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Medication adherence and rejection rates in older versus younger adult liver transplant recipients

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Abstract

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All authors were meaningfully involved in the study design, data acquisition, data analysis and interpretation, and manuscript preparation. Emily Leven,[1] participated in determining study concept and design, acquisition of data, analysis and interpretation of data, and preparation of manuscript.
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CONFLICT OF INTEREST

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A growing number of older adults are undergoing liver transplantation (LT) in the US. In some settings, it is thought that adherence declines with age. This retrospective study examined adherence and clinical outcomes in older versus younger adult LT recipients. Medical records of adult LT recipients from 2009–2012 from a single urban center were reviewed. The medication level variability index (MLVI) was the pre-defined primary outcome, with nonadherence defined as MLVI >2.5. The secondary outcome was incidence of rejection. Outcomes were evaluated starting one year post-LT until 2015. 42/248 patients were ≥65 at transplant. Older adults had significantly better adherence than younger ones (65% ≥65 were adherent vs. 42% younger adults; Chi-Square two-tailed p=0.02). Survival analyses of rejection between age groups censored by time since transplant showed no difference among the four age groups (χ^2 = 0.84, p=0.84). Older age was not found to be a risk factor for reduced adherence or graft rejection in patients surviving at least one year post-LT.

Keywords

medication adherence; biomarkers; graft rejection

INTRODUCTION

Liver transplantation (LT) in older adults (≥65 years old) in the United States is increasingly being performed, and this trend is expected to continue.[1–3] A growing older population, expanded selection criteria for organ recipients, and advances in treatment for common causes of liver disease are all contributing factors.[1,4] Increasing general life expectancy rates predispose more patients to ultimately develop decompensated liver disease or hepatocellular carcinoma, which are the major indications for LT. Because older adults are considered to have unique physiological and psychosocial characteristics, it becomes increasingly important to investigate outcomes and risk factors in this particular group of patients.[5,6]

Many factors, such as premorbid medical conditions, influence post-LT outcomes in adults.[1,7] The degree of adherence to medical recommendations is amongst the most consistently reported determinants of posttransplant outcomes. Although not all studies demonstrate evidence of lower rates of adherence in older adults,[8–10] many suggest that nonadherence rates increase with depression; lack of daily structure; social isolation; visual or auditory impairment; decreased physical health, cognitive function and memory; longer time since diagnosis; and increased number of medications, side effects, and doses per day.[8,11–14] All of these are more common in older adults, and many are also present after liver transplant. Indeed, nonadherence to immunosuppressants occurs in 15–40% of adults 6 months to more than 5 years post-LT and one study of older adult (55+) kidney transplant recipients reported nonadherence in as many as 86% of patients 1 year after transplant.[15–17]

Older adults tend to present a higher surgical risk for transplantation due to medical co-morbidities. Therefore, they are generally considered to require more rigorous medical eligibility screening.[1,2,7] While it is known that the higher surgical risk may lead to greater morbidity in the immediate post-operative period, it is not clear whether older patients are

more or less adherent in the long term posttransplant period as compared with their younger peers. The answer to this question might be helpful to transplant centers contemplating decision-making parameters predicated upon recipient age, and may also prioritize resource allocation for psychosocial support for these recipients.

To examine the relative risk for nonadherence and poor outcomes in younger versus older adult recipients who are long-term survivors of LT, we conducted a retrospective chart review of adult LT recipients. Nonadherence to tacrolimus (TAC) immunosuppressive therapy was determined via a validated biomarker of serum drug level fluctuation, the medication level variability index (MLVI). We investigated whether older adults demonstrated differences in TAC adherence compared to younger adult LT recipients (pre-defined primary outcome measure) a year or more posttransplant.

METHODS

Patients and Procedures

All available medical records of adult liver transplant recipients from the Recanati Miller Transplantation Institute (RMTI) and Mount Sinai Medical Center between 2009 and 2013 were identified (n=423). The final sample consisted of 248 patients based on the following inclusion criteria: underwent LT between 2009–2013, were prescribed TAC for maintenance immunosuppression between 2009–2015, were at least 1 year post-LT, and had at least 3 outpatient post-LT TAC levels. A CONSORT-like diagram demonstrating the selection process is presented in Figure 1. A waiver of informed consent was approved by the Institutional Review Board at the Icahn School of Medicine at Mount Sinai.

