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Frailty is Associated with Increased Rates of Acute Cellular Rejection Within 3 Months After Liver Transplantation

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Abstract

Introduction: Frailty, a state of decreased physiologic reserve, has been associated with dysregulation of the immune system. We hypothesized that frailty is associated with differential rates of acute cellular rejection (ACR) in LT recipients.

Methods: Included were LT recipients from 2014-16 who had a pre-LT frailty assessment using the Liver Frailty index (LFI). Frailty was defined as a LFI ≥ 4.5. ACR at 3 months was ascertained from pathology reports and immunosuppression regimens were collected from chart review.

Results: 241 LT recipients were included: 46 (19%) were classified as frail pre-LT. Median tacrolimus trough levels, mycophenolate doses, and corticosteroid doses at discharge and 3-months were similar between frail and non-frail patients. Within 3 months post-LT, 7 (15%) frail patients versus 10 (5%) non-frail patients experienced ACR (p=0.02). In univariable analysis, frailty was associated with a 3.3 times higher odds of ACR at 3 months (95% CI 1.2, 9.3, p=0.02). Bivariable analyses was conducted with co-variates that were associated with acute cellular rejection in univariable analysis or have been previously associated with either frailty (age, female sex) or acute cellular rejection (MELD, ascites), as well as relevant immunosuppression variables. In bivariable analysis, frailty remained significantly associated with acute cellular rejection at 3 months with an odds ratio relatively similar to the unadjusted value.

Conclusion: In conclusion, frailty is associated with an increased rate of ACR within 3 months, despite similar immunosuppression regimens, suggesting that frailty should be considered in immediate post-LT management.

Keywords

Immunosuppression; post-transplant outcomes; patient characteristics; rejection; frailty

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INTRODUCTION

Frailty, a state of decreased physiologic reserve and increased vulnerability to health stressors, has emerged as a critical predictor of outcomes in liver transplantation [1-8]. Patients with cirrhosis are particularly vulnerable to developing frailty due to the combination of systemic inflammation from the underlying chronic liver disease in combination with under-nutrition and muscle wasting that result from hepatic synthetic dysfunction [6]. In fact, frailty has been found to be prevalent in up to 17% of patients with cirrhosis [3, 7].

Studies have demonstrated that frailty is associated with dysregulation of multiple physiologic systems including the immune system, with frail patients exhibiting an inflammatory phenotype even in absence of cirrhosis [2, 9, 10]. Specifically, studies of older adults have found that those displaying the frail phenotype have higher systemic inflammation as measured by markers such as CRP, IL-6, and sTNF-RII to name a few [11-13]. Perhaps related to this physiologic dysregulation, frailty has also been associated with increased rates of medication intolerance among the community dwelling geriatric population due to pharmacokinetic changes [14, 15].

Known risk factors for acute cellular rejection in liver transplant recipients include young recipient age, longer cold ischemic time, and older donor age [16, 17]. CMV is also well understood to be a potent up-regulator of alloantigen, increasing the risk of both acute and chronic graft rejection [18]. Within the kidney transplant population, frailty has also been found to be associated with an increased rate of mycophenolate dose reduction, which was independently associated with an increased risk of death-censored graft loss [19]. There have been no studies to our knowledge to evaluate the association between frailty and acute cellular rejection in the liver transplant population.

Based on the association between frailty and both immune dysregulation and medication intolerance, we hypothesized that frailty would be associated with early acute cellular rejection in liver transplant recipients. We predict that frailty improves post-liver transplant with the resolution of cirrhotic pathophysiology; the potential increased risk of acute cellular rejection should thus resolve as well. In this study, we aimed to test this hypothesis.

MATERIALS AND METHODS

Patients and baseline data collection

We evaluated data on patients who underwent liver transplantation at a single center from 1/1/2014 to 12/31/2016 who had an outpatient assessment of physical frailty prior to liver transplantation. Excluded were patients who did not have cirrhosis as their underlying etiology for liver transplantation. Patients with hepatocellular carcinoma were included in the study if they had underlying cirrhosis.

