Fatigue, Pain, and Other Physical Symptoms of Living Liver Donors in the Adult-to-Adult Living Donor Liver Transplantation Cohort Study

Zeeshan Butt,[1*] Andrea F. DiMartini,[2] Qian Liu,[3] Mary Ann Simpson,[4] Abigail R. Smith,[3,5] Jarcy Zee,[3] Brenda W. Gillespie,[5] Susan Holtzman,[6] Daniela Ladner,[1] Kim Olthoff,[7] Robert A. Fisher,[8] Silvia Hafliger,[9] Chris E. Freise,[10] Mercedes Susan Mandell,[11] Averell H. Sherker,[12] and Mary Amanda Dew[2]

[1]Departments of Medical Social Sciences, Surgery, and Psychiatry and Behavioral Sciences, Northwestern University, Chicago, IL; [2]Departments of Psychiatry, Psychology, Epidemiology, Biostatistics, and Clinical and Translational Science, University of Pittsburgh, Pittsburgh, PA; [3]Arbor Research Collaborative for Health, Ann Arbor, MI; [4]Department of Transplantation, Lahey Hospital and Medical Center, Burlington, MA; [5]Department of Biostatistics, University of Michigan, Ann Arbor, MI; [6]Department of Psychology, University of British Columbia, Kelowna, British Columbia Canada; [7]Department of Surgery, University of Pennsylvania, Philadelphia, PA; [8]Division of Transplantation, The Transplant Institute Beth Israel Deaconess Medical Center, Harvard University, Boston, MA; [9]Department of Psychiatry, Columbia University, New York, NY; [10]Departments of Medicine and Surgery, University of California at San Francisco, San Francisco, CA; [11]Department of Medicine, University of Colorado, Denver, Aurora, CO; and [12]National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD

Little is known about living liver donors' perceptions of their physical well-being following the procedure. We collected data on donor fatigue, pain, and other relevant physical outcomes as part of the prospective, multicenter Adult-to-Adult Living Donor Liver Transplantation Cohort Study consortium. A total of 271 (91%) of 297 eligible donors were interviewed at least once before donation and 3, 6, 12, and 24 months after donation using validated measures when available. Repeated measures regression models were used to identify potential predictors of worse physical outcomes. We found that donors reported more fatigue immediately after surgery that improved by 2 years after donation, but not to predonation levels. A similar pattern was seen across a number of other physical outcomes. Abdominal or back pain and interference from their pain were rated relatively low on average at all study points. However, 21% of donors did report clinically significant pain at some point during postdonation study follow-up. Across multiple outcomes, female donors, donors whose recipients died, donors with longer hospital stays after surgery, and those whose families discouraged donation were at risk for worse physical well-being outcomes. In conclusion, although not readily modifiable, we have identified risk factors that may help identify donors at risk for worse physical outcomes for targeted intervention.

Liver Transplantation 24 1221–1232 2018 AASLD.
Received February 1, 2018; accepted April 10, 2018.

Liver transplantation is the only lifesaving intervention for patients with end-stage liver disease and certain patients with hepatocellular carcinoma. However, there is a shortage of available deceased donors for liver transplantation. One strategy to alleviate the shortage of liver grafts has been the introduction of living donor liver transplantation (LDLT). Living liver donors (LLDs) are typically healthy adults who do not derive any personal medical benefit from the procedure. Therefore, in order to justify exposing LLDs to such an operation, it is imperative to understand not only the clinical outcomes of the surgery, but the physical impact of donation from the donor's perspective.

The potential mortality and morbidity risks of LDLT have been described.[1,2] Donor death is the most serious complication for LLD, with estimated

Abbreviations: A2ALL, Adult-to-Adult Living Donor Liver Transplantation Cohort Study; BMI, body mass index; BPI, Brief Pain Inventory; CI, confidence interval; FACIT-F, Functional Assessment of Chronic Illness Therapy – Fatigue subscale; LDLT, living donor liver transplantation; LLD, living liver donor; MCS, mental component summary; NA, not available; OR, odds ratio; PCS, physical component summary; PHQ-9, Patient Health Questionnaire-9; PROMIS, Patient-Reported Outcomes Measurement Information System; SD, standard deviation; SF-36, Short Form 36.

mortality of <0.5%.[3] Short-term postoperative complications after LDLT have also been well characterized, with Abecassis et al.[2] reporting a 39% overall morbidity among right lobe donors, and 2.8% of patients experiencing Clavien grade 3 (ie, resulting in residual or lasting functional disability) or 4 (ie, leading to transplant or death) complications, whereas the remaining reported more minor, grade 1 and 2 complications. The median follow-up period ranged from 1.8 to 3.4 years after donation, depending on the cohort.[2] Notably, nearly four-fifths of these complications resolved within 3 months of presentation. Patient perceptions of their physical well-being are also important outcomes of LLD but can be difficult to quantify.[4] In particular, the impact of donation on LLD fatigue, pain, and other physical outcomes is not well understood beyond the first year after donation.[5,6]

The majority of research to date has employed single-center, cross-sectional designs to characterize donor symptoms during the first year after donation. Before donation, LLD physical well-being is often equal to or significantly higher than normative adult populations.[7,8] Not surprisingly, donors experience the most impact on their physical well-being within the first 3 months of donation and report returning to near normal levels by 1 year after donation.[5] According to Hsu et al.,[9] in their sample of donors with median postsurgery follow-up of 25.9 months, the most common physical complaints in donors included throbbing, itching, and/or numbness around the surgical site, followed by reduced general physical vigor, sleep disturbance, and slowed reaction ability. The most prominent symptoms within 1 month of donation in 1 LLD cohort included bloating and loss of muscle tone.[7] In another cohort, in the 6-12 months after donation, the most common complaints were a change in body image, increased tiredness, and fatigue.[8,10] Few studies have described the timeline of symptom resolution in this population. Additionally, most longitudinal studies follow donors only up to 1 year, leaving questions regarding the longer-term impact of donation on physical well-being.

