

The Implications of Donor Gender on the Post-Liver Transplant Prognosis of Patients with Nonalcoholic Steatohepatitis: An UNOS-Based Study

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Background and Aims

In nonalcoholic steatohepatitis (NASH), there are thought to be metabolic pathways that are influenced by sex hormones and other gender-specific comorbidities, which shape the phenotypic manifestations of NASH. In the height of recent interests surrounding recipient-gender donor mismatch and its post-transplant implications, further effort is required to understand the prognostic effects of gender discordance on the post-liver transplant (LT) prognosis of NASH patients.

Methods

The 2005-2019 UNOS registry was queried to isolate NASH patients. Recipients aged 18 or younger, those with multi-organ transplants, and those with living donor transplants were excluded. The resulting sample was stratified using donor gender and compared to post-LT outcomes via Cox regression analysis (adjusting for MELD and covariates). Secondary analysis included the recipient gender-restricted subgroups, which were stratified using donor gender and compared to the endpoints. For each comparison, cumulative hazard curves were drawn and Log-rank p-values were calculated.

Results

There was a total of 11585 NASH patients, from which there were 6778 recipients with male donors and 4807 recipients with female donors. The median follow-up period 3.02 years. In the primary analysis, recipients with male donors (compared to those with female donors) were younger (58.1 vs. 58.8 years, $p < 0.001$), likely to have male recipients (62.5% vs. 49.1%, $p < 0.001$), and had higher MELD score (22.90 vs. 22.50, $p = 0.02$). No significant differences were found along all-cause mortality (adjusted hazard ratio (aHR) 0.97 95%CI 0.90-1.05) or graft failure (aHR 1.04 95%CI 0.84-1.29). However, recipients with male donors had a higher risk of death due to myocardial infarction death (MI) (aHR 2.32 95%CI 1.01-5.31) and NASH recurrence (aHR 4.76 95%CI 1.04-21.76). These results were reflected in the case-incidence rates, expressed per 1000 person-years (MI death: 0.86 vs 0.39; NASH recurrence death: 0.45 vs 0.10). In the male recipient-restricted subpopulation, having a recipient-donor gender mismatch (female donors vs male donors) did not correlate with general outcomes (all-cause mortality: aHR 1.00 95%CI 0.9-1.11; graft failure: 0.90 95%CI 0.67-1.22) or the specific-causes of death. On the other hand, in the female recipient-restricted subpopulation, having a recipient-donor gender mismatch (male donors vs female donors) was associated with lower risk of sepsis-related deaths (aHR 0.69 95%CI 0.49-0.97), which was reflected in the case incidence rates (5.57 versus 8.97 deaths).

Conclusion

The findings show that recipients with male donors are generally at a higher risk of deaths due to MI and NASH recurrence, but a protective effect was observed against sepsis-induced death in male-donor-to-female-recipient gender-mismatch cases. Further studies are needed to understand the pathophysiological bases behind these findings.

Univariate Analysis

Comparison of Donor Gender: Male vs Female

Characteristics	Male Donors	Female Donors	P-value
Number of Patients	n = 6778	n = 4807	
Recipient Demographics			
Age (year)	58.10 ± 9.17	58.80 ± 9.12	< 0.001 ***
Recipient-Donor Gender Matching (%)	4237 (62.50)	2360 (49.10)	< 0.001 ***
Race			0.004 **
White (%)	5459 (80.50)	3740 (77.80)	
Black (%)	177 (2.61)	147 (3.06)	
Hispanic (%)	933 (13.80)	727 (15.10)	
Asian (%)	127 (1.87)	120 (2.50)	
Other (%)	82 (1.21)	73 (1.52)	
BMI (kg/m ²)	31.40 (6.04)	30.90 ± 6.20	< 0.001 ***
Hepatic Variables			
MELD Scores	22.90 ± 8.87	22.50 ± 8.89	0.02 *
Donor Demographics			
Donor Age (years)	41.70 ± 17.10	47.80 ± 16.60	< 0.001 ***
Donor Race			< 0.001 ***
White (%)	4361 (64.30)	3238 (67.40)	
Black (%)	1267 (18.70)	904 (18.80)	
Hispanic (%)	864 (12.70)	446 (9.28)	
Asian (%)	147 (2.17)	124 (2.58)	
Other (%)	139 (2.05)	95 (1.98)	
Donor BMI (kg/m ²)	27.70 ± 5.91	29.20 ± 7.78	< 0.001 ***
† Fisher's Test			

Cox Iterations for Clinical Endpoints

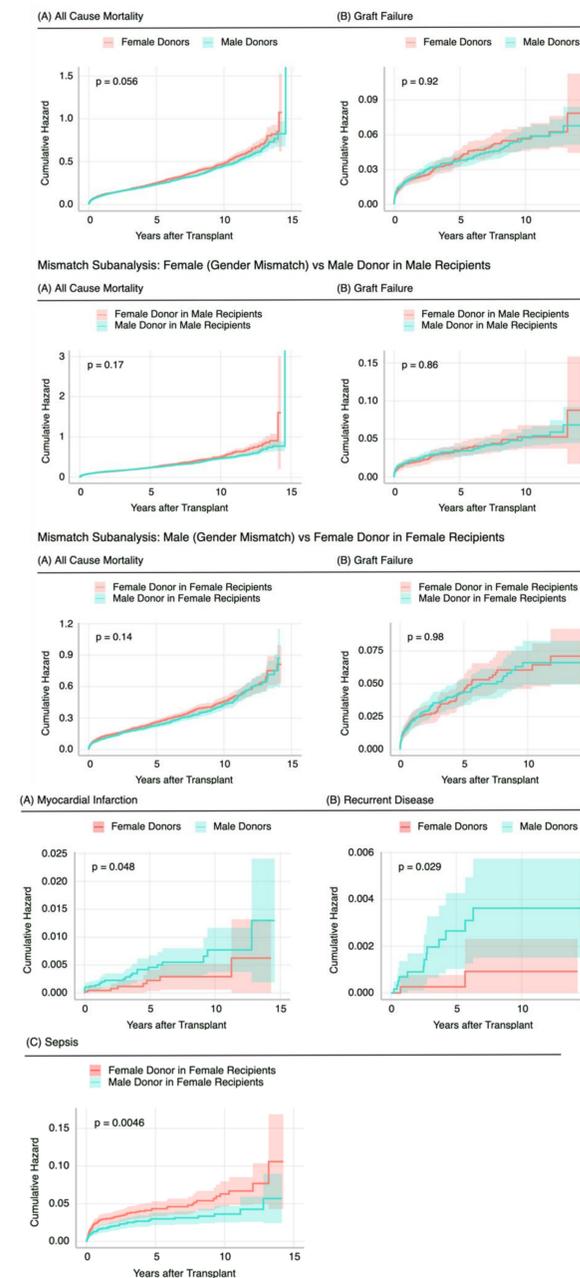
Male vs Female Donor			
(A) All-cause Mortality		(B) Graft Failure	
Incidence Rates per 1000 Person-Years		Incidence Rates per 1000 Person-Years	
Male Donor	3.03 (1.01 - 6.98)	Male Donor	3.03 (1.01 - 6.98)
Female Donor	3.01 (1.00 - 6.90)	Female Donor	3.01 (1.00 - 6.90)
Sequential Cox Regression Analysis		Sequential Cox Regression Analysis	
Model	p-value	aHR	95% CI
1	0.20	0.95	(0.88 - 1.03)
2	0.20	0.95	(0.88 - 1.03)
3	0.15	0.94	(0.87 - 1.02)
†FM	0.45	0.97	(0.90 - 1.05)
Mismatch Subanalysis: Female (Gender Mismatch) vs Male Donor in Male Recipients		Mismatch Subanalysis: Female (Gender Mismatch) vs Male Donor in Male Recipients	
(A) All-cause Mortality		(B) Graft Failure	
Incidence Rates per 1000 Person-Years		Incidence Rates per 1000 Person-Years	
Male Donor in Male Recipients	3.02 (1.00 - 6.97)	Male Donor in Male Recipients	3.02 (1.00 - 6.97)
Female Donor in Male Recipients	3.06 (1.00 - 6.94)	Female Donor in Male Recipients	3.06 (1.00 - 6.94)
Sequential Cox Regression Analysis		Sequential Cox Regression Analysis	
Model	p-value	aHR	95% CI
1	0.56	0.97	(0.87 - 1.08)
2	0.54	0.97	(0.87 - 1.08)
3	0.51	0.97	(0.87 - 1.07)
†FM	0.99	1.00	(0.9 - 1.11)
Male vs Female Donor			
(A) Death due to Recurrent Nonhepatitis		(B) Death due to Myocardial Infarction	
Incidence Rates per 1000 Person-Years		Incidence Rates per 1000 Person-Years	
Male Donor	0.45 (0.24 - 0.77)	Male Donor	0.86 (0.56 - 1.27)
Female Donor	0.10 (0.01 - 0.36)	Female Donor	0.39 (0.17 - 0.78)
Sequential Cox Regression Analysis		Sequential Cox Regression Analysis	
Model	p-value	aHR	95% CI
1	0.04 *	4.88	(1.09 - 21.79)
2	0.04 *	4.79	(1.07 - 21.40)
3	0.05 *	4.53	(1.01 - 20.25)
†FM	0.04 *	4.76	(1.04 - 21.76)
Mismatch Subanalysis: Male (Gender Mismatch) vs Female Donor in Female Recipients			
(C) Death due to Sepsis			
Incidence Rates per 1000 Person-Years			
Male Donor in Female Recipients	5.57 (4.26 - 7.15)		
Female Donor in Female Recipients	8.97 (7.24 - 10.99)		
Sequential Cox Regression Analysis			
Model	p-value	aHR	95% CI
1	0.004 *	0.62	(0.45 - 0.85)
2	0.004 *	0.62	(0.45 - 0.86)
3	0.004 *	0.62	(0.45 - 0.86)
†FM	0.03 *	0.69	(0.49 - 0.97)

* p < 0.05, ** p < 0.01, *** p < 0.001

† FM indicates Final Model

Model 1 includes VOI (variable of interest) and demographics, model 2 includes VOI, demographics, comorbidities, and medications, model 3 includes VOI, demographics, comorbidities, medications, and biomarkers, and the final model includes VOI, demographics, comorbidities, medications, biomarkers, and donor information

Prognostic Curves for Clinical Endpoints



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