

The outcomes of marginal donor hearts compared with ideal donors: a single-center experience in Iran

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Background: Heart transplantation has been considered the gold-standard treatment for patients with end-stage heart failure. This study assessed the survival outcomes of marginal donor hearts compared with ideal donor hearts in Iran.

Methods: This retrospective study is based on the follow-up data of heart donors and recipients in the Sina Hospital Organ Procurement Unit. Among the 93 participants, 75 were categorized as ideal donors (group A) and 18 as marginal donors (group B). Group C included heart recipients who received a standard organ, and group D included heart recipients who received a marginal one. To analyze differences in patient characteristics among the groups, posttransplant heart survival was assessed in all groups. All data were obtained from the hospital records.

Results: The mean age of the donors was 26.27±11.44 years (median age, 28 years). The marginal age showed a significant association with donor age. The age of recipients had a significant effect on survival days in the ideal group. Most patients survived for at least 1 year, with a median of 645 days in recipients from marginal donors and 689 days in recipients from ideal donors.

Conclusions: Considering the lack of organ availability in Iran, it may be possible to use marginal donors for marginal recipients, therefore reducing the number of people on the waitlist. We also recommend establishing a national marginal donor system specifically for Iranian patients to extend the donor pool.

Keywords: Heart transplantation; Graft survival; Organ donation; Organ transplantation

HIGHLIGHTS

- As heart transplantation progresses as an effective treatment, expansion of donor pool is considered to meet the high demand for available organs.
- The use of marginal donors increases organ availability; however, it should be considered that the results may not replicate those obtained with ideal donors those obtained with ideal donors.
- Sex matching between donors and recipients can be concluded that it decreases the negative impacts of marginal donor on survival.
- There was no significant difference between survival rates of ideal and marginal groups.

INTRODUCTION

Heart transplantation has been considered the gold-standard treatment for patients with end-stage heart failure, provided that a careful selection process is followed to assess candidacy [1]. In addition, the increased survival rate and quality of life for patients undergoing transplantation during recent decades have contributed to the success of heart transplantation [2,3]. The annual number of heart transplants has remained steady at 3,500–4,500 worldwide and, notably, half were performed in the United States [4,5]. In 2018, only 100 heart transplants were performed in Iran, despite 2,500 patients on the waiting list. This significant difference in one year led to an increase in the wait time and in the mortality rate of patients on the waiting list [6]. According to Mandegar et al. [7], in Iran, the mean survival rate for heart transplant recipients was 6.6 ± 0.87 years.

The major cause of brain death in potential organ donors in Iran is head trauma (including motor vehicle accidents), especially in the age range of 20 to 40 years. Based on reports from the Ministry of Health on the number of accidents and deaths due to trauma, the age of donors is increasing [8]. Concurrently, the number of patients on heart transplant waiting lists is growing due to the increased number of patients with cardiovascular diseases, dilated cardiomyopathy, and hypertension. Considering the limited number of brain death donors in the ideal age range with high-performance cardiovascular function, resources other than ideal donors should be considered for patients on the waiting list [9-11].

The age limit restrictions for organ donors vary slightly in different countries and medical centers, though these standards have expanded due to the increased need for organs and longer wait times. In addition to the age of the donor, other controversial eligibility issues such as smoking habits and communicable diseases (e.g., hepatitis C) have been addressed in different studies [12]. In Iran the upper age limit is usually between 40 and 50 years for donors. Marginal donors are defined as patients between 40 and 50 years or less than 40 years with risk factors such as drug abuse, a history of smoking, hypertension, diabetes mellitus, dyslipidemia, a family history of coronary artery disease, or high-dose inotrope treatment [13] indicating a potentially poor outcome based on follow-up echocardiography and coronary angiography. In recent years in Iran, harvests from marginal donors for heart transplants have been performed based on careful and complementary tests such as angiography at the Sina Hospital Organ Procurement Unit (OPU), a pioneer of procuring organs in the country.

Studies have shown that donations from older donors (>50 years) can be conducted for older (>60 years) recipients to avoid organ waste and to offer the patient a chance for survival [7,14-16]. An analysis by the United Network for Organ Sharing (UNOS) used a propensity score analysis to evaluate the postoperative outcomes of recipients of donor hearts with left ventricular ejection fractions <40% (reduced), 40%–50% (borderline), and $\geq 50\%$ (normal) and the results showed equivalent odds of primary graft failure and death at 1 year in all three groups [17]. Several studies have demonstrated no significant difference in the survival rate of patients who received organs from older donors [1,18-21]. The characteristics of potential ideal donors in Iran are detailed in Table 1 [15].

