

Relation of Age to Risk of Major Rejections, Allograft Vasculopathy, and Long-Term Mortality in a Contemporary Cohort of Patients Undergoing Heart Transplantation

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ABSTRACT

Background: In 2006, the International Society for Heart and Lung Transplantation amended the guidelines for the upper age limit of heart transplantation (HTx) from 55 years to 70 years and older for carefully selected patients. However, the relation of age to outcomes following of HTx has not been well studied.

Objectives: To investigate the impact of recipient age on the occurrence of rejections, vasculopathy, and mortality after HTx.

Methods: Study population comprised all consecutive 291 patients who underwent HTx between 1991–2016 and were followed at our center. Patients were categorized by age tertiles: < 46 years (mean 31.4 ± 11.7, range 16–45, n=90), 46–57 years (mean 51.4 ± 3.2, range 46–56, n=92), and ≥ 57 years (mean 61.6 ± 3.4, range 57–73, n=109).

Results: Patients aged ≥ 57 years were more often males and had more pre-HTx co-morbidities including hypertension, diabetes, dyslipidemia, and history of smoking ($P < 0.05$) compared to the younger age groups. Kaplan-Meier analysis by age tertiles showed the rates of major rejections and vasculopathy at 15 years were similar among the three age groups. Mortality rates at 15 years were directly related to the age groups (39%, 52%, 62% log-rank, $P = 0.01$). However, the association between age and mortality was no longer statistically significant after multivariate analysis (hazard ratio 1.01, 95% confidence interval 1.00–1.03).

Conclusions: In a contemporary cohort of patients undergoing HTx, recipient age does not significantly impact the risk of major rejections, vasculopathy, and long-term mortality.

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KEY WORDS: cardiac allograft vasculopathy, elderly, heart transplantation (HTx)

Initially, advanced age was a contraindication to HTx, and was restricted to recipients younger than 50 years of years due to unfavorable long-term outcomes that were adversely influenced by advanced age [3]. For many years there has been a debate whether HTx is justified for older recipients. Opponents claim that expanding the upper age limit will result in a distort of the recipient demand/donor supply and will produce an increased mortality for all patients awaiting cardiac transplantation. However, as a consequent of improved outcomes of HTx, the upper limit of recipient age has been liberalized, and the 2016 International Society for Heart and Lung Transplantation (ISHLT) criteria for HTx include as a class IIb and level of evidence C, carefully selected patients older than 70 years of age [4–7].

HTx for advanced age recipients raise many important moral, ethical, and practical issues. To date, the relationship of age to outcomes following of HTx has not been well studied with inconsistent results [5,7–9]. We investigated the impact of recipient age on the occurrence of rejections, vasculopathy, and mortality during long-term follow-up after HTx.

PATIENTS AND METHODS

STUDY POPULATION AND REGISTRY DESIGN

Between 1991 and 2017, 291 patients who underwent HTx were prospectively followed and registered at the tertiary center of the Sheba HTx Registry. Patients were categorized by age tertiles: < 46 years (n=90), 46–57 years (n=92), and ≥ 57 years (n=109). Data for each patient were systematically recorded at enrollment to the study and during each subsequent visit or medical contact. Clinical data were recorded on prospectively designed forms and included comprehensive information regarding the transplantation procedure, immunosuppression, occurrence of major cardiac events, and treatment during long-term follow-up. Donor data were recorded from the National Organ Transplantation Center, as well as from the hospitals records in which the donations were made. The study was approved by the institutional review board.

Advances in the treatment of heart failure in the last two decades have led to significant increases in the life span of patients. Consequently, the characteristics of heart transplantation (HTx) candidates have changed toward an older population who present with more co-morbidities [1]. The great advance in mechanical circulatory support devices has not yet resulted in a true alternative to HTx and is implanted frequently as a bridge for transplant. Currently, nearly half of the HTx candidates are bridged to transplant with a mechanical circulatory support device [2].

