Association of frailty with postoperative outcomes following thoracic transplantation: A national analysis

Shineui Kim, BA,[a] Sara Sakowitz, MS, MPH,[a] Joseph Hadaya, MD, PhD,[a,b] Joanna Curry, BA,[a] Nikhil L. Chervu, MS, MD,[a,b] Syed Shahyan Bakhtiyar, MD,[c] Saad Mallick, MD,[a] Nam Yong Cho, BS,[a] and Peyman Benharash, MD[a,b]

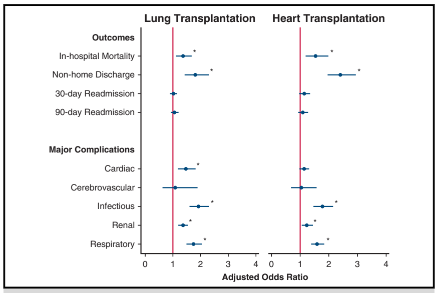
ABSTRACT

Objective: Frailty has been repeatedly associated with inferior outcomes after surgical hospitalizations. However, a thorough evaluation of the impact of frailty on the clinical and financial outcomes of patients undergoing solid-organ thoracic transplantation is sparse in the literature. We evaluated the association of frailty, as determined by an administrative tool, with postoperative outcomes and healthcare resource use after heart or lung transplantation.

Methods: The Nationwide Readmissions Database was used to identify all adult hospitalizations for heart or lung transplant from 2014 to 2020. Patients were grouped as frail or nonfrail using International Classification of Diseases codes associated with conditions in the Johns Hopkins Adjusted Clinical Groups cluster. Multivariable regression models were developed to evaluate the association of frailty status on in-hospital mortality, complications, length of stay, costs, and unplanned readmissions.

Results: Of an estimated 35,862 heart or lung transplant recipients, 7316 (20.4%) were considered frail. After multivariable adjustment, frailty in heart transplantation was associated with greater odds of in-hospital mortality (adjusted odds ratio, 1.54; 95% CI, 1.19-1.99) and infectious complications (adjusted odds ratio, 1.77; 95% CI, 1.45-2.15; $P < .001$). Frailty in lung transplantation was also associated with higher odds of in-hospital mortality (adjusted odds ratio, 1.38; 95% CI, 1.11-1.69) and infectious complications (adjusted odds ratio, 1.93; 95% CI, 1.60-2.31). In addition, frailty in both heart transplantation and lung transplantation was associated with increased postoperative length of stay and greater costs.

Conclusions: Among transplant recipients, those classified as frail were associated with increased in-hospital mortality, perioperative complications, and resource use. (JTCVS Open 2023;16:1038-48)



Frailty status is associated with inferior outcomes after HT and LT.

CENTRAL MESSAGE

Frailty is associated with inferior outcomes in HT and LT. The inclusion of a frailty indicator may optimize targeted resource allocation and intensive perioperative management.

PERSPECTIVE

Frailty, characterized by a decline in physiological reserve and resilience to stressors, has consistently demonstrated an association with poorer clinical outcomes across various surgical procedures. This study used a nationally representative cohort of HT and LT recipients, and identified frailty status to be associated with increased in-hospital mortality and complications.

Advancements in organ preservation, pretransplant and post-transplant care, and immunosuppression have established solid-organ transplantation as the definitive treatment modality for patients with end-stage organ failure.[1] Based on a comprehensive 25-year analysis, heart transplantation (HT) and lung transplantation (LT) were estimated to yield an average increase in life expectancy of 11 and 8.3 years per patient, respectively.[2,3] As the field of transplant

From the [a]Cardiovascular Outcomes Research Laboratories (CORELAB), David Geffen School of Medicine, and [b]Department of Surgery, David Geffen School of Medicine at UCLA, University of California Los Angeles, Los Angeles, Calif; and [c]Department of Surgery, University of Colorado Anschutz Medical Center, Aurora, Colo.

Read at the 49th Annual Meeting of the Western Thoracic Surgical Association, Coeur d'Alene, Idaho, June 21-24, 2023.

Received for publication June 19, 2023; revisions received Sept 11, 2023; accepted for publication Oct 10, 2023; available ahead of print Nov 16, 2023.

Address for reprints: Peyman Benharash, MD, UCLA Division of Cardiac Surgery, 62-249 Center for Health Sciences, Los Angeles, CA 90095 (E-mail: pbenharash@mednet.ucla.edu).

2666-2736

https://doi.org/10.1016/j.xjon.2023.10.011

Abbreviations and Acronyms

ACG	= Adjusted Clinical Group
AOR	= adjusted odds ratio
HT	= heart transplantation
ICD-9/10	= International Classification of Diseases, 9th and 10th Revisions
LOS	= length of stay
LT	= lung transplantation
NRD	= Nationwide Readmissions Database

medicine continues to expand, the concept of frailty assumes increasing significance, particularly given the potential impact of aging and immunosenescence on post-transplantation outcomes.[4]

Accurate assessment of preoperative risk has been increasingly used across surgical disciplines and is commonly used to inform shared-decision making and counsel patients regarding treatment options.[5] In the case of organ transplantation, such assessment may also inform waitlist management and prioritization.[6] Although factors including chronological age and comorbidities have traditionally been used to assess operative risk, frailty has recently garnered interest as a strong predictor of perioperative outcomes.[7] An exact definition lacking, frailty has been described as a decline in physiological function and reserve.[8] Studies encompassing a broad range of operations, including emergency general surgery and cardiothoracic surgery, have found a strong association between frailty and inferior clinical outcomes.[9] Among 537 kidney transplant recipients, McAdams-DeMarco and colleagues[10] found frailty to be associated with a 200% decrease in long-term survival.

Although single-institutional studies have explored the association of frailty with outcomes in thoracic transplantation, a nationally representative study may provide a comprehensive and contemporary analysis.[11-16] The present study used a nationally representative cohort to examine the association of frailty with in-hospital clinical and financial outcomes of HT and LT.

MATERIAL AND METHODS

This was a retrospective cohort study of the 2014-2020 Nationwide Readmissions Database (NRD). The NRD is the largest all-payer readmissions database and produces accurate estimates for approximately 60% of all hospitalization in the United States. By using hospital identifiers, patients can be tracked across admissions within each calendar in the NRD.[17] All adult (≥18 years) hospitalizations entailing HT or LT were identified using relevant International Classification of Diseases, 9th/10th Revision (ICD-9/10) procedural codes (Table E1). Patients who underwent both HT and LT were excluded (0.2%). Entries missing key data for sex, age, status of mortality, income, and payer were further excluded (1.5% for HT, 1.7% for LT, Figure 1).

