ORIGINAL ARTICLE

Association Between Sarcopenia and the Risk of Serious Infection Among Adults Undergoing Liver Transplantation

Robert W. Krell,[1] **Daniel R. Kaul,**[2,3] **Andrew R. Martin,**[2,3] **Michael J. Englesbe,**[1,4] **Christopher J. Sonnenday,**[1,4] **Shijie Cai,**[1,4,5] **and Preeti N. Malani**[2,3,6,7]

[1]*Department of Surgery,* [2]*Department of Internal Medicine,* [3]*Division of Infectious Diseases,* [4]*Section of Transplantation Surgery,* [5]*Department of Biostatistics, and* [6]*Division of Geriatric and Palliative Medicine, University of Michigan Health System, Ann Arbor, MI; and* [7]*Geriatrics Research Education and Clinical Center, Veterans Affairs Ann Arbor Healthcare System, Ann Arbor, MI*

Although sarcopenia (muscle loss) is associated with increased mortality after liver transplantation, its influence on other complications is less well understood. We examined the association between sarcopenia and the risk of severe posttransplant infections among adult liver transplant recipients. By calculating the total psoas area (TPA) on preoperative computed tomography scans, we assessed sarcopenia among 207 liver transplant recipients. The presence or absence of a severe posttransplant infection was determined by a review of the medical chart. The influence of posttransplant infections on overall survival was also assessed. We identified 196 episodes of severe infections among 111 patients. Fifty-six patients had more than 1 infection. The median time to the development of an infection was 27 days (interquartile range = 13-62 days). When the patients were grouped by TPA tertiles, patients in the lowest tertile had a greater than 4-fold higher chance of developing a severe infection in comparison with patients in the highest tertile (odds ratio = 4.6, 95% confidence interval = 2.25-9.53). In a multivariate analysis, recipient age (hazard ratio = 1.04, $P = 0.02$), pretransplant TPA (hazard ratio = 0.38, $P < 0.01$), and pretransplant total bilirubin level (hazard ratio = 1.05, $P = 0.02$) were independently associated with the risk of developing severe infections. Patients with severe posttransplant infections had worse 1-year survival than patients without infections (76% versus 92%, $P = 0.003$). In conclusion, among patients undergoing liver transplantation, a lower TPA was associated with a heightened risk for posttransplant infectious complications and mortality. Future efforts should focus on approaches for assessing and mitigating vulnerability in patients undergoing transplantation. *Liver Transpl 19:1396-1402, 2013.* © 2013 AASLD.

Liver transplants are costly and highly morbid procedures. With increased efforts at providing efficient and effective care, much attention has been given to identifying patients who require more intense resource utilization during the perioperative period. One such group of patients is the medically frail.[1-4] Although often considered a normal facet of aging, this heightened state of vulnerability (known as frailty) plays a role in susceptibility to a wide range of illnesses, including infections.[5,6] Although there are many proposed ways for establishing the presence or absence of frailty, sarcopenia (muscle loss) has gained attention recently because of its reproducibility and its demonstrated link with increased

mortality and morbidity risk across diverse patient groups.[7-10]

Although the influence of sarcopenia on the overall health of older adults has been well recognized, the potential impact of frailty on surgical outcomes has only recently generated interest. Sarcopenia has been used to evaluate perioperative risk across several patient populations. Sarcopenic patients appear to be at increased risk for major postoperative complications and death after a variety of surgical procedures, including liver transplantation.[11-14]

Previously, we described the relationship between sarcopenia and post–liver transplant survival.[15] Although we observed a robust association between sarcopenia and increased mortality, other clinical outcomes of interest were not considered. An improved understanding of the influence of sarcopenia on posttransplant risk can inform the development of better management strategies for this vulnerable population. In that context, we examined the relationship between sarcopenia and infectious complications after liver transplantation.

PATIENTS AND METHODS

Setting and Study Population

The University of Michigan Health System (UMHS) is a 931-bed, tertiary care medical center with an active liver transplantation program. The UMHS liver transplant program began in 1985 and now performs both pediatric and adult liver transplants. Our study population included all adult patients who underwent liver transplantation between June 2002 and August 2008 and also underwent a preoperative abdominal/pelvic computed tomography (CT) scan during the 90 days before transplantation.

