
APPENDICES

Appendix A. Additional Tables and Figures

Table A1 Results of Balance and Bias Reduction Achieved per Each Propensity Score Variable

Table A1 Results of Balance and Bias Reduction Achieved per Each Propensity Score Variable⁷⁸

Variable (Pre-Index)	Unmatched Matched	Mean		%bias	%reduct bias	t-test		V _e (T) / V _e (C)
		LT	MM			t	p> t	
Ln(N of HAE)	U	1.5081	.85468	124.6		8.31	0.000	2.56**
	M	1.2264	.99374	44.4	64.4	1.52	0.132	1.00
% NH ₄ >399 μmol/L	U	.29747	.21938	20.9		1.43	0.153	0.78*
	M	.35435	.36923	-4.0	80.9	-0.13	0.900	0.85
Parent Edu (No College)	U	.21782	.10465	31.0		2.09	0.038	1.89*
	M	.27586	.21397	16.9	45.3	0.49	0.624	1.14
Parent Edu (Not Provided)	U	.26733	.5	-49.0		-3.36	0.001	0.75*
	M	.34483	.39994	-11.6	76.3	-0.40	0.688	0.89
Parent Edu (Some College)	U	.16832	.09302	22.4		1.51	0.133	1.39*
	M	.06897	.05673	3.6	83.7	0.17	0.864	1.12
Birth Decade	U	2.1485	1.8488	34.2		2.37	0.019	0.56*
	M	2.1207	2.1335	-1.5	95.7	-0.06	0.951	0.94
Ln(Max. HAE LOS)	U	3.0537	2.5174	59.9		4.06	0.000	1.18
	M	2.863	2.8145	5.4	91.0	0.18	0.858	1.16
UCD Type (Proximal v. Distal)	U	.52475	.33721	38.4		2.61	0.010	1.12
	M	.53448	.46734	13.7	64.2	0.47	0.639	0.98
% NH ₄ 150-399 μmol/L	U	.33002	.17409	45.3		3.09	0.002	0.81
	M	.27922	.23676	12.3	72.8	0.42	0.679	0.83
Ln(N of HAE LOS > 8days)	U	.72825	.45272	73.0		4.94	0.000	1.04
	M	.5538	.55296	0.2	99.7	0.01	0.993	1.18
Birth Decade ²	U	5.1188	4.4302	22.3		1.53	0.129	0.79*
	M	5.0172	5.0837	-2.2	90.3	-0.08	0.936	0.96
Ln(Max. HAE LOS) ²	U	10.213	7.0341	63.1		4.24	0.000	1.90*
	M	9.1285	8.6955	8.6	86.4	0.28	0.783	1.62*
Ln(N of HAE) x No College	U	.35183	.10373	43.6		2.90	0.004	4.28**
	M	.42718	.26342	28.8	34.0	0.78	0.440	1.51*
Birth Decade x %NH ₄ 150-399 μmol/L	U	.72376	.38837	40.3		2.77	0.006	0.69*
	M	.60629	.5129	11.2	72.2	0.39	0.696	0.86
Ln(Max. HAE LOS) x Some College	U	.53322	.19585	34.1		2.27	0.024	2.52**
	M	.17836	.15835	2.0	94.1	0.11	0.915	0.97
UCD Type x Ln(N of HAE LOS > 8days)	U	.41359	.1612	64.0		4.29	0.000	2.59**
	M	.32267	.28899	8.5	86.7	0.34	0.734	1.01
%NH ₄ 150-399 μmol/L x Ln(N HAE LOS > 8ds)	U	.22616	.07339	62.2		4.20	0.000	1.22
	M	.1232	.10509	7.4	88.1	0.30	0.765	0.78*
%NH ₄ 150-399 μmol/L x Birth Decade ²	U	1.7031	1.0182	30.1		2.07	0.040	0.63*
	M	1.431	1.2148	9.5	68.4	0.34	0.733	0.96

* if 'of concern', i.e. variance ratio (V_e(T) / V_e(C)) in [0.5, 0.8) or (1.25, 2]

** if 'bad', i.e. variance ratio <0.5 or >2

%bias is the % difference in sample means in LT vs MM as a percent of the square root of the sample variances in LT and MM

%reductbias is % difference in %bias in the matched (M) and unmatched (U) samples.