Patients were classified into frail and nonfrail groups based on the previously validated Johns Hopkins Adjusted Clinical Groups (ACG) indicator.[18] Briefly, this binary indicator identifies frailty from administrative data using a cluster of diagnoses that include malnutrition, dementia, impaired vision, decubitus ulcer, incontinence, weight loss, falls, difficulty walking, lack of social support, and barriers to healthcare access. The ACG has been extensively used to study associations of frailty with outcomes after various surgical procedures (Table 1).[18]

Patient and hospital characteristics were defined according to the NRD Data Dictionary.[19] The Van Walraven modification of the Elixhauser Comorbidity Index was calculated to numerically capture the overall burden of chronic conditions.[20] Specific comorbidities were further ascertained using ICD-9/10 diagnosis codes.[21] Perioperative complications were categorized as cardiac (cardiac arrest, ventricular fibrillation, ventricular tachycardia, tamponade, and myocardial infarction), cerebrovascular (intracranial hemorrhage, acute ischemic complication, and stroke), infectious (sepsis and surgical site infection), renal (acute kidney injury and end-stage renal disease), and respiratory (pneumonia, acute respiratory distress syndrome, respiratory failure, pneumothorax, and prolonged ventilation).[21] Transplant-related complications such as graft failure and rejection were not included in this study because related ICD diagnosis codes were found to be inaccurate.[22] Hospitalization costs were calculated by applying center-specific cost-to-charge ratios to overall index hospitalization charges and then adjusted for inflation to 2020 using the Personal Health Index.[23]

The primary outcome of interest was in-hospital mortality. Secondary outcomes included perioperative complications, postoperative length of stay (LOS), index hospitalization costs, and unplanned readmissions within 30 and 90 days of initial discharge.

Continuous variables are presented as means with SD if normally distributed or medians with interquartile range if non-normally distributed. Categorical variables are reported as percentages. The adjusted Wald, Mann–Whitney *U*, and Pearson's chi-square tests were used for comparisons of 2 groups, as appropriate. Cuzick's nonparametric rank-based test was used to evaluate the significance of temporal trends (*nptrend*).[24] Covariate selection for regression models was guided by Elastic net regularization. This technique minimizes collinearity and enhances generalizability by applying a penalized least-squares algorithm.[25] The selected covariates identified through Elastic net regularization were further used in entropy balancing to account for intergroup differences. Unlike propensity score matching, entropy balancing creates sample weights to meet predetermined balance criteria while preserving the entire study population for analysis.[26-28] After entropy balancing, multivariable logistic and linear regression models were developed to assess the independent associations between frailty and selected outcomes. Models were evaluated using receiver operating characteristics curves and calibration plots. Regression outputs are reported as adjusted odds ratios (AORs) or beta coefficients (β) with 95% CI. Statistical significance was set at an alpha of 0.05.

All statistical analyses were performed using Stata 16.1 (StataCorp LLC). This study was considered exempt from full review by the Institutional Review Board at the University of California, Los Angeles.

RESULTS

Throughout the study period, the proportion of frail patients who underwent HT increased from 10.1% (n = 237) in 2014 to 17.4% (n = 609) in 2020 (*nptrend* < .001; Figure 2). Likewise, the proportion of frail patients who underwent LT increased from 13.9% (n = 228) in 2014 to 30.0% (n = 739) in 2020 (*nptrend* < .001). For both HT and LT, the proportion of frail patients with malnutrition decreased while those with dementia has increased significant (*nptrend* = .02; Table E2).

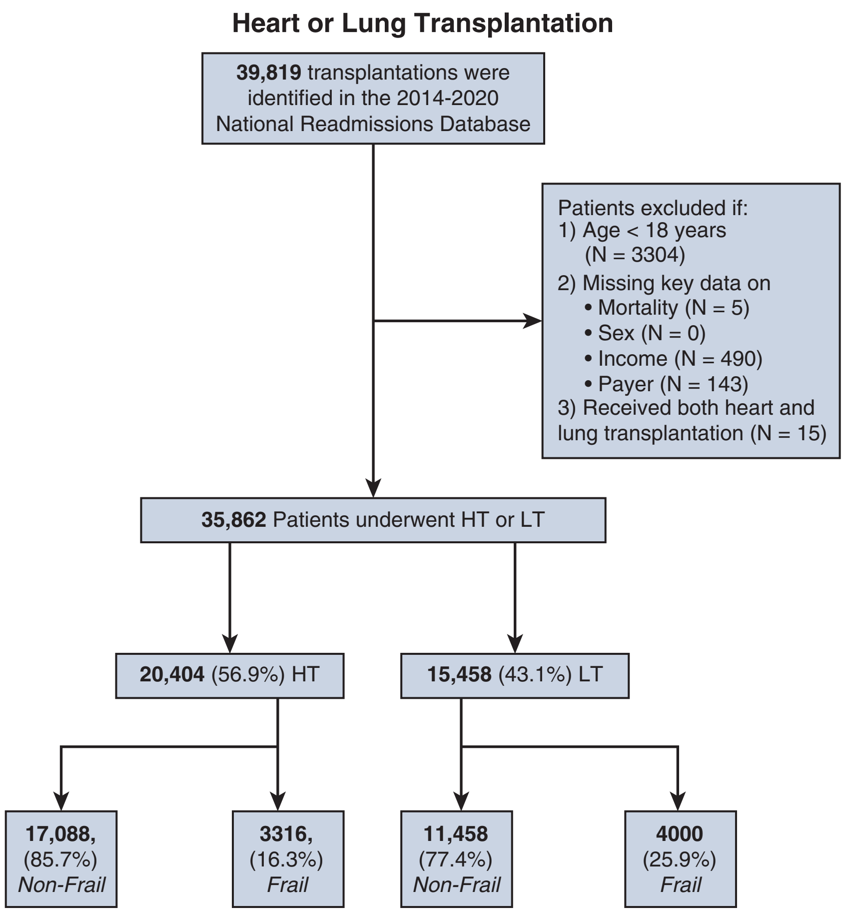


FIGURE 1. Study flowchart of survey-weighted estimates. Of 20,404 HTs and 15,458 LTs identified in the 2014-2020 NRD, 3316 patients (16.3%) and 4000 patients (25.9%) were considered frail, respectively. All estimates represent survey-weighted methodology. *HT*, Heart transplantation; *LT*, lung transplantation.

Of an estimated 20,404 patients undergoing HT, 3316 (16.3%) were considered frail. Frail HT recipients were on average older (58 [48-64] years vs 56 years [46-63], $P = .004$), of similar sex distribution (26.5% vs 26.7% female, $P = .85$), and had a greater burden of chronic medical conditions, as defined by the Elixhauser Comorbidity Index (5 [4-6] vs 5 [4-6], $P < .001$; Table 2). Frail patients more frequently presented with dialysis dependence (10.2% vs 5.7%, $P < .001$), liver disease (16.1% vs 9.9%, $P < .001$), and weight loss (73.5% vs 5.6%, $P < .001$) compared with nonfrail patients.