To improve our explanation of the risks of surgery to LLDs, we must have better information about the incidence and time course of donors' fatigue, pain, and other relevant physical outcomes. We have previously reported the perceived psychological, social, and economic outcomes in LLDs.[11,12] The purpose of the present longitudinal study was to evaluate LLD perception of their physical outcomes and potential predictors of these outcomes in a prospective, multicenter observational study.

Address reprint requests to Zeeshan Butt, Ph.D., Departments of Medical Social Sciences, Surgery, and Psychiatry and Behavioral Sciences, Northwestern University Feinberg School of Medicine, 633 North Saint Clair Street, 19th Floor, Chicago, IL 60611. Telephone: 312-503-7708; E-mail: z-butt@northwestern.edu

This study was supported by the National Institute of Diabetes and Digestive and Kidney Diseases through cooperative agreements (grants U01-DK62444, U01-DK62467, U01-DK62483, U01-DK62484, U01-DK62494, U01-DK62496, U01-DK62498, U01-DK62505, U01-DK62531, U01-DK62536, U01-DK85515, U01-DK85563, and U01-DK85587). Additional support was provided by Health Resources and Services Administration and the American Society of Transplant Surgeons.

This study was presented in part at the annual meeting of the American Transplant Congress, Boston, MA, June 15, 2016.

This is publication number #41 of the Adult-to-Adult Living Donor Liver Transplantation Cohort Study.

See the Supporting Information for the list of participating institutions.

Additional supporting information may be found in the online version of this article.

View this article online at wileyonlinelibrary.com.

DOI 10.1002/lt.25185

Patients and Methods

STUDY DESIGN

The Adult-to-Adult Living Donor Liver Transplantation Cohort Study (A2ALL) consortium consists of 9 North American transplant centers with data collected on potential LLDs and their recipients. These centers started study enrollment on a staggered basis from February to July 2011 and ended enrollment on January 31, 2014. Because our study was observational, screening protocols or other practices were not standardized across centers. However, all centers followed the medical and psychosocial evaluation and exclusion criteria for selecting LLD that are now included in the current US national policy.[13] Data for this analysis were obtained from eligible LLDs prospectively enrolled in the A2ALL study. Potential donors were considered eligible for the present study if they were English speaking, were scheduled to donate during the study enrollment period, and were approached for participation on or before their scheduled

donation date. The study was approved a priori by the institutional review boards/research ethics board and privacy boards of the University of Michigan Data Coordinating Center and each of the 9 participating transplant centers.

PROCEDURE

Potential LLDs were approached by transplant center study coordinators to obtain informed consent. Trained survey center interviewers then contacted consented participants within 1 month prior to donation and at 3, 6, 12, and 24 months after donation. Donors who did not reach a postdonation interview time point by the end of the study on July 15, 2014 were administratively censored (n = 29 at 1 year plus another 66 at 2 years after donation). Each interview took approximately 45 minutes to complete and was facilitated by use of a computer-assisted telephone interview to streamline data recording and storage. Participants were compensated with US $20 for each completed interview. Site and study-wide quality assurance and retraining were implemented for the duration of the study. Clinical information, including donor hospitalizations and complications, was collected prospectively within A2ALL.

MEASURES

Primary Physical Outcomes

Functional Assessment of Chronic Illness Therapy – Fatigue Subscale. The Functional Assessment of Chronic Illness Therapy – Fatigue subscale (FACIT-F) is a 13-item scale that asks respondents to rate statements regarding their fatigue experience and its impact on their daily lives. Using conventional scoring, the FACIT-F subscale ranges from 0 to 52 with lower scores indicating greater levels of fatigue. Originally developed for use with cancer patients,[14,15] the scale has been successfully tested for use in the general population and other chronic illness populations.[16,17] In the current study, we converted FACIT-F scores to Patient-Reported Outcomes Measurement Information System (PROMIS) T scores (mean ± standard deviation [SD], 50 ± 10) for modeling to reduce skewness of the score distribution and defined clinically significant fatigue as >0.5 SD above the normative mean.[18,19] This allows for comparison to future studies using PROMIS and the PROMIS general population norms.[18] The converted fatigue scale has a possible range of 30.3-83.5 with higher scores indicating greater levels of fatigue.

Brief Pain Inventory, Pain Intensity, and Interference. The Brief Pain Inventory (BPI) is a self-reported instrument that assesses the severity of pain and its impact on daily functions. It has been validated in patients with cancer and other chronic illnesses.[20] Donors provided a single-item rating for the level of abdominal or back pain they experienced at the time of assessment, ranging from 0 = no pain to 10= pain "as bad as you can imagine." Pain interference was summarized by the mean of the 7 interference items that range from 0 to 10. Patients who reported no pain were assigned 0 on pain interference.

Number of Current Physical Symptoms Attributed to Donation. Donors were asked to identify how many physical symptoms they experienced in the past month that could be attributed to the donation. Specifically, donors were asked approximately 10 possible clinical signs and symptoms, including bleeding, pain, itching, tension, numbness, and infection at surgical site. They were also asked about abdominal pain, low back pain, abdominal bloating/swelling, and decreased stomach tone. A count was used to quantify these symptoms, ranging from 0 to 10.

Short Form 36 Physical Component Summary. The Short Form 36 (SF-36) is 1 of the most widely used general measures of health status. The 36-item instrument can be summarized by 2 aggregated scores—the Physical Component Summary (PCS) and mental component summary (MCS)—which explain 80%-85% of the score variance.[21,22] Scores are standardized to a general population (mean ± SD, 50 ± 10). Higher scores indicate better health-related quality of life. Our focus for the present study was PCS scores.