Outcomes

The development of severe infections (primarily health care–associated and opportunistic infections) within 180 days of transplantation was the primary outcome of interest. The presence or absence of infections and associated organisms was determined by a review of each recipient's medical records. We defined severe infections as infections requiring hospitalization or intravenous or prolonged courses of antimicrobials or infections resulting in persistent disability or death. We focused on severe infections because more minor infections (eg, mild cellulitis and uncomplicated urinary tract infections) are generally of limited clinical consequence. We defined health care–associated infections and opportunistic infections with established Centers for Disease Control and Prevention/National Healthcare Safety Network and American Society of Transplantation criteria.[16,17] From a practical standpoint, minor infections are also nearly impossible to ascertain in a retrospective manner. We recorded the time to the diagnosis of infection and mortality as secondary outcomes.

Independent Variables

Our primary exposure of interest was sarcopenia, which was measured with each patient's total psoas area (TPA). We computed each patient's TPA from preoperative abdominal/pelvic CT scans as previously described.[15] In brief, we calculated the cross-sectional area of both psoas muscles at the level of the fourth lumbar vertebra via a standardized computer algorithm. Other patient characteristics, including the demographics, height, weight, body mass index (BMI), indication for liver transplantation, preoperative laboratory values, and presence of portal vein thrombosis, were recorded. Preoperative laboratory values were used to calculate the Model for End-Stage Liver Disease (MELD) scores for patients.

Statistical Analysis

To account for known sex influences on TPA in our analysis, we first grouped patients into sex-stratified TPA tertiles so that each tertile contained similar proportions of men and women.[9,18] We then compared patient demographics, preoperative characteristics, and preoperative laboratory values as well as donor characteristics across TPA tertiles with 1-way analyses of variance (for continuous variables) and Pearson chi-square tests (for categorical variables). We included all transplant indications when we were comparing indications across TPA tertiles. Next, we compared patient demographics, characteristics, and laboratory values as well as donor characteristics across groups by the presence of severe posttransplant infections with unpaired t tests for continuous variables and with Pearson chi-square tests or Fisher's exact test for categorical variables. When we were comparing groups according to infections, we considered only a patient's primary indication for transplantation if he or she had multiple indications. We further categorized primary transplant indications into 1 of 3 categories [hepatocellular carcinoma (HCC) without hepatitis C virus infection, hepatitis C virus, and other] for bivariate analyses and further modeling.

To examine the relationship between TPA and posttransplant severe infections, we first used logistic regression to calculate the unadjusted odds ratio (OR) for developing severe infections by the TPA tertile level. We then entered all variables with $P < 0.2$ in the univariate analysis into a Cox proportional hazards regression with backwards stepwise selection to identify independent risk factors for developing a severe posttransplant infection. We examined risk factors for developing bacterial, fungal, and viral infections with the same method.

For the survival analysis, we calculated the days from transplantation to death. We elected to censor survival at the end of the study period or the last date of follow-up, whichever occurred first. We estimated survival functions with the Kaplan-Meier method and stratified patients across the presence of severe infections. Finally, we compared survival curves and 1-year survival rates between groups (infected or not infected) with a log-rank test.

TABLE 1.   Characteristics of Liver Transplant Recipients at UMHS From June 2002 to July 2008 With Preoperative CT Scans Stratified by TPA Tertiles (n = 207)