Data Collection

Psychosocial and demographic variables were collected from two electronic medical record (EMR) systems: OTTR Solid Organ Transplant System (for patients undergoing LT prior to 2011) and EpicCare (for patients undergoing transplant in 2011 or later). Similar information was available from each EMR, and records from OTTR were linked to EpicCare records when the institution transitioned its EMR system.

The standard practice in our center is for all recipients to undergo an evaluation with a licensed clinical social worker prior to LT listing. For patients whose records were found in OTTR, social work evaluations were documented in a standard electronic template and included information on race, marital status (single, married, divorced/separated, widowed), employment status (working, not working, retired), type of insurance coverage (Medicare, Medicaid, private), presence of social support, history of psychiatric illness, history of substance abuse, and prior legal convictions. A similar, but not identical, template was used by the EpicCare platform. While it may have differed in presentation and placement in the more recent EMR format, the clinical content of the actual evaluation did not differ during the study period.

The review of medical records included sex, age at the time of transplant, indication for liver transplant, and primary reason for LT, and TAC levels drawn regularly for dose adjustment as a part of standard of care post-LT management.

Outcome Measures

The primary outcome was nonadherence in the period beginning one year after LT as measured by MLVI. To compute the MLVI, we followed the standard procedure described elsewhere [17:] we calculated a standard deviation of each patient's TAC levels measured over time as part of standard of care follow-up. A minimum of three levels from different time points was used to calculate the MLVI (all available levels were used if >3 were available). The MLVI has been independently validated as a predictor of poor post-LT outcomes in adult and pediatric LT recipients with levels ≥2.5 considered nonadherent and associated with allograft rejection.[18,19] Outpatient serum TAC levels drawn at least one year post-LT were used to calculate MLVI scores. MLVI scores >2.5 have been shown to predict graft rejection in adult and pediatric LT recipients.[18–20] Only outpatient values were used to calculate MLVI, as hospitalized patients are not responsible for their own medication management, and serum TAC levels would not, therefore, reflect individual adherence. A secondary outcome was biopsy-proven graft rejection.

Statistical Analyses

All analyses were conducted using IBM SPSS Statistics package, 20th edition. Descriptive statistics were used to characterize the sample. Predefined age groups followed UNOS categories: 18–34, 35–49, 50–64, ≥65 years old. Preliminary analyses were conducted to examine baseline difference on demographic variables between the age groups. The primary analysis looked at the MLVI as a dichotomy, comparing age groups and categorical outcomes (MLVI threshold and occurrence of rejection). To look at the relationship between time to rejection and age, we used a Kaplan-Meier survival analysis, although it may be somewhat limited by a small "n" in subgroups, especially upon long-term follow-up. In this approach, differences in follow-up are addressed by presenting "censored" or extrapolated findings. Analysis of variance using ANOVA was utilized to compare age groups and time of follow-up. A "*p*" value of less than 0.5 was chosen as the level of significance.

RESULTS

The mean age at transplant for the study cohort was 56.1 years (SD: 10.54, Range: 19–74). The groups differed in highest level of education attained, employment status, type of insurance, and sex (Table 1). Therefore, we examined whether these variables were associated with our primary outcome, MLVI. There were no significant Chi-Square associations between MLVI threshold and education, employment status, insurance, or sex. One-way ANOVAs revealed that MLVI measured continuously was not associated with any of these variables either. No significant differences existed in the baseline psychosocial variables amongst the four age groups. The absolute range of time since transplant was 1.34 – 5.78 years. The average time since transplant in all subjects was 3.61 years (3.63 years in younger adults and 3.49 years in older adults, $t(247) = 1.05$, $p = 0.29$). The mean number of tacrolimus levels used to calculate MLVI in patients who experienced rejection was 25.7 (SD = 19.0) and 17.5 (SD = 12.6) in patients who did not experience rejection. Data collection began after the first year, meaning that tacrolimus levels over an average of 2.61 years were used to calculate adherence. Time since transplant captured in data collection was similar amongst all groups (ANOVA, $F(3, 244) = 0.38$, $p = 0.77$).