Secondary Physical Outcomes

A number of secondary physical outcomes were explored by donor report, including the following: the number of postdonation health-related worries endorsed (4 items including worries about physical effects of donation, current health, future health, and never feeling 100% well again; and Cronbach's alpha of 0.75, suggesting adequate internal consistency reliability), ability to do physical activities as well since

donation, whether the donor is back to normal physically, whether recovery was slower than expected (versus as expected or faster than expected), any current donation-related medical problems, a rating of how physically stressful the donation was, and any overall negative feelings about donation (versus neutral or positive feelings).

Potential Predictors of Physical Outcomes

Potential predictors of physical outcomes included predonation survey items to assess donor experiences during the predonation process.[23] These instruments included psychosocial background, represented by donation history, donation decision-making items including whether there were other possible donors for the candidate, ambivalence to donate (a 7-item scale with Cronbach's alpha = 0.57 in the present sample), whether someone encouraged or discouraged the donation, anticipated longterm health effects of donation, feeling life would be more worthwhile, and if the donor felt like a "black sheep" (ie, experienced any family disapproval for their decision). Simmons' 11 items pertaining to motivations to donate were averaged to summarize the strength of motivation to donate (Cronbach's alpha = 0.77). The scale ranged from 1 (weak motivation to donate) to 7 (strong motivation to donate). Other potential predictors included the Campbell global life satisfaction item, which captures how donors feel about life as a whole,[24] the MCS and PCS scores from the SF-36, and the Patient Health Questionnaire-9 (PHQ-9) depression score (Cronbach's alpha = 0.73).

Additional potential predictors included donor demographics (age, sex, race/ethnicity, education, marital status, and household income before donation), clinical characteristics (predonation body mass index [BMI], length of donation hospital stay, postdonation hospitalizations within the first month, and postoperative complications within the first month), donor relation to the recipient (first-degree relative, spouse/partner, other biological or nonbiological relative, or unrelated), and whether the donor learned of recipient death prior to a given survey time point.

Surgical variables including the lobe donated and laparoscopic versus open surgery were also examined. However, they were only analyzed descriptively and were not considered as potential covariates in the modeling. In part, this was due to a lack of within-center variability on these variables. To help address this, the center was included as a predictor in sensitivity analysis models.

STATISTICAL ANALYSIS

Comparisons of demographic characteristics between respondents and nonrespondents have been previously published.[11,12] Nonrespondents included potential donors who did not consent to the study and actual donors who were not interviewed.

Descriptive statistics were used to describe physical outcomes at each assessment time point. We calculated means and SDs for continuous variables and percentages for dichotomous variables. For continuous outcomes, we compared 3 months after donation versus before donation and 2 years after donation versus before donation using paired t test and adjusted for multiple comparisons using the Bonferroni correction. For dichotomous outcomes, we also estimated endorsement cumulatively by calculating the percentage who endorsed the outcome at any time after donation.

We sought to investigate changes in physical outcomes following donation and to identify predictors of physical outcomes. To do so, we fit repeated measures liner, logistic, or negative binomial regressions using data from donors who completed a predonation survey and at least 1 postdonation survey. Outcomes endorsed by <10% of donors at every time point were not modeled to avoid limited generalizability with sparse outcomes. For each of the models above, generalized estimating equations models with sandwich standard error estimators were used to characterize the correlation among the repeated measures. Postdonation time point was included as a categorical variable (3 months, 6 months, 1 year, and 2 years after donation) and was retained in all regression models to show the outcome trajectories over time, even if it was not statistically significant. Variable selection was guided by the method of best subsets adjusting for time point.[25] Predictors were retained in models if P values were <0.05. Categorical predictors were retained if overall tests (over all levels) were <0.05, or if Bonferroni-corrected pairwise tests against the reference category were significant. Model assumptions, eg, functional forms for continuous covariates and residual distributions, were checked and were met in all models.

For descriptive analyses assessing the prevalence of physical outcomes, as a sensitivity analysis, we also performed the analyses only among patients who completed all interviews to evaluate whether missed or refused surveys had any impact on the results. For modeling, we conducted sensitivity analyses to examine whether the center was associated with outcomes by evaluating the overall P values of the center in the final models. We

also assessed whether controlling for centers in the final models changed the effects of other predictors.

All analyses were performed using SAS, version 9.4 (SAS Institute, Inc., Cary, NC).

Results

Study attrition as well as the demographics and clinical characteristics of respondents and nonrespondents have been published previously.[11,12] In brief, out of 297 eligible donors, 271 (91.2%) were interviewed at least once during study follow-up; 19 did not consent; and 7 consented but were not interviewed due to administrative errors or refusals. Among those interviewed, 253, 250, 241, 201, and 139 were interviewed before donation, 3, 6, 12, and 24 months after donation, respectively, making a total of 245 interviewed both before and after donation, 8 interviewed only before donation, and 18 interviewed only after donation.

The 271 donors who were interviewed were mostly female (57%), white (80%), married (63%), and employed full time (61%). Slightly more than half donated to a first-degree relative (53%). The majority (84%) of donors had right lobe hepatectomies, and 35% had laparoscopic surgery. During the first month after donation, 19% had 1 or more postoperative complications, and 8% had 1 or more hospitalizations. During the study follow-up, 27 (10%) donors reported recipient death. Respondents were similar to the 26 donors who did not consent or were not interviewed on sex, age, and race/ethnicity. Comparisons on clinical variables including recipient death were not possible because we did not have information on those variables for nonrespondents.