TABLE 1. Johns Hopkins Adjusted Clinical Groups frailty-defining diagnosis clusters

Cluster	Percentage of frail cohort, %	
	Lung	Heart
Malnutrition or catabolic illness	68.3	62.8
Dementia	21.9	23.7
Severe vision impairment	0.2	0.2
Decubitus ulcer	5.0	8.9
Incontinence of urine	0	0
Weight loss	2.6	1.8
Fecal incontinence	0.3	0.2
Social support needs	0.1	0.1
Difficulty walking	1.5	2.2
Fall	0	0.2

Of an estimated 15,458 patients undergoing LT, 4000 (25.9%) were considered frail. Frail LT recipients were on average younger (59 [45-65] years vs 61 years [53-66], $P < .001$), were more commonly female (43.8% vs 39.7% female, $P = .006$), and had a higher median Elixhauser Comorbidity Index (4 [3-5] vs 3 [2-4], $P < .001$; Table 2). Frail patients demonstrated comparable rates of liver disease (6.0% vs 5.0%, $P = .10$) and coagulopathy (31.9% vs 29.5%, $P = .08$), but more often faced dialysis dependence (2.8% vs 1.0%, $P < .001$) and weight loss (80.8% vs 10.5%, $P < .001$) compared with nonfrail patients. Of note, frail patients less frequently underwent single LT (23.5% vs 35.1%, $P < .001$) compared with nonfrail patients.

TABLE 2. Comparison of baseline patient and hospital characteristics between nonfrail and frail patients

Characteristics	Lung transplantation			Heart transplantation		
	Nonfrail (N = 11,458)	Frail (N = 4000)	P value	Nonfrail (N = 17,088)	Frail (N = 3316)	P value
Age (y, median, IQR)	61 [53-66]	59 [45-65]	<.001*	56 [46-63]	58 [48-64]	.004*
Female (%)	4548 (39.7)	1753 (43.8)	.006*	4568 (26.7)	879 (26.5)	.85
Elixhauser score (median, IQR)	3 [2-4]	4 [3-5]	<.001*	5 [4-6]	5 [4-6]	<.001*
Income quartile (%)			.16			.57
0-25th	2199 (19.2)	844 (21.1)		3978 (23.3)	714 (21.5)	
26th-50th	2903 (25.3)	906 (22.6)		4516 (26.4)	887 (26.7)	
51st-75th	3155 (27.5)	1074 (26.9)		4378 (25.6)	883 (26.6)	
76th-100th	3201 (27.9)	1176 (29.4)		4216 (24.7)	833 (25.1)	
Primary payer (%)			.03*			.31
Private	5153 (45.0)	1716 (42.9)		7507 (43.9)	1445 (43.6)	
Medicare	5051 (44.1)	1793 (44.8)		6473 (37.9)	1333 (40.2)	
Medicaid	632 (5.5)	315 (7.9)		2023 (11.8)	358 (10.8)	
Other payer	621 (5.4)	177 (4.4)		1085 (6.4)	180 (5.4)	
Single LT (%)	4017 (35.1)	941 (23.5)	<.001*			
Comorbidities (%)						
Anemia	255 (2.2)	90 (2.3)	.94	601 (3.5)	66 (2.0)	.002*
Cerebrovascular disease	756 (6.6)	469 (11.7)	<.001*	1362 (8.0)	485 (14.6)	<.001*
Coagulopathy	3377 (29.5)	1277 (31.9)	.08	6740 (39.4)	1184 (35.7)	.01*
Diabetes	1429 (12.5)	310 (7.8)	<.001*	3457 (20.2)	435 (13.1)	<.001*
Dialysis dependence	113 (1.0)	111 (2.8)	<.001*	968 (5.7)	339 (10.2)	<.001*
Hypothyroidism	799 (7.0)	180 (4.5)	<.001*	1192 (7.0)	136 (4.1)	<.001*
Liver disease	575 (5.0)	241 (6.0)	.10	1691 (9.9)	534 (16.1)	<.001*
Obesity	695 (6.1)	117 (2.9)	<.001*	980 (5.7)	73 (2.2)	<.001*
Peripheral vascular disorders	345 (3.0)	98 (2.5)	.28	4533 (26.5)	711 (21.4)	<.001*
Pulmonary circulation disorders	3998 (34.9)	1073 (26.8)	<.001*	3535 (20.7)	436 (13.1)	<.001*
Weight loss	1198 (10.5)	3232 (80.8)	<.001*	961 (5.6)	2437 (73.5)	<.001*

IQR, Interquartile range; *LT*, lung transplant. *$P < .05$.

Compared with nonfrail recipients, frail HT recipients faced greater unadjusted rates of in-hospital mortality (9.8% vs 4.6%, $P < .001$; Table 3), as well as infectious (8.1% vs 6.4%, $P = .04$), renal (65.3% vs 58.0%, $P < .001$), and respiratory complications (39.1% vs 28.2%, $P < .001$). The frail cohort also demonstrated greater duration of postoperative hospitalization (23 [15-42] days vs 15 days [11-22], $P < .001$) and increased median hospitalization costs ($268,000 [171,000-446,000] vs 181,000 [126,000-279,000], $P < .001$). The frail and nonfrail cohorts experienced similar rates of 90-day (23.4% vs 21.7%, $P = .14$) nonelective readmissions.

After risk adjustment, frailty in HT remained independently associated with greater odds of in-hospital mortality (AOR, 1.54; 95% CI, 1.19-1.99, $P = .001$). Further, frailty was linked with greater odds of infectious (AOR, 1.77; 95% CI, 1.46-2.15, $P < .001$), renal (AOR, 1.23; 95% CI, 1.05-1.45, $P = .01$), and respiratory complications (AOR, 1.59; 95% CI, 1.38-1.84, $P < .001$; Figure 3). In addition, the frail cohort demonstrated a 13-day increase in LOS (95% CI, 10.9-15.2 days, $P < .001$) and an $86,000 incremental increase in per-patient expenditures (95% CI, 69,000-105,000, $P < .001$). Frailty in HT was associated with more than a 2-fold increase in odds of nonhome discharge (AOR, 2.40; 95% CI, 1.96-2.95, $P < .001$). Odds of 30- and 90-day nonelective readmissions were similar between groups (Figure 3). Risk-adjusted predictors of increase in postoperative length of stay and nonhome discharge are shown in supplementary tables (Tables E3 and E4).

Among those who underwent LT, the frail cohort exhibited greater unadjusted rates of mortality (6.1% vs 4.3%, $P = .004$) as well as cardiac (9.1% vs 6.2%, $P < .001$), infectious (18.1% vs 8.5%, $P < .01$), renal (44.3% vs 34.1%, $P < .001$), and respiratory complications (50.9% vs 38.3%, $P < .001$; Table 3). The frail cohort also exhibited longer postoperative LOS (26 [16-47] days vs 16 days [11-26], $P < .001$) and higher median hospitalization costs ($231,000 [$156,000-$379,000] vs $159,000 [$118,000-$235,000], $P < .001$). Frail and nonfrail patients had similar rates of 30 (24.1% vs 23.0%, $P = .31$) and 90-day (30.7% vs 29.2%, $P = .22$) nonelective readmission.