Forty-two patients (17% of all LT recipients) were ≥65 years old at the time of transplant. The mean age of older adults was 68.7 years (SD 2.45, range 65–74 years); 21 older adult LT recipients (50%) were male. Outcomes and indications for transplant by age group are shown in table 2.

The most common primary indications for LT in older adults were hepatitis C virus (HCV) (n=17), hepatocellular carcinoma (n=8), and non-alcoholic fatty liver disease (NAFLD) (n=6). Overall, nonadherence was high (50.8% of all subjects), though it is difficult to compare to other studies that measured adherence using different tools and over different periods of time.[15–17] Despite the relatively high overall prevalence of nonadherence identified in the period beginning at least one year post-LT, older adults had significantly better rates of TAC adherence than younger adults as measured by the lower percentage of above-threshold MLVI scores in older adults (65% of recipients ≥65 were adherent vs. 42% of younger recipients; $\chi^2 = 5.89$, p=0.02).

When analyzed as a continuous variable, MLVI scores among the four groups were not significantly different (ANOVA, F (3, 244) = 2.24, p = 0.08). In addition, this analysis was repeated controlling for demographic variables (education, employment status, insurance, and sex); the model remained nonsignificant, F (3, 217) = 1.48, p = 0.18. Finally, we ran Kaplan-Meier survival analyses with rejection as the “status” variable and “age groups” as the factor. When censoring by time since transplant, there was no difference between the four age groups, $\chi^2 = 0.84$, p=0.84 (Figure 2).

There was a modest positive correlation between MLVI and the number of levels used to calculate an MLVI score for each patient (Pearson’s correlation = 0.17, p < 0.01).

Of those patients who were excluded due to mortality within the first year after LT, older adults were overrepresented. Thirty-four percent of transplanted older adults died within 1 year, as compared to 16% of younger adults (Fisher’s Exact p<0.01). Complete chart reviews were not performed for excluded patients, but it is known that these patients did not differ significantly from those included in the study with respect to sex ($\chi^2 = 0.57$, two-tailed *p* value = 0.45) or age at time of transplant (t(422) = 1.49, p = 0.13).

Thirteen patients died in the follow-up period beyond one year post-LT, with no significant difference between older and younger adults (8 younger adults and 5 older adults, Fisher’s exact p = 0.05). Death after one year post-LT was not a reason for exclusion.

DISCUSSION

To our knowledge, this is the first study to look at older age as a potential risk factor for medication nonadherence in liver transplant recipients, and one of few studies to consider recipients older than 65. The fact that we found older age to be a protective factor for nonadherence, not a risk, has implications for transplant decision-making and resource allocation in transplant clinics. While, as expected, [7,21] older adults were a medically high-risk group (as they were more likely to die within the first year post-LT), they were not high-risk as far as adherence is concerned. Instead, we found that older liver transplant recipients displayed significantly better adherence to their immunosuppressant regimens than younger

adults and no increased risk for rejection. These findings are consistent with other studies that indicate that older age is correlated with better adherence in a transplant setting,[22–24] particularly when compared with young adult transplant recipients (<20 year old). However, since transplantation of older adults is a relatively new practice, these studies primarily include data from much younger patients than those examined in the current study and there is a relative dearth of data on older adult adherence in transplant settings. However, in non-transplant settings, older adults are often considered to be a high-risk group when it comes to adherence and chronic disease management.[8,12,17,23,25] In one study showing a correlation between overall adherence to posttransplant regimens and increasing age, the "accidental noncompliers" in the study group were significantly older than those patients whose nonadherence was purposeful, though the "older" group had an average age of 44, much younger than the older adults considered in the current study.[23]

Our study groups, as would be expected, differed in characteristics that are closely tied to age, such as highest level of education attained, employment status, and insurance (in the United States, insurance carriers change with age as patients become eligible for Medicare). Such differences are expected when patients of different ages are compared. There was also a difference in sex, attributable to the fact that about 67% of our young adult recipients were males whereas only 50% were men in the adult cohort. The overall study population contained about 64% male recipients, which is consistent with national listing and transplant data (based on OPTN data as of May 1, 2016). The drop in males in the older age group may reflect some degree of sampling error, but is likely at least partially explained by the shorter life expectancy in American males.[26] Additionally, among liver transplant recipients, more males have liver disease related to primary sclerosing cholangitis, alcohol, and hepatitis C complicated by a higher percentage of non-alcoholic fatty liver compared to females.