PHYSICAL OUTCOME CHARACTERISTICS

Table 1 shows the outcome characteristics by predonation and postdonation time points. The average FACIT-F (conventional) score ranged from 43.31 to 47.95 over the follow-up period, with 2%-15% reporting impaired levels of fatigue (defined as 0.5 SD, or 5 points, above the PROMIS normative mean). The average level of abdominal or back pain was low at all study time points, and donors reported minimal interference as measured by the BPI pain interference scale. Although the mean level of abdominal or back pain was low, 4%-13% of donors reported moderate to severe pain (defined as 4 or higher on a pain scale from 0 to 10) at some point during the study. Across all the postdonation time points, the average number of physical symptoms attributed to donation ranged from 2.30 to 4.59. In addition, the average PCS ranged from 48.19 to 56.20, with 2.8% to 28.8% of donors reporting impaired PCS (defined as 0.5 SD below the US normative mean).

With respect to the trajectories of these primary physical outcomes over time, FACIT-F, level of abdominal or back pain, pain interference, and PCS showed increased impairment from before donation to 3 months after donation (all significant based on paired *t* tests). These physical quality-of-life measures improved from 6 months to 2 years after donation but still did not reach predonation levels by 2 years after donation (only statistically significant for pain, based on paired *t* tests; Table 1). These trends were confirmed for FACIT-F and level of abdominal or back pain in adjusted model results, which showed statistically significant differences across time and highest levels of adverse outcomes at 3 months after donation (Table 2). The number of physical symptoms decreased over time from 3 months to 2 years after donation ($P < 0.001$).

The proportion of donors who reported that they were unable to do some physical activities as well since donation decreased from 3 months to 2 years after donation. The same was true for the proportion of donors who recovered more slowly than expected and for the proportion of donors who reported they recovered more slowly than expected (Table 1). In adjusted models, these outcomes had statistically significant differences across time points and were worst at 3 months after donation (Table 3). Donors reported an average of 0.68-0.98 health-related worries (range from 0 to 4), and the average number of health-related worries also showed a decreasing trend. In contrast, the proportion of donors reporting current donation-related medical problems (20% or higher across time points) and that the donation was physically stressful (43% or higher across time points) remained relatively constant over time ($P > 0.05$ in adjusted models). Finally, only a small minority of donors (1%-4%) reported overall negative feelings about donation.

We also investigated whether donors with worse outcomes in 1 physical domain also reported worse symptoms in other domains by reviewing the correlation among outcomes at 3 months and 2 years after donation (see Supporting Table 2). At 3 months after donation, the largest correlation between outcomes

TABLE 1. Physical Outcome Characteristics Over Time

Outcome	Before Donation (n = 253)	3 Months After Donation (n = 250)	6 Months After Donation (n = 241)	1 Year After Donation (n = 201)	2 Years After Donation (n = 139)	Cumulative Results: Endorsement at Any After Donation Time Point (n = 263)*
Primary outcomes						
FACIT-F†						
Raw scores (0 = high, 52 = low)	47.95 ± 4.20	43.31 ± 7.57	45.40 ± 7.41	45.82 ± 7.83	46.88 ± 5.96	—
PROMIS T-scores (30.3 = low fatigue to 83.5 = high fatigue, normative mean = 50, SD = 10)	40.25 ± 6.37	45.83 ± 7.90	43.00 ± 8.33	42.49 ± 8.33	41.26 ± 7.49	—
Clinically significant fatigue (>0.5 SD, >5 points above the PROMIS normative mean)	5 (2.0)	37 (14.8)	21 (8.8)	15 (7.5)	6 (4.3)	54 (20.5)
Level of abdominal or back pain‡						
Raw scores (0 = no pain, 10 = worst pain imaginable)	0.51 ± 1.27	1.20 ± 1.78	1.00 ± 1.72	0.86 ± 1.78	0.79 ± 1.63	—
Clinically significant pain (≥4)	11 (4.3)	32 (12.8)	20 (8.3)	20 (10.0)	11 (7.9)	56 (21.3)
BPI pain interference‡,§						
Raw scores (0 = low, 10 = high)	0.18 ± 0.67	0.49 ± 1.04	0.32 ± 0.92	0.41 ± 1.23	0.28 ± 0.80	—
Clinically significant interference (≥4)	2 (0.8)	4 (1.6)	3 (1.3)	8 (4.0)	1 (0.7)	14 (5.3)
Number of current physical symptoms attributed to donation (0 to 10)‡	—	4.59 ± 2.07	3.39 ± 2.12	2.96 ± 2.04	2.30 ± 2.08	—
SF-36 PCS Score						
Raw scores (US mean = 50, SD = 10, higher is better)‡,§	56.20 ± 3.88	48.19 ± 7.48	53.65 ± 6.31	55.03 ± 5.37	54.98 ± 4.38	—
Impaired (>0.5 SD, >5 points below mean)‡	7 (2.8)	72 (28.8)	28 (11.7)	10 (5.0)	7 (5.0)	88 (33.5)
Secondary outcomes						
Number of postdonation health-related worries (0-4)‡,‖	—	0.98 ± 1.25	0.90 ± 1.26	0.74 ± 1.18	0.68 ± 1.19	—
Unable to do some physical activities as well since donation¶	—	145 (58.2)	80 (33.5)	40 (19.9)	18 (12.9)	160 (60.8)
Still not physically back to normal‡	—	90 (36.0)	45 (18.8)	18 (9.0)	6 (4.3)	107 (40.7)
Recovered slower or much slower than expected#	—	87 (34.8)	66 (27.5)	58 (29.0)	35 (25.2)	109 (41.4)
Current donation-related medical problems‡	—	50 (20.0)	54 (22.5)	41 (20.4)	28 (20.1)	97 (36.9)
Donation was physically stressful**	—	120 (48.0)	109 (45.2)	100 (50.0)	60 (43.2)	164 (62.4)
Overall negative feelings about donation††	—	4 (1.6)	3 (1.3)	3 (1.5)	6 (4.3)	8 (3.0)

NOTE: Data are given as n (%) and mean ± SD. Sensitivity analyses among donors who completed all 5 surveys (n = 118) showed results similar to those who completed at least 1 survey (n = 271).

*This may be underestimated given that some respondents did not respond at all time points.