After risk adjustment, frailty in LT remained associated with greater odds of in-hospital mortality (AOR, 1.38;

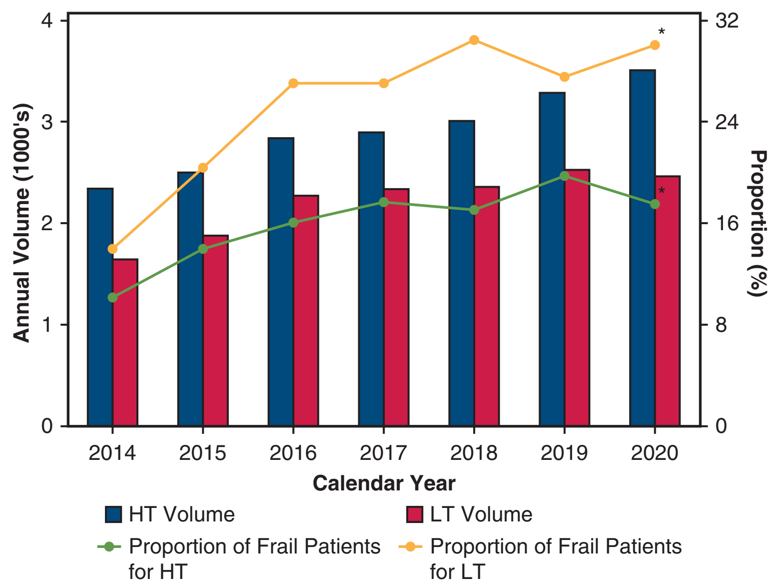


FIGURE 2. National trends in proportion of frail patients who received LT and HT from 2014 to 2020. The proportion of frail patients undergoing thoracic transplantation significantly increased across the time period. *HT*, Heart transplantation; *LT*, lung transplantation. **nptrend* < .001.

95% CI, 1.11-1.69, $P = .004$). Frailty was further associated with greater odds of cardiac (AOR, 1.47; 95% CI, 1.18-1.83, $P = .001$), infectious (AOR, 1.93; 95% CI, 1.60-2.31, $P < .001$), renal (AOR, 1.36; 95% CI, 1.19-1.55, $P < .001$), and respiratory complications (AOR, 1.75; 95% CI, 1.49-2.05, $P < .001$; Figure 3). In addition, frailty was linked with a 14-day increase in LOS (95% CI, 10.9-15.2, $P < .001$) and a $79,000 increase in risk-adjusted costs (95% CI, 59,000-99,000, $P < .001$), but similar odds of 30-day and 90-day nonelective readmissions (Figure 3).

DISCUSSION

In the present nationally representative study, we examined the association of frailty with several clinical and financial end points after thoracic transplantation. The proportion of transplant recipients identified as frailty through at least one frailty domain increased significantly over the study period, reaching approximately 17% and 30% of HT and LT recipients, respectively. After adjusting for patient and hospital characteristics, frailty remained associated with increased odds of mortality and perioperative complications. Frailty was associated with greater postoperative LOS and hospitalization costs but did not alter the odds of unplanned readmissions. Although several dated single-institution studies have previously considered frailty in HT and LT,[11-16] the present work provides a comprehensive and contemporary analysis of acute clinical and financial outcomes. With implications for more accurate risk stratification and shared decision-making, our findings merit further discussion.

In the present work, we found an association between frailty and greater in-hospital mortality after HT and LT. In a single institution study of 100 LT recipients, Montgomery and colleagues[29] found frailty, evaluating using physical features, to be associated with increased odds of 1-year mortality. Throughout analysis solely evaluating in-hospital outcomes, frailty likely has an effect on mid- and long-term outcomes. Consistent with this notion, in a prospective cohort study of 386 LT recipients, frailty, defined using physical features, was associated with a with a 10-fold increase in risk of mortality within the first year after transplantation.[11] Likewise, among 140 HT recipients, frailty was associated with mortality not just at 1 month but also at 12 months post-transplantation.[12] On the other hand, Singer and colleagues[11] reported frail and nonfrail patients face similar survival beyond the first post-transplantation year. The present analysis builds on the literature by using a large, nationally representative cohort and a readily available frailty tool to evaluate the impact of frailty on thoracic transplantation. Our data suggest that frail patients face greater mortality even during the transplantation hospitalization. Although it might be tempting to consider deprioritizing frail patients for transplantation, the central question should revolve around how to support and optimize their candidacy. Recent studies suggest that certain elements commonly associated with frailty are modifiable, such as malnutrition, sarcopenia, and chronic deconditioning.[13] Such efforts have been commonly used in thoracic transplantation and may consist of preoperative rehabilitation and participation in nutrition programs, among others.[14] Particularly for frail patients undergoing thoracic transplantation, prehabilitation interventions may improve muscle strength, endurance, and overall physical function, potentially mitigating the severity of frailty. Addressing malnutrition through dietary

TABLE 3. Unadjusted and risk-adjusted clinical outcomes and resource use stratified by frailty

Outcomes	Lung transplantation					
	Unadjusted			Risk adjusted		
	Nonfrail	Frail	*P* value	Frail	95% CI	*P* value
Clinical outcomes	(%)	(%)		(AOR/β)		
In-hospital mortality	4.3	6.1	.004*	1.38	1.11-1.69	.004*
Major complications						
Cardiac	6.2	9.1	<.001*	1.47	1.18-1.83	.001*
Cerebrovascular	1.4	2.0	.13	1.09	0.62-1.90	.77
Infectious	8.5	18.1	<.001*	1.93	1.60-2.31	<.001*
Renal	34.1	44.3	<.001*	1.36	1.19-1.55	<.001*
Respiratory	38.3	50.9	<.001*	1.75	1.49-2.05	<.001*
Resource use						
Length of stay (d, median [IQR])	16 [11-26]	26 [16-47]	<.001*	13.7	11.4-16.1	<.001*
Costs (USD $1000, median [IQR])	159 [118-235]	231 [156-379]	<.001*	79.2	59.2-99.2	<.001*
Nonhome discharge	8.7	16.1	<.001*	1.81	1.42-2.32	<.001*
30-d nonelective readmission	23.0	24.1	.31	1.02	0.89-1.17	.79
90-d nonelective readmission	29.2	30.7	.22	1.06	0.92-1.21	.42
	Heart transplantation					
	Unadjusted			Risk adjusted		
	Nonfrail	Frail	*P* value	Frail	95% CI	*P* value
Clinical outcomes	(%)	(%)		(AOR/β)		
In-hospital mortality	4.6	9.8	<.001*	1.54	1.19-1.99	.001*
Major complications						
Cardiac	39.0	40.1	.45	1.14	0.98-1.32	.09
Cerebrovascular	2.1	2.6	.33	1.04	0.68-1.58	.86
Infectious	6.4	8.1	.04*	1.77	1.46-2.15	<.001*
Renal	58.0	65.3	<.001*	1.23	1.05-1.45	.01*
Respiratory	28.2	39.1	<.001*	1.59	1.38-1.84	<.001*
Resource use						
Length of stay (d, median [IQR])	15 [11-22]	23 [15-42]	<.001*	13.0	10.9-15.2	<.001*
Costs (USD $1000, median [IQR])	181 [126-279]	268 [171-446]	<.001*	86.3	67.7-104.9	<.001*
Nonhome discharge	9.1	24.5	<.001*	2.40	1.96-2.95	<.001*
30-d nonelective readmission	15.9	18.6	.01*	1.14	0.97-1.35	.12
90-d nonelective readmission	21.7	23.4	.14	1.09	0.93-1.28	.26