Data regarding demographics were extracted from the clinic visit note from the same day as the objective frailty measurement. Patients were considered to have a diagnosis of hypertension, diabetes, or coronary artery disease if was reported in their electronic health

record. Patients were ascertained to have CMV infection if they had a positive CMV PCR and were started on treatment for CMV.

Frailty assessment

Frailty was assessed at an outpatient clinic visit prior to liver transplantation using the Liver Frailty Index, which consists of 3 performance-based tests [6]:

1. Grip strength: the average of three trials, measured in the patient's dominant hand using a hand dynamometer;
2. Timed chair stands: measured as the number of seconds it takes to rise to a full standing position and return to a seated position with the patient's arms folded across the chest;
3. Balance testing: measured as the number of seconds that the patient can balance in three positions (feet placed side-to-side, semi-tandem, and tandem) for a maximum of 10 seconds each.

With these three individual tests of frailty, the Liver Frailty Index was calculated using the following equation (calculator available at: http://liverfrailtyindex.ucsf.edu):

$$(-0.330 * \text{gender-adjusted grip strength}) + (-2.529 * \text{number of chair stands per second}) + (-0.040 * \text{balance time}) + 6$$

Patients were categorized as frail based on previously established cut-offs if they had a liver frailty index score of ≥ 4.5 at the time of their last assessment prior to liver transplant [6].

Acute Cellular Rejection

Patients were classified as having experienced acute cellular rejection if they had a liver biopsy within 3 months post-transplant with an official pathologist final interpretation that acute cellular rejection was present, *and* if they received treatment specifically for acute rejection with a change in immunosuppression. We also collected data regarding histologic diagnosis of rejection on biopsy, rejection grade, and clinical response (i.e. changes in immunosuppression) from the electronic health record. Grade of acute cellular rejection was ascertained using the Banff schema, looking for evidence of portal inflammation, bile duct inflammation, and subendothelial inflammation of portal veins or terminal hepatic venules on core needle biopsy. Liver biopsies were performed when there was clinical or biochemical suspicion of acute cellular rejection; no protocol biopsies were performed. We selected this time frame of 3 months post-transplant as we hypothesized that the effects of frailty related to the pre-transplant pathophysiology might resolve beyond the 3-month time frame after receiving a new liver.

Immunosuppression

The standard immunosuppression regimen at the time of transplant at our center is high-dosed solumedrol and mycophenolate, with the addition of tacrolimus on post-operative day 2-4, depending upon renal function. Data on mycophenolate, tacrolimus, cyclosporine, sirolimus, everolimus, and corticosteroid dosages and associated trough levels were

collected from medical chart review at time of discharge and 3 months (+/− 1 month) at post-liver transplant follow up appointments. If the patient had multiple appointments in the 3 month time interval, the appointment closest to 3 months post-liver transplant was selected.

Mycophenolate dose reduction was defined as mycophenolate mofetil (Cellcept) reduced to less than 1000 mg/day and mycophenolic acid (Myfortic) reduced to less than 720 mg/day. Discontinuation of either medication was also considered mycophenolate dose reduction. Patients were categorized as having mycophenolate dose reduction if they experienced a qualifying dose reduction at any point prior to the selected time interval.

Statistical Analysis

Baseline demographics were presented as medians [interquartile ranges (IQR)] for continuous variables or percentages for categorical variables and compared by frailty status using Wilcoxon rank sum or chi-square tests. To minimize the risk of overfitting models, only univariable and bivariable logistic regression were performed using variables that may confound the relationship between frailty and acute cellular rejection. Co-variates evaluated in bivariable models included those that were significantly associated with acute cellular rejection in univariable analysis, or those that have previously been associated with either frailty (age, female sex) or acute cellular rejection (MELD, ascites). Statistical significance was defined by a cutoff p-value of <0.05.

Statistical analyses were performed using Stata (v15, SE). The University of California, San Francisco institutional review board approved this study.