The primary objective of the study was to determine whether patients who received a marginal donor heart had different outcomes in terms of survival compared with patients who received an ideal donor heart, with the goal of finding an appropriate solution to the shortage of donor organs and to reduce wait times for recipients.

METHODS

This research was approved by the Tehran University of Medical Sciences ethics center (No. IR.TUMS.IKHC.REC.1399.359). Written consent was obtained from the

Table 1. Factors impacting the definition and usability of ideal cardiac donors

Factor	Detail
Age	<40 yr
No history of chest trauma	
No history of cardiac disease	
No prolonged hypotension or hypoxemia during pre-harvest time	
Appropriate hemodynamics	
Mean arterial pressure	>60 mmHg
Central venous pressure	Between 8 and 12 mmHg
Inotropic support (dopamine or dobutamine)	Less than 10 µg/kg/min
Normal electrocardiogram	
Normal echocardiogram	
Normal cardiac angiography (if indicated by donor age and history)	
Negative serology (hepatitis B surface antigen, hepatitis C virus, and HIV)	

HIV, human immunodeficiency virus.

families of deceased donors and the heart recipients before entering the study, and no organs were obtained from prisoners.

Study Subjects

This study was a retrospective analysis based on the follow-up data of heart donors and recipients at the Sina Hospital OPU. Over a period of 2 years, 93 hearts were harvested from 302 deceased organ donors. Among the donors, 75 were categorized as ideal donors (group A) and 18 were marginal donors (group B).

Study Protocol

To identify possible differences among the groups, the differences in the patient characteristics between the two donor groups (A and B) were assessed based on post-transplant heart survival in the two recipient groups (C and D). Group C included heart recipients of a standard organ, and group D comprised heart recipients of a marginal organ. All recipients had undergone heart transplant surgery for the first time. A summary of the sampling is provided in Fig. 1.

Demographic information on the donors was obtained from the hospital records, including their age, sex, smoking habits, drug abuse, alcohol consumption, history of surgery, history of cardiopulmonary resuscitation (CPR), ischemic time, and type and amount of inotrope intake.

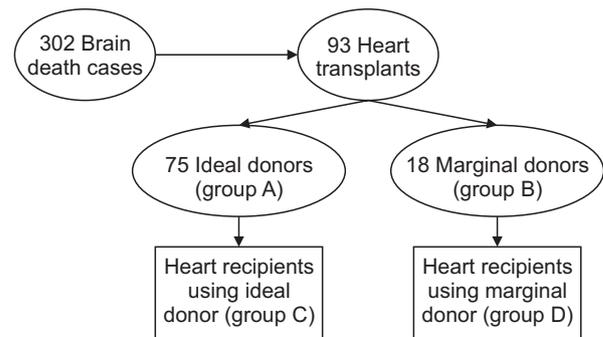


Fig. 1. Flowchart of study population selection.

The eligibility of heart donors was confirmed based on clinical, laboratory, and imaging evaluations including echocardiography. In marginal donors, final eligibility confirmation was based on angiography results. The ischemic time for all hearts was 60–90 minutes. Upon arrival of the heart at the destination hospital, the procedure was begun immediately.

Exclusion Criteria

Candidates were excluded if they had received multiple organ transplants, had hepatitis B or C, had unfavorable angiography results, and if families did not give consent.

Data Collection

After heart transplantation, the recipients' information, including age and sex, was extracted from their hospital records. After discharge from the tertiary hospital, all recipients were admitted to our department at 1 month and 1 year after transplant and were followed up through face-to-face interviews.

Statistical Analysis

SPSS ver. 16 (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. Normality was accessed by the Shapiro-Wilk test. Continuous variables are presented as means±standard deviation, and categorical variables are presented as percentages. The chi-square test, Fisher's exact test, or linear regression was used to compare variables. A two-tailed P-value <0.05 was considered to indicate statistical significance.