Characteristic	Tertile 1 (n = 69)	Tertile 2 (n = 69)	Tertile 3 (n = 69)	P Value
Age at transplant (years)*	52.0 ± 9.8	52.0 ± 10.2	51.1 ± 9.6	0.82
TPA: males (mm^2)*†	1499.2 ± 309.9	2224.8 ± 157.8	2915.7 ± 381.5	<0.01
TPA: females (mm^2)*†	954.3 ± 225.3	1423.1 ± 120.5	1978.8 ± 282.0	<0.01
Race [n (%)]				
White	53 (76.8)	61 (88.4)	54 (78.3)	0.17
African American	5 (7.2)	7 (10.1)	11 (15.9)	0.30
Other	11 (15.9)	1 (1.4)	4 (5.8)	
Preoperative BMI (kg/m^2)*	26.5 ± 5.6	27.5 ± 6.4	29.3 ± 6.3	0.03
Indication for transplantation [n (%)]‡				
Hepatitis C virus	22 (31.9)	19 (27.5)	13 (18.8)	0.21
Hepatitis B virus	2 (2.9)	2 (2.9)	5 (7.2)	0.35
HCC	10 (14.5)	16 (23.2)	26 (37.7)	0.01
Alcoholic cirrhosis	11 (15.9)	11 (15.9)	8 (11.6)	0.70
Primary sclerosing cholangitis	6 (8.7)	5 (7.2)	10 (14.5)	0.33
Primary biliary cirrhosis	6 (8.7)	4 (5.8)	5 (7.2)	0.81
Autoimmune hepatitis	4 (5.8)	3 (4.3)	4 (5.8)	0.91
Nonalcoholic steatohepatitis	2 (2.9)	3 (4.3)	3 (4.3)	0.88
Fulminant hepatitis failure	1 (1.4)	2 (2.9)	1 (1.4)	0.78
Alpha-1 antitrypsin deficiency	1 (1.4)	2 (2.9)	0	0.36
Wilson's disease	0	1 (1.4)	1 (1.4)	0.60
Other	9 (13.0)	6 (8.7)	4 (5.8)	0.33
Need for pretransplant dialysis [n (%)]	6 (8.7)	1 (1.4)	3 (4.3)	0.13
Preoperative laboratory values*				
MELD score	22.7 ± 7.9	18.7 ± 8.2	18.0 ± 6.2	<0.01
International normalized ratio	1.6 ± 0.7	1.5 ± 1.0	1.5 ± 0.4	0.15
Creatinine (mg/dL)	1.9 ± 1.3	1.3 ± 0.9	1.2 ± 0.7	<0.01
Total bilirubin (mg/dL)	4.2	4.0	3.2	0.44
Donor age (years)*	42.2 ± 18.0	36.6 ± 17.2	39.7 ± 15.6	0.17

*The data are presented as means and standard deviations.
†Measured at the fourth lumbar vertebra.
‡The n values refer to the total number of diagnoses. Twenty one patients had more than 1 indication for transplantation. Hepatitis C virus–infected patients were divided by the presence and absence of HCC.

We considered a 2-tailed P value < 0.05 to be significant. All statistical analyses were performed with SAS 9.2 (SAS Institute, Cary, NC). This study was approved by the University of Michigan institutional review board.

RESULTS

Patient Characteristics

Between June 2002 and August 2008, 509 adult patients underwent liver transplantation at UMHS; 207 of these patients (40.7%) underwent abdominal CT scanning within the 90 days before transplantation. These 207 patients formed our overall study cohort. The mean age of the cohort was 51.7 ± 9.8 years; 129 patients (62.3%) were male. The majority of the patients (81.2%) were white. The most frequent indications for transplantation were hepatitis C virus (26.1%), HCC (25.1%), and alcoholic cirrhosis (14.5%). Twenty one patients had more than 1 indication for transplantation.

Patient characteristics across TPA tertiles are presented in Table 1. Patients with high TPAs had a higher mean BMI than patients with low TPAs (29.3 versus 26.5 kg/m^2, $P = 0.03$), were more likely to have a diagnosis of HCC (37.7% versus 14.5%, $P = 0.01$), and had a lower mean MELD score (18.0 versus 22.7, $P < 0.01$; Table 1).

Table 2 shows differences between patients who developed severe posttransplant infections and those who did not. Infected patients had a higher mean MELD score than patients who did not have a severe infection (21.8 versus 17.4, $P < 0.01$), a lower mean albumin level (2.7 versus 2.9 g/dL, $P = 0.04$), and a lower TPA (1762.4 versus 2116 mm^2, $P < 0.01$). In addition, infected patients were less likely to have HCC as an indication for transplantation (15.3% versus 36.5%, $P < 0.01$; Table 2). Overall, patients with severe posttransplant infections had a higher mortality rate (36.0%) than patients without infections (18.8%, $P < 0.01$).