†Missing n = 2 at 6 months.

‡Missing n = 1 at 6 months.

§PCS was not modeled because it is not donation specific. BPI pain interference was not modeled due to high skewness even after transformation and few endorsements of clinical significant interference.

‖Health-related worries include worries about physical effects of donation, current health, future health, and never feeling 100% well again.

¶Missing n = 1 at 3 months and n = 2 at 6 months.

#Missing n = 1 at 6 months and n = 1 at 1 year.

**Missing n = 1 at 1 year.

††Missing n = 4 at 6 months.

TABLE 2. Predictors of Primary Physical Outcomes from Repeated Measures Linear Regression Models (n = 245)

	FACIT-F Scale (Scale of 30.3 = Low Fatigue to 83.5 = High Fatigue; PROMIS T Converted)[†]		Level of Abdominal/Back Pain (Scale of 0 = no pain to 10 = Pain as Bad as You Can Imagine)		Number of Current Physical Symptoms Attributed to Donation (0-10)	
Predictors[*]	Estimate (95% CI)	*P* Value	Estimate (95% CI)	*P* Value	Estimate (95% CI)	*P* Value
Postdonation time point		<0.001		0.010		<0.001
3 months versus 2 years	4.00 (2.80-5.20)	<0.001	0.41 (0.11-0.71)	0.007	2.25 (1.95-2.55)	<0.001
6 months versus 2 years	1.30 (0.10-2.50)	0.03	0.16 (-0.12-0.45)	0.27	1.03 (0.74-1.33)	<0.001
1 year versus 2 years	0.76 (–0.20-1.73)	0.12	0.01 (–0.30-0.32)	0.95	0.58 (0.28-0.89)	<0.001
Recipient death (time dependent)	3.62 (1.23-6.01)	0.003	0.68 (0.18-1.19)	0.008	1.04 (0.42-1.66)	0.001
Female versus male	2.23 (0.80-3.65)	0.002	0.29 (0.01-0.57)	0.04	0.68 (0.27-1.08)	0.001
Married or had longtime partner before donation	1.75 (0.28-3.21)	0.02				
Length of hospital stay (per day)	0.49 (0.12-0.86)	0.009			0.22 (0.12-0.32)	<0.001
Had postoperative complications during the first month after donation			0.73 (0.36-1.11)	<0.001		
Predonation predictors						
Level of abdominal/back pain at predonation (scale of 0 = no pain to 10 = pain as bad as you can imagine)	NA	NA	0.32 (0.20-0.44)	<0.001	NA	NA
FACIT-F scale at predonation (per 10-unit increase on a scale of 30.3 to 83.5; PROMIS T converted)	4.83 (3.69-5.98)	<0.001	NA	NA	NA	NA
MCS before donation (per 10-unit increase on a scale of 1 to 100)			–0.51 (–0.73 to –0.28)	<0.001	–0.64 (–0.95 to –0.34)	<0.001
PCS before donation (per 10-unit increase on a scale of 1 to 100)			–0.56 (–0.98 to –0.14)	0.009	–1.01 (–1.56 to –0.45)	<0.001
Black sheep donor	2.39 (0.79-3.99)	0.003				
Anyone discouraged donor to donate					0.45 (0.05-0.85)	0.03
If donated, I will feel my life is more worthwhile (scale of 1 = very unlikely to 10 = very likely)	0.30 (0.05-0.55)	0.02				
Household income (per US $10,000 increase)[‡]			–0.04 (–0.07 to –0.01)	0.009		

[*]Variables tested but not significant: donor's age at donation, race/ethnicity, education, BMI, rehospitalized within 30 days after donation, donor recipient relationship, Simmons psychosocial background (donation history), Simmons donation decision-making items (other possible donors, ambivalence scale, anyone encouraged donor to donate, and anticipated longterm health effects of donation), Simmons motivation for donating, Campbell global life satisfaction item, and PHQ-9.
[†]FACIT-F scores were converted to PROMIS T scores for modeling in order to reduce skewness of the distribution. The direction of FACIT-F score (higher score = lower fatigue) is flipped in the PROMIS T–converted score (higher score = higher fatigue).
[‡]In the level of abdominal/back pain model where household income was significant, adjusting for household size did not change results and household size was not statistically significant.

was between pain, as measured by the BPI, and level of abdominal/back pain (r = 0.71), with other intercorrelations more modest. A similar pattern was found at 2 years after donation (r = 0.68). Results from sensitivity analyses among donors who completed all 5 surveys (n = 118) showed similar results. Outcomes data for the donors who completed all surveys are included in Supporting Table 1.

PREDICTORS OF PHYSICAL OUTCOMES

Donors who were female, who were married or had a longterm partner before donation, who were hospitalized longer during the donation surgery, and whose recipient had died reported more fatigue. Predonation fatigue, history of family disapproval (black sheep

TABLE 3. Predictors of Secondary Physical Outcomes from Repeated Measures Logistic/Negative Binomial Regression Models (n = 245)

