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Is timing everything? Examining operative time in lung transplants from 2006 to 2023

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donor-cross clamp time;
burnout;
ex vivo lung perfusion;
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BACKGROUND: Several studies have tried to find a link between timing of lung transplant surgery and patient outcomes. However, there has been conflicting results. This study sought to evaluate the association of operative times and recipient outcomes.

METHODS: Primary adults lung transplants were identified from the United Network for Organ Sharing Database. Patients were stratified based on time of lung transplant: T1 (12 AM-6 AM); T2 (6 AM-12 PM); T3 (12 PM-6 PM); T4 (6 PM-12 AM). Groups were assessed with comparative statistics. Long-term survival was evaluated using Kaplan-Meier methods and a multivariate Cox proportional hazard model.

RESULTS: Within the T4 group, there was a significant increase in length of stay and incidence of primary graft dysfunction, though minor. Unadjusted survival analysis with Kaplan-Meier methods demonstrated that there was no significant difference in long-term survival among the 4 groups ($p = 0.55$). Following adjustment, no operative time was independently associated with decreased long-term mortality. Variables that were significantly associated with increased long-term mortality included recipient diabetes, creatinine, hospitalization status, intensive care unit status, cigarette use, and donation after circulatory death donor status.

CONCLUSIONS: Though operative times during the T4 period were associated with increased peri-operative complications, this had no effect on long-term survival. While thoracic transplantation can safely occur no matter what time of day, transplantation should preferentially be performed during normal surgical work hours for the longevity and work life balance of transplant providers and surgeons.

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Background

Operative timing for lung transplantation is dependent on a multitude of factors, and in contrast to elective practices can be rather unpredictable. Pending donor family, operative team, and operative room availability, organ procurements have the possibility to occur at any time of the day. This ultimately requires careful coordination within the transplant team, a commitment to teamwork, and dedication from all providers. The ever-adjusting schedule of thoracic transplantation surgery necessitates grueling hours and affects every member of the team physically and emotionally. Transplant surgeons and fellows experience an alarming amount of burnout and fatigue.[1-3] This fatigue may contribute to operative outcomes, as

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some single institutions have found nighttime surgeries among lung transplant patients were associated with higher postoperative morbidity, decreased long-term survival, and decreased chronic lung allograft dysfunction (CLAD) free survival.[4] Small case series have claimed early morning lung transplants, between 4 AM and 8 AM, have a higher incidence of primary graft dysfunction (PGD) development in the recipient at 72 hours.[5] However, large database studies examining lung transplantation have found there is no significant association between operative timing and short-term mortality.[6] Ultimately, the heterogeneity of data surrounding lungs transplantation makes it difficult to draw conclusions on appropriate timing of operations.

Due to an ongoing interest in making lung transplantation a more sustainable field on not only surgeons, but the rest of the transplantation team, we sought to further determine if timing of transplantation affected patient outcomes. Specifically, in this current analysis, we evaluated the potential role of operative times (i.e., time of implantation) on short-term outcomes and long-term survival following lung transplantation.

Material and Methods

Study population

Adult lung transplants from June 1, 2006, to March 30, 2023, were identified from the United Network for Organ Sharing (UNOS)/Organ Procurement and Transplant Network Database. Recipients were excluded if they had previous lung transplant, multiorgan transplant, or had insufficient donor data. Patients were then stratified based on time of operation (i.e., time of implantation, which was calculated by adding the ischemic time to the time of cross clamp[6]) and split into 4 groups: T1 (12 AM-6 AM); T2 (6 AM-12 PM); T3 (12 PM-6 PM); T4 (6 PM-12 AM), based on normal work schedules throughout the hospital. To further analyze the impact of ex vivo lung perfusion (EVLP) on operative timing, a subgroup analysis was conducted looking specifically at this patient population. Additionally, while recently advanced cooler technology has been developed to transport lungs following procurement,[7,8] the use of these coolers is not available within the UNOS database.

Variables

Baseline donor, recipient, and transplant variables were compared between the 4 groups. Recipient variables included age, sex, race, body mass index (BMI), weight, smoking history, diabetes, creatinine, diagnosis, blood group, lung allocation score (LAS), pulmonary artery pressure, cardiac output, pulmonary capillary wedge pressure, days on wait list, and preoperative dialysis, ventilator, and extracorporeal membrane oxygenation (ECMO) use. Donor variables included age, sex, race, coronary artery disease, smoking history, diabetes, diabetes duration, hypertension, BMI, cause of death, infection, creatinine, myocardial infarction, and PaO_2:FiO_2 (PF) ratio. Transplant variables included EVLP perfusion location, EVLP perfusion time, distance traveled, ischemic time, and transplant laterality.

Outcomes

The primary outcome was long-term survival post-transplant. Secondary outcomes included length of stay (LOS), grade 3 PGD