Ve(T) - variance in the treated group

Ve(C) - variance in the untreated or control group

Table A2. Stratum Mean Propensity Score Balance within Three Propensity Score Stata

Stratum 1

Two-Sample t-test with Equal Variances

Group	Obs	Mean	Std. Err.	Std. Dev.	[95% Conf. Interval]	
MM	33	-1.7176	.1274261	.7320071	-1.977158	-1.458041
LT	5	-2.131752	.2666098	.5961576	-2.871979	-1.391524
combined	38	-1.772093	.1172015	.7224785	-2.009566	-1.534621
diff		.4141521	.3446552		-.284841	1.113145

diff = mean(No) - mean(Yes) t = 1.2016
 Ho: diff = 0 degrees of freedom = 36

Ha: diff < 0 Ha: diff != 0 Ha: diff > 0
 Pr(T < t) = 0.8813 Pr(|T| > |t|) = 0.2373 Pr(T > t) = 0.1187

Stratum 2

Two-Sample t-test with Equal Variances

Group	Obs	Mean	Std. Err.	Std. Dev.	[95% Conf. Interval]	
MM	14	-.0312503	.1200428	.4491592	-.2905871	.2280865
LT	14	.0491227	.1332641	.4986285	-.2387768	.3370223
combined	28	.0089362	.0883422	.467463	-.172327	.1901995
diff		-.080373	.1793588		-.4490504	.2883044

diff = mean(No) - mean(Yes) t = -0.4481
 Ho: diff = 0 degrees of freedom = 26

Ha: diff < 0 Ha: diff != 0 Ha: diff > 0
 Pr(T < t) = 0.3289 Pr(|T| > |t|) = 0.6578 Pr(T > t) = 0.6711

Stratum 3

Two-Sample t-test with Equal Variances

Group	Obs	Mean	Std. Err.	Std. Dev.	[95% Conf. Interval]	
MM	4	2.055689	.6191165	1.238233	.0853839	4.025994
LT	39	2.208801	.1483275	.9263051	1.908527	2.509074
combined	43	2.194558	.1436941	.9422652	1.904571	2.484544
diff		-.1531118	.5001289		-1.163143	.8569191

diff = mean(No) - mean(Yes) t = -0.3061
Ho: diff = 0 degrees of freedom = 41

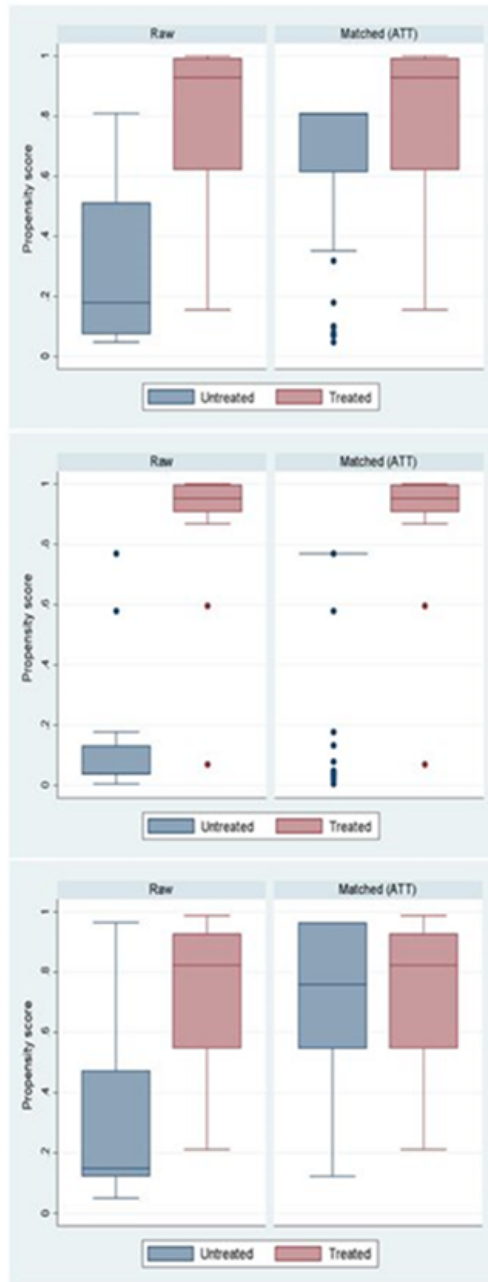
Ha: diff < 0 Ha: diff != 0 Ha: diff > 0
Pr(T < t) = 0.3805 Pr(|T| > |t|) = 0.7610 Pr(T > t) = 0.6195

