Improved survival after lung transplantation for adults requiring preoperative invasive mechanical ventilation: A national cohort study

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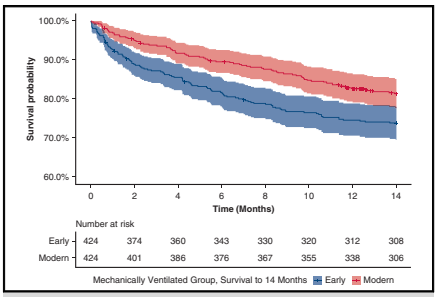
ABSTRACT

Objective: Early survival after lung transplantation has improved in the last decade. Mechanically ventilated recipients are known to be at greater risk for early post-transplant mortality. We hypothesized that post-transplant survival in mechanically ventilated recipients has improved over time.

Methods: Using a national registry, we compared hazard of death at 30 days, 4 and 14 months, 3 and 5 years, and overall for adults on mechanical ventilation who underwent lung or heart–lung transplantation from May 4, 2011, to April 4, 2018 (modern group) with those undergoing transplantation from May 4, 2005, to May 3, 2011 (early group). We quantified the impact of mechanical ventilation on survival using population-attributable fractions. We also compared mechanically ventilated recipients with nonmechanically ventilated recipients.

Results: Mechanically ventilated recipients from the modern group had lower hazard of death than recipients in the early group at all time-points, lowest at 30-days post-transplant (hazard ratio, 0.04; 95% confidence interval, 0.02-0.08). In the modern period, mechanically ventilated recipients had greater hazard of death than nonmechanically ventilated recipients at 30 days' post-transplant (9.53; 4.57-19.86). For mechanically ventilated recipients, the population attributable fraction was lower in the modern group compared to the earlier group (0.6% vs 5.7%).

Conclusions: While mechanically ventilated recipients remain at high risk, survival in this patient population has improved over time. This may reflect improvements in perioperative recipient management. (J Thorac Cardiovasc Surg 2020;160:1385-95)



Kaplan–Meier curves comparing survival between the early and modern time periods.

CENTRAL MESSAGE

The last decade has shown significant improvements in survival for lung transplantation in mechanically ventilated recipients.

PERSPECTIVE

Pretransplant mechanical ventilation is a known risk factor for post-transplant mortality, with ongoing concerns about survival and resource use. However, short- and long-term survival in this patient population has significantly improved over time.

See Commentaries on pages 1396 and 1397.

THOR

Pretransplant mechanical ventilation (MV) remains a known risk factor for increased post-transplant mortality.[1-3] Recipients requiring preoperative MV have worse 6-month postoperative mortality than those not requiring invasive support.[4] Since the introduction of the Lung Allocation Score (LAS) in 2005, the number of sick patients being bridged to transplant has increased, as LAS prioritizes medical urgency and estimated survival over time on the waitlist.[4-6] Bridging strategies have evolved beyond invasive MV to include extracorporeal membrane oxygenation (ECMO), not only on its own but also in addition to invasive MV.[7] Consequently, concerns about recipient survival and resource use have thus led to the classification of recipient preoperative MV as a relative contraindication to lung transplantation.[6,8]

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Abbreviations and Acronyms

AF = attributable fraction
BMI = body mass index
CI = confidence interval
ECMO = extracorporeal membrane oxygenation
FEV1 = forced expiratory volume in 1 second
HR = hazard ratio
LAS = Lung Allocation Score
MV = mechanical ventilation/mechanically ventilated
NMV = nonmechanically ventilated
OR = odds ratio
OPTN = Organ Procurement and Transplantation Network
pCO_2 = partial pressure of carbon dioxide

Scanning this QR code will take you to the article title page to access supplementary information.

Recent advances in recipient postoperative management such as low tidal volume ventilation, early mobilization, and rehabilitation[5,9] could contribute to improved outcomes in this select cohort of patients. Mobilizing patients on ECMO as a bridge to transplant,[10] in addition to patients with prolonged need for mechanical ventilation, has demonstrated patient benefit.[11] We hypothesized that over the last decade, outcomes for recipients requiring preoperative invasive MV have improved. We specifically asked the following questions: (1) have outcomes for MV recipients improved over time, (2) what baseline characteristics in the MV group are associated with 30-day mortality, and (3) are MV recipient outcomes similar to nonmechanically ventilated (NMV) recipient outcomes. To answer these questions, we performed a retrospective analysis using data from the Organ Procurement and Transplantation Network (OPTN) registry supplied by the United Network for Organ Sharing.