CI, Confidence interval; *AOR*, adjusted odds ratio; β, beta coefficient; *IQR*, interquartile range. *$P < .05$.

interventions can also ameliorate patient's nutritional status and optimize their preoperative condition.[13] Although preoperative measures may influence elements of physical strength, undergoing HT or LT may also improve physical strength and functional status. For example, Rozenberg and colleagues[15] found frail candidates to demonstrate significant improvements in both physical strength and quality of life within just 6 months after transplantation. Therefore, there is a pressing need for novel interventions aimed at optimizing this cohort of patients for transplantation process. Ultimately, programs that seek to enhance patient function and both prevent and ameliorate sequelae in the peritransplantation period hold the potential to prolong survival among these patients.

In our analysis, we found frailty to be associated with greater odds of perioperative complications, with an approximately 2-fold increase in odds of infection. Frailty is commonly associated with a chronic, gradual immune dysfunction,[16] wherein patients experience a low-grade proinflammatory state, characterized by elevated levels of interleukin-6, tissue necrosis factor alpha, and C-reactive protein, among other inflammatory markers.[30] Neutrophil chemotactic activity is thought to be particularly impaired, leading to reduced defense against bacterial infections.[30] Likewise, a recent work by Singer and colleagues[31] demonstrated frailty, as measured by the short physical performance battery, to be associated with chronic lung allograft dysfunction after LT. Such inflammatory factors may render frail patients more susceptible to posttransplant infections, given their weakened immune response.[32] Further, frail patients frequently exhibit sarcopenia, generalized weakness, and slow gait.[13] For example, in an Australian study of 395 LT candidates, frailty was associated with decreased 6-minute walk distance.[33] These

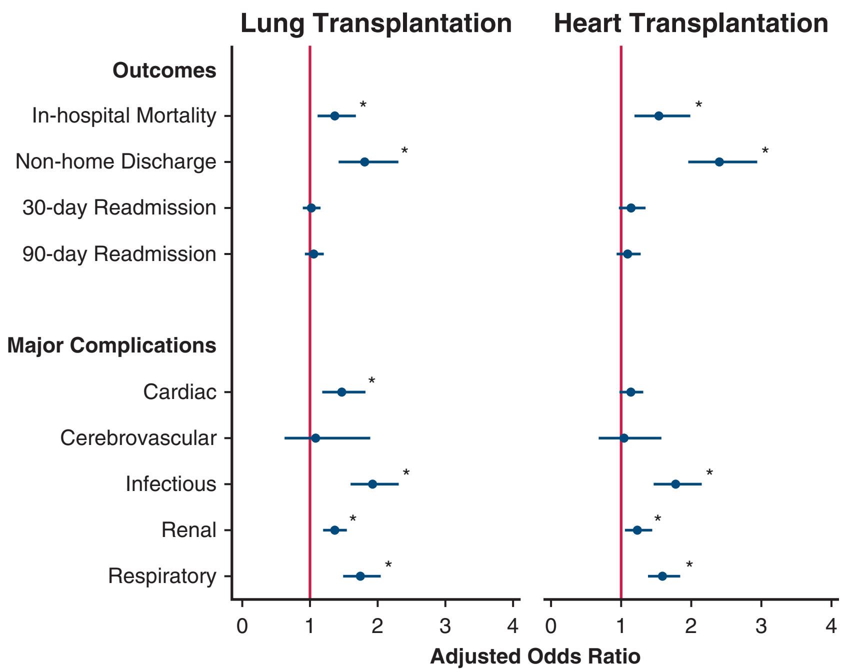


FIGURE 3. Association of frailty status on risk-adjusted outcomes. After risk adjustment, patients considered frail faced greater odds of in-hospital mortality, perioperative complications, and nonhome discharge. Reference: nonfrailty status. *Error bars* represent 95% CIs. $^*P < .01$.

physical aspects may yield reduced mobility in the immediate post-transplant period, leading to postoperative atelectasis, respiratory congestion, and prolonged recovery. Inadequate mobilization of secretions due to sarcopenia, chronic fatigue, and deconditioning may increase the likelihood for development of pneumonia. Such factors may lead to aspiration and ineffective aeration of lungs, and may increase the probability of acute respiratory distress syndrome, as seen in our analysis study. Finally, frailty has been associated with impaired hemodynamic function and fluid balance, contributing to chronic dehydration and greater predisposition to AKI.[34] Of note, incidence of AKI among frail patients has been independently linked with greater short-term mortality.[34] Therefore, implementation of targeted strategies to prevent post-transplant AKI incidence among this complex population may be particularly relevant for future study.

Lastly, we found transplant recipient frailty to be linked with longer postoperative LOS, as well as increased hospitalization costs and likelihood of nonhome discharge. This finding is in disagreement with 2 single-institution studies of 50 and 144 LT recipients, respectively, which reported similar LOS irrespective of frailty status.[15,33] However, these studies relied on exclusively physical measures of frailty and may have been underpowered to detect a significant effect. Moreover, the present work relies on administrative data and coding of various comorbidities to deduce the presence of frailty. Nonetheless, mechanistic studies to better delineate the role of frailty in transplantation are needed to develop directed interventions for this group. Moreover, we noted an approximately 2-fold increase in the likelihood of nonhome discharge in the presence of frailty. Nonhome discharge has been linked with increased risk for unplanned readmissions and greater long-term hospitalization costs after several operations.[35] The incorporation of frailty in pretransplant risk assessment, prehabilitation when feasible, and development of home-health programs for frail patients may help reduce rates of nonhome discharge. Of note, we found a similar likelihood of nonelective readmission among frail patients, relative to others. This observation can be due to several factors, including the notion that patients considered frail may undergo rehabilitation programs after successful transplantation, potentially improving physical health and decreasing the readmission risk.[14] Additionally, the transplantation process itself has been found to enhance physical strength and functional status, as supported by Rozenberg and colleagues,[15] who found frail candidates demonstrated significant improvements shortly after transplantation. These findings emphasize that frail patients who survive the immediate transplantation hospitalization may perform similarly with regard to postdischarge care relative to their nonfrail counterparts. Ultimately, given the increasing prevalence of frailty, novel approaches are needed to reduce the growing resource use burden and develop specific and informed care pathways for frail patients undergoing transplantation.