Table A3. Unadjusted Visual Skills Result by Treatment Group in Common Support Sample

Outcome	Group	N	Mean	95% CI
Beery VMI	LT	22	77.3	70.5, 84.1
	MM	15	73.7	62.1, 85.2
Beery Visual Perception	LT	18	83.8	74.0, 93.7
	MM	14	86.3	73.6, 99.0
Performance IQ	LT	20	82.9	73.8, 92.0
	MM	16	81.8	71.2, 92.3

Table A4. Matched and Adjusted Visual Skills Result in LT Compared to MM

Outcome	Analysis Method	Liver Transplant Treatment Effect		
		Difference	95% CI	p-value
Beery VMI (LT=22, MM=15)				
	Unadjusted	3.7	-8.4, 15.7	0.54
	Propensity Score Adjusted	0.3	-30.0, 30.6	0.98
	Ridge Matched and Adjusted*	-2.0	-27.4, 23.4	0.88
Beery Visual Perception*(LT=18, MM=14)				
	Unadjusted	-2.5	-17.6, 12.7	0.74
	Propensity Score Adjusted	-14.2	-42.3, 13.9	0.32
	Ridge Matched and Adjusted*	-12.7	-56.3, 31.0	0.57
Performance IQ (LT=20, MM=16)				
	Unadjusted	1.2	-12.2, 14.5	0.86
	Propensity Score Adjusted	13.8	-6.9, 34.4	0.19
	Ridge Matched and Adjusted*	8.1	-60.7, 76.9	0.82



**in addition to propensity scores, results are adjusted for index age and age assessed.*

Table A5. Relationship between Age at Liver Transplant And Visual Skills

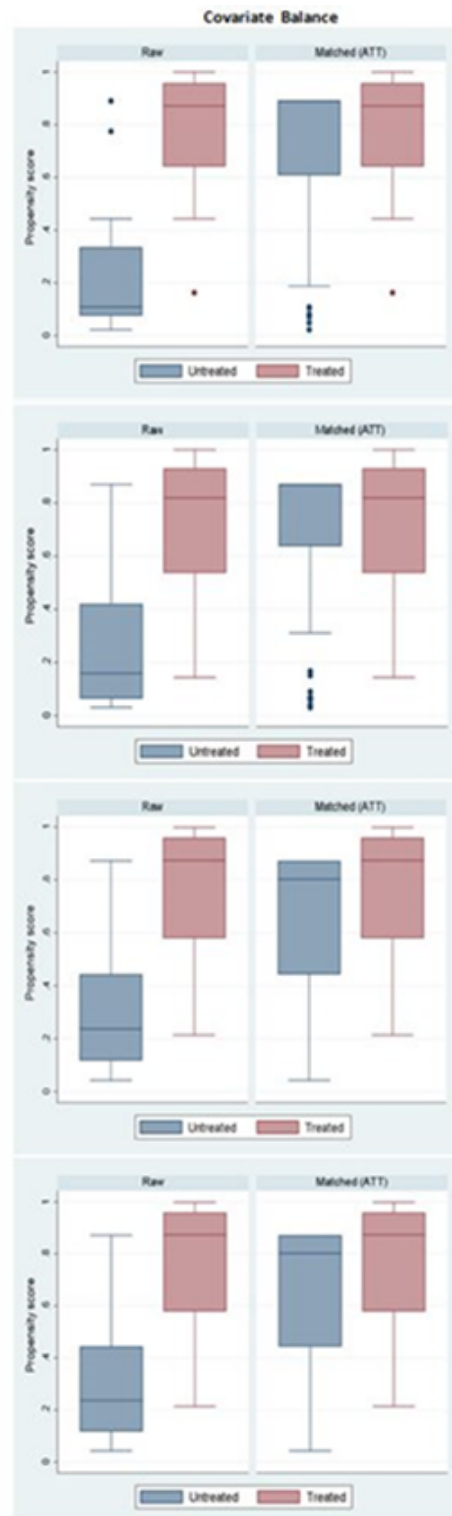
Outcome	Age Group	Result by Age at Transplant		
		N	Mean	95% CI
Beery VMI	<1 yr	11	80.6	72.8, 88.4
	1 - <3 yrs	8	78	65.7, 90.2
	3+ yrs	3	63.5	41.6, 85.4
Beery Visual Perception*	<1 yr	8	92.6	77.1, 108.1
	1 - <3 yrs	7	74.9	58.1, 91.7
	3+ yrs	3	81.3	60.5, 102.0
Performance IQ	<1 yr	8	90.6	71.6, 109.7
	1 - <3 yrs	7	83.1	75.2, 91.1
	3+ yrs	3	68.7	55.2, 82.2