Posttransplant Infections

We identified 196 severe infectious episodes among 111 patients. Fifty-six patients had more than 1

TABLE 2.   Characteristics of Liver Transplant Recipients With Infections and Liver Transplant Recipients W ithout Infections

Characteristic	Infection (n = 111)	No Infection (n = 96)	P Value
Age at transplant (years)*	52.3 ± 8.8	50.9 ± 10.8	0.30
Male [n (%)]	64 (57.7)	65 (67.7)	0.14
Race [n (%)]			
White	91 (82.0)	77 (80.2)	0.75
African American	11 (9.9)	12 (12.5)	0.66
Other	9 (8.1)	7 (7.3)	
Indication for transplantation [n (%)]†			
Hepatitis C virus without HCC	34 (30.6)	20 (20.8)	0.11
HCC	17 (15.3)	35 (36.5)	<0.01
Other	60 (54.1)	41 (42.7)	0.10
Need for pretransplant dialysis [n (%)]	8 (7.2)	2 (2.1)	0.11
Preoperative laboratory values*			
MELD score	21.8 ± 7.8	17.4 ± 6.9	<0.01
International normalized ratio	1.6 ± 0.6	1.6 ± 0.9	0.91
Creatinine (mg/dL)	1.7 ± 1.2	1.2 ± 0.7	<0.01
Total bilirubin (mg/dL)	7.6 ± 8.5	4.9 ± 6.6	<0.01
Serum albumin (g/dL)	2.7 ± 0.6	2.9 ± 0.7	0.04
BMI (kg/m^2)*	28.0 ± 5.7	27.5 ± 6.7	0.56
TPA (mm^2)*‡	1762.4 ± 701	2116 ± 643.3	<0.01
Donor age (years)*	40.4 ± 17.2	38.4 ± 16.8	0.43
Portal vein thrombosis [n (%)]	3 (2.7)	7 (7.3)	0.35
Mortality [n (%)]	40 (36.0)	18 (18.8)	<0.01

*The data are presented as means and standard deviations.
†The n values indicate the primary indications for transplantation as recorded in the patient charts. Patients with multiple indications for transplantation were assigned a primary indication for the bivariate analysis.
‡Measured at the fourth lumbar vertebra.

infection. The median time to the first infectious episode was 27 days (interquartile range = 13-62 days); 53.1% of infections occurred within 30 days of transplantation, and 73.9% occurred within 60 days of transplantation.

The most common infectious episodes were bloodstream infections (n = 48), intra-abdominal infections (n = 65), and pneumonia (n = 14). In addition, there were 15 opportunistic infections, the majority of which (60.0%) were related to cytomegalovirus (CMV). Details on the types of infections and associated microorganisms are displayed in Table 3.

Risk Factors for Developing Severe Posttransplant Infections

As shown in Table 4, a decreasing TPA (more sarcopenia) was associated with increased odds of developing any infection [OR for tertile 1 versus tertile 3 = 4.6, 95% confidence interval (CI) = 2.25-9.53] or any bacterial infection (OR for tertile 1 versus tertile 3 = 5.2, 95% CI = 2.5-10.8; OR for tertile 2 versus tertile 3 = 2.5, 95% CI = 1.2-5.1). The results of a multivariate Cox proportional hazards regression are presented in Table 4. We identified the following variables as independent risk factors for developing a serious infection: recipient age (hazard ratio for developing any infection = 1.04, P = 0.02), pretransplant TPA (hazard ratio with an increasing TPA tertile = 0.38,

P < 0.01), and pretransplant total bilirubin level (hazard ratio = 1.05, P = 0.02; Table 5). Each of these factors remained statistically significant when infectious episodes were stratified by the pathogen type (bacterial, fungal, or viral).

Survival

Fifty-eight patients died during the study period. Patients with severe infections had more than twice the odds of posttransplant mortality than patients without infections (OR = 2.4, 95% CI = 1.3-4.6). Patients with any infection had a lower 1-year survival rate than patients without infections [76% versus 92%, P = 0.003 (log-rank test)].