Study Limitations

Our study has several important limitations. Because of its administrative nature, the NRD lacks access to laboratory and imaging studies, as well as the recipient's

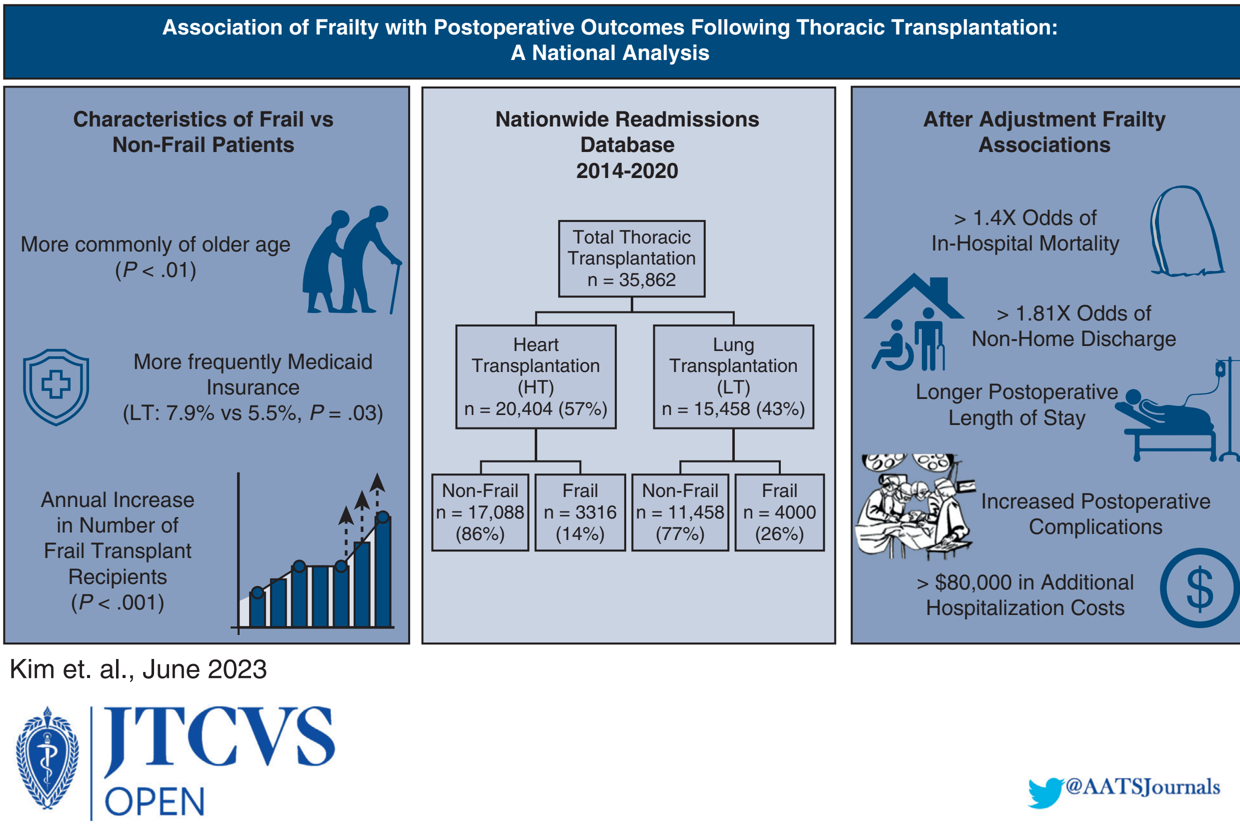


FIGURE 4. Frailty status is associated with inferior clinical and financial outcomes after HT and LT. Frail transplant recipients faced greater odds of in-hospital mortality, perioperative complications, and nonhome discharge. Patients considered frail also incur greater hospitalization costs and LOS compared with nonfrail patients.

transplant status and waiting times before the transplantation. It is important to recognize that there is a significant overlap between the concepts of frailty and comorbidity. A crucial distinction is that frailty encompasses a patient's overall physiological reserve, whereas comorbidity represents a specific medical condition. In addition, characteristics of donors were not available for study and could not be compared across frail and nonfrail groups. Although the frailty indicator we used has been extensively validated across numerous contexts, other clinical markers of frailty such as hypoalbuminemia or sarcopenia could not be assessed and warrant further study. The diagnosis of dementia used in the present study encompasses a broad spectrum of cognitive dysfunction, but the NRD lacks granular end points to assess the degree of cognitive dysfunction associated with dementia. Further, the NRD does not provide fine-grained details about the specific destination of nonhome discharge, such as whether the patients were transferred to a skilled nursing facility, rehabilitation center, or hospice. The binary nature of the Johns Hopkins ACG indicator limits the ability to analyze frailty on a continuum, which could have provided a more insightful analysis of patient outcomes. Nonetheless, the Johns Hopkins indicator has been externally validated in conjunction with the Vulnerable Elderly Scale and encompasses a multifaceted approach to defining frailty.[18] Last, our study was limited to short-term outcomes and could not consider long-term survival because the NRD only tracks admissions within each calendar year. However, single-center studies have indicated the greatest impact of frailty may occur in the immediate post-transplant period. Nonetheless, we used a large, nationally representative database to consider the impact of frailty on acute outcomes among the largest cohort of thoracic transplant recipients to date.

CONCLUSIONS

The present work offers the first national perspective of the impact of frailty on short-term outcomes after thoracic transplantation (Figure 4). We found frailty to be increasing in prevalence among patients undergoing HT and LT. Frailty remained associated with greater mortality, complications, and resource use after adjustment for age and comorbid conditions. This study underscores the significance of incorporating frailty into risk stratification models and candidate selection to benefit shared decision-making among clinicians, patients, and their families. Additional work is needed to develop interventions to prevent and treat complications among frail patients. Further, future studies should consider novel approaches to modify frailty in the pretransplantation process to better optimize patients for potentially lifesaving transplantation.