Table A6. Unadjusted Motor Skills Result by Treatment Group in Common Support Sample

Outcome	Group	N	Mean	95% CI
Grooved Pegboard, Dominant Hand	LT	16	72.3	59.0, 85.7
	MM	13	71.6	56.8, 81.2
Grooved Pegboard, NonDominant Hand	LT	15	77.2	64.2, 90.3
	MM	14	73.9	59.2, 88.6
Grip Strength, Dominant Hand	LT	15	83.1	66.6, 99.7
	MM	11	72.9	59.0, 86.8
Grip Strength, NonDominant Hand	LT	15	89.1	74.5, 103.7
	MM	11	74.9	62.4, 87.3

Table A7. Matched and Adjusted Motor Skills Result in LT Compared to MM

Outcome	Analysis Method	Liver Transplant Treatment Effect		
		Difference	95% CI	p-value
Grooved Pegboard, Dominant (LT=16, MM=13)				
	Unadjusted	0.7	-18.3, 19.7	0.94
	Propensity Score Adjusted	-32.2	-68.7, 4.3	0.08
	Ridge Matched and Adjusted*	-27.4	-116.1, 61.3	0.55
Grooved Pegboard, Non Dominant (LT=15, MM=14)				
	Unadjusted	3.3	-15.3, 22.0	0.72
	Propensity Score Adjusted	-7.9	-62.7, 47.0	0.78
	Ridge Matched and Adjusted*	-7.9	-58.6, 42.8	0.76
Grip Strength, Dominant (LT=15, MM=11)				
	Unadjusted	10.2	-11.4, 31.9	0.34
	Propensity Score Adjusted	4.2	-25.6, 34.1	0.78
	Ridge Matched and Adjusted*	6.9	-57.3, 110.7	0.83
Grip Strength, Non Dominant (LT=15, MM=11)				
	Unadjusted	14.2	-4.9, 33.4	0.14
	Propensity Score Adjusted	10.5	-19.8, 40.8	0.5
	Ridge Matched and Adjusted*	10	-33.2, 53.2	0.65



*in addition to propensity scores, results are adjusted for index age and age assessed.

Table A8. Relationship between Age at Liver Transplant And Motor Skills

Outcome	Result by Age at Transplant			
	Age Group	N	Mean	95% CI
Grooved Pegboard, Dominant				
	<1 yr	8	75.8	57.6, 93.9
	1 - <3 yrs	4	79	64.1, 93.8
	3+ yrs	4	53.1	37.6, 68.6
Grooved Pegboard, Non Dominant				
	<1 yr	7	86.9	76.8, 96.9
	1 - <3 yrs	4	79.5	62.4, 96.5
	3+ yrs	4	58.2	42.1, 74.4
Grip Strength, Dominant				
	<1 yr	7	80.8	56.5, 105.0
	1 - <3 yrs	4	77.8	60.6, 94.9
	3+ yrs	4	92.7	72.1, 113.3
Grip Strength, Non Dominant				
	<1 yr	7	90.3	71.3, 109.4
	1 - <3 yrs	4	86.1	76.5, 95.7
	3+ yrs	4	90	74.3, 105.6

Table A9. Unadjusted Attention/Executive Function by Treatment Group in Common Support Sample

Outcome	Group	N	Mean	95% CI
CBCL Attention				
	LT	23	117	109.9, 124.0
	MM	17	119.4	112.6, 126.3
BRIEF Inhibition				
	LT	19	118.4	108.5, 128.3
	MM	14	117.3	106.5, 128.0
BRIEF Working Memory				
	LT	27	123.7	115.7, 131.8
	MM	18	120.9	110.8, 131.1
BRIEF Shift				
	LT	27	114.2	105.3, 123.1
	MM	18	108.2	99.9, 116.5
BRIEF GEC				
	LT	27	119.3	111.5, 127.2
	MM	17	117.2	107.5, 126.9

CBCL – Child Behavior Checklist

BRIEF – Behavior Rating Inventory of Executive Function

Table A10. Matched and Adjusted Attention/Executive Function in LT Compared to MM