DISCUSSION

The need for evidence-based methods for reducing perioperative risk among vulnerable populations remains critical. This issue continues to garner much attention from policymakers and medical leaders.[19] Sarcopenia is a reproducible marker of vulnerability and is closely linked to increased mortality and morbidity risk across diverse patient and procedure groups. The preceding results suggest that pretransplant sarcopenia, measured by TPA, was associated with an increased risk of serious posttransplant infections among a cohort of patients undergoing liver

TABLE 3.   Microorganisms Associated With Severe Infections Among Patients Undergoing Liver Transplantation

Type of Infection	n	Type of Infection	n
Bloodstream/central line–associated bloodstream infections (n = 48)		Pneumonia (n = 14)	
Staphylococcus aureus	5	*Pseudomonas aeruginosa*	4
Coagulase-negative *Staphylococcus*	6	*Klebsiella oxytoca*	1
Enterococcus faecalis	5	*Candida glabrata*	1
Vancomycin-resistant *Enterococcus*	6	Polymicrobial	2
Morganella morganii	1	No organism isolated	6
Pseudomonas aeruginosa	3	Urinary tract infections (n = 8)	
Escherichia coli	3	Vancomycin-resistant *Enterococcus*	2
Klebsiella pneumoniae	2	*Escherichia coli*	2
Candida albicans	5	*Klebsiella pneumoniae*	2
Candida glabrata	5	*Enterobacter* species	1
Alpha-hemolytic *Streptococcus*	1	Polymicrobial	1
Streptococcus milleri	1	Colitis (n = 31)	
Serratia maltophilia	1	*Clostridium difficile*	30
Polymicrobial	4	*Klebsiella pneumonia*	1
Intra-abdominal infections (n = 65)		Opportunistic infections (n = 15)	
Staphylococcus aureus	3	Epstein-Barr virus	1
Vancomycin-sensitive *Enterococcus*	6	CMV*	9
Vancomycin-resistant *Enterococcus*	14	Disseminated histoplasmosis	1
Alpha-hemolytic *Streptococcus*	1	*Cryptococcus* peritonitis	1
Pseudomonas aeruginosa	3	*Cryptococcus* fungemia	1
Klebsiella oxytoca	2	*Aspergillus* pneumonia	1
Klebsiella pneumoniae	2	*Aspergillus* osteomyelitis	1
Candida albicans	2	Other (n = 6)	
Candida glabrata	3	St. Louis encephalitis virus	1
Polymicrobial	22	Cutaneous herpes simplex	2
No organism isolated	7	Herpes zoster	2
Surgical site infections (n = 9)		Influenza A virus	1
Staphylococcus aureus	3		
Escherichia coli	1		
Enterobacter cloacae	1		
Polymicrobial	2		
No organism isolated	2		

*CMV infections included CMV colitis (4), CMV hepatitis (1), and disseminated CMV infections (4).

transplantation. In addition, we observed that patients with severe posttransplant infections had decreased survival in comparison with recipients without infections.

This work adds to a growing body of literature highlighting the negative influence of sarcopenia on patient outcomes. Previous research has suggested that frailty in general and sarcopenia in particular are associated with poor outcomes after strokes, hip fractures, and both elective and cancer operations.[4,11-13,20] Although

we used TPA to quantify sarcopenia, other frailty measures have demonstrated similar outcomes. For example, Kaido et al.[14] used bioelectrical impedance analysis to assess sarcopenia in a cohort of 124 adult patients undergoing living donor liver transplantation. Their findings mirror our results; low skeletal muscle mass was independently associated with posttransplant mortality.

Our findings are novel in the demonstration of an association between sarcopenia and an increased risk

TABLE 4.   Unadjusted ORs for Developing Any Serious Infection After Liver Transplantation by TPA Tertiles

	ORs for Developing a Severe Infection After Transplantation*			
TPA Tertiles	Any Infection	Bacterial Infection	Fungal Infection	Viral Infection
First versus third	4.6 (2.25-9.53)	5.2 (2.53-10.8)	2.8 (0.82-9.25)	0.70 (0.21-2.30)
Second versus third	1.9 (0.97-3.80)	2.5 (1.25-5.09)	1.5 (0.42-5.75)	0.70 (0.21-2.30)

*The ranges within parentheses are 95% CIs.

TABLE 5.   Multivariate Analysis of Preoperative Risk Factors Associated With the Development of a Severe Infection After Liver Transplantation (n = 207).