Conflict of Interest Statement

P.B. received fees from AtriCure as a surgical proctor. This manuscript does not discuss any related products or services. All other authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

References

1. Rana A, Gruessner A, Agopian VG, Khalpey Z, Riaz IB, Kaplan B, et al. Survival benefit of solid-organ transplant in the United States. *JAMA Surg*. 2015;150:252-9. https://doi.org/10.1001/jamasurg.2014.2038
2. Global Burden of Cardiovascular Diseases Collaboration, Roth GA, Johnson CO, Abate KH, Abd-Allah F, Ahmed M, et al. The burden of cardiovascular diseases among US states, 1990-2016. *JAMA Cardiol*. 2018;3:375-89. https://doi.org/10.1001/jamacardio.2018.0385
3. ISHLT. The International Society for Heart & Lung Transplantation–CME information. Accessed June 17, 2023. https://ishlt.org/ishlt2023/2023-annual-meeting-and-scientific-sessions/scientific-program/cme-information?viewmode=0
4. Schaenman JM, Diamond JM, Greenland JR, Gries C, Kennedy CC, Parulekar AD, et al. Frailty and aging-associated syndromes in lung transplant candidates and recipients. *Am J Transplant*. 2021;21:2018-24. https://doi.org/10.1111/ajt.16439
5. Schulze PC, Jiang J, Yang J, Cheema FH, Schaeffle K, Kato TS, et al. Preoperative assessment of high-risk candidates to predict survival after heart transplantation. *Circ Heart Fail*. 2013;6:527-34. https://doi.org/10.1161/CIRCHEARTFAILURE.112.000092
6. Tabriziani H, Baron P, Abudayyeh I, Lipkowitz M. Cardiac risk assessment for end-stage renal disease patients on the renal transplant waiting list. *Clin Kidney J*. 2019;12:576-85. https://doi.org/10.1093/ckj/sfz039
7. Makary MA, Segev DL, Pronovost PJ, Syin D, Bandeen-Roche K, Patel P, et al. Frailty as a predictor of surgical outcomes in older patients. *J Am Coll Surg*. 2010;210:901-8. https://doi.org/10.1016/j.jamcollsurg.2010.01.028
8. Fried LP, Cohen AA, Xue QL, Walston J, Bandeen-Roche K, Varadhan R. The physical frailty syndrome as a transition from homeostatic symphony to cacophony. *Nat Aging*. 2021;1:36-46. https://doi.org/10.1038/s43587-020-00017-z
9. Dobaria V, Hadaya J, Sanaiha Y, Aguayo E, Sareh S, Benharash P. The pragmatic impact of frailty on outcomes of coronary artery bypass grafting. *Ann Thorac Surg*. 2021;112:108-15. https://doi.org/10.1016/j.athoracsur.2020.08.028
10. McAdams-DeMarco MA, Law A, King E, Orandi B, Salter M, Gupta N, et al. Frailty and mortality in kidney transplant recipients. *Am J Transplant*. 2015;15:149-54. https://doi.org/10.1111/ajt.12992
11. Singer JP, Diamond JM, Anderson MR, Katz PP, Covinsky K, Oyster M, et al. Frailty phenotypes and mortality after lung transplantation: a prospective cohort study. *Am J Transplant*. 2018;18:1995-2004. https://doi.org/10.1111/ajt.14873
12. Macdonald PS, Gorrie N, Brennan X, Aili SR, De Silva R, Jha SR, et al. The impact of frailty on mortality after heart transplantation. *J Heart Lung Transplant*. 2021;40:87-94. https://doi.org/10.1016/j.healun.2020.11.007
13. Sanchez-Lorente D, Navarro-Ripoll R, Guzman R, Moises J, Gimeno E, Boada M, et al. Prehabilitation in thoracic surgery. *J Thorac Dis*. 2018;10(Suppl 22):S2593-600. https://doi.org/10.21037/jtd.2018.08.18
14. Varughese R, Rozenberg D, Singer LG. An update on frailty in lung transplantation. *Curr Opin Organ Transplant*. 2020;25:274. https://doi.org/10.1097/MOT.0000000000000762
15. Rozenberg D, Mathur S, Wickerson L, Chowdhury NA, Singer LG. Frailty and clinical benefits with lung transplantation. *J Heart Lung Transplant*. 2018;37:1245-53. https://doi.org/10.1016/j.healun.2018.06.005
16. Shaw AC, Joshi S, Greenwood H, Panda A, Lord JM. Aging of the innate immune system. *Curr Opin Immunol*. 2010;22:507-13. https://doi.org/10.1016/j.coi.2010.05.003
17. NRD overview. Accessed May 13, 2023. https://hcup-us.ahrq.gov/nrdoverview.jsp
18. Sternberg SA, Bentur N, Abrams C, Spalter T, Karpati T, Lemberger J, et al. Identifying frail older people using predictive modeling. *Am J Manag Care*. 2012;18:e392-7.
19. NRD description of data elements. Accessed May 10, 2023. https://hcup-us.ahrq.gov/db/nation/nrd/nrdddde.jsp
20. van Walraven C, Austin PC, Jennings A, Quan H, Forster AJ. A modification of the Elixhauser comorbidity measures into a point system for hospital death using administrative data. *Med Care*. 2009;47:626-33.
21. Madrigal J, Tran Z, Hadaya J, Sanaiha Y, Benharash P. Impact of chronic lymphocytic leukemia on outcomes and readmissions after cardiac operations. *Ann Thorac Surg*. 2022;114:152-9. https://doi.org/10.1016/j.athoracsur.2021.07.059
22. Massicotte-Azarniouch D, Sood MM, Fergusson DA, Knoll GA. Validation of the International Classification of Disease 10th Revision Codes for kidney transplant rejection and failure. *Can J Kidney Health Dis*. 2020;7:2054358120977390. https://doi.org/10.1177/2054358120977390
23. Cost-to-charge ratio files. Accessed May 15, 2023. https://hcup-us.ahrq.gov/db/ccr/costtocharge.jsp
24. Cuzick J. A Wilcoxon-type test for trend. *Stat Med*. 1985;4:87-90. https://doi.org/10.1002/sim.4780040112
25. Zou H, Hastie T. Regularization and variable selection via the elastic net. *J R Stat Soc Series B Stat Methodol*. 2005;67:301-20. https://doi.org/10.1111/j.1467-9868.2005.00503.x
26. King G, Nielsen R. Why propensity scores should not be used for matching. *Polit Anal*. 2019;27:435-54. https://doi.org/10.1017/pan.2019.11
27. Zhao Q, Percival D. Entropy balancing is doubly robust. *J Causal Inference*. 2017;5:1-19. https://doi.org/10.1515/jci-2016-0010
28. Harvey RA, Hayden JD, Kamble PS, Bouchard JR, Huang JC. A comparison of entropy balance and probability weighting methods to generalize observational cohorts to a population: a simulation and empirical example. *Pharmacoepidemiol Drug Saf*. 2017;26:368-77. https://doi.org/10.1002/pds.4121
29. Montgomery E, Macdonald PS, Newton PJ, Chang S, Jha SR, Hannu MK, et al. Frailty as a predictor of mortality in patients with interstitial lung disease referred for lung transplantation. *Transplantation*. 2020;104:864. https://doi.org/10.1097/TP.0000000000002901
30. Sapey E, Greenwood H, Walton G, Mann E, Love A, Aaronson N, et al. Phosphoinositide 3-kinase inhibition restores neutrophil accuracy in the elderly: toward targeted treatments for immunosenescence. *Blood*. 2014;123:239-48. https://doi.org/10.1182/blood-2013-08-519520
31. Singer JP, Gao Y, Huang CY, Kordahl RC, Sriram A, Hays SR, et al. The association between frailty and chronic lung allograft dysfunction after lung transplantation. *Transplantation*. 2023;107:2255-61. https://doi.org/10.1097/TP.0000000000004672
32. Trindade AJ. Frailty: a strong impact on lung transplant outcomes? *Transplantation*. 2023;107:2101-2. https://doi.org/10.1097/TP.0000000000004673
33. Wilson ME, Vakil AP, Kandel P, Undavalli C, Dunlay SM, Kennedy CC. Pretransplant frailty is associated with decreased survival after lung transplantation. *J Heart Lung Transplant*. 2016;35:173-8. https://doi.org/10.1016/j.healun.2015.10.014
34. Morton S, Isted A, Avery P, Wang J. Is frailty a predictor of outcomes in elderly inpatients with acute kidney injury? a prospective cohort study. *Am J Med*. 2018;131:1251-6.e2. https://doi.org/10.1016/j.amjmed.2018.03.012
35. Merkow RP, Ju MH, Chung JW, Hall BL, Cohen ME, Williams MV, et al. Underlying reasons associated with hospital readmission following surgery in the United States. *J Vasc Surg*. 2015;62:265. https://doi.org/10.1016/j.jvs.2015.05.023