Our findings expand on earlier reports showing that those who survived were no more likely to experience graft rejection than younger adults, [4,27,28] and add that older patients have better adherence to their medication regimens compared to younger patients. Our data do not provide information regarding the medical selection of transplant candidates at our center. However, consistent with prior literature,[1,4] in those older adults who were deemed medically eligible and fit for transplant, our results continue to support the idea that the long-term management of older adult transplant recipients need not involve a particularly higher concern for persistently increased needs for psychosocial supports compared to younger adult recipients.

Furthermore, the finding that the older adults experienced both the highest rates of adherence and the lowest rates of graft rejection is consistent with prior studies that consistently show that the MLVI predicts rejection in children and adults,[18,29,30] although the association between this marker and rejection was not specifically examined in older adults prior to the present study.

If TAC levels used to calculate MLVI were a string of random numbers, it would be expected that the variability, and therefore the MLVI, would be smaller when more variables are available for the calculation. However, blood levels are not random numbers. We found a modest *positive* correlation (Pearson's coefficient = 0.17) between the MLVI and the number

of levels used to calculate it in our sample, establishing that it is not the case that more levels were associated with a lower MLVI. It is possible that patients with aberrant (too high or too low) results were tested more frequently, though this hypothesis cannot be conclusively stated from the current data.. Prior work using the MLVI as a measurement of adherence showed that the number of blood levels used to calculate the MLVI did not vary significantly between subjects found to be adherent vs. nonadherent, and so, in clinical settings, the MLVI is not affected by the number of input values used to calculate it.[18] This insight also suggests that adherence to a recommendation to measure blood levels in transplant settings is not the same as adherence to the medication: patients do get tested, even when they are not taking their medications as prescribed.

One year post-LT was chosen as the designated starting point because prior studies show that immunosuppressant adherence within the first year is generally high, dropping off as more time elapses.[23,31] Furthermore, graft rejections prior to the one year mark are not considered to be primarily related to nonadherence.[31] Tacrolimus levels are measured frequently for dose-adjustment in the first few weeks and months post-LT, and resultant variability would falsely elevate the MLVI in a time period when the expected adherence rates in all patients would be similarly high, despite the possibility of drop offs in adherence later in the posttransplant course.

Strengths of this study include a sample reflective of “real world” patient selection (as opposed to prospective trials evaluating outcomes in a controlled study environment) and outcomes at a center with a relatively large population of older adult LT recipients and long-term follow-up data. Though the overall number of patients in this study is somewhat small, our data include a relatively large proportion of older adult LT recipients: 17% of study patients were 65+ years old at the time of transplant compared to 12.5% of all U.S. patients undergoing liver transplantation during our study period (based on OPTN data of liver transplant recipients from 2009–2013). The MLVI measure of adherence is another major strength of this study as it is a validated, objective biomarker of adherence. It has been validated in several independent cohorts of transplant recipients, across different ages and different organs; it is therefore the most widely studied objective adherence measure in transplant medicine.[18,20,32–34] Furthermore, the use of state-mandated social work evaluations allowed access to demographic and psychosocial variables for all patients from standardized templates

There is no gold standard for adherence assessment in transplant settings. Besides the MLVI, other methods are sometimes used to assess adherence, such as self-reports, electronic monitoring devices, and pill counts. The reason there is no gold standard is that each method has its weaknesses and strengths, as reviewed elsewhere[20]. Our study used only the MLVI to assess adherence, and it is possible that, had we used another method, it would have resulted in different findings. One limitation to our study was its retrospective design, which did not allow for a prospective evaluation of endpoints. However, since evaluation processes are standardized in our center, the shortcomings of the retrospective design are mitigated to some extent, while also allowing us to examine an unbiased clinical sample. While our sample included a relatively large number of older adult recipients, the overall sample size was only 248 patients. In addition to the relatively small “n”, generalizability may be limited