	Number of Health-Related Worries (Count of 0-4)		Unable to Do Some Physical Activities as Well Since Donation		Still Not Physically Back to Normal		Recovered Slower or Much Slower Than Expected (2 or Lower on a Scale of 1 - Much Slower Than Expected to 3 - as Expected to 5 - Much Faster)		Current Donation-Related Medical Problems		Donation Was Physically Stressful (2 or Lower on a Scale of 1 - Very Stressful to 4 - Not at All Stressful)	
Predictors*	Rate Ratio (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Postdonation time point		0.003		<0.001		<0.001		0.005		0.45		0.22
3 months versus 2 years	**1.31 (1.02-1.68)**	**0.04**	**11.05 (6.37-19.15)**	**<0.001**	**12.20 (5.41-27.47)**	**<0.001**	**1.76 (1.27-2.45)**	**<0.001**	0.84 (0.52-1.35)	0.48	**1.45 (0.95-2.20)**	**0.08**
6 months versus 2 years	**1.22 (0.96-1.56)**	**0.12**	**3.66 (2.09-6.40)**	**<0.001**	**4.96 (2.13-11.54)**	**<0.001**	**1.19 (0.86-1.64)**	**0.30**	**1.13 (0.73-1.75)**	**0.59**	**1.22 (0.83-1.78)**	**0.31**
1 year versus 2 years	0.90 (0.70-1.17)	0.47	**1.63 (0.97-2.73)**	**0.05**	**1.98 (0.85-4.63)**	**0.10**	**1.28 (0.94-1.75)**	**0.12**	0.94 (0.63-1.39)	0.75	**1.45 (0.97-2.17)**	**0.07**
Donor recipient relationship (reference = other biological or nonbiological relative)												0.01
First-degree relative											**2.30 (1.32-4.01)**	**0.003**
Spouse/partner											**4.60 (1.53-13.84)**	**0.02**
Unrelated											**1.75 (0.86-3.56)**	**0.12**
Recipient death (time-dependent)					**3.55 (1.88-6.68)**	**0.01**					**2.15 (1.05-4.40)**	**0.04**
Female versus male	**1.39 (1.03-1.87)**	**0.03**					**2.15 (1.28-3.60)**	**0.003**				
Age at donation (per 10-year increase)	0.81 (0.70-0.94)	0.004										
BMI at donation				0.05								
25.0-29.9 versus <24.9 kg/m^2			**1.82 (1.12-2.98)**	**0.017**								
≥30 versus <24.9 kg/m^2			**1.20 (0.62-2.32)**	**0.60**								
Length of hospital stay (per day)	**1.13 (1.07-1.20)**	**0.002**	**1.32 (1.15-1.52)**	**<0.001**	**1.63 (1.39-1.92)**	**<0.001**	**1.31 (1.10-1.55)**	**0.005**			**1.16 (1.01-1.32)**	**0.02**
Hospitalized during the first month after donation											**3.25 (1.34-7.90)**	**0.01**

TABLE 3. (Continued)

Predictors*	Number of Health-Related Worries (Count of 0-4)		Unable to Do Some Physical Activities as Well Since Donation		Still Not Physically Back to Normal		Recovered Slower or Much Slower Than Expected (2 or Lower on a Scale of 1 - Much Slower Than Expected to 3 - as Expected to 5 - Much Faster)		Current Donation-Related Medical Problems		Donation Was Physically Stressful (2 or Lower on a Scale of 1 - Very Stressful to 4 - Not at All Stressful)	
	Rate Ratio (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Had postoperative complications during the first month after donation									**2.33 (1.32-4.14)**	**0.01**		
Predonation predictors												
MCS before donation (per 10 increase on scale 1-100)	0.79 (0.67-0.93)	0.01			0.72 (0.54-0.95)	0.049					0.41 (0.27-0.60)	<0.001
Ambivalence to donate (scale of 0 - no ambivalence to 7 - ambivalence)	**1.17 (1.06-1.28)**	**0.003**									**1.23 (1.05-1.45)**	**0.01**
Anticipated longterm health effects from donation	**2.00 (1.48-2.70)**	**<0.001**									**2.03 (1.26-3.25)**	**0.004**
Black sheep donor			**1.73 (1.06-2.80)**	**0.03**								
Anyone discouraged donor to donate									**1.89 (1.17-3.05)**	**0.01**		
Household income (per $10,000 increase)†							**1.06 (1.00-1.12)**	**0.04**				

NOTE: Rate ratios or ORs of >1 are in bold.

*Variables tested but not significant: donor demographics (race/ethnicity, education, marital status), clinical characteristics (hospitalized within 1st month after donation, donation complications within 1st month), Simmons psychosocial background (donation history), Simmons donation decision-making items (other possible donors, anyone encouraged donor to donate, anticipated feeling life would be more worthwhile after donation), Simmons strength of motivation to donate, PHQ-9 depression score, and SF-36 PCS.

†In the level of abdominal/back pain model where household income was significant, adjusting for household size did not change results and household size was not statistically significant.

donor), and anticipation that life would be more worthwhile after donation were also associated with more fatigue (Table 2).

Female sex, recipient death prior to survey administration, postoperative complications in the first month after donation, and higher level of abdominal/back pain before donation were associated with higher levels of postdonation pain. In contrast, better predonation MCS and PCS (higher scores) and higher household income were associated with lower postdonation pain (Table 2).

Significant predictors of physical symptoms attributed to donation included recipient death, female sex, and longer hospital stay for donation surgery, whereas better predonation MCS and PCS were associated with fewer symptoms (Table 2). Donors discouraged to donate also had more physical symptoms attributed to donation on average.

Table 3 shows model results for secondary physical outcomes. Longer hospital stay for donation surgery was significantly associated with all secondary outcomes except for current donation-related medical problems. Donors with BMI of 25.0-29.9 kg/m^2 compared with those with BMI of ≤24.9 kg/m^2 and donors who were "black sheep" were more likely to report being unable to do some physical activities as well since donation. Donors whose recipients died were more likely to report being not physically back to normal, whereas donors with better MCS before donation were less likely to report this outcome. Additionally, female sex and higher household income were associated with higher odds of recovering slower than expected.

Predictors of other secondary outcomes including donation-related medical problems, number of health-related worries, and if donation was physically stressful are presented in Table 3.

Model results for both primary and secondary outcomes were unchanged when adjusting for transplant center, and the center effect was only significant in predicting 1 outcome: number of physical symptoms after donation (overall *P* value = 0.04). For this outcome, comparing all other centers to the 1 with the largest number of donors (n = 90), the differences in mean number of physical symptoms ranged from –0.60 to 0.74.