IMMUNOSUPPRESSION

All patients were treated with a triple-drug regimen. Maintenance immunosuppression comprised a combination therapy including prednisone, an antimetabolite, and a calcineurin inhibitor. Conversion to everolimus was based on the patient risk profile including cytomegalovirus infection, renal failure, allograft vasculopathy, and malignancy risk. All patients received induction therapy consisting of anti-thymocyte globulin.

REJECTIONS, SURVEILLANCE, AND CLASSIFICATION

Rejections were diagnosed by routine or clinically indicated endomyocardial biopsy, classified according to the revised ISHLT classification system for rejection [10]. Biopsies obtained before the institution of the revised ISHLT rejection grading system were reclassified according to the new system. Routine endomyocardial biopsies were performed every week for the first 4 weeks post HTx, twice a month during the second and third months, once a month for the following 3 months, and thereafter every 3 months until the end of the first year. From the end of the first year until the end of the fifth year, biopsies were performed annually. The following rejection scores were calculated for each patient: total rejection score (TRS), taking into account the severity of the rejection, was calculated as 0R=0, 1R=1, 2R=2, and 3R=3; and any rejection score (ARS) was calculated as 0R=0, 1R=1, 2R=1, 3R=1, and represented the total number of rejections regardless of severity experienced by the patient. All scores were normalized by dividing the cumulative scores for the total number of biopsy specimens taken for each patient throughout the study period [11].

CARDIAC ALLOGRAFT VASCULOPATHY

The institutional post-transplant care protocol included annual invasive coronary angiography for the first 5 years following HTx, including echocardiogram and right heart catheterization. Cardiac allograft vasculopathy (CAV), diagnosed by coronary angiography, and invasive hemodynamic assessment were performed annually, along with clinical assessment and echocardiography, combined according to the recommended ISHLT standardized nomenclature for CAV [12].

OUTCOME MEASURES

Primary outcomes included: all-cause mortality, CAV, and major rejections. Mortality data were obtained from the Population Registry of the State of Israel, where all deaths are required by law to be registered. Secondary outcomes included the occurrence of major adverse events (acute coronary syndrome or coronary revascularization, congestive heart failure, pacemaker implantation, stroke, new-onset peripheral vascular disease). The study periods over the study decade were categorized as early (before 2000) vs. late (2000 or after).

STATISTICAL ANALYSIS

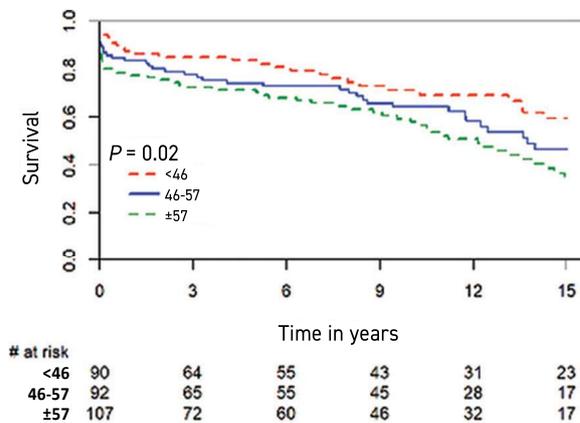
The primary analysis used age as a continuous variable, but for descriptive purposes the study population was divided into tertiles of age (< 46 years, 46–57 years, and ≥ 57 years). Data are presented as mean ± standard deviation if normally distributed, or as median (interquartile range). Categorical variables are given as frequencies and percentages. Continuous variables were tested with the *t*-test for normal distribution, and Mann-Whitney-Wilcoxon for abnormal distributed variables. A Chi-square test was used for comparison of categorical variables across age tertiles. In addition, we compared patients who underwent HTx in the early years (before 2000) vs. late period (2000 or later).

To identify factors associated with mortality and for major rejection among the entire cohort, a multivariable logistic regression model was constructed. Candidate covariates are presented in Table 1. Results are presented as odds ratio (OR) and 95% confidence interval (95%CI).