due to possible selection bias in that included patients may inherently differ compared to excluded patients (particularly those who lack sufficient tacrolimus levels to measure MLVI) and the fact that all patients were treated at a single, urban, expert tertiary care center with a rigorous medical and psychosocial evaluation and follow-up protocol. Furthermore, though all patients were required to have adequate social supports in place prior to transplant listing, the extent and quality of these supports is neither quantifiable nor available in patient records. The social supports requirement has its underpinnings in the theory that social support impacts a patient's ability to adhere to his/her treatment plan as a whole (including doctor's visits, medication regimens, dietary/behavioral modifications, etc.), yet we cannot assess a quantifiable relationship between adherence to tacrolimus and quality/extent of social support in the current study. Another limitation is that we do not have access to information predating subject enrollment. Therefore, we could have missed pre-enrollment nonadherence or adverse outcomes in any of the investigated groups.

Although prior research does document that adherence gets worse over time in transplant recipients, we still think that it is surprising that in our sample, it appears that nonadherence was worse between the ages of 50–64; young adults had better adherence. We are not sure what could explain this trajectory, other than the general deterioration of adherence noted elsewhere.[7] Our primary interest, and focus, in this study was the very old age group. Secondary findings such as this one, although intriguing, will have to be replicated in studies that are directed to answer the question of progression of adherence in the less-than-very-old age group, before they are considered further.

Possible reasons for the higher rates of adherence seen in older adults in this study include: more extensive screening for medical clearance prior to transplant listing or closer post-LT follow up for older adults; possible age-related changes in immunity that make it more difficult to mount a rejection response; potentially better health literacy and health habits of adults who reach older age prior to requiring a transplant; more family/home health worker involvement in older adult post-LT care and possibly different attitudes toward transplant in patients of different ages. Although selection bias might also be an explanation (in that the most nonadherent patients might have died within the first year), we consider this unlikely because adherence in the first year after transplantation is actually considered to be better, rather than worse, as compared to later in the transplant survivor's course. [31] For similar reasons, we hypothesize that the overrepresentation of older adults in patients excluded due to death within the first year after transplant is not related to worse adherence, but rather, to the increased medical risk that older patients may carry into transplant surgery and recovery. Although this study did not seek to identify explanations for differences in first year mortality between the groups, future studies may explore these aspects further.

In summary, we found that adults receiving a liver transplant at the age of 65 or older and surviving at least one year are a resilient group of patients who demonstrate better immunosuppressant adherence with no increased rejection risk as compared with younger adults. These results might have implications for resource allocation of ancillary services in transplant programs, and suggest that transplantation of older adults should not be withheld on the basis of age alone.