Key Words: clinical outcomes, frailty, heart transplantation, lung transplantation

TABLE E1. International Classification of Diseases 10th Revision codes for identification of procedures

Procedure or complication	ICD codes
Heart transplantation	ICD-9: 37.51 ICD-10: 02YA0Z0, 02YA0Z1, 02YA0Z2
Lung transplantation	ICD-9: 33.5, 33.50, 33.51, 33.52 ICD-10: 0BYC0Z0, 0BYC0Z1, 0BYC0Z2, 0BYD0Z0, 0BYD0Z1, 0BYD0Z2, 0BYF0Z0, 0BYF0Z1, 0BYF0Z2, 0BYG0Z0, 0BYG0Z1, 0BYG0Z2, 0BYH0Z0, 0BYH0Z1, 0BYH0Z2, 0BYJ0Z0, 0BYJ0Z1, 0BYJ0Z2, 0BYK0Z0, 0BYK0Z1, 0BYK0Z2, 0BYL0Z0, 0BYL0Z1, 0BYL0Z2, 0BYM0Z0, 0BYM0Z1, 0BYM0Z2

ICD, International Classification of Diseases.

TABLE E2. Trends in proportions of frail patients with malnutrition, dementia, or other criteria of frailty over the study period 2014-2020

Years	Malnutrition*	Dementia*	Others
2014	70.9	19.3	9.8
2015	76.7	18.2	5.1
2016	60.5	26.5	13.0
2017	63.5	25.4	11.1
2018	64.9	27.0	8.1
2019	66.4	25.3	8.3
2020	64.4	28.1	7.5

*$Nptrend = .02$.

TABLE E3. Risk-adjusted predictors of increase in postoperative length of stay

Predictors	Lung transplantation			Heart transplantation		
	LOS (β)	95% CI	P value	LOS (β)	95% CI	P < .001
Elixhauser Index	1.42	[0.66-2.17]	<.001*	−0.11	[–0.72 to 0.49]	.71
Age	0.14	[0.07-0.21]	<.001*	0.11	[0.06-0.16]	<.001*
Payer						
Private Insurance (ref)						
Medicare	1.87	[0.17-3.57]	.03*	2.43	[1.21-3.65]	<.001*
Medicaid	2.82	[–0.03 to 5.68]	.05	1.98	[0.44-3.52]	.01*
Self/other payer	0.02	[–5.64 to 5.69]	.99	−3.48	[–5.15 to −1.80]	<.001*
Bed						
Large (ref)						
Medium	13.5	[1.61-25.4]	.03*	−0.56	[–3.44 to 2.33]	.71
Small	15.7	[0.34-30.1]	.05*	−0.58	[–5.15 to −1.80]	<.001*
Comorbidities						
Anemia	−6.17	[–8.64 to −3.70]	<.001*	−4.38	[–6.15 to −2.61]	<.001*
Congestive heart failure	3.48	[1.22-5.73]	.003*	−12.4	[–17.9 to −6.88]	<.001*
Coronary artery disease	−7.96	[–9.64 to −6.29]	<.001*	−3.95	[–5.14 to −2.76]	<.001*
Peripheral vascular disease	1.81	[–2.88 to 6.50]	.45	−2.89	[–4.10 to −1.68]	<.001*
Diabetes	−5.89	[–7.60 to −4.18]	<.001*	−3.76	[–4.92 to −2.59]	<.001*
Chronic kidney disease	87.0	[73.5-100.4]	<.001*	25.2	[19.5-30.9]	<.001*
Liver disease	1.70	[–1.68 to 5.08]	.32	3.84	[1.66-6.03]	.001*

LOS, Length of stay; *CI*, confidence interval. **P* < .05.

TABLE E4. Risk-adjusted predictors of nonhome discharge

Predictors	Lung transplantation			Heart transplantation		
	AOR	95% CI	P value	AOR	95% CI	P < .001
Elixhauser Index	1.25	1.13-1.39	<.001*	1.26	1.15-1.38	<.001*
Age	1.04	1.03-1.05	<.001*	1.05	1.04-1.05	<.001*
Payer						
Private Insurance (ref)						
Medicare	0.90	0.74-1.09	.29	1.16	0.98-1.38	.08
Medicaid	0.64	0.40-1.03	.06	0.92	0.67-1.26	.60
Self/other payer	7.66	3.41-17.2	<.001*	4.15	2.48-6.94	<.001*
Bed						
Large (ref)						
Medium	1.10	0.52-2.34	.81	1.23	0.92-1.65	.17
Small	1.51	0.59-3.90	.39	1.13	0.62-2.07	.69
Comorbidities						
Anemia	0.74	0.36-1.48	.39	0.44	0.24-0.79	.006*
Congestive heart failure	1.22	0.96-1.56	.11	0.51	0.34-0.75	.001*
Coronary artery disease	0.76	0.54-1.07	.12	0.69	0.57-0.83	<.001*
Peripheral vascular disease	0.66	0.40-1.11	.11	0.78	0.64-0.94	.009*
Diabetes	0.69	0.52-0.90	.008*	0.53	0.42-0.67	<.001*
Chronic kidney disease	4.34	2.47-7.61	<.001*	2.53	2.02-3.15	<.001*
Liver disease	1.17	0.83-1.64	.36	1.34	1.05-1.71	.02*

AOR, Adjusted odds ratio; *CI*, confidence interval. **P* < .05.