heart transplantation should not be contraindicated by a patient's calendar age but rather by comorbidities.

Recent single-center studies have proven that with careful patient selection, heart transplantation can be performed in the elderly with similar survival rates as those in younger recipients.[11,12,19] These studies are consistent with the results of the present study, demonstrating that older patients were not associated with increased midterm mortality.

Limitations

The present study shows the experience of a single institution with 126 patients, but it includes all consecutive patients with a median follow-up of 18.9 (1st quartile: 8.1; 3rd quartile: 37.4) months. More precise evaluation of both left and right cardiac function now can be performed using strain and 3-dimensional echocardiography. These resources were not available at the time of this study.

The acceptability criteria applied were the same for all patients; however, a subjective selection bias could exist in the evaluation of older patients to avoid selecting borderline recipients with several risk factors besides advanced age. It is possible that with a larger cohort of patients, age might be demonstrated as a predictor, but its importance likely would be inferior to other associated features. Finally, confirmation of the authors' hypothesis would be required in a different and larger population for external validation.

Conclusion

In summary, the authors observed that in patients undergoing heart transplantation, survival was more likely related to preoperative relative PH, CPB duration, and postoperative RV failure than to recipient age. Additional studies are required to

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Table 7
Main Studies Comparing Younger and Older Recipients for Heart Transplantation

Reference	Study Period	Number of Patients	Age Group (n)	Survival	Secondary Outcomes/Comments
Awad et al[4]	1988-2012	704	< 70 y (659) ≥ 70 y (45)	No significant difference	Only high creatinine level was identified as a predictor of 10-year mortality
Cooper et al[23]	1987-2014	50,432	18-59 y (36,190) 60-69 y (13,527) ≥ 70 y (715)	Decreased survival in older patients Recipients in their 70s had similar outcomes to recipients in their 60s in 1995-2014 period	Older patients received suboptimal organs Patients ≥ 70 years old had fewer rejection episodes
Prieto et al[19]	2003-2013	248	≥ 65 y (45) > 65 y (203)	No significant difference	Higher incidence of cardiac allograft vasculopathy and more serious infections in the first year in older recipients
George et al[25]	2005-2011	12,273	< 70 y (11,996) ≥ 70 y (277)	Decreased survival in older patients	≥ 70 y bridged to transplantation had similar outcome of younger patients
Goldstein et al[26]	1998-2010	6,139	≥ 70 y (332) 60-69 y (5,807)	Decreased survival in older patients	≥ 70 y received nonidentical ABO match and older donors
Daneshvar et al[11]	1988-2009	519	≥ 70 y (37) 60-69 y (206) ≤ 60 y (276)	No significant difference	No significant difference in redo surgery for bleeding, dialysis, and prolonged intubation
Weiss et al[3]	1999-2006	14,401	≥ 60 y (4,273) < 60 y (10,128)	Decreased survival in older patients	Older patients had more infections, ARF, and longer LOS but fewer rejections MPAP was related to mortality
Marelli et al[15]	1995-2001	530	≥ 62 y (182) < 62 y (348)	No significant difference	Elderly patients had increased risk of renal failure and cancer
Tjang et al[28]	1989-2004	1,262	< 55 y (540) ≥ 55 y (722)	Decreased survival in older patients	RV failure was a cause of death, but it was not analyzed in univariate or multivariate analyses
Forni et al[13]	1994-2005	272	≤ 60 y (197) > 60 y (75)	No significant difference, despite that older recipients received marginal donor hearts	No difference in perioperative mortality, rejection, infection, neoplasia, and chronic renal failure
Crespo-Leiro et al[10]	1991-2003	445	> 65 y (42) ≤ 65 y (403)	No significant difference	No greater risk of rejection or malignancy in patients > 65 y
Nagendran et al[18]	1990-2000	275	< 60 y (225) ≥ 60 y (50)	No significant difference	Similar rates of rejection, transplant coronary artery disease, infection, and malignancy
Favaloro et al[24]	1993-2003	178	≥ 60 y (36) < 60 y (142)	Decreased survival in older patients	Long-term survival conditional on survival to 1 year was not significantly different
Morgan et al[16]	1992-2003	824	≥ 70 y (10) < 70 y (814)	No significant difference	Age should not be contraindication to OHT
Zuckermann et al[20]	1989-2001	882	18-60 y (679) 60-65 y (137) > 65 y (66)	No significant difference	Fewer rejection episodes in the older group
Demers et al[12]	1986-2001	484	≥ 60 y (81) < 60 y (403)	No significant difference	Older patients had fewer rejections but more cancer
Morgan et al[17]	1992-2002	126	> 65 y (63) < 65 y (63)	No significant difference	Post-transplantation coronary artery disease was greater in the older group
Baran et al[5]	1989-2002	250	18-45 y (70) 46-59 y (107) ≥ 60 y (73)	No significant difference	Similar rejection between the age groups
Peraira et al[27]	1984-2002	560	≤ 60 y (465) > 60 y (95)	No significant difference Subanalysis: > 65 y had worse survival	Lower acute rejection episodes and viral infections in older recipients
Blanche et al[6]	1994-1999	113	≥ 70 y (15) < 70 y (98)	No significant difference	No effect of age on morbidity or mortality
Borkon et al[21]	1985-1997	153	≤ 55 y (110) > 55 y (43)	Decreased survival in older patients	Older patients demonstrated higher incidence of infection
Coffman et al[9]	1988-1993	111	< 60 y (71) ≥ 60 y (40)	No significant difference	Greater improvement in quality of life and lower rejections in older patients

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Table 7 (*continued*)

Reference	Study Period	Number of Patients	Age Group (n)	Survival	Secondary Outcomes/Comments
Bull et al[22]	1985-1994	527	≤ 60 y (426) > 60 y (101)	Decreased survival in older patients	Patients > 60 y demonstrated fewer rejection episodes and were more likely to die of infection or cancer
Blanche et al[7]	1988-1995	180	< 70 y (174) ≥ 70 y (6)	No significant difference	Small number of septuagenarians
Frazier et al[14]	1982-1987	200	≤ 60 y (172) > 60 y (28)	No significant difference	Pediatric population was included
Carrier et al[8]	1979-1985	62	> 50 y (13) < 50 y (49)	No significant difference	Rigidly defined age criterion is not acceptable

Abbreviations: ARF, acute renal failure; LOS, length of stay.

determine the extent through which relative PH could be reversible and may represent a potential therapeutic avenue in order to improve OHT survival. Older patients should be selected carefully, taking into consideration preoperative factors other than age.

Acknowledgments

The authors thank the anesthesiologists, cardiac surgeons, and perfusionist colleagues for their significant contribution to the Heart Transplant Program. They cared for a large number of the patients described in this article.

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