Effect of Jewish-Arab Ancestry and Gender Matching on Clinical Outcome of Lung Transplantation in Israel

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ABSTRACT: **Background:** Studies in lung transplantation demonstrate that the ancestry and gender dissimilarities of donor–recipients lead to a decrease in survival of the recipient.

Objectives: To evaluate the survival of lung transplant recipients in Israel based on whether the donors and recipients are of Jewish or Arab ancestry, as well as survival based on gender match or mismatch.

Methods: We performed a retrospective observational cohort study of 345 lung transplant recipients at the Rabin Medical Center, Petah Tikva, Israel between January 1997 and January 2013. We compared the survival of lung transplant recipients in two ancestry categories: ancestry matched (Jewish donors to Jewish recipients or Arab donors to Arab recipients) and ancestry mismatched (Jewish donors to Arab recipients and vice versa). We also compared the survival among the four gender donor and recipient combinations (male to male, female to female, male to female, and female to male).

Results: Survival analysis revealed no significant differences between the two ancestry groups ($P = 0.51$) and among the four gender combinations ($P = 0.58$). On Cox multivariate analysis, younger donor age was the only significant parameter for longer survival (hazards ratio 1.025, 95% confidence interval 1.012–1.037).

Conclusions: Gender and ancestry mismatches in these two Israeli populations do not appear to alter the clinical outcomes following lung transplantation.

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The first successful clinical lung transplantation was performed in 1963 [1]. Since then, lung transplantation has become an available treatment for a variety of end-stage lung diseases. Remarkable progress has been made through thoracic surgical techniques, advances in immunosuppressive therapy and improved donor–recipient genetic matching [2].

Ancestry differences in long-term survival after solid organ transplantation are well recognized [3-6]. Studies have demonstrated that transplantation between an African-American and European-American has led to shorter survival of lung transplant recipients [7-9]. However, transplantation between African-American and African-American individuals led to longer recipient survival [3]

The effect of gender mismatch on lung transplantation outcomes has received less attention, despite extensive studies in other solid organ transplantations. In transplantations of liver [10], kidney [11] and heart [12], the female donor to male recipient combination has been consistently associated with poor survival. In lung transplantation the results are mixed; while two studies supported this finding [13,14], in others it was insignificant [15-17] or was even found contradictory [18]. The aim of the present study was to evaluate the effect of donor–recipient ancestry and gender matching on survival after lung transplantation in Israel.

PATIENTS AND METHODS

We performed a retrospective single-center cohort study of the 345 lung transplantations performed at Rabin Medical Center. This medical center is the national center for lung transplantation in Israel since 1997. Included in the study were all individuals undergoing lung transplantation between January 1997 and January 2013.

The lung transplants were divided into two groups according to recipient and donor ancestry origin. Ancestry-matched transplantation was defined as Jewish donor to Jewish recipient or Arab donor to Arab recipient. Ancestry-mismatched transplantation was defined as Jewish donor to Arab recipient or Arab donor to Jewish recipient. Donor–recipient pairs were also distributed into four groups according to donor and recipient gender: gender-matched transplantation groups comprised male donors to male recipients (MM), or female donors to female recipients (FF). Gender-mismatched transplantation groups comprised male donors to female recipients (MF) or female donors to male recipients (FM). The study received ethics approval from the Rabin Medical Center Institutional Review Board.

STATISTICAL ANALYSIS

Descriptive data were expressed as the mean and standard deviation (SD), number of patients (n) and percentage (%). The

Table 1. Baseline patient characteristics

	Gender match		Gender mismatch					
	MM	FF	MF	FM	*P*	Ancestry match	Ancestry mismatch	*P*
n	158	97	45	45		252	93	
Recipient								
Age (years)	54.7±11.9	50.2±13.5	49.3±15.7	48.6±17.4	0.08	52.8±13.3	52.2±13.1	NS
Transplant type								
Left lung	39.2%	34%	22.2%	26.7%	0.01	34.1%	39.7%	NS
Right lung	39.9%	37.1%	31.1%	31.1%		39.3%	30.1%	
Double/heart-lung	20.9%	28.9%	46.7%	42.2%		26.5%	30.1%	
Diagnosis								
Emphysema	30.6%	24%	22.2%	31.1%	0.002	28%	27.4%	NS
Fibrosis	40.1%	39.6%	28.9%	24.4%		37%	43.8%	
Cystic fibrosis	4.5%	8.3%	24.4%	22.2%		9.5%	9.6%	
Others	24.8%	28.1%	24.4%	22.2%		25.6%	19.2%	
Donor								
Age (years)	45±17.6	46.1±17	46.2±14.4	35.5±19.4	0.05	46.1±17.8	38.8±15.9	0.003

MM = male to male, FF= female to female, MF = male to female, FM = female to male, NS = not significant

differences between ancestry and gender groups were examined using the chi-square tests for categorical variables and ANOVA test for continuous variables. Statistical significance was set at $P < 0.05$. Survival analysis was calculated by the Kaplan-Meier method and Cox regression to determine statistical difference between groups. Statistical analyses were performed using SAS version 9.2 software (SAS Institute Inc., Cary, NC, USA).