RESULTS

General Characteristics of the Study Subjects

In this retrospective study of heart transplant recipients (n=93), we identified 75 who received transplants from

Table 2. Baseline characteristics of brain death cases in marginal donor and ideal donor groups

Characteristics	Ideal donor group (n=75)	Marginal donor group (n=18)	P-value ^{a)}
Donor status			
Age (yr)	22.91±9.6 (23)	40.27±6.27 (41.5)	0.008
Sex			0.001
Male	58 (77.3)	16 (88.9)	
Female	17 (22.7)	2 (11.1)	
Smoking			0.001
Yes	0	10 (55.6)	
No	75 (100)	8 (44.4)	
CPR			0.001
Yes	12 (16)	4 (22.2)	
No	63 (84)	14 (77.8)	
Cause of brain death			0.001
Head trauma	50 (66.6)	14 (77.8)	
ICH-IVH	13 (17.3)	4 (22.2)	
Toxicity	5 (6.7)	0	
Tumor	2 (2.7)	0	
Others	5 (6.7)	0	
Addiction			0.001
Yes	0	4 (22.2)	
No	75 (100)	14 (77.8)	
Recipient status			
Age at transplant (yr)	29.16±18.1 (27)	33.5±16.6 (35.5)	0.001
Sex			0.001
Male	55 (73.3)	13 (72.2)	
Female	20 (26.7)	5 (27.8)	
Sex mismatch type			0.001
None	46 (61.3)	10 (55.6)	
Male to female	21 (28.0)	6 (33.3)	
Female to male	8 (10.7)	2 (11.1)	
Status			0.001
Stable	49 (65.3)	9 (50.0)	
Died in <365 days	18 (24.0)	6 (33.3)	
Died in >365 days	8 (10.7)	3 (16.7)	

Values are presented as mean±standard deviation (median) or number (%). CPR, cardiopulmonary resuscitation; ICH, intracranial hemorrhage; IVH, intraventricular hemorrhage.

^{a)}P<0.05 indicates statistical significance.

ideal donors (group A). The mean age of the donors was 26.27±11.44 years (median age, 28 years). The mean age of the ideal donors and marginal donors was 22.91±9.6 years (median, 23 years) and 40.27±6.27 years (median, 41.5 years), respectively. Fifty-eight ideal donors (77.3%) were men, and four marginal donors (22.2%) had a history of addiction. Sixty-eight of the recipients (73.1%) were male. The donor and recipient characteristics and the results of the normality of data are shown in Table 2.

Survival Rate in the Two Groups

There were no significant differences in the relationship between donors' sex and the survival rate of the recipients (P=0.24). Moreover, the recipients' sex did not affect their survival (P=0.92). Based on sex, no differences were observed for recipient-donor matches between the marginal and ideal donor groups (P=0.425). In addition, there was no difference in the status of recipients whose donor died due to head trauma or intracranial hemorrhage (ICH) (P=0.99). In our analysis, the donors' use of alcohol did not change transplant outcomes in the marginal donor group (P=0.43). There was no difference according to whether recipients had received pretransplant CPR (P=0.20), and no significant association was found between donors who received CPR and the recipients' survival rate (P=0.59).

Linear regression (Table 3) showed a significant relationship between the survival rate and the recipients' age (P<0.001) but no significant differences between survival rates in group C and D (recipient from ideal donor and recipient from marginal donor: group D). Most patients survived for at least 1 year, and the median survival was 645 days and 689 days in recipients from marginal and ideal donors, respectively. Specifically, of the 93 patients who were discharged from the hospital after transplantation, 18 patients who had undergone an ideal donor heart transplant died. Fourteen died within the first month posttransplant and four patients died after 1 year. In addition, five patients who had undergone a marginal donor transplant died within the first month and one patient died after 1 year. No significant differences were found in the endpoints between recipients in the marginal donor group and recipients in the ideal donor group (P=0.175).

Table 3. Linear regression of donor and recipient age, sex, and survival days in group C and D

Variable	Unstandardized coefficient		Standardized coefficients beta	t	P-value
	B	Beta			
Survival	0.000	0.000	-0.123	-1.055	0.295
Donor age	0.023	0.003	0.654	7.399	0.000 ^{a)}
Donor sex	-0.088	0.082	-0.090	-1.074	0.286
Recipient sex	0.093	0.077	0.103	1.202	0.233
Recipient age	-0.003	0.002	-0.153	-1.614	0.110
Recipient status	0.003	0.092	0.003	0.029	0.977

group C, recipient from ideal donor; group D, recipient from marginal donor.

^{a)}P<0.05 indicates statistical significance.

DISCUSSION

As heart transplantation progresses as an effective treatment for end-stage heart failure, physicians have considered relaxing the exclusion criteria and expanding the donor pool to meet the high demand for available organs [18-20]. Although heart transplantation from marginal donors is a relatively new topic in Iran, protocols regarding the suitability of potential cardiac donors have been modified over the years. Donors older than 40 to 50 years old or those with a positive history of drug abuse and smoking have recently been considered suitable. However, potential donors with chronic diseases like hepatitis B and C or high-grade tumors are not yet eligible candidate.

In our study, the most prevalent cause of brain death was head trauma, followed by non-traumatic ICH. In marginal donors, the most prevalent cause of brain death was also trauma and brain hemorrhage. These findings were similar to the study of Mizraji et al. [22]. Based on previous studies, age is one of the most important factors in choosing donors. Considering the organ shortage, the acceptable age range for organ harvest has increased [23]. According to Morgan et al. [24], older age is an independent risk factor for 1-year mortality, but the upper limit of the acceptable age range continues to increase as time progresses.

In our study, age as a continuous variable or as a categorical variable with a cutoff value of 50 years did not affect short and intermediate-term survival rates or the incidence of mechanical support. Although matching a young donor with a young recipient is a basic principle of donor selection, in this study there were 18 patients with an average age of 33.5 years who received hearts from donors 40.2 years or older.

According to the findings of previous studies, recipi-

ents of older donor hearts are exposed to the highest level of risk within the first postoperative month; therefore, precise care should be provided during that time [24]. However, Morgan et al. [24] did not report any significant difference between younger and older donor groups when assessing posttransplant complications such as sepsis and acute rejection. Moreover, they reported no difference in the first-year survival rates between the two groups. The findings of Drinkwater et al. [20] were similar to our study.

In a cohort study by Blanche et al. [25], two donor groups were compared who were similar to our cohort in all demographic data, except age (>50 years and <50 years), with recipient groups that were also similar. Their study recommended using donors older than 50 years and showed no difference in the survival rates of the two groups. According to the UNOS heart transplant registry, the donor-recipient predicted heart mass ratio, but not the weight or height ratio, is associated with survival [26]. Furthermore, sex matching between donors and recipients is very important. In our study, the sex was matched in 46 patients (61.3%) in group C and in 10 patients (55.56%) in group D. Considering the absence of a significant difference between the survival rates of the two groups, it can be concluded that sex match decreases the negative impacts of a marginal donor on survival.

Ayesta et al. [27] has shown that matched groups (female/female [F/F] and male/male [M/M]) were associated with higher recipient survival rates. In contrast, Antelmi et al. [28] suggested that a male donor organ for a female recipient is permissible. An analysis by the International Society for Heart and Lung Transplantation demonstrated that both mismatched groups (F/M and M/F) showed lower survival rates. A meta-analysis conducted by Ayesta et al. [27] and a retrospective cohort study by Reed et al. [26]

assessed the relationship between sex mismatch and survival of heart recipients and concluded that sex mismatch increased 1-year mortality in men, but not in women. In our study, female recipients exhibited a higher mortality rate overall than male recipients. Wang et al. [29] demonstrated that female recipients of hearts from marginal donors may have lower survival rates than those who receive hearts from ideal donors.

Taking into consideration the limited number of subjects due to the novelty of the topic in Iran, our study showed no significant difference between the survival rates of the ideal and marginal groups. However, according to Felker et al. [30], a marginal donor heart graft is only acceptable when it offers a greater chance of survival than that achieved with existing conventional therapies. Based on prior experience and considering the limited availability of resources such as artificial devices for cardiac support, heart transplantation using appropriate marginal donors is a valuable treatment for end-stage heart failure patients in Iran. Although the use of marginal donors increases organ availability, it should be considered that the results may not replicate those obtained with ideal donors. Overall, due to the lack of organ availability in Iran, the use of marginal donors for marginal recipients can reduce the number of people on the waiting list. We also recommend establishing a national marginal donor system that is appropriate for Iranian patients and extends the donor pool. The small number of marginal cases in our study underscores the need for further studies that include data from other centers and have longer follow-up time frames.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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