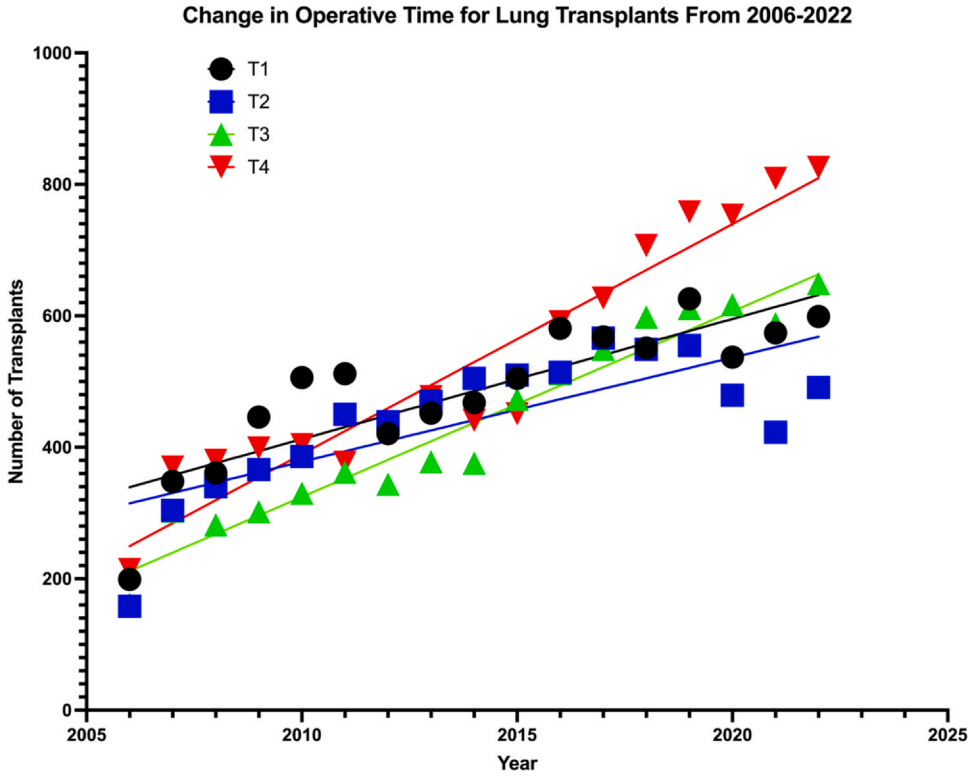

Figure 1 Trend of total lung transplants in each operative time group from 2006 to 2022. T1 (12 AM-6 AM) in black; T2 (6 AM-12 PM) in blue; T3 (12 PM-6 PM) in green; T4 (6 PM-12 AM) in red. Thick solid lines represent the overall trend for each group.

Table 1 Recipient Demographics and Baseline Characteristics

Variable	T1 (12 AM-6 AM) ($n = 8,402$)	T2 (6 AM-12 PM) ($n = 7,622$)	T3 (12 PM-6 PM) ($n = 7,622$)	T4 (6 PM-12 AM) ($n = 9,195$)	p-value
Age (years)	60 (14)	61 (13)	61 (14)	61 (14)	0.19
Male sex	5,069 (60.3%)	4,561 (59.8%)	4,621 (60.6%)	5,510 (59.9%)	0.72
Race					0.48
White	6,618 (78.8%)	6,076 (79.7%)	6,125 (80.4%)	7,283 (79.2%)	
Black	786 (9.4%)	699 (9.2%)	675 (8.9%)	830 (9%)	
Hispanic	747 (8.9%)	633 (8.3%)	594 (7.8%)	791 (8.6%)	
Asian	190 (2.3%)	157 (2.1%)	170 (2.2%)	224 (2.4%	
Other	61 (0.7%)	57 (0.7%)	58 (0.8%)	67 (0.7%)	
BMI (kg/m^2)	25.7 (6.9)	25.8 (6.6)	25.8 (6.9)	25.8 (6.7)	0.73
Weight (kg)	74.4 (24.4)	74.4 (24)	74.4 (23.9)	74.1 (24)	0.92
Former smoker > 20 pack years	4,911 (59%)	4,520 (59.8%)	4,476 (59.25)	5,305 (58.2%)	0.21
Diabetes	33 (0.39%)	35 (0.46%)	25 (0.33%)	28 (0.31%)	0.63
Creatinine (mg/dl)	0.8 (0.3)	0.8 (0.3)	0.8 (0.3)	0.8 (0.3)	0.05
Preoperative dialysis	24 (0.3)	26 (0.3)	20 (0.3)	24 (0.3)	0.59
Diagnosis					0.09
Cystic fibrosis/ Immunodeficiency	335 (4%)	287 (3.8%)	355 (4.7%)	375 (4.1%)	
Obstructive lung disease	767 (9.1%)	693 (9.1%)	701 (9.2%)	774 (8.4%)	
Pulmonary vascular disease	2,286 (27.2%)	2,143 (28.1%)	2,072 (27.2%)	2,510 (27.3%)	
Restrictive lung disease	5,014 (59.7%)	4,499 (59%)	4,494 (59%)	5,536 (60.2%)	
Blood group					0.44
A	3,249 (38.7%)	3,030 (39.8%)	3,061 (40.2%)	3,629 (39.5%)	
B	940 (11.2%)	844 (11.1%)	887 (11.6%)	1014 (11%)	
AB	332 (4%)	302 (4%)	277 (3.6%)	336 (3.7%)	
O	3,881 (46.2%)	3,446 (45.2%)	3,397 (44.6%)	4,216 (45.9%)	
LAS	38 (11.3)	38 (11.6)	37.8 (11.5)	37.9 (11.3)	0.56
Mean pulmonary artery pressure (mm Hg)	16 (10)	17 (10)	16 (10)	16 (10)	0.045
Cardiac output	5.2 (1.71)	5.2 (1.72)	5.2 (1.72)	5.2 (1.73)	0.32
PCWP	10 (7)	10 (7)	10 (7)	10 (7)	0.23
Days on wait list	50 (141)	53 (153.8)	49 (143)	49 (139)	0.10
Preoperative ventilator	509 (6.1%)	442 (5.8%)	426 (5.6%)	535 (5.8%)	0.66
Preoperative ECMO	384 (4.6%)	332 (4.4%)	396 (5.2%)	457 (5%)	0.06

Abbreviations: BMI, body mass index; ECMO, extracorporeal membrane oxygen; LAS, lung allocation score; PCWP, pulmonary capillary wedge pressure.
Data presented as median (interquartile range) for continuous variables and number (%) for categorical variables.

at 72 hours (PGD3, defined as PF < 200 or requiring ECMO), ECMO use at 72 hours post-transplant, intubation 72 hours post-transplant, reintubation, inhaled nitric oxide (NO) at 72 hours, acute rejection before discharge, postoperative dialysis, stroke, airway dehiscence, and cause of death.

Calculation

Variables were assessed for normality and then compared using analysis of variance (continuous parametric) or Kruskal-Wallis test (continuous nonparametric) or the chi-square test (categorical). Continuous variables were presented as median (interquartile range [IQR]) or n, % for categorical variables. To determine trends overtime, a simple linear regression was created.

Unadjusted long-term survival was assessed using Kaplan-Meier methods with the log-rank test. To adjust for recipient, donor, and transplant variables, a multivariable shared frailty Cox proportional hazard model was created. Recipient variables included age, gender, ethnicity, BMI, smoking history, diabetes, creatinine, glomerular filtration rate, preoperative dialysis, diagnosis prior to transplant, blood group, hospital status, ECMO, LAS, preoperative ventilator, and time on the waitlist. Donor variables included were age, sex, ethnicity, coronary artery disease, diabetes, BMI, infection, creatinine, history of myocardial infarction, donation after circulatory death (DCD) status, and PF ratio. Transplant-related variables included were yearly center volume, distance traveled to transplant center, and ischemia time in hours and era. Variables were chosen based on clinical experience.