Discussion

We conducted a multicenter, prospective study of LLD clinical and perceived well-being to evaluate their perceptions of their physical outcomes and to determine predictors of key outcomes, such as fatigue, pain, and other unique physical symptoms over time. In our cohort, donors reported worsening fatigue immediately after surgery that approached predonation levels (2% impaired) by 2 years after donation, with 4%-15% of our cohort reporting impaired levels of fatigue after surgery. We observed a similar pattern using a broad measure of donor-reported physical well-being and more pointed questions about ability to perform physical activities, feeling physically back to normal, and recovering more slowly than expected. These findings support and extend findings from previous reviews of donor physical symptoms and well-being.[5,6] Although in some respect, these findings may seem intuitive or predictable, ours is 1 of the largest cohorts of LLDs to actually substantiate this clinical wisdom with data from a large, multisite cohort, using prospective assessments. Our findings suggest actionable steps that may benefit future LDLT outcomes.

We found relatively few donation-related health worries and quite low levels of negative feelings about donation. Abdominal or back pain was also rated relatively low, on average, at all study time points and donors reported low levels of interference, as measured by the BPI. Indeed, we have found that living donors who are further out from their donation—3-10 years after donation—experience clinically significant pain at levels similar to the general population.[26] Although these data are useful and reassuring for donor education, a sizable minority—up to 21% of donors—reported clinically significant pain at some point. These findings suggest somewhat lower pain in our cohort compared with other single-center reports on donor pain.[27] Nonetheless, our prior work in this area[28] suggests that there may still be benefit to adjusting pain control strategies to be more aligned with expert analgesic recommendations for postoperative pain. Identification and optimization of pain control earlier after donation may improve longterm pain outcomes for LLDs. Regarding other physical outcomes, it is worrisome that by 1 year following donation, 20% or more of donors still reported being unable to do some physical activities as well since donation, were recovering slower than expected, or felt they had donation-related medical problems. Interventions to improve these outcomes may be considered, but at the least, better predonation education about recovery is needed.

We modeled potential predictors of our primary and secondary outcomes to help identify donors who

may be at risk for poor perceptions of their donor experience. Notably, some factors, like incision type, showed lack of variability within center and were not included as covariates in modeling. However, our sensitivity analyses showed that outcomes were similar across centers and a previous report with a shorter follow-up found that pain perceptions were not impacted by laparoscopic versus open incision.[28] We identified some risk factors that cut across multiple outcomes, including female donors, those whose recipients died, donors with longer surgery hospital stays, and those whose families discouraged donation. Although these risk factors may not be easily modifiable, they do help to identify donors that may warrant more prophylactic care to help ensure optimal symptom management. Donors' health-related quality of life, as measured by the MCS and PCS summaries of the SF-36, also predicted many donor physical outcomes. This may be because both general and donation-specific outcomes were assessed by the same method (ie, self-report). However, our findings confirm associations found in smaller sample studies and in studies looking at the association of quality of life with donor medical comorbidities.[6]

We recognize that our study has several important limitations. First, we only studied adult-to-adult LDLTs from the United States and Canada. It would not be appropriate to generalize our findings to adult-to-child donors or to other geographical areas. Second, given our naturalistic, nonrandomized design, we cannot be certain that factors we identify as risks for specific outcomes were in fact causative factors. For example, we found that higher household income is associated with lower postdonation pain but also with slower recovery. It is possible that donors with higher incomes may have work that requires less physical exertion and at the same time may have higher expectations regarding their recoveries. However, strong inference of these individual findings warrants replication. We were also not able to model all physical symptoms assessed because of low levels of endorsement and data skewness, which may be in part due to only having 2-year data for half of our enrolled donors. However, this amount of missing data was likely at random, as most were administratively censored due to donors not reaching this time point by study completion. Although we did look at the impact of recipient death on donor pain, fatigue, and other physical outcomes, we did not assess the degree to which other nonfatal recipient outcomes, such as graft rejection or alcohol recidivism, impacted donor symptoms. Finally, although we have previously described the analgesic and other medication use in a short-term follow-up report, we did not collect comprehensive medication use for this entire donor sample.[28] Although we assessed or recorded many potential covariates, some variability in outcomes may be related to unmeasured factors. That said, our study has several strengths, including the large, multicenter, prospective design and the use of standardized patient-reported outcomes to describe the sample over time.

Although our data do provide reassurances for LDLT candidates, their families, and their health care providers about postdonation fatigue, pain, and other patient-centered physical outcomes, our report also highlights the potential for targeted, longterm follow-up of donors to help optimize these outcomes. Although it may not be the case that all LLDs and their families require longterm follow-up and education, our data suggest that we can identify donors at risk for physical symptoms that may benefit from more active surveillance and intervention. Some of this targeted follow-up may be symptom specific,[28] but there may also be promise in addressing predonation factors that may influence patients' postdonation physical symptoms.[29] There may also be value in adapting symptom control interventions used in other populations for use among LLDs.[30–32]

REFERENCES

1) Miyagi S, Kawagishi N, Fujimori K, Sekiguchi S, Fukumori T, Akamatsu Y, Satomi S. Risks of donation and quality of donors' life after living donor liver transplantation. Transpl Int 2005;18:47-51.
2) Abecassis MM, Fisher RA, Olthoff KM, Freise CE, Rodrigo DR, Samstein B, et al. Complications of living donor hepatic lobectomy--a comprehensive report. Am J Transplant 2012;12:1208-1217.
3) Quintini C, Hashimoto K, Uso TD, Miller C. Is there an advantage of living over deceased donation in liver transplantation? Transpl Int 2013;26:11-19.
4) Butt Z, Parikh ND, Skaro AI, Ladner D, Cella D. Quality of life, risk assessment, and safety research in liver transplantation: new frontiers in health services and outcomes research. Curr Opin Organ Transplant 2012;17:241-247.
5) Parikh ND, Ladner D, Abecassis M, Butt Z. Quality of life for donors after living donor liver transplantation: a review of the literature. Liver Transpl 2010;16:1352-1358.
6) Dew MA, Butt Z, Humar A, DiMartini AF. Long-term medical and psychosocial outcomes in living liver donors. Am J Transplant 2017;17:880-892.
7) Verbesey JE, Simpson MA, Pomposelli JJ, Richman E, Bracken AM, Garrigan K, et al. Living donor adult liver transplantation: a longitudinal study of the donor's quality of life. Am J Transplant 2005;5:2770-2777.