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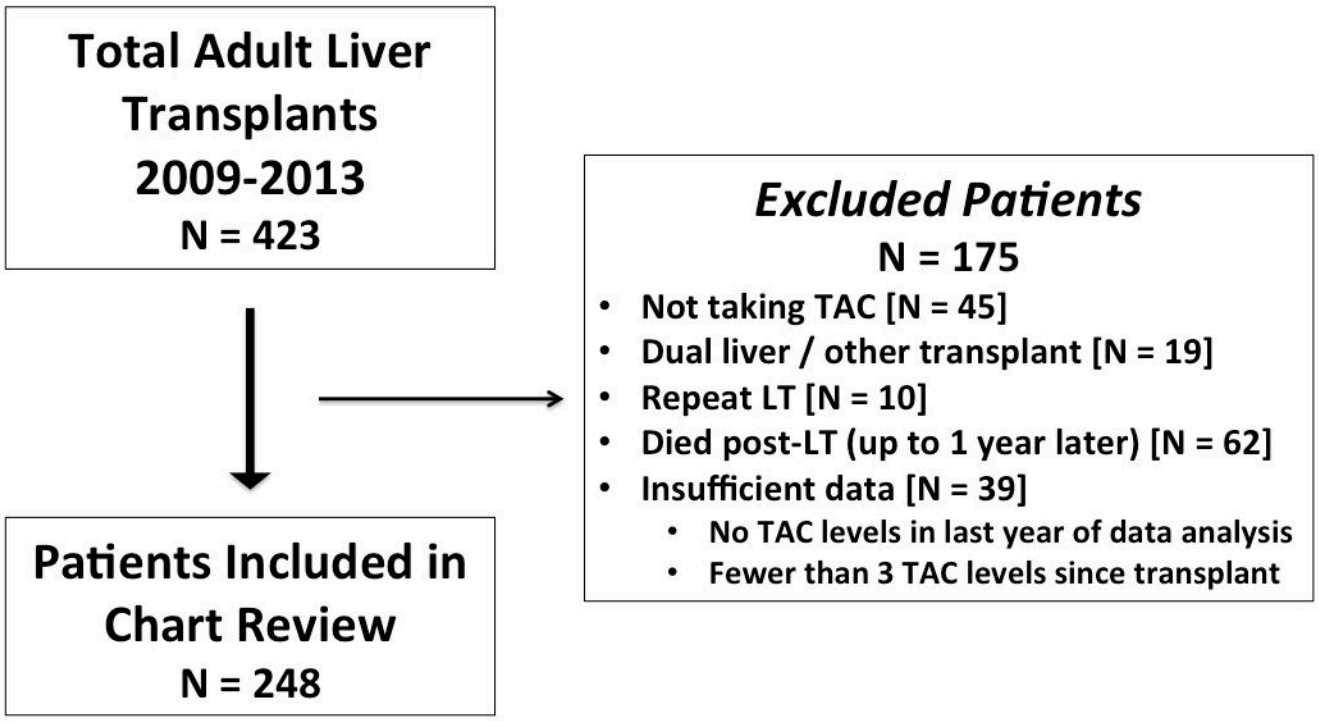

Figure 1. Inclusion/Exclusion Criteria for the Study Patients

423 patient charts eligible for review. 175 excluded based on exclusion criteria. Complete chart reviews were not performed for excluded patients, but it is known that these patients did not differ significantly from those included in the study with respect to sex ($\chi^2 = 0.57$, two-tailed p value = 0.45) or age at time of transplant ($t(422) = 1.49$, $p = 0.13$). 248 patients included in final study population. N= number of patients; TAC = Tacrolimus; LT = liver transplant