Outcome	Analysis Method	Liver Transplant Treatment Effect			Covariate Balance
		Difference	95% CI	p-value	
CBCL Attention (LT=23, MM=17)					
	Unadjusted	-2.5	-12.3, 7.4	0.62	
	Propensity Score Adjusted	0.7	-11.8, 13.2	0.91	
	Ridge Matched and Adjusted*	7.2	-18.0, 32.5	0.57	
BRIEF Inhibition (LT=19, MM=14)					
	Unadjusted	1.1	-13.0, 15.3	0.87	
	Propensity Score Adjusted	-3	-18.7, 12.8	0.71	
	Ridge Matched and Adjusted*	9.4	-142.1, 161.0	0.9	
BRIEF Working Memory (LT=27, MM=18)					
	Unadjusted	2.8	-9.7, 15.3	0.65	
	Propensity Score Adjusted	14.3	-2.6, 31.2	0.1	
	Ridge Matched and Adjusted*	1.3	-32.4, 35.0	0.94	
BRIEF Shift (LT=27, MM=18)					
	Unadjusted	6.1	-6.4, 18.6	0.33	
	Propensity Score Adjusted	21	8.1, 34.0	0.001	
	Ridge Matched and Adjusted*	3.4	-20.0, 26.8	0.77	
BRIEF GEC (LT=27, MM=17)					
	Unadjusted	2.1	-10.1, 14.3	0.73	
	Propensity Score Adjusted	18.4	-4.1, 32.7	0.01	
	Ridge Matched and Adjusted*	-1.9	-34.6, 30.8	0.91	

*in addition to propensity scores, results are adjusted for index age and age assessed.

Table A11. Relationship between Age at Liver Transplant And Attention/Executive Function

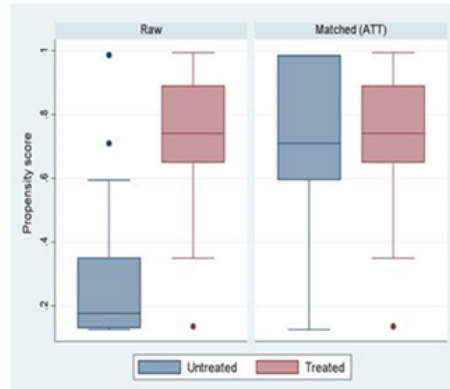
Outcome	Result by Age at Transplant			
	Age Group	N	Mean	95% CI
CBCL Attention	<1 yr	9	117	104.5, 129.4
	1 - <3 yrs	8	113	100.3, 125.7
	3+ yrs	6	122.3	111.8, 132.7
BRIEF Inhibition	<1 yr	7	114.6	97.5, 131.7
	1 - <3 yrs	6	120.7	97.0, 144.3
	3+ yrs	6	120.5	105.0, 136.0
BRIEF Working Memory	<1 yr	12	123.3	110.9, 135.7
	1 - <3 yrs	8	114.5	96.1, 122.0
	3+ yrs	7	134.9	123.2, 146.6
BRIEF Shift	<1 yr	12	118.3	106.5, 130.2
	1 - <3 yrs	8	117.9	98.6, 137.1
	3+ yrs	7	103	89.2, 116.7
BRIEF GEC	<1 yr	12	120.4	107.8, 133.1
	1 - <3 yrs	8	117.3	99.3, 135.3
	3+ yrs	7	119.8	110.2, 129.4

Table A12. Unadjusted Emotional/Behavioral Function by Treatment Group in CSS

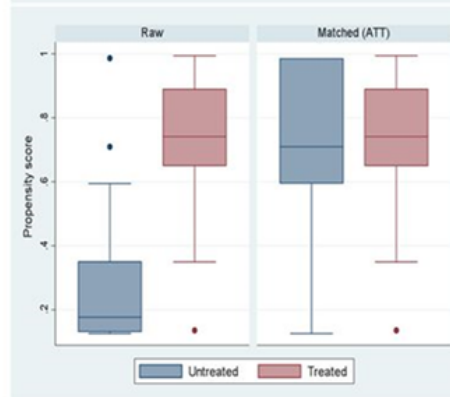
Outcome	Group	N	Mean	95% CI
CBCL Internalizing	LT	20	107.1	100.3, 113.9
	MM	18	105.2	96.9, 113.6
CBCL Externalizing	LT	20	105.4	98.3, 112.5
	MM	18	107.3	100.6, 114.1