Table 1. Baseline population characteristics of the study population

	Age < 46 (N=90)	Age 46–57 (N=92)	Age ≥ 57 (N=109)	P value
Gender: male (%)	64 (71)	81 (88)	97 (89)	0.001
Age (years), mean ± SD	31.4 ± 11.7	51.4 ± 3.2	61.6 ± 3.3	< 0.001
Weight (kg), mean ± SD	66.2 ± 22.5	74 ± 12.9	77 ± 15.4	< 0.001
Height (cm), mean ± SD	165.7 ± 28.2	170.7 ± 15	168.6 ± 19	0.293
Ischemic etiology for HTx (%)	71 (81)	26 (28)	22 (20)	< 0.001
Hypertension (%)	14 (16)	38 (43)	61 (56)	< 0.001
Diabetes (%)	8 (9)	16 (18)	35 (32)	< 0.001
Dyslipidemia (%)	20 (22)	47 (53)	68 (63)	< 0.001
Past Smoker (%)	16 (18)	45 (51)	66 (61)	< 0.001
Creatinine (mg/dl), mean ± SD	1.14 ± 0.52	1.33 ± 0.61	2.04 ± 5.46	0.198
Bilirubin (mg/dl), mean ± SD	1.42 ± 2.3	1.51 ± 3.62	1.14 ± 0.98	0.631
Late period (> 2000) (%)	60 (67)	56 (61)	74 (68)	0.551
Blood type (%)				0.041
A	32 (43)	27 (39)	34 (45)	
AB	4 (5)	15 (21)	7 (9)	
B	18 (24)	9 (13)	20 (27)	
O	21 (28)	19 (27)	14 (19)	

HTx = heart transplantation, SD = standard deviation

Figure 1. Kaplan-Meier analysis for survival by age tertiles

Statistical significance was assumed when the null hypothesis could be rejected at $P < 0.05$. All P values are the results of two-sided tests. Statistical analyses were conducted using R Core Team (2015), a language and environment for statistical computing, R Foundation for Statistical Computing, Vienna, Austria, URL <http://www.R-project.org/> (Version 3.4.1).

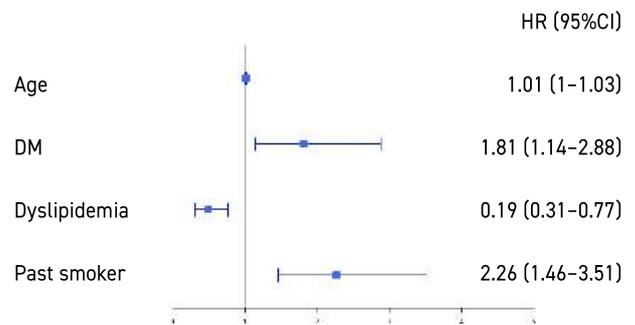
RESULTS

PATIENT CHARACTERISTICS

The current analysis was based on 291 patients, who were classified into three groups according to tertiles age: < 46 years ($n=90$), 46–57 years ($n=92$), and ≥ 57 years ($n=109$). Patients aged ≥ 57 years were more often males, more likely to have ischemic cardiomyopathy as an indication for HTx, had more pre-HTx co-morbidities including hypertension, diabetes, dyslipidemia, and history of smoking compared to the younger age-groups. The tertiles age distribution was similar in the early period (before 1 January 2000) and in the late period (1 January 2000 and thereafter). Baseline clinical characteristics of the study patients by the age tertiles are shown in Table 1. Donor baseline characteristics were similar in all groups in terms of age and hemodynamics prior to the HTx; however, donors for the younger recipient were more often males [Table 1].

SURVIVAL ANALYSIS

Unadjusted Kaplan-Meier survival analysis by age tertiles showed that overall survival was significantly higher among younger patients and mortality was directly related to the age-groups. Thus, at 15 years of follow-up, the respective rates of survival were 70% in the youngest tertile, 59% in the middle tertile, and 50% in the oldest tertile (log-rank $P = 0.02$ for the comparison between the three groups during follow-up) [Figure 1].