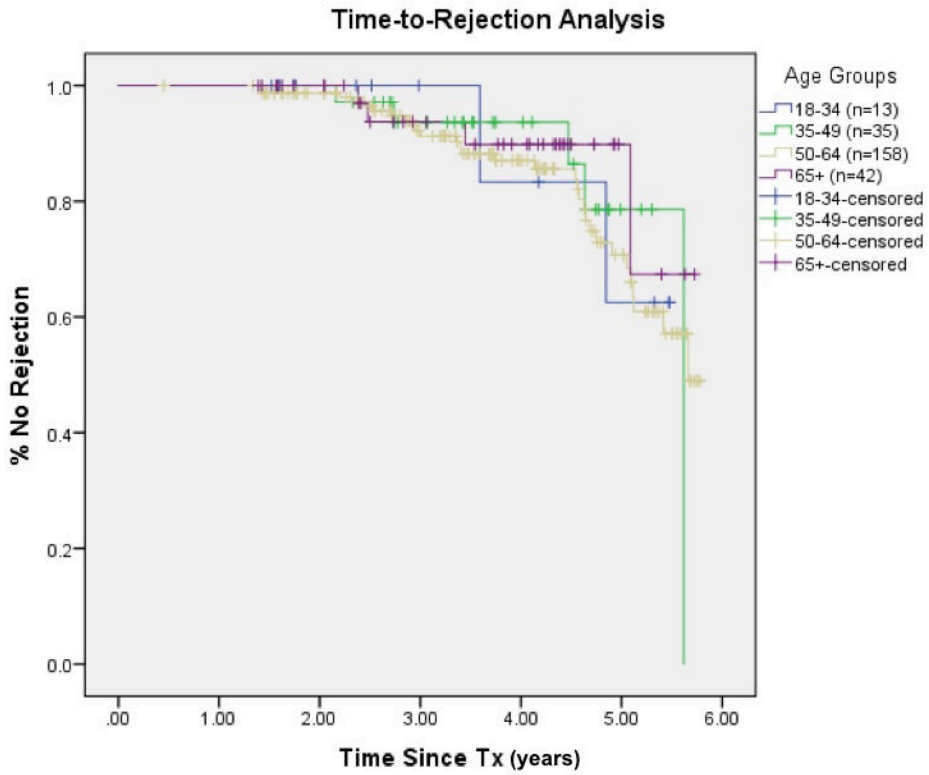

Figure 2. Time-to-rejection analysis by age group

Kaplan-Meier survival analyses with rejection as the "status" variable and "age groups" as the factor. When censored by time since transplant, there was still no difference between the four age groups, $\chi^2 = 0.84$, p=0.84.

Table 1

Patient Demographics

	Younger Adults	Older Adults
Sex *		
Male	137	21
Female	67	21
Race		
White	83	18
Hispanic	42	13
Black	32	3
Asian	33	6
Other	15	0
Marital Status		
Married	121	27
Significant Other	17	0
Divorced/Separated	15	5
Single	50	8
Widowed	1	2
Highest level of completed education *		
Graduate	15	4
College	57	9
High School	102	14
Less than high school	17	11
Employment *		
No	99	10
Yes	72	6
Retired	22	25
Insurance *		
Medicaid	54	13
Medicare	39	19
Private	112	10

* significant difference between two groups

Table 2

LT Outcomes, Indications and MLVI by Age Group

Age	N	MLVI	Nonadherence (MLVI >2.5)	Indications for LT	
(yrs)	*n (% total pop)*	*(mean, SD)*	*n (% age group)*	*Condition*	*n (% age group)*
18–34	13 (5.2%)	2.36 (1.57)	5 (38.5%)	Fulminant Hepatic Failure	5 (38%)
				Hepatitis C Virus	2 (15%)
				Primary Sclerosing Cholangitis	2 (15%)
				Hepatitis B virus	1 (1%)
				Autoimmune Hepatitis	1 (1%)
				Alcoholic Liver Disease	1 (1%)
				Other	1 (1%)
35–49	35 (19.4%)	2.79 (1.44)	16 (44.4%)	Hepatitis C Virus	8 (23%)
				Hepatitis B Virus	7 (20%)
				Alcoholic Liver Disease	5 (14%)
				Primary Sclerosing Cholangitis	4 (11%)
				Fulminant Hepatic Failure	3 (9%)
				Other	3 (9%)
				Nonalcoholic Fatty Liver Disease	2 (6%)
				Hepatocellular Carcinoma	1 (3%)
				Primary Biliary Cirrhosis	1 (3%)
				Alcoholic Liver Disease w/Hepatitis C Virus	1 (3%)
50–64	158 (63.7%)	3.00 (1.59)	91 (57.6%)	Hepatitis C Virus	79 (50%)
				Hepatitis B Virus	25 (16%)
				Hepatocellular Carcinoma	11 (7%)
				Alcoholic Liver Disease with Hepatitis C Virus	11 (7%)
				Fulminant Hepatic Failure	6 (4%)
				Alcoholic Liver Disease	6 (4%)
				Primary Biliary Cirrhosis	5 (3%)
				Nonalcoholic Fatty Liver Disease	5 (3%)
				Autoimmune Hepatitis	4 (3%)

Age	N	MLVI	Nonadherence (MLVI >2.5)	Indications for LT	
(yrs)	*n (% total pop)*	*(mean, SD)*	*n (% age group)*	*Condition*	*n (% age group)*
65+	42 (16.9%)	2.53 (1.50)	15 (34.9%)	Primary Sclerosing Cholangitis	3 (2%)
				Other	3 (2%)
				Hepatitis C Virus	17 (40%)
				Hepatocellular Carcinoma	8 (19%)
				Non-Alcoholic Fatty Liver Disease	6 (14%)
				Hepatitis B virus	4 (10%)
				Primary Biliary Cirrhosis	3 (7%)
				Alcoholic Liver Disease	2 (5%)
				Alcoholic Liver Disease w/Hepatitis C Virus	2 (5%)