Variable	Hazard Ratios for Developing a Severe Infection After Transplantation*			
	Any Infection	Bacterial Infection	Fungal Infection	Viral Infection
Age at transplantation (years)	1.04 (1.01-1.08)†	1.04 (1.01-1.08)†	1.04 (1.01-1.08)†	1.04 (1.01-1.08)†
BMI (kg/m^2)	1.04 (0.99-1.08)	1.04 (0.99-1.08)	1.04 (1.00-1.09)	1.03 (0.99-1.08)
Pretransplant serum creatinine (mg/dL)	0.84 (0.61-1.13)	0.83 (0.61-1.13)	0.86 (0.64-1.17)	0.88 (0.65-1.19)
Pretransplant total bilirubin (mg/dL)	1.05 (1.01-1.10)†	1.05 (1.00-1.09)†	1.05 (1.00-1.09)†	1.05 (1.01-1.09)†
Preoperative TPA (mm^2)	0.38 (0.23-0.65)†	0.38 † (0.23-0.65)	0.35 (0.21-0.59)†	0.34 (0.20-0.58)†
Preoperative MELD score	0.99 (0.93-1.05)	0.99 (0.94-1.05)	0.99 (0.94-1.05)	0.99 (0.94-1.05)

NOTE: The results are presented for all infections (any infections) and subsets (bacterial, fungal, and viral pathogens). Details are provided in Table 3.
*The ranges within parentheses are 95% CIs.
†$P < 0.05$.

of infectious complications after liver transplantation. Infectious complications are significant sources of morbidity and mortality for liver transplant recipients; the potential influence of sarcopenia on infection-related outcomes deserves further investigation.[21] Improving our understanding of how sarcopenia contributes to an individual patient's risk and subsequent outcomes will be fundamental to developing effective countermeasures for risk reduction and management.

Some investigators have suggested that preoperative risk stratification for identifying patients with the highest risk can help to inform patient conversations and enact more intensive preoperative preparation, which is sometimes called prehabilitation.[22-25] Among patients awaiting liver transplantation, this may not be feasible because of the sporadic nature of organ availability and the poor overall health of transplant candidates. An alternative strategy may be to use measures of frailty such as sarcopenia to preemptively identify patients for more intensive postoperative monitoring and care specifically related to infection. Such measures might include the use of different perioperative antimicrobial regimens or approaches to infection prophylaxis, an early intensive care unit transfer for sarcopenic patients who experience complications, or extra vigilance in terms of removing lines and devices as soon as possible. Further investigations should help to clarify which management strategies would be most efficacious for mitigating or managing these patients' increased morbidity and mortality risk.

Our study has several important limitations. First, we analyzed a relatively small cohort from a single transplant center. Future studies should include larger numbers of patients from multiple institutions and use prospectively recorded data. In addition, we assessed only liver transplant candidates who had preoperative abdominal/pelvic CT scans, and this could have resulted in a selection bias because patients who had preoperative CT scans and patients who did not may have been inherently different. As such, our results may not apply to a broader population of liver transplant recipients. We did not attempt to investigate differences in microbiology or in sites of infection across TPA levels or the potential effects of antimicrobial treatment. Notably, all patients received standard perioperative infection prophylaxis, which consisted of ampicillin and sulbactam or vancomycin and levofloxacin (in the setting of a penicillin allergy). We also did not account for the potential impact of pretransplant infections or more minor postoperative infections. Other clinical factors such as immunosuppression regimens were also not considered, although most patients, at least initially, received similar regimens according to our standard protocol (which includes steroid induction, tacrolimus, mycophenolate, and steroid maintenance followed by a reduction in the steroid dose over approximately 3 months). Finally, there was possibly an ascertainment bias for infections that might have occurred outside UMHS (and not been reported).

Although the association between sarcopenia, infection, and mortality was striking, we cannot infer causality from these results. Nonetheless, the mechanism is biologically plausible, and this work lends additional support to the importance of frailty to outcomes after liver transplantation. Further work should examine other potential mechanisms for increased mortality among sarcopenic patients as well as factors that may have confounded these results. Finally, although sarcopenia is a consistent marker of increased risk, it remains unclear whether it can be mitigated or improved, especially in a population as ill as our study cohort was.

Sarcopenia, measured by TPA, seems to provide a convenient and relatively simple way of assessing a patient's physiological reserve, and it may identify those at increased risk for posttransplant

complications and mortality. Specifically, those patients with smaller TPAs seem to be at higher risk for developing severe infections. Besides larger confirmatory studies, there is a critical need to better understand the best way to assess and mitigate vulnerability in this extremely high-risk patient population.

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