Figure 2. Hazard ratios for mortality by multivariable analysis with a stepwise selection

DM = diabetes mellitus, HR = hazard ratio, CI = confidence interval

In a multivariate analysis, diabetes mellitus (HR 1.81, 95%CI 1.14–2.88, $P = 0.012$), the absent of dyslipidemia (HR 0.49, 95%CI 0.31–0.77, $P = 0.002$) and history of smoking (HR 2.26, 95%CI 1.46–3.51, $P < 0.001$) were risk factors for overall mortality, with no effect of age (HR 1.01, 95%CI 0.99–1.03, per 1-year age increment; $P = 0.083$) [Figure 2].

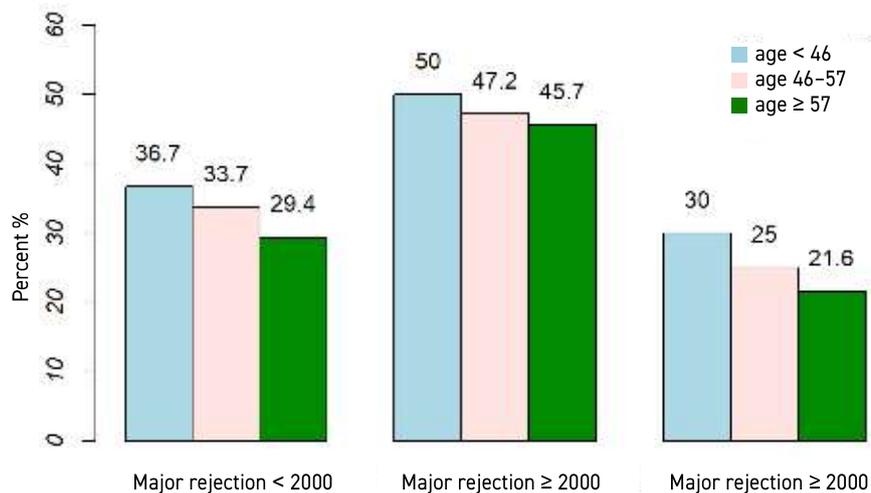
MAJOR ADVERSE EVENTS AT FOLLOW-UP

The rates of major rejections and CAV at 15 years of follow-up were similar among the youngest, middle and oldest age-groups (70% vs. 75.3% vs. 68.4%, $P = 0.605$; and 20% vs. 25% vs. 15.6%, $P = 0.251$; respectively) [Figure 1, Figure 2]. No significant differences were found regarding major adverse events (MACE) assessed separately or as combined end points. At 15 years of follow-up, the respective rates of MACE were 67% in the < 46 years group, 69% in the 46–57 years group, and 76% in the ≥ 57 years group ($P = 0.325$).

TRENDS IN OUTCOMES IN THE EARLY AND LATE PERIODS

HTx patients in the early period compared to the late period were more often male, and more likely to have ischemic cardiomyopathy as an indication for HTx, smoked, however they had less diabetes mellitus. Other baseline characteristics were similar between the two periods in terms of recipients age, donors age, hypertension, dyslipidemia, and body mass indexes [Table 2]. Among older patients aged ≥ 57 years, those in the early period had less diabetes mellitus; however, all other baseline characteristics were similar between the two periods [Table 3]. Major rejection rate was seen mostly in the youngest tertile followed by the middle tertile and the oldest tertile in both periods; however, it was demonstrated in a higher probability in the early period as compared to the late period [Figure 3]. Multivariate analysis has shown that the only predictor for major rejection was HTx in the early period (HR 2.04, 95%CI 1.37–3.03, $P < 0.001$).

Figure 3. Major rejection by age tertiles and period



DISCUSSION

This retrospective study describes several cardinal findings regarding HTx in the elderly population. We showed that: although the rate of long-term mortality increases with higher age tertiles, it was not increased in HTx patients compared to the natural history of increased age in the general population; in a contemporary cohort of patients undergoing HTx, the rejections and CAV; and while the tertiles age distribution was similar in the early and late periods, the probability of major rejections was higher in the early period.