RESULTS

Characteristics of the entire patient population (Table 1)

A total of 241 LT recipients were included. Baseline characteristics of the cohort are shown in Table 1. To briefly summarize, median (IQR) age was 60 years (54-65), 37% were female, 54% were non-Hispanic white, and median body mass index was 28 kg/m^2. Fifty-five percent of patients had Hepatitis C as their primary etiology of liver disease, 14% had alcoholic hepatitis, and 10% had non-alcoholic steatohepatitis. Rates of hypertension, diabetes, and coronary artery disease were 44%, 27%, and 7% respectively. In this outpatient cohort, median MELDNa was 20 and albumin was 3.1 g/dL. Only one, non-frail patient experienced and was treated for an active CMV infection within 3 months post liver transplant.

Comparison of baseline characteristics by frailty status (Table 1)

The median time from last frailty assessment to transplant was 66 days (34-122); 46 (19%) were classified as frail. Compared to non-frail patients, frail patients were more likely to be female (50% vs 33%) and to be Hispanic white (40% vs 25%). Frail patients were less likely to have chronic hepatitis C as their primary etiology of liver disease (43% vs. 58%) but more likely to have non-alcoholic steatohepatitis (20% vs 8%). Frail patients also had higher median MELDNa (25.5 vs 19) and a higher incidence of ascites and hepatic encephalopathy

(52% and 50% vs 24% and 27% respectively). However frail and non-frail patients were similar by age, BMI, diabetes incidence, and coronary artery disease incidence.

Immunosuppression

Immunosuppression characteristics are summarized in Table 2. The median tacrolimus trough during the first 10 days post-liver transplant was 4.8 ng/ml. The median tacrolimus trough among non-frail patients was 4.8 ng/ml, and among frail patients was 4.6 ng/ml (p=0.26). Only 3 patients were on cyclosporine during the first 10 days post-liver transplant.

The vast majority (98%) of frail and non-frail patients were on a combination of mycophenolate, corticosteroids and tacrolimus on discharge after liver transplant. By 3 months, 78% of frail patients and 81% of non-frail patients remained on this triple-drug regimen combination. On discharge post-liver transplant, only 2% of patients were on sirolimus or everolimus; at 3 months, 12% of non-frail patients and 15% of frail patients were on one of these medications.

The median tacrolimus trough among all patients at discharge post-liver transplant was 6.6 ng/ml; the median mycophenolate dose was 2000 mg, and the median corticosteroid dose was 20 mg. At 3 months, the median tacrolimus trough was 6.9 ng/ml, median mycophenolate dose was 2000 mg, and median corticosteroid dose was 5 mg (Table 2). There were no significant differences in median tacrolimus trough levels, mycophenolate doses, or corticosteroid doses at discharge or 3-months [p>0.05 for comparisons between frail and non-frail].

At time of discharge from the hospital post-liver transplant, 5% of patients had experienced mycophenolate dose reduction, with no significant difference between frail and non-frail patients (7% vs 5%, p=0.58). By 3 months post-liver transplant, 30% of patients had experienced mycophenolate dose reduction, with no difference between frail and non-frail patients (Table 2).

Associations between acute cellular rejection and frailty

Within the first 3 months post-LT, 7 (15%) frail patients versus 10 (5%) (p= 0.02) non-frail patients experienced acute cellular rejection. These rejection episodes occurred a median of 8 days after liver transplant, and median number of biopsies for this group was 2. Of the 17 patients who experienced acute cellular rejection in the first 3 months post liver transplantation, 6 experienced mild rejection, 10 experienced moderate rejection, and 1 experienced severe rejection. Severity of rejection episodes did not differ by frailty status (p=0.34).

In response to the rejection episodes, 45% of these patients received IV steroids, 30% saw an increase in their regular immunosuppression medication dosages, 10% received thymoglobulin, and 15% received a combination of steroid and another medication. In univariable logistic regression, frailty was associated with a 3.3 times higher odds of acute cellular rejection at 3 months (95%CI 1.2, 9.3, p=0.02); age (OR 0.9), time from last frailty assessment to transplant (days) (OR 1.0), Black race (OR 3.4), alcoholic liver disease (OR 2.5), autoimmune disease (OR 2.7), “other” etiology (OR 7.2), diabetes (OR 0.4), and INR

(OR 0.4) were also associated with acute cellular rejection by 3 months with a p-value<0.20. To further explore the association between frailty and acute cellular rejection, we conducted bivariable analyses with the variables that were significantly associated with acute cellular rejection in univariable analysis or have been previously associated with either frailty (age, female sex) or acute cellular rejection (MELD, ascites) as well as relevant immunosuppression variables. While bilirubin level and ascites are both established risk factors for acute cellular rejection, they were not significantly associated with acute cellular rejection in univariable regression in our cohort and as such were excluded from bivariable analyses. In these bivariable analyses, frailty remained significantly associated with acute cellular rejection with an odds ratio relatively similar to the unadjusted value (Table 3).

Among the 17 patients who had experienced acute cellular rejection by 3 months, only 2 had experienced mycophenolate dose reduction by the time of discharge post-LT or at their 3-month follow up appointment. The were no differences in immunosuppression regimens between those who did and did not experience acute cellular rejection – and the vast majority of patients (100% of those who experienced acute cellular rejection vs. 98% of those who did not experience acute cellular rejection; p=0.53) were on a combination of mycophenolate, corticosteroids, and tacrolimus on discharge post-liver transplant. There was no significant difference in the median tacrolimus trough level during the first 10 days post-liver transplant between those who experienced acute cellular rejection within 3 months (5.5 ng/ml) and those who did not (4.7 ng/ml) (p=0.30). At 3-month follow-up, 80% of patients who did not experience acute cellular rejection and 76% of patients who did experience acute cellular rejection by 3 months were on a combination of mycophenolate, corticosteroids, and tacrolimus (p=0.70).

DISCUSSION

Frailty has increasingly been understood to be an immune-mediated phenomenon, associated with dysregulation of the immune system and decline in physiologic reserve. We, therefore, hypothesized that this would lead to differential rates of acute cellular rejection. Indeed, in this study of 241 liver transplant recipients, we observed that frail patients had three-fold higher adjusted odds of acute cellular rejection within 3 months after liver transplantation compared to non-frail patients.

Our data support past studies which have identified the biological underpinnings of frailty as one of immune activation, with effects that linger into the early post-transplant time-frame [20]. There is substantial evidence pointing to frailty as a heightened inflammatory state, and biomarkers such as sTNF-RII have even been found to be predictive of frailty status [21]. These past findings of immune activation in frailty syndrome are consistent with our observation of increased rates of acute cellular rejection among frail patients.

It is possible that under-immunosuppression could have led to higher rates of ACR in frail patients. Our findings are similar to observations in frail kidney transplant patients, who experienced *higher* rates of mycophenolate dose reduction than non-frail recipients [19]. However, in our study, neither the number of immunosuppression medications nor the median doses of immunosuppressive medications differed between frail and non-frail liver

transplant recipients at the time of discharge or 3-month follow up. Both conclusions have significant implications for clinical practice, providing compelling reasons to pursue future prospective studies to investigate this association in a large, multi-center cohort of liver transplant recipients.

We acknowledge the following limitations to our study. To determine frailty status, we used the last frailty measurement prior to liver-transplant, which was closer to the time of transplant for frail patients then non-frail patients. As such, we acknowledge that by time of transplant, frailty status may have changed for some patients. In addition, frailty may also have changed shortly after liver transplantation which could confound the association between frailty and acute cellular rejection that we found, but data on 3-month post-transplant frailty were not available on many of the patients included in this study [22]. We also retrospectively collected data regarding immunosuppression, so we were only able to collect information about immunosuppression as documented in progress notes. As such, our data may not reflect complete trends in immunosuppression. Furthermore, we only collected immunosuppression regimens and doses at specific time points (e.g., discharge and 3-months) rather than continuously, and therefore, may have missed transient periods of relative under-immunosuppression. In addition, we relied solely on liver biopsy data to ascertain episodes of acute cellular rejection, and it may have been possible that patients experienced acute cellular rejection that was treated empirically rather than evaluated formally with a liver biopsy. However, we do not believe that empiric treatment of acute rejection would have occurred differentially in frail compared with non-frail patients. Finally, our study was limited by a relatively small number of acute cellular rejection events which precluded multivariable adjustment; therefore, our findings warrant confirmation in larger, multi-center cohorts.

Despite these limitations, our data have important implications for the management of frail patients undergoing liver transplantation. Anecdotally, frail patients may be perceived to have less robust immune systems and therefore, lower need for high dose or aggressive immunosuppression. They may also be perceived to have a lower tolerance for immunosuppressive medications. Our data demonstrate that they, in fact, experience *higher* rates of acute cellular rejection. While much research needs to be done to explore the underlying cause of our findings, whether it be physiologic or due to provider behavior resulting in under-immunosuppression, our clinical data provide the necessary first step to justify such research. Furthermore, our findings suggest that the frail phenotype may play a crucial role in risk stratification for studies involving early post-transplant immunosuppression interventions.

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List of abbreviations:

ACR	acute cellular rejection
LFI	liver frailty index
LT	liver transplant
MDR	mycophenolate dose reduction

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Table 1.

Characteristics of the 241 patients with cirrhosis included in this study.

Characteristic		All n=241	By Frailty Status		p-value
			Not Frail n=195 (81%)	Frail n=46 (19%)	
Age, years		60 (54-65)	61 (55-65)	58.5 (53-63)	0.09
Female		37%	33%	50%	0.04
Time from last frailty assessment to transplant (days)		66 (34-122)	71 (38-132)	48 (30-95)	0.046
Race/Ethnicity	**Non-Hispanic White**	54%	55%	52%	0.046
	Black	5%	6%	0%	
	Hispanic White	28%	25%	40%	
	Asian/Pacific Islander	8%	9%	4%	
	Other	5%	6%	4%	
Body mass index, kg/m^2		28 (25-32)	27 (24-32)	29 (25-33)	0.17
Etiology of liver disease	**Chronic hepatitis C**	55%	58%	43%	0.25
	Alcohol	14%	13%	15%	
	Non-alcoholic steatohepatitis	10%	8%	20%	
	HBV	5%	5%	4%	
	Autoimmune/Cholestatic	13%	13%	13%	
	Other	3%	3%	4%	
Hypertension		44%	46%	37%	0.29
Diabetes		27%	26%	28%	0.77
Coronary artery disease		7%	7%	7%	0.88
MELDNa		20 (15-28)	19 (14-26)	26 (19-34)	<0.001
Total bilirubin, mg/dL		3.7 (1.8-8.8)	3.4 (1.7-7.5)	4.6 (3.3-14.8)	0.01
Creatinine, mg/dL†		1.1 (0.8-1.4)	1.0 (0.8-1.3)	1.4 (0.9-1.8)	0.03
INR		1.7 (1.4-2.1)	1.7 (1.4-2.1)	2 (1.6-2.3)	0.02
Sodium, mEq/L		137 (132-140)	137 (135-140)	136 (134-139)	0.19
Albumin, g/dL		3.1 (2.7-3.7)	3.1 (2.7-3.8)	3.1 (2.8-3.5)	0.55
Dialysis		15%	13%	24%	0.07

Characteristic	All n=241	By Frailty Status		p-value
		Not Frail n=195 (81%)	Frail n=46 (19%)	
Ascites	29%	24%	52%	<0.001
Hepatic encephalopathy	32%	27%	48%	0.007
CMV infection	0.4%	0.5%	0%	0.63
Operation post-transplant	15%	11%	33%	<0.001

Table 2.

Immunosuppression use in 241 patients with cirrhosis included in this study.

		All		By Frailty Status				
				Not Frail n=195 (81%)		Frail n=46 (19%)		
		N	Median Dose or Trough, IQR	N	Median Dose or Trough, IQR	N	Median Dose or Trough, IQR	p-value
Mycophenolate Mofetil Dose	**Discharge**	228 (95%)	2000 (2000-2000)	186 (95%)	2000 (2000-2500)	42 (91%)	2000 (2000-2000)	0.47
	3 month	185 (77%)	1500 (1000-2000)	151 (77%)	1500 (1000-1500)	34 (74%)	1000 (1000-1500)	0.14
Mycophenolic Acid Dose	**Discharge**	11 (5%)	1440 (1080-1440)	8 (4%)	1440 (1080-1440)	3 (7%)	1440 (1080-1480)	0.65
	3 month	30 (12%)	870 (720-1440)	24 (12%)	720 (720-1080)	6 (13%)	1260 (1080-1440)	0.14
Mycophenolate Dose Reduction **	**Discharge**	12 (5%)		9 (5%)		3 (7%)		0.58
	3 month	66 (28%)		53 (28%)		13 (29%)		0.86
Steroid Dose	**Discharge**	238 (99%)	20 (20-20)	194 (99%)	20 (20-20)	45 (98%)	20 (15-20)	0.42
	3 month	232 (96%)	5(5-5)	188 (96%)	5(5-5)	44 (96%)	5(5-5)	0.08
Tacrolimus Trough	**Discharge**	239 (99%)	6.6 (4.6-8.4)	194 (99%)	6.55 (4.5-8.3)	45 (98%)	6.8 (5.2-8.8)	0.18
	3 month	237 (98%)	6.6 (4.9-8.6)	192 (98%)	6.9 (5-8.7)	45 (98%)	6 (4.2-8)	0.22
Cyclosporine Trough	**Discharge**	4 (2%)	88.5 (54-182)	3 (2%)	122 (55-242)	1 (2%)	53 (53-53)	0.18
	3 month	9 (4%)	133 (58-160)	7 (4%)	120 (51-160)	2 (4%)	225.5 (145-306)	0.24
Sirolimus or Everolimus	**Discharge**	6 (2%)		5 (3%)		1 (2%)		
	3 month	31 (13%)		24 (12%)		7 (15%)		

* Median (interquartile range) or %

** Mycophenolate Dose Reduction defined as Mycophenolate < 1000 mg daily and Myfortic < 720 mg daily

Table 3.

Bivariable odds of acute cellular rejection associated with frailty, defined by the Liver Frailty Index ≥4.5.

Adjusted for		Odds ratio (95% CI) p-value associated with frailty
No adjustment		3.3 (1.2-9.3) 0.02
Age		3.1 (1.0-9.0) 0.04
Female		3.2 (1.1-8.9) 0.03
Time from last frailty assessment to transplant (days)		2.9 (1.0-8.1) 0.046
Black race		3.9 (1.4-11.5) 0.01
Alcoholic liver disease		3.3 (1.2-9.2) 0.02
Autoimmune etiology		3.4 (1.2-9.4) 0.02
“Other” etiology		3.2 (1.1-9.2) 0.03
Diabetes		3.4 (1.2-9.7) 0.02
MELD		3.6 (1.2-11) 0.03
INR		4.5 (1.5-13.1) 0.01
Ascites		3.7 (1.3-11.0) 0.02
Steroid dose, mg	**Discharge**	4.4 (1.4-14.5) 0.01
	3 months	3.3 (1.2-9.2) 0.02
Mycophenolate Mofetil dose, mg	**Discharge**	3.4 (1.1-10.3) 0.03
	3 months	4.3 (1.3-13.8) 0.02
Tacrolimus trough, ng/ml	**Discharge**	3.4 (1.2-9.5) 0.02
	3 months	4.4 (1.4-14) 0.01