All statistical analyses were performed with R version 3.6.2 (R Core Team, Vienna, Austria), SAS version 9.4 (SAS Institute, Cary, NC), and Prism version 10 (GraphPad, La Jolla, CA). Statistical significance was set at $p < 0.05$ for all analyses.

Table 2 Donor Characteristics

Variable	T1 (12 AM-6 AM) ($n = 8,402$)	T2 (6 AM-12 PM) ($n = 7,622$)	T3 (12 PM-6 PM) ($n = 7,622$)	T4 (6 PM-12 AM) ($n = 9,195$)	p-value
Age	33 (23)	33 (24)	34 (24)	33 (24)	0.17
Male sex	5,156 (61.4%)	4,620 (60.6%)	4,529 (59.4%)	5,526 (60.1%)	0.08
Ethnicity					< 0.01
White	4,998 (59.5%)	4,574 (60%)	4,740 (62.2%)	5,661 (61.6%)	
Black	1,576 (18.8%)	1,426 (18.7%)	1,444 (18.9%)	1,655 (18%)	
Hispanic	1,501 (17.9%)	1,295 (17%)	1,184 (15.5%)	1,515 (16.5%)	
Asian	248 (3%)	249 (3.3%)	197 (2.6%)	258 (2.8%)	
Other	79 (0.9%)	78 (1%)	57 (0.7%)	106 (1.2%)	
Coronary artery disease	187 (2.3%)	176 (2.3%)	200 (2.7%)	222 (2.5%)	0.40
Smoking history	703 (8.4%)	684 (9%)	654 (8.6%)	733 (8%)	0.13
Diabetes	642 (7.6%)	574 (7.5%)	602 (7.9%)	752 (8.2%)	0.31
Donor diabetes duration					0.03
0-5 years	227 (35.4%)	204 (35.5%)	224 (37.2%)	238 (31.6%)	
6-10 years	120 (18.7%)	104 (18.1%)	83 (13.8%)	156 (20.7%)	
> 10 years	224 (34.9%)	221 (38.5%)	241 (40%)	286 (38%)	
Hypertension	1,929 (23%)	1,815 (23.8%)	1,865 (24.5%)	2,221 (24.2%)	0.12
Body mass index	25.4 (6.6)	25.5 (6.5)	25.6(6.8)	25.4 (6.7)	0.64
Donor cause of death					0.20
Neuro (seizure/CVA)	376 (4.5%)	346 (4.5%)	349 (4.6%)	417 (4.5%)	
Drug overdose	644 (7.7%)	588 (7.7%)	603 (7.9%)	687 (7.5%)	
Asphyxiation	23 (0.3%)	22 (0.3%)	28 (0.4%)	24 (0.3%)	
Cardiovascular	898 (10.7%)	774 (10.2%)	825 (10.8%)	1,096 (11.9%)	
Trauma (GSW/stab/ blunt)	2,712 (32.3%)	2,475 (32.5%)	2,466 (32.4%)	2,975 (32.4%)	
Drowning	290 (3.5%)	274 (3.6%)	292 (3.8%)	355 (3.9%)	
Other	3,459 (41.2%)	3,143 (41.2%)	3,059 (40.1%)	3,641 (39.6%)	
Donor bloodstream Infection	692 (8.2%)	609 (8%)	639 (8.4%)	723 (7.9%)	0.61
Donor clinical infection	5,764 (69%)	5,357 (70.7%)	5,311 (70.3%)	6,325 (69.2%)	0.07
Donor pulmonary infection	5,169 (61.5%)	4,761 (62.5%)	4,736 (62.1%)	5,688 (61.9%)	0.65
Donor creatinine	1 (0.7)	1 (0.7)	1 (0.7)	1 (0.7)	0.30
Donor MI history	154 (1.8%)	138 (1.8%)	135 (1.8%)	166 (1.8%)	0.99
PF ratio	418 (189)	425 (181.3)	424 (161)	424 (175)	0.004

Abbreviations: BMI, body mass index; CDC, Center for Disease Control; CVA, cerebral vascular accident; DCD, donation after circulatory death; GSW, gun shot wound; MI, Myocardial Infarction; PF, PaO_2:FiO_2.

Data presented as median (interquartile range) for continuous variables and number (%) for categorical variables.

Results

After querying UNOS database, a total of 32,841 lung transplant recipients were identified. Regarding lung transplant recipients, there were 8,402 (25.6%) patients in T1, 7,622 (23.2%) in T2, 7,622 (23.2%) in T3, and 9,195 (30%) in T4. Overtime, operative times occurring within the T3 and T4 had the sharper increases in total transplants compared to those in the T1 and T2 groups (Figure 1).

There were no differences in baseline demographics or medical comorbidities among the recipients ($p > 0.05$ for all groups). Those in the T2 group had significantly higher mean pulmonary artery pressure (median [M]: 17 mm Hg, IQR: 10 mm Hg, $p = 0.045$). LAS was comparable among the groups as well. Though diagnosis prior to transplant did not differ significantly amongst the groups, those in T3 had the highest incidence of cystic fibrosis/immunodeficient patients (4.7%) and obstructive lung disease (9.2%), while those in the T2 group had the highest incidence of pulmonary vascular disease (28.1%) and those in T4 had the highest incidence of restrictive lung disease (60.2%; $p > 0.05$) (Table 1). Donors in T3 were more often White (62.2%) and suffered from diabetes for more than 10 years (40%) ($p < 0.05$ for both). Though donors in the T1 group had significantly lower PF ratios (M: 418, IQR: 189, $p = 0.004$), all groups had PF ratios above 400. There were no further differences in baseline demographics, medical comorbidities, nor cause of death among donors (Table 2).