Table A13. Matched and Adjusted Emotional/Behavioral Function in LT Compared to MM

Outcome	Analysis Method	Liver Transplant Treatment Effect		
		Difference	95% CI	p-value
CBCL Internalizing (LT=20, MM=18)				
	Unadjusted	1.9	-8.4, 12.2	0.71
	Propensity Score Adjusted	8.8	-8.9, 26.5	0.77
	Ridge Matched and Adjusted*	9.2	-21.5, 39.9	0.56



CBCL Externalizing (LT=20, MM=18)				
	Unadjusted	-1.9	-11.4, 7.5	0.68
	Propensity Score Adjusted	-2.9	-17.4, 11.6	0.7
	Ridge Matched and Adjusted*	8.1	-6.0, 22.1	0.26



**in addition to propensity scores, results are adjusted for index age and age assessed.*

Table A14. Relationship Between Age at Liver Transplant And Emotional/Behavioral Function

Outcome	Result by Age at Transplant			
	Age Group	N	Mean	95% CI
CBCL Internalizing				
	<1 yr	8	115.7	105.0, 126.5
	1 - <3 yrs	6	107.6	96.7, 118.5
	3+ yrs	6	95.2	84.7, 105.7
CBCL Externalizing				
	<1 yr	8	108.7	99.3, 118.1
	1 - <3 yrs	6	102.5	83.6, 121.3
	3+ yrs	6	104	93.0, 114.9

Missing Values and Multiple Imputations

Table A15: Number and Percent of Missing Values Per Characteristic Among All Eligible

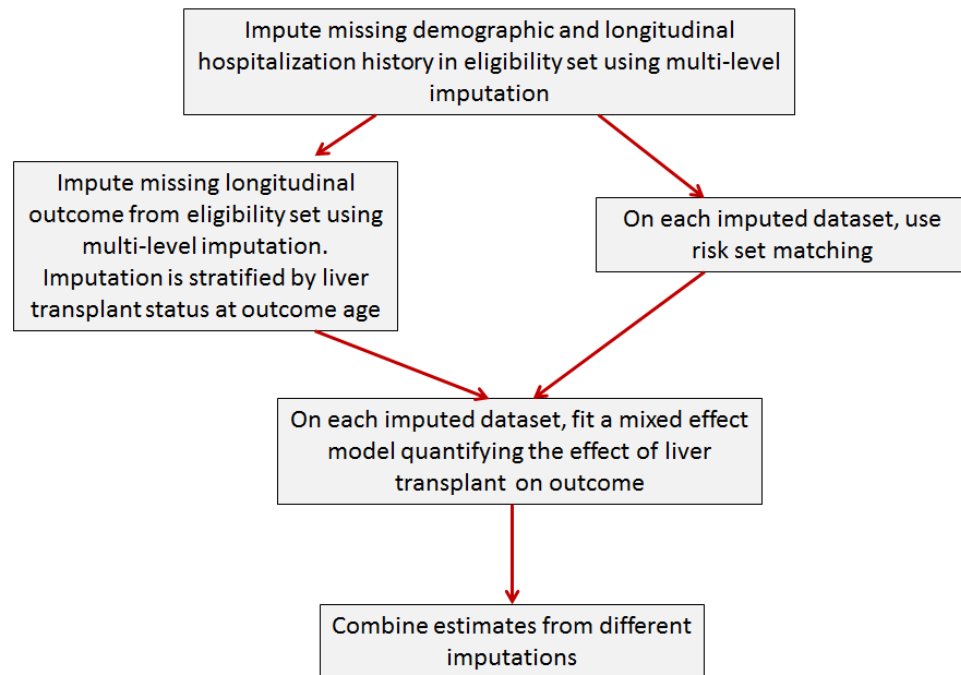
Characteristics	Missing Records	Total Records	% Missing
Demographic¹			
Sex	38	283	13
Parent Education	121	283	43
Medical History²			
Length of Stay	28	1004	3
Maximum Ammonia	36	1004	4
Coma or Intracranial Pressure	348	1004	35
Quality of Life³			
Total	151	1335	11
Physical Health	177	1335	13
Psychosocial Health	170	1335	13
Family	1088	1335	81

¹ one record for demographic characteristics is a distinct eligible subject

² one record for medical history is for one distinct hospitalization visit for one eligible subject

³ one record for quality of life is for one distinct visit for an eligible subject

Figure A1. Multiple Imputations to Impute Missing Characteristics



Imputation Method

Table A15 summarizes the extent of missing-ness for the variables that were imputed in our procedures. As we see in Table A15, two demographic characteristics had missing values among all eligible, 13% of subjects had missing sex value and 43% of subjects had missing parent education value. Three medical history covariates had missing values among hospitalization periods for eligible subjects: 3% of hospitalization periods had a missing discharge date or length of stay (LOS) variable, 4% of hospitalization periods had missing maximum ammonia measurement, and 35% of hospitalization periods had missing dichotomous composite variables indicating whether coma or intracranial pressure (ICP) occurred during hospital stay.

The overall imputation process is summarized in Figure A1. In *miceadds* library in R, demographic and medical history variables were imputed using two-level imputations, stratified by LT status, and using the information on complete variables, UCD diagnosis, birth decade, and hospital admission age. First level variables included demographic variables, sex, and parent education; each was imputed using predictive mean matching. Second level variables included medical history variables, LOS, maximum ammonia, and coma or ICP. Length of stay and maximum ammonia were imputed on the log scale using two-level normal model with homogeneous within-group variances. Coma or ICP was imputed using two-level predictive mean matching. The second-level longitudinal variable accounted for the subject identifier as a clustering variable.

In *miceadds* library in R, quality of life (QOL) variables were imputed using two-level imputations, stratified by LT status, using complete or imputed demographic and medical history covariates as well as

age at the time of the questionnaire visit and any available QOL measure. For those eligible with missing any QOL measurement, the measurement was imputed at an age prior to the end of follow-up. As with medical history variables, longitudinal QOL measures were imputed using predictive mean matching accounting for the subject identifier as a clustering variable.

The confidence intervals for each outcome combined confidence intervals from each imputation using the library *Amelia* in R⁹⁸. We did five imputations of covariates to evaluate the outcome of death and 25 imputations to evaluate the outcomes of QOL (imputing both covariates and outcomes). This is consistent or exceeds the classic guidelines for the number of imputations by Rubin, 1987⁹⁹. We did not optimize the number of imputations, following for example more recent guidelines recommending calibrating the number of imputations to the fraction of missing information^{100,101}, because we did not see the value-added in running more imputations to increase the efficiency of a small estimate that would not change our conclusions.

Figures 2A-6A show results for every imputed dataset. Note that family quality of life had the most missing values and the high variability in estimates between imputations for this outcome reflects that.

Figure 2A. Estimated Average Treatment Effect +/- 95% CI by Imputation in LT for All-Cause Mortality

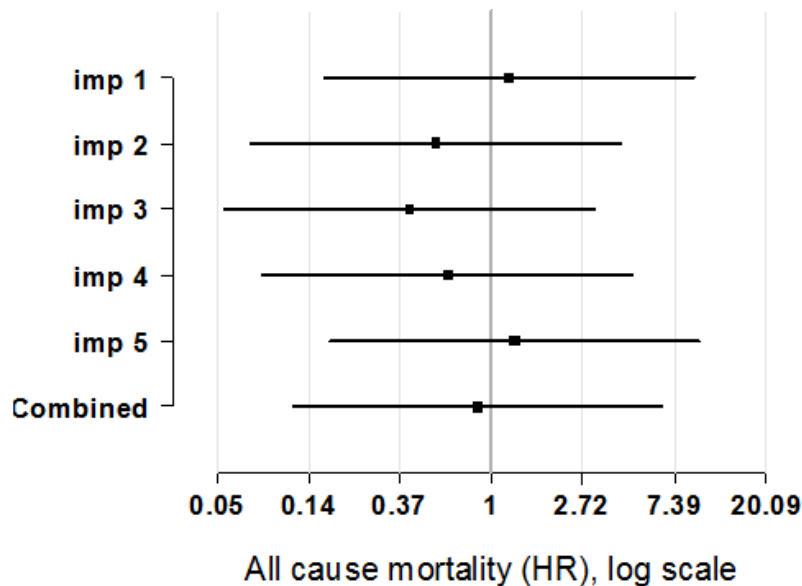


Figure 3A. Estimated Average Treatment Effect \pm 95% CI by Imputation in LT, Total Quality of Life (QOL)

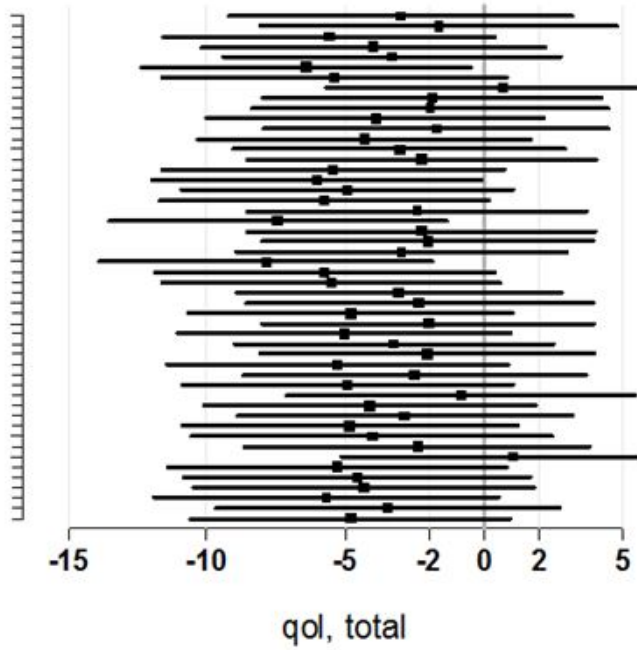


Figure 4A. Estimated Average Treatment Effect \pm 95% CI by Imputation in LT for Psychosocial Health QOL

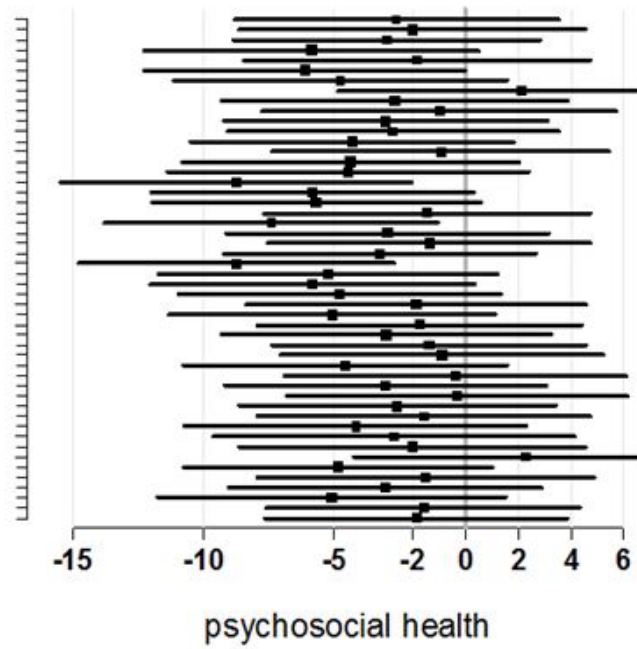


Figure 5A. Estimated Average Treatment Effect $\pm 95\%$ CI by Imputation in LT for Physical Health QOL

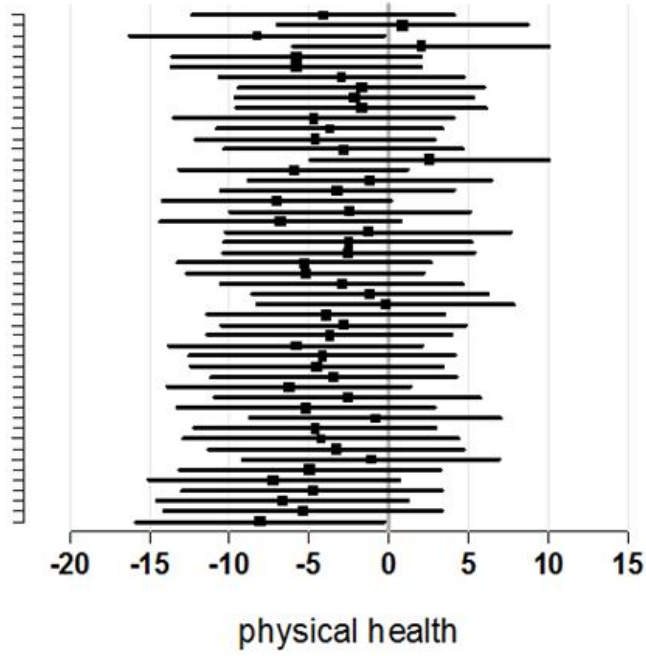


Figure 6A. Estimated Average Treatment Effect $\pm 95\%$ CI by Imputation in LT for Family QOL