Chronologic age does not strictly correlate with physiologic age in every case. We reported in the current study that other risk factors were more correlated to late mortality than age itself. Our study supports the recommendations made by international and national societies for the abolition of age as an excluding criterion for listing candidates for transplants [13]. We believe that age alone should not disqualify patients from consideration for HTx. The challenge for transplant physicians is to establish objective parameters that accurately predict the recipient's response to the trauma of the operation and the need for lifelong immunosuppression. In the last two decades HTx recipients have been transplanted at an older age and with steadily increasing co-morbidities (25% have diabetes mellitus, 45% have hypertension, 46% have had prior sternotomy, 7% have had malignancy, and 33% are allosensitized) [2].

We showed that diabetes is an independent risk factor for mortality after HTx. It is known that it is mainly due to accelerating coronary artery disease; however, in some cases it is secondary to diabetic cardiomyopathy and nephropathy [14].

Although the presence of insulin treatment is a marker for more advanced disease, its underlying biological mechanism has not been fully elucidated. It may be related to the impact of a procoagulant imbalance, chronic exposure to high glucose levels, and direct effects of hyperinsulinemia.

Of interest, endogenous hyperinsulinemia has been associated with increased long-term mortality in patients without diabetes [15]. Accordingly, the high-risk population of diabetic patients may require specific and/or more intense cardiovascular protective therapies after HTx. Further studies are needed to examine whether novel interventions, such as GLP-1 analogues or SGLT2 inhibitors, can improve their long-term outcomes.

An interesting finding was that the absence of dyslipidemia was associated with increased mortality. We believe that it is due to the effect of statin therapy in patients presenting with dyslipidemia. A recent publication has shown that pre-HTx statin therapy was independently associated with a reduced risk for primary graft dysfunction and mortality, and that statins have a beneficial prognostic impact on heart failure patients awaiting HTx [16].

The actuarial survival of patients after all other cardiac surgeries is influenced by the age of the patient, and there is no logical reason why HTx should be different. There are also factors associated with long-term immunosuppression in older patients that could be expected to adversely influence survival and major adverse outcomes. The concept of an alternative list for older patients and high-risk recipients and use of marginal donor hearts for the alternative list has been raised in the last few years but in turn introduces many theoretical and practical concerns. Our results do not support this concept. Establishing an alternative list should not be widely adopted

without more convincing data to support this approach. We believe that the challenge to match donor and recipient risks should persist for all donor hearts including the marginal and nonmarginal hearts and for low- and high-risk recipients with a single waiting list of recipients. Furthermore, the creation of an alternate list seems to disadvantage the patients on this list by giving them second-rate hearts; conversely, if the hearts are acceptable, then the standard list patients are disadvantaged by not being given the chance for the hearts. In a situation in which every candidate is examined on an individual basis, there is no point in an exclusionary rule on a basis of age which entirely relies on generalized statistical assumptions rather than particular examination of the patient under consideration [13].

LIMITATIONS

The major limitation of our study lies in its observational nature. Not all possible confounders were recorded or adjusted for this single-center study.

CONCLUSIONS

Our findings suggest that, in a contemporary cohort of patients undergoing HTx, recipient age does not significantly impact the risk of major rejections, CAV, and long-term mortality. High-risk population with co-morbidities may require specific and/or more intense cardiovascular protective therapies after HTx. Despite advanced age, appropriate candidates for HTx should be allowed placement on the transplantation waiting list after careful evaluation and screening as transplantation remains their best option for long-term survival.

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Capsule

Sites of vulnerability in SARS-CoV-2

Antibodies that neutralize severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) could be an important tool in treating coronavirus disease-2019 (COVID-19). **Brouwer** and colleagues isolated 403 monoclonal antibodies from three convalescent COVID-19 patients. They show that the patients had strong immune responses against the viral spike protein, a complex that

binds to receptors on the host cell. A subset of antibodies was able to neutralize the virus. Competition and electron microscopy studies showed that these antibodies target diverse epitopes on the spike, with the two most potent targeting the domain that binds the host receptor.

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Eitan Israeli