RESULTS

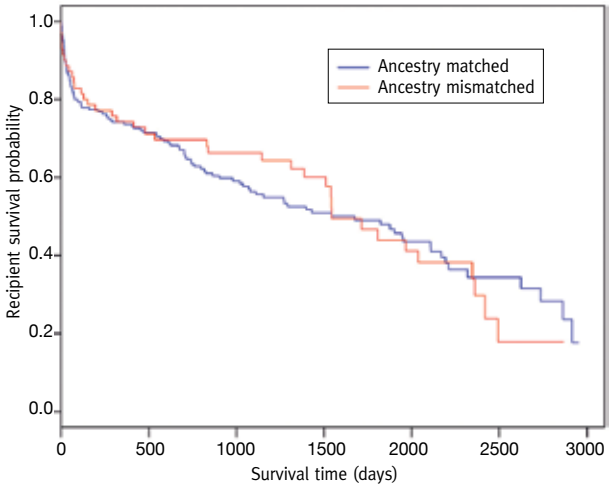
Baseline characteristics for 345 lung transplant patients are listed in Table 1. A total of 252 donor–recipient pairs belonged to the ancestry-matched group, while 93 pairs belonged to the ancestry-mismatched group. There was a significant difference between the donor age of the two groups (46.1 ± 17.8 vs. 38.8 ± 15.9 years, $P < 0.003$). Recipient age, transplantation type (single lung versus double lung) and disease diagnosis leading to transplantation showed no statistically significant differences.

Significant differences were found among the gender combinations in several categories: transplant type ($P = 0.01$), diagnosis ($P = 0.002$), recipient's age ($P = 0.008$) and donor's age ($P = 0.05$). The recipient's age in increasing order was 49.3 (MF), 50.2 (FF), 54.7 (MM) and 48.6 (FM) years. The donor's age in increasing order was 35.5 (FM), 46.1 (FF), 46.2 (MF) and 45 (MM) years. On multivariate analysis, younger age of the lung donor was the only significant parameter for increased survival (hazards ratio 1.025, 95% confidence interval 1.012–1.037).

SURVIVAL ANALYSIS

Kaplan-Meier survival analysis showed no statistically significant difference in survival between ancestry-matched and mismatched groups ($P = 0.51$) [Figure 1]. In addition, no significant survival difference was found between the gender-matched and mismatched groups ($P = 0.18$) [Figure 2]. When comparing four survival curves for each gender combination, only the male donor to male recipient had a trend to increased survival but it did not reach statistical significance ($P = 0.58$) [Figure 3]. The other gender combinations had the same survival trends.

Figure 1. Kaplan-Meier estimate of survival comparing the matched and mismatched ancestry combinations. Matched combinations include Jewish to Jewish or Arab to Arab, while mismatched combinations include Jewish to Arab or Arab to Jewish ($P = 0.51$)



DISCUSSION

We studied the effects of donor-recipient ancestry and gender matching on outcome following lung transplantation. No

Figure 2. Kaplan-Meier estimate of survival comparing the matched and mismatched gender combinations. Matched combinations include male to male (MM) and female to female (FF), while mismatched combinations include male to female (MF) and female to male (FM) ($P = 0.18$)

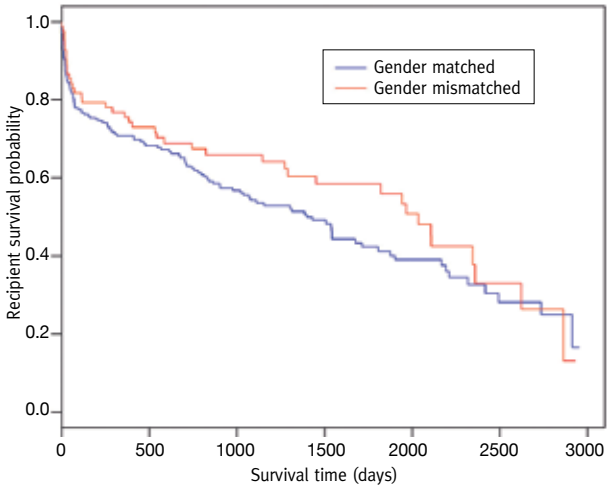
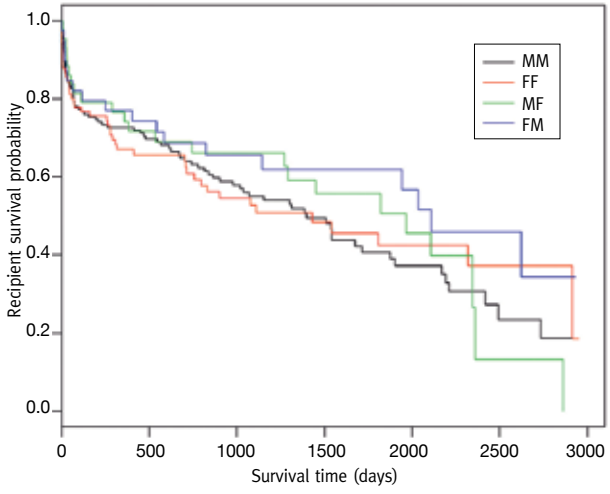