8) Chan SC, Liu CL, Lo CM, Lam BK, Lee EW, Fan ST. Donor quality of life before and after adult-to-adult right liver live donor liver transplantation. Liver Transpl 2006;12:1529-1536.
9) Hsu HT, Hwang SL, Lee PH, Chen SC. Impact of liver donation on quality of life and physical and psychological distress. Transplant Proc 2006;38:2102-2105.
10) Walter M, Bronner E, Pascher A, Steinmüller T, Neuhaus P, Klapp BF, Danzer G. Psychosocial outcome of living donors after living donor liver transplantation: a pilot study. Clin Transplant 2002;16:339-344.
11) DiMartini A, Dew MA, Liu Q, Simpson MA, Ladner DP, Smith AR, et al. Social and financial outcomes of living liver donation: A prospective investigation within the Adult-to-Adult Living Donor Liver Transplantation Cohort Study 2 (A2ALL-2). Am J Transplant 2017;17:1081-1096.
12) Butt Z, Dew MA, Liu Q, Simpson MA, Smith AR, Zee J, et al. Psychological outcomes of living liver donors from a multicenter prospective study: results from the Adult-to-Adult Living Donor Liver Transplantation Cohort Study 2 (A2ALL-2). Am J Transplant 2017;17:1267-1277.
13) Organ Procurement and Transplantation Network/United Network for Organ Sharing (OPTN/UNOS). OPTN Policies, Policy 14: Living donation. Updated 12/1/15. http://optn.transplant.hrsa.gov/governance/policies/. Accessed February 9, 2016.
14) Yellen SB, Cella DF, Webster K, Blendowski C, Kaplan E. Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system. JPain Symptom Manage 1997;13:63-74.
15) Cella D. The Functional Assessment of Cancer Therapy-Anemia (FACT-An) Scale: a new tool for the assessment of outcomes in cancer anemia and fatigue. Semin Hematol 1997;34(suppl 2):13-19.
16) Butt Z, Lai JS, Rao D, Heinemann AW, Bill A, Cella D. Measurement of fatigue in cancer, stroke, and HIV using the Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) scale. JPsychosom Res 2013;74:64-68.
17) Cella D, Eton DT, Lai JS, Peterman AH, Merkel DE. Combining anchor and distribution-based methods to derive minimal clinically important differences on the Functional Assessment of Cancer Therapy (FACT) anemia and fatigue scales. JPain Symptom Manage 2002;24:547-561.
18) Lai JS, Cella D, Yanez B, Stone A. Linking fatigue measures on a common reporting metric. JPain Symptom Manage 2014;48:639-648.
19) Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. Med Care 2003;41:582-592.
20) Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. Ann Acad Med Singapore 1994;23:129-138.
21) Jay CL, Butt Z, Ladner DP, Skaro AI, Abecassis MM. A review of quality of life instruments used in liver transplantation. JHepatol 2009;51:949-959.
22) Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. conceptual framework and item selection. Med Care 1992;30:473-483.
23) Simmons R, Simmons R, Marine SK. Gift of Life: The Effect of Organ Transplantation on Individual, Family, and Societal Dynamics. New Brunswick, NJ: Transaction Books; 1987.
24) Campbell A, Converse P, Rodgers N. The Quality of American Life: Perceptions, Evaluations, and Satisfactions. New York, NY: Russell Sage Foundation; 1976.
25) Harrell FE. Regression Modeling Strategies: With Applications to Linear Models, Logistic Regression, and Survival Analysis. Springer Series in Statistics. New York, NY: Springer; 2001.
26) Dew MA, Butt Z, Liu Q, Simpson MA, Zee J, Ladner DP, et al. Prevalence and predictors of patient-reported long-term mental and physical health after donation in the Adult-to-Adult Living Donor Liver Transplantation Cohort Study. Transplantation 2018;102:105-118.
27) Holtzman S, Clarke HA, McCluskey SA, Turcotte K, Grant D, Katz J. Acute and chronic postsurgical pain after living liver donation: incidence and predictors. Liver Transpl 2014;20: 1336-1346.
28) Mandell MS, Smith AR, Dew MA, Gordon DB, Holtzman S, Howell T, et al. Early postoperative pain and its predictors in the Adult to Adult Living Donor Liver Transplantation Cohort Study. Transplantation 2016;100:2362-2371.
29) Dew MA, DiMartini AF, DeVito Dabbs AJ, Zuckoff A, Tan HP, McNulty ML, et al. Preventive intervention for living donor psychosocial outcomes: feasibility and efficacy in a randomized controlled trial. Am J Transplant 2013;13:2672-2684.
30) Owen JE, O'Carroll Bantum E, Pagano IS, Stanton A. Randomized trial of a social networking intervention for cancer-related distress. Ann Behav Med 2017;51:661-672.
31) Rolving N, Nielsen CV, Christensen FB, Holm R, Bünger CE, Oestergaard LG. Does a preoperative cognitive-behavioral intervention affect disability, pain behavior, pain, and return to work the first year after lumbar spinal fusion surgery? Spine (Phila Pa 1976) 2015;40:593-600.
32) Hoffman AJ, Brintnall RA, Given BA, von Eye A, Jones LW, Brown JK. Using perceived self-efficacy to improve fatigue and fatigability in postsurgical lung cancer patients: a pilot randomized controlled trial. Cancer Nurs 2017;40:1-12.