Regarding transplant characteristics and operative outcomes, those in the T3 had a significantly higher incidence of bilateral lung transplants (73.7%) among the groups ($p < 0.0001$). Those in the T4 had significantly longer distance traveled for the donor allograft (M: 163 nautical miles [NM], IQR 288 NM, $p = 0.03$), longer LOS (M: 18 days, IQR: 18 days, $p < 0.0001$), higher incidence of PGD3 (11.3%, $p = 0.02$), and higher incidence of inhaled NO at 72 hours (9.3%, $p < 0.0001$). Those in the T2 group had significantly higher ischemic times when compared to the

Table 3 Operative Characteristics and Postoperative Outcomes

Variable	T1 (12 AM-6 AM) ($n = 8,402$)	T2 (6 AM-12 PM) ($n = 7,622$)	T3 (12 PM-6 PM) ($n = 7,622$)	T4 (6 PM-12 AM) ($n = 9,195$)	p-value
Bilateral transplant	6,003 (71.4%)	5,420 (71.1%)	5,620 (73.7%)	6,687 (72.7%)	< 0.0001
Distance traveled (nautical miles)	147 (283)	153 (286)	157 (289)	163 (288)	0.03
Ischemia time (hours)	5.2 (2.1)	5.3 (2.2)	5.2 (2.3)	5.2(2.1)	< 0.0001
Length of stay post-transplant (days)	17 (16)	17 (17)	17 (17)	18 (18)	< 0.0001
PGD3 at 72 hours	866 (10.3%)	755 (9.9%)	802 (10.5%)	1039 (11.3%)	0.02
ECMO at 72 hours	400 (8.4%)	336 (7.8%)	385 (8.1%)	443 (7.7%)	0.63
Intubated at 72 hours	1,494 (31.2%)	1,247 (29.1%)	1,504 (31.5%)	1,764 (30.7%)	0.06
Reintubated	1,486 (17.9%)	1,353 (18%)	1,368 (18.3%)	1,726 (19%)	0.58
Inhaled NO at 72 hours	447 (9.4%)	346 (8.1%)	459 (9.6%)	532 (9.3%)	< 0.0001
Postoperative dialysis	615 (7.4%)	497 (6.6%)	535 (7.1%)	643 (7%)	0.26
Postoperative stroke	195 (2.3%)	166 (2.2%)	187 (2.5%)	219 (2.4%)	0.69
Postoperative airway Dehiscence	133 (1.6%)	102 (1.4%)	122 (1.6%)	138 (1.5%)	0.51
Acute rejection before Discharge	625 (7.5%	592 (7.9%)	594 (7.9%)	707 (7.8%)	0.79
Cause of death					0.80
Graft failure	741 (18.3%)	623 (16.9%)	577 (16.7%)	709 (17.5%)	
Cardiovascular	297 (7.3%)	254 (6.9%)	268 (7.8%)	303 (7.5%)	
Cerebrovascular	118 (2.9%)	117 (3.2%)	96 (2.8%)	129 (3.2%)	
Pulmonary	731 (18%)	710 (19.2%)	622 (18%)	750 (18.5%	
Infection (to included COVID-19)	774 (19.1%)	726 (19.7%)	686 (19.9%)	751 (18.5%)	
Malignancy	433 (10.7%)	407 (11%)	365 (10.6%)	433 (10.7%)	
Other	956 (23.6%)	854 (23.1%)	837 (24.3%)	988 (24.3%)	

Abbreviations: ECMO, extracorporeal membrane oxygenation; PGD3, grade 3 primary graft dysfunction.
Data presented as median (interquartile range) for continuous variables and number (%) for categorical variables.

other groups (M: 5.33 hours, IQR: 2.2 hours, $p < 0.0001$). Postoperative dialysis, stroke, airway dehiscence, acute rejection before discharge, and cause of death did not differ significantly between groups ($p > 0.05$ for all) (Table 3). Unadjusted survival analysis with Kaplan-Meier methods demonstrated that there was no significant difference in long-term survival among the 5 groups ($p = 0.55$). Survival at 1 year was T1 87.3%, T2 87%, T3 87.9%, and T4 87.7%. Survival at 10 years was T1 30.1%, T2 30%, T3 29.3%, and T4 30.9% (Figure 2).

Following adjustment, no operative time was independently associated with decreased long-term mortality (Figure 3). Some variables that were significantly associated with increased long-term mortality included recipient diabetes (hazard ratio [HR]: 1.11, 95% CI: 1.07-1.12, $p < 0.001$), creatinine (HR: 1.08, 95% CI: 1.04-1.12, $p < 0.001$), hospitalization status (HR: 1.15, 95% CI: 1.08-1.22, $p < 0.001$), ICU status (HR: 1.16, 95% CI: 1.08-1.25, $p < 0.001$) and donor ethnicity black (HR: 1.2, 95% CI: 1.15-1.26, $p < 0.001$) or Hispanic/Latino ethnicity (HR: 1.09, 95% CI: 1.04-1.14, $p < 0.001$ diabetes), cigarette use (HR: 1.09, 95% CI: 1.03-1.16, $p = 0.002$), and DCD status (HR: 1.15, 95% CI: 1.04-1.26, $p = 0.007$). Variables that were significantly associated with decreased long-term mortality included the era 2011-2017 (HR: 0.93, 95% CI: 0.89-0.97, $p < 0.001$).

There were 735 recipients who received allografts that were evaluated by EVLP: 165 (22.4%) in T1, 215 (29.4%) in T2, 190 (25.9%) in T3 and 164 (22.3%) in T4. There were no significant differences in where EVLP took place, that is, organ procurement organization, transplant center, or external perfusion center. Additionally, perfusion time was similar for all groups; however, those in the T2 group had significantly longer ischemic times (12.6 hours, $p = 0.0002$) (Table 4). Those in T1 had the highest incidence of inhaled NO at 72 hours (18.8%, $p = 0.01$). There were no differences in PGD3 rates nor cause of death. Unadjusted survival analysis with Kaplan-Meier methods demonstrated that there was no significant difference in long-term survival among the 5 groups ($p = 0.74$). Survival at 1 year was: T1 82.4%, T2 85.1%, T3 83.5%, and T4 87.6%. Survival at 3 years was: T1 68.2%, T2 69%, T3 61.6%, and T4 68.9% (Figure 4). Again, no operative time was independently associated with increased long-term mortality, while recipient female sex (HR: 1.84, 95% CI: 1.24-2.72, $p = 0.002$) and DCD status (HR: 1.45, 95% CI: 1.01-2.09, $p = 0.043$) were (Figure 5).

Discussion

On both unadjusted and adjusted analysis, long-term mortality did not differ significantly among the groups; however, those in the T4 groups did have longer LOS (1 day longer) and PGD3 incidence (~1% higher) compared to the

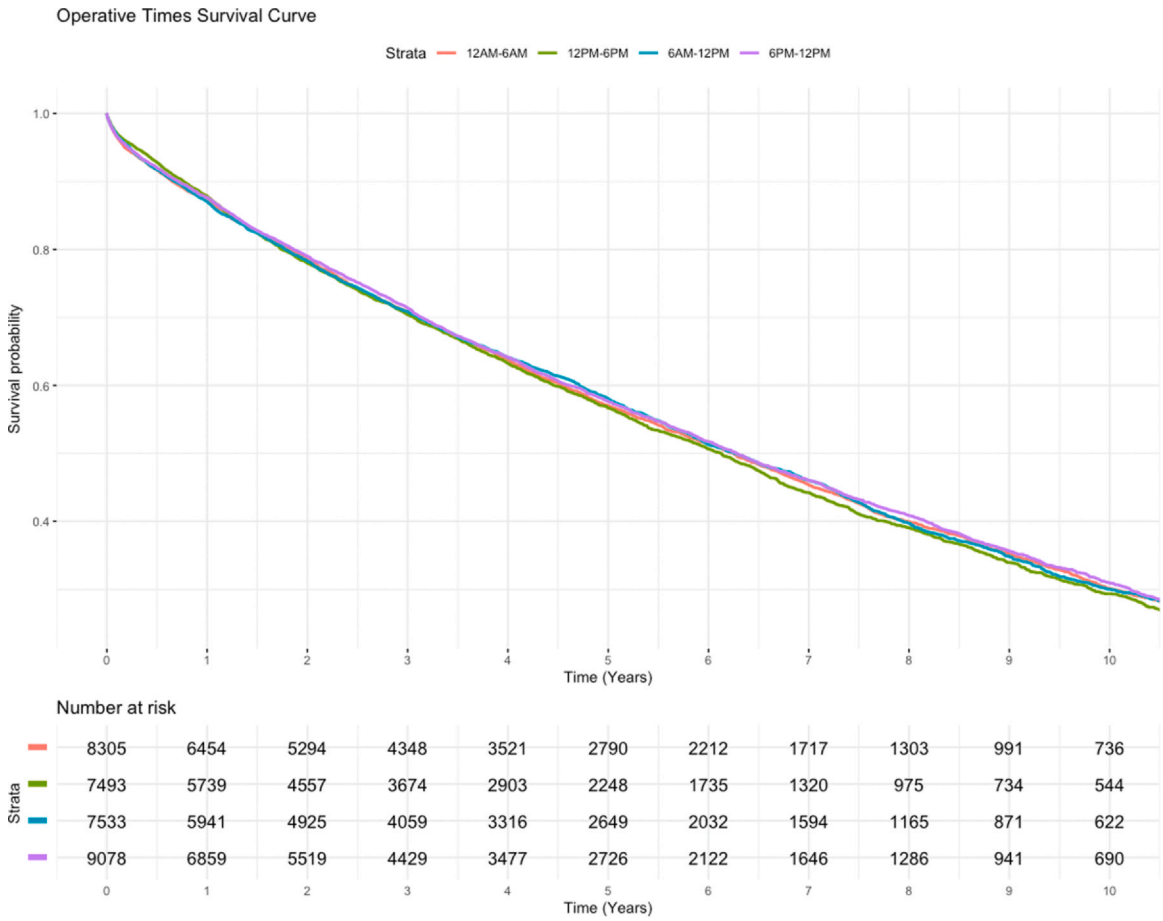

Figure 2 Kaplan-Meier curves demonstrating survival for patients in each operative time category. Survival at 1 year was T1 87.3% (95% confidence interval [CI]: 86.5%-88%), T2 87% (95% CI: 86.3%-87.8%), T3 87.9% (95% CI: 87.1%-88.6%), and T4 87.7% (95% CI: 87%-88.3%). Survival at 3 years was T1 70.8% (95% CI: 69.8%-71.9%), T2 70.9% (95% CI: 69.8%-72%), T3 70.4% (95% CI: 69.2%-71.6%), and T4 71.4% (95% CI: 70.4%-72.4%). Survival at 10 years was T1 30.1% (95% CI: 28.7%-31.6%), T2 30% (95% CI: 28.5%-31.6%), T3 29.3% (95% CI: 27.8%-31%), and T4 30.9% (95% CI: 29.5%-32.5%).

reset of the groups. Recently, Cunningham et al showed that lungs reperfused between 4 AM and 8 AM had a higher incidence of PGD after transplantation,[5] while in this study the time of 6 PM-12 AM was associated with a slight increase in PGD3 development. Though there are differences in the timing of reperfusion leading increased PGD development between the 2 studies, both reperfusion times can be considered outside normal work hours. While there were few significant differences between baseline group characteristics or differences in ischemic times within our study that would offer explanation, a possible explanation could be human factors within the transplant community. Transplant surgeons often find themselves on call 4-days a week and work upward of 70 hours per week consistently.[9,10] Furthermore, these surgeons typically sleep far less than the average American, just around 6-hours a night.[11] Importantly, surgeons are not the only members of the team that suffer either as transplant coordinators,[12] pharmacists,[13] nurses,[14] and additional operative staff and team members experience high levels of distress, fatigue and can contribute to increase risk of operative errors, or post-operative care lapses. The attentiveness of the surgeon, operative staff, and receiving team could be diminished during these hours leading to increases in complications.[4,15]

However, despite a slight increase in PGD3 incidence, we did not see significant differences in long-term mortality that would be expected from an increased incidence of PGD[5,16,17] or a large difference in overall LOS. Overall, we believe that these results reflect other studies results in terms of our inability to draw specific conclusions based on operative timing.[6,18] Traditional thought has perpetuated the paradigm that transplantation can occur safely at any hour of the day due inherent to the nature of transplantation surgery and centers alike. Transplantation is a highly scrutinized specialty, and centers must provide high-level care around the clock. As opposed to most other surgery specialties, everyone on the team (nurses, anesthesiologists, social workers, ICU personnel, PACU personnel, perfusionists) are all highly specialized and trained specifically for transplantation. Frequently, emergent operations that occur in other surgical fields pull in different OR members from different subspecialties and ask them to deal with broader pathology. This rarely is the case in transplant, as usually most OR members are part of the transplant team; however, short staffing in recent years is making this less rare.[19] Additionally, prospective transplant recipients are closely followed in the outpatient office and undergo extensive peri-operative testing which lowers the chances an

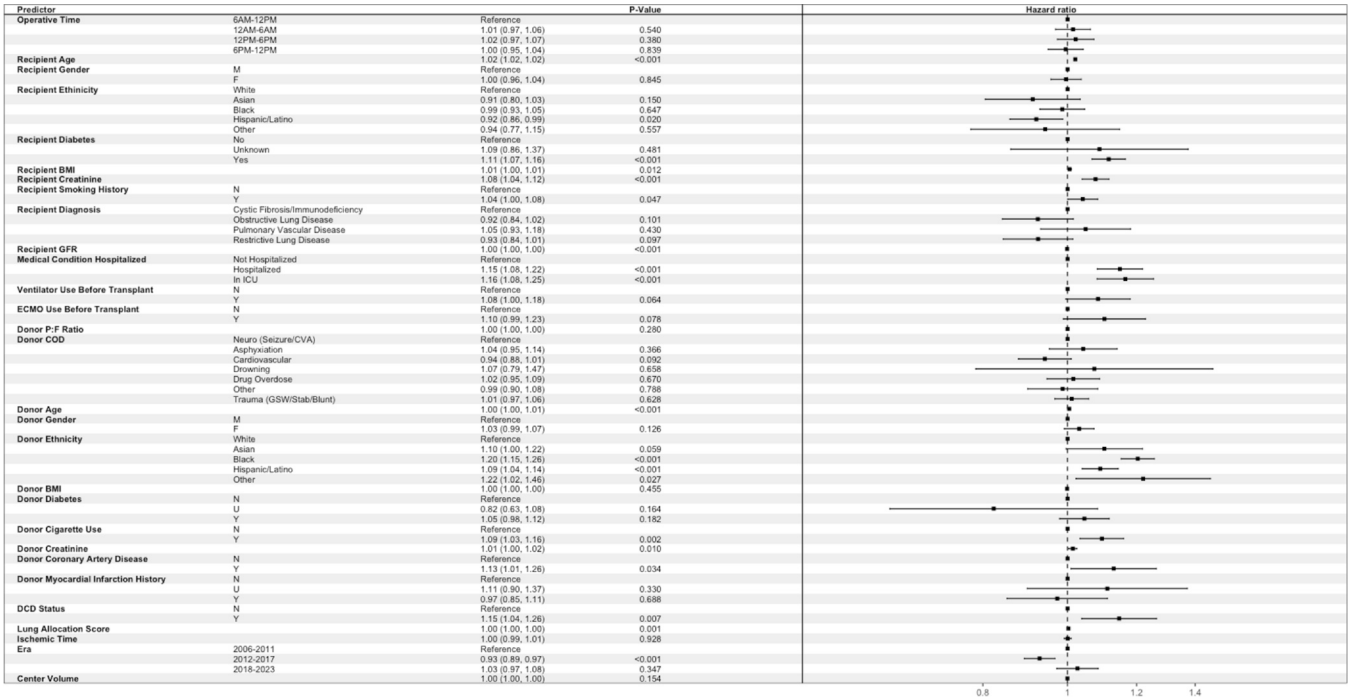

Figure 3 Forest plot of Cox regression for survival. BMI, body mass index; CVA, cerebral vascular accident; DCD, donation after circulatory death; ECMO, extracorporeal membrane oxygen; GFR, glomerular filtration rate; GSW, gun shot wound; ICU, intensive care unit; LAS, lung allocation score; P:F ratio, PaO_2:FiO_2 ratio.

Table 4 Operative Characteristics and Postoperative Outcomes for Ex Vivo Lung Perfusion Cohort

Variable	T1 (12 AM-6 AM) ($n = 165$)	T2 (6 AM-12 PM) ($n = 216$)	T3 (12 PM-6 PM) ($n = 190$)	T4 (6 PM-12 AM) ($n = 164$)	p-value
Perfused by:					0.64
OPO	10 (6.1%)	13 (6%)	8 (4.2%)	7 (4.3%)	
Transplant program	102 (61.8%)	134 (62%)	115 (60.8%)	112 (69.1%)	
External perfusion center	53 (32.1%)	69 (31.9%)	66 (34.9%)	43 (26.5%)	
Perfusion time (minutes), median, IQR	254.5 (128)	237 (151)	255 (233)	254 (200.3)	0.28
Distance traveled (nautical miles)	269 (336)	270 (348)	215 (358.5)	227 (408.25)	0.52
Ischemia time (hours)	10.6 (5.3)	12.6 (5.3)	12.4 (5.8)	11.3 (7)	0.0002
Length of stay post-transplant (days)	26 (25.5)	21 (24)	22 (26)	22 (31.5)	0.40
PGD3 at 72 hours	48 (29.1%)	45 (20.8%)	45 (23.7%)	34 (20.7%)	0.22
ECMO at 72 hours	31 (18.8%)	31 (14.6%)	33 (17.5%)	25 (15.4%)	0.69
Intubated at 72 hours	80 (48.5%)	87 (40.8%)	97 (51.1%)	69 (42.3%)	0.14
Reintubated	42 (25.5%)	47 (22.1%)	41 (21.6%)	35 (21.5%)	0.65
Inhaled NO at 72 hours	31 (18.8)	15 (7%)	32 (16.9%)	24 (14.8%)	0.01
Postoperative dialysis	25 (15.2%)	27 (12.7%)	26 (13.8%)	21 (13%)	0.91
Postoperative stroke	5 (3%)	9 (4.2%)	3 (1.6%)	3 (1.8%)	0.35
Postoperative airway dehiscence	2 (1.2%)	3 (1.4%)	4 (2.1%)	4 (2.5%)	0.80
Acute rejection before discharge	19 (11.5%)	24 (11.3%)	18 (9.5%)	10 (6.1%)	0.31
Cause of death					0.76
Graft failure	6 (13.6%)	10 (15.4%)	9 (19.6%)	3 (8.3%)	
Cardiovascular	3 (6.8%)	6 (9.2%)	4 (8.7%	5 (13.9%)	
Cerebrovascular	3 (6.8%)	4 (6.2%)	4 (8.7%)	2 (5.6%)	
Pulmonary	5 (11.4%)	9 (13.8%)	10 (21.7%)	3 (8.3%)	
Infection (to included COVID-19)	13 (29.5%)	17 (26.2%)	14 (30.4%)	10 (27.8%)	
Malignancy	1 (2.3%)	2 (3.1%)	0 (0)	2 (5.6%)	
Other	13 (29.5%)	17 (26.2%)	5 (10.9%)	11 (30.6%)	

Abbreviations: ECMO, extracorporeal membrane oxygenation; IQR, interquartile range; OPO, Organ Procurement Organization; PGD, grade 3 primary graft dysfunction.

Data presented as median (interquartile range) for continuous variables and number (%) for categorical variables.

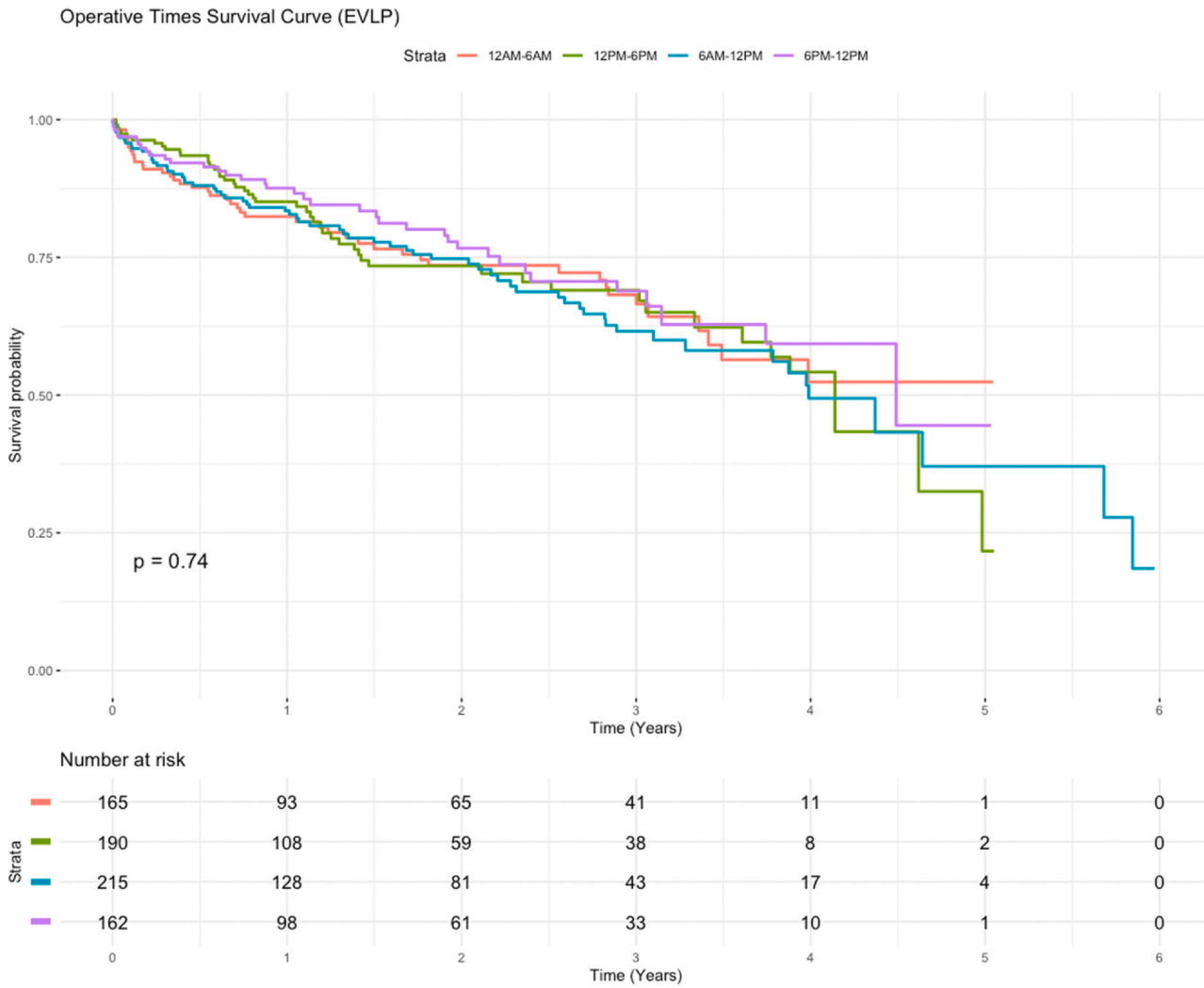

Figure 4 Kaplan-Meier curves demonstrating survival for patients in each operative time category for ex vivo lung perfusion (EVLP) recipients. Survival at 1 year was: T1 82.4% (95% confidence interval [CI]: 76.5%-88.8%), T2 85.1% (95% CI: 79.8%-90.7%), T3 83.5% (95% CI: 78.4%-88.9%), and T4 87.6% (95% CI: 82.3%-93.2%). Survival at 3 years was T1 68.2% (95% CI: 69.8%-71.9%), T2 69% (95% CI: 60.8%-78.3%), T3 61.6% (95% CI: 53.7%-70.7%), and T4 68.9% (95% CI: 60%-79.2%).

undiagnosed ailment negatively affects outcomes is much lower than traditional emergent cases.[20]

Although several different conclusions can be reached regarding the effect of procurement timing on patient outcomes, we believe that because thoracic organ procurement can occur safely, night or day with near equivocal outcomes and as such focus should be shifted to provider lifestyle and satisfaction. Disturbingly, close to 35% of transplant and cardiothoracic surgeons exhibit symptoms of depression and report experiencing suicidal ideation at rates ranging from 4.1% to 7.3%.[9] This grueling workload, combined with erratic schedules, sleep deprivation, and the inability to plan for personal events, has contributed substantially to the alarming rates of burnout.[1-3,21-23] As further evidence of this burnout, almost 40% of married transplant surgeons reported marital distress.[23] While the effects on current providers are clear, the effects on the next generation of transplant surgeons are becoming apparent as well, as transplant fellowships are currently some of the least competitive and sought-after training among surgical fellows.[24] High rates of burnout and lack of sleep have been shown to contribute to medical errors and poor patient outcomes.[25-28] Burnout can be combated through many avenues on the individual, institutional, and national scale.[29] Besides these traditional methods of combating burnout among transplant providers, additional strives in transplant technology might allow for a better work-life balance.

Advances in EVLP may offer clinicians not only valuable time to repair and assess organs,[30-32] but time away from the hospital. Within our EVLP cohort, there was no difference in unadjusted survival, and furthermore upon adjustment no operative time was independently associated with decreased survival. Additionally, the differences seen in PGD3 incidence or LOS were not apparent. While the incidence of PGD3 was increased in the EVLP cohort compared to the total cohort, this is not a new finding.[33-35] The use of EVLP can perhaps suspend the ischemic time making it a valuable technology in the long-term preservation of allografts.[36] With the advent of multiday organ preservation utilizing ELVP,[37,38] the concept of organ banking and a novel "semielective" transplant practice are

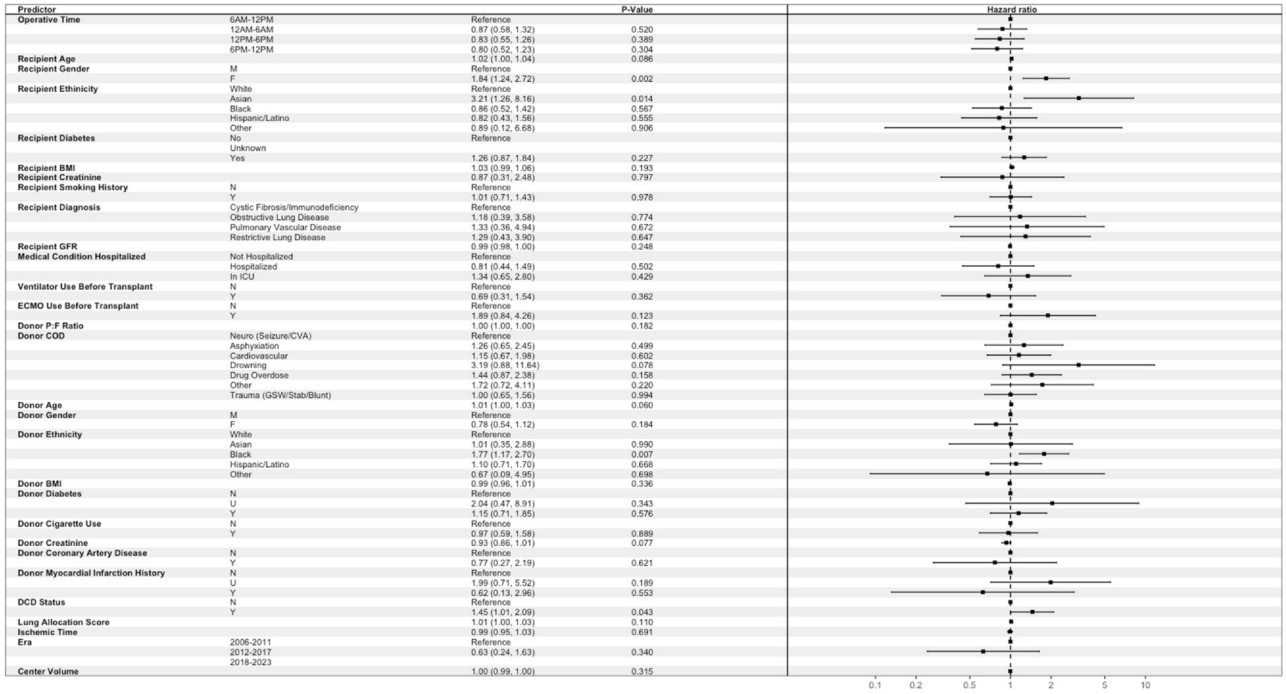

Figure 5 Forest plot of Cox regression for survival for ex vivo lung perfusion (EVLP) recipients. BMI, body mass index; CVA, cerebral vascular accident; DCD, donation after circulatory death; ECMO, extracorporeal membrane oxygen; GFR, glomerular filtration rate; GSW, gun shot wound; ICU, intensive care unit; LAS, lung allocation score; P:F ratio, PaO_2:FiO_2 ratio.

becoming more achievable. Additionally, cooler preservation technology has greatly progressed in recent years with the advent of 10°C preservation[37,39] as well as technologies, such as Lungguard Paragonix,[7] which allow for the prolonged preservation of lung allografts without the cost of EVLP. Overall, these technologies have several advantages for providers, hospitals, and patients. Transplants could occur within daytime hours reducing the stress of unpredictable schedules and interrupted sleep. Patients, and especially those in rural areas, would have greater flexibility for hospital travel and admission. Hospitals additionally would face reduce costs as the need for nighttime surgeries, perfusions, and ICU care would decrease. With the conclusions of our study, as well as the progression and perfection of EVLP and preservation coolers alike, we believe transplantation in the future will be a more sustainable career field.

Limitations

This study has inherent limitations that affect any large database, including lack of granular data, its retrospective nature, and its subject to information and selection bias. Data regarding the treatment of acute rejection as well as other peri-operative complications, and the long-term impact of morbidity, such as dialysis and rejection, were not available thus limiting inferences regarding quality of life. Due to the above limitations, we were unable to use the International Society for Heart and Lung Transplantation definition of PGD,[40] and given the lack of radiographic data, and some missingness in the PaO_2 and FiO_2, there may be bias that influenced the rate observed. Furthermore, data regarding CLAD were not available, which prevented examination of the impact of procurement timing on CLAD. Finally, the timing of the operation detailed in this manuscript is only a surrogate of the timing of the reimplantation, as exact operative times are unavailable within the UNOS database, and therefore this is the best estimation one can make within the UNOS database.[6] There are several instances that we cannot account for in this manuscript to include the use of coolers that prolong the ischemic time or prolonged explant procedures that further delay implant time in the recipient.

Conclusions

Although operative times during the T4 time-period were associated with an increased LOS and incidence of PGD3, this had no effect on long-term survival. While thoracic transplantation can safely occur no matter what time of day, transplantation should preferentially be performed during normal surgical work hours for the longevity and work-life balance of transplant providers and surgeons. Improving the lifestyle of transplant surgeons and providers will not only allow the field to grow but will undoubtedly decrease the burden placed on the health care system and workers.

Disclosure statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Bryan A. Whitson reports a relationship with National Institutes of Health that includes funding grants. Bryan A. Whitson reports a relationship with TransMedics Inc that includes board membership. B.A.W. serves on the Clinical Events Committee of TransMedics OCS. Hua Zhu reports a relationship with National Institutes of Health that includes funding grants. AMG is a prior consultant for Abbvie Pharmaceuticals.

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