Figure 3. Kaplan-Meier estimate of survival comparing the four gender combinations: male to male (MM), male to female (MF), female to male (FM), and female to female (FF) ($P = 0.58$)



significant association between donor–recipient ancestry and gender matching with improved survival was observed. This suggests that ancestry and gender matching in Israel were not independent risks factors for patient survival.

ANCESTRY MATCHING

In contrast to our observations, the effect of donor–recipient ancestry matching on clinical outcome has been studied for kidney [3], liver [4], pancreas [5] and heart [6] transplantation. These studies have reported enhanced survival of graft and patient with ancestry-matched transplantations. Few ancestry studies have been performed in lung transplantation [7-9]. These studies reported that patients who received ancestry-matched lung transplants (European-American ancestry donor to European-American ancestry recipient) had improved 30 day [7], 90 day, 1 and 2 year survival [8], and overall survival rates [9]. However, there was a significant decrease in survival for European-American ancestry recipients who received African-American donor lungs [7].

The independent effect of ancestry on survival has several potential explanations. First, ethnic minorities with poorer socioeconomic status may have limited access to medical care [19]. Secondly, African-American patients showed increased graft loss, which could be related to immunologic hyper-responsiveness [20]. Thirdly, some studies show that African-Americans exhibit differential expression of angiotensin-converting enzyme on vascular endothelium, which could potentially predispose them to a more severe ischemic reperfusion injury [21]. Fourthly, African-American donors with APOL1 two risk variants exhibit a markedly decreased kidney allograft survival compared with African-Americans with APOL1 0 or 1 risk allele and European-Americans. Although APOL1 has been detected in the normal lung, the role of these variants in lung transplantation has not been studied [22]. Finally, the genetic basis for all these explanations may originate from the fact that different ethnic groups are more likely to display greater histocompatibility polymorphisms [23].

This is the first study to examine the impact of ancestry matching of Israeli Jews and Arabs on clinical outcome following solid organ transplantation. A possible explanation for these results could be that since contemporary Jews originated in the Middle East, Jews and Arabs in Israel have a related genome-wide structure [24]. The similar genetic structure was recently demonstrated using principal component and structure-like analyses [25]. Another explanation could be related to our relatively small sample (n=354) with low heterogeneity to enable demonstration of a statistically significant difference.

GENDER MATCHING

The influence of gender matching on clinical outcome after lung transplantation has been the subject of a small number of studies [13-18]. Studies of liver [10], kidney [11] and heart [12] transplantation have shown a decreased graft survival in many cases of female donors to male recipients [10-12]. Two large lung transplant studies also suggest a decreased survival among female donors to male recipients [13,14], with increased survival among female donors to female recipients. The first was an American study (n=9651 patients) [13] from the International Society of Heart and Lung Transplantation Registry (ISHLT), and the other was a French multicenter study (n=785 patients) [14]. However, in the current study on lung transplantation in Israel we were unable to show a significant association between donor and recipient gender match and increased survival. In

contrast, we found a tendency towards increased survival in the group of female donors to male recipients. These results may be explained by the significantly younger age of female recipients (48.6 ± 17.4 years) and male donors (35.5 ± 19.4 years) as compared to the other combinations [Table 1]. In the multivariate analysis, younger age at donation was seen as the only parameter that predicted longer survival. Other reasons for the increased survival in the group of female donors to male recipients can be attributed to the different incidence of pre-transplantation diagnosis, type of operation, and smaller sample with low homogeneity of the patient population. Similarly, three other small studies did not demonstrate an association between donor and recipient gender match [15-17].

In conclusion, we were unable to demonstrate an association between donor–recipient Jewish-Arab ancestry and gender match on clinical outcomes after lung transplantation in Israel in contrast to that reported in other lung transplant cohorts.

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