METHODS

Overview and Study Population

We performed a retrospective analysis using national data from the OPTN Database as of June 10, 2019, supplied by United Network for Organ Sharing, and collected in strict compliance with the International Society for Heart and Lung Transplantation ethical guidelines. The "THORACIC_-DATA" dataset was used. We included all adults age 18 or older who underwent lung transplantation between May 4, 2005, and April 4, 2018. Patients who underwent heart–lung transplantation, retransplantation, or bridged with ECMO were excluded (Figure 1). Preoperative invasive MV was defined as MV at the time of organ matching, and all baseline recipient variables were recorded at the time of donor matching and transplantation and extracted from the transplant recipient registry. To ensure appropriate time for follow-up, the last transplant included occurred on April 4, 2018, 14 months before the last date of follow-up in the dataset. The time point of 14 months was chosen given recent evidence that recipients in the post-LAS era might experience a drop in survival after reaching the 12-month survival metric.[12] Recipients were placed into an early group (May 4, 2005, to May 3, 2011), or a modern group (May 4, 2011, to April 4, 2018), designed to divide the available data and maximize the number of MV recipients included without wildly disproportionate numbers between groups.

Outcome Measure

Days of survival were calculated by subtracting the date of death from the date of transplant. For those recipients lacking a death date as well as a follow-up date at least 14 months after their transplant, survival was right-censored 1 day after the end of the study period (April 4, 2018). The primary outcome was mortality at 30 days, 4, and 14 months post-transplantation in the MV group, compared between the early and modern periods. Time-points were chosen to encapsulate the immediate perioperative period (30 days), early survival (4 months), as well as survival after the 12-month metric (14 months). Three-year, 5-year, and overall survival were also included. For all 14-month endpoints, conditional survival to 4 months was also tested. Baseline variables were compared between early and modern MV groups, as well as between MV and NMV recipients in the modern group. Secondary outcomes included the association of baseline characteristics in the MV group with 30-day mortality, as well as mortality outcomes in the modern group, compared between MV and NMV recipients. Sensitivity analyses of survival to 6 months, as well as conditional survival to 6 months for 14-month endpoints, were conducted to evaluate the sensitivity of our results to our chosen time-points. Given that recipients on ECMO at time of transplantation were excluded from the analysis, the survival analyses were also repeated including patients bridged with ECMO. Finally, to quantify the impact of mechanical ventilation on mortality, we calculated the population attributable fraction (AF) to estimate the fraction of all cases that would not have occurred without the exposure (MV). This calculation was done for the early group and the modern group separately.

Statistical Analysis

Baseline characteristics. Given the non-normal distribution of the continuous variables, they were expressed as median values with interquartile range (25%, 75%), and compared using the Wilcoxon rank-sum test. Categorical variables were compared using χ^2 or Fisher exact tests. To test the association of baseline characteristics with 30-day mortality in the MV group, multivariable logistic regression was used, and results were expressed as odds ratios (OR). Death data at 30 days were complete. Variables included in the model were chosen via backwards and forwards stepwise regression and clinical judgment (age, sex, body mass index [BMI], LAS, diagnosis, center volume, single vs double transplant, waitlist time, serum creatinine, partial pressure of carbon dioxide (pCO_2), % predicted forced expiratory volume in 1 second [FEV1], ischemic time, donor height, and donor BMI).

Matching. To address potential confounders given recipient differences between the 2 time periods as well as between MV and NMV groups, propensity score matching was used for all Cox regression analyses. Propensity score development was completed using 39 variables extracted from the OPTN database and 3 total groups were matched for 4 different comparisons: in the MV population, early versus modern recipients were matched to compare baseline characteristics and to compare mortality; in the NMV population, early versus modern recipients were matched to compare mortality; in the modern population, MV and NMV recipients were matched to compare mortality. Even with matching,

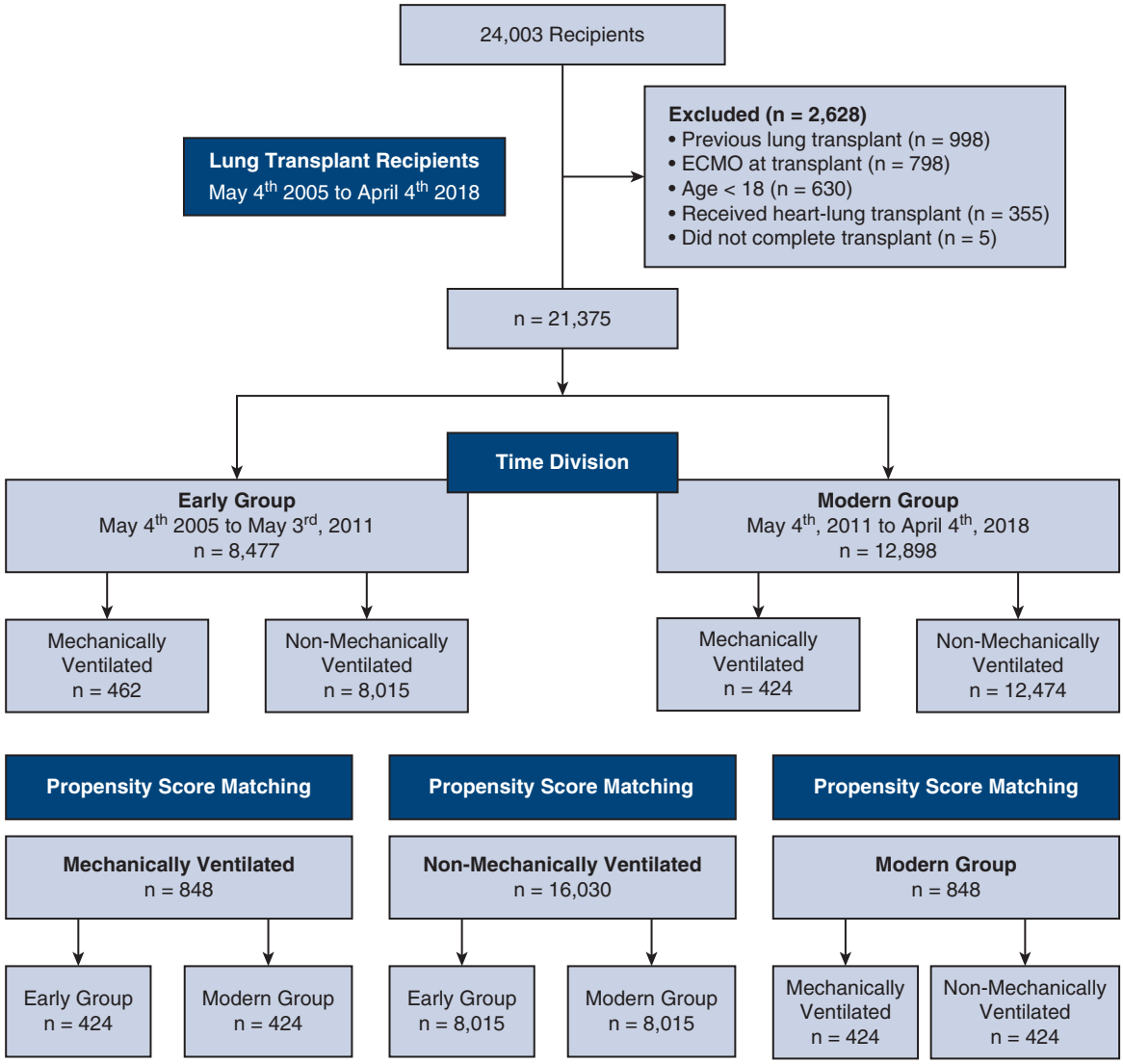


FIGURE 1. Consort diagram demonstrating recipient selection from the Organ Procurement and Transplantation Network registry. Numbers of excluded and unmatched recipients are shown, as well as early and modern group division into mechanically ventilated and nonmechanically ventilated recipients. *ECMO*, Extracorporeal membrane oxygenation.

recipients between groups remained unbalanced (Table E1, Figures E1 and E2). Thus, additional covariates (listed under "Survival analyses") were added to the Cox regression models.

Survival analyses. Kaplan–Meier plots were used to visualize unadjusted survival to 30 days and 14 months. Hazard of death at all time points was evaluated using multivariable Cox proportional hazards models. All Cox models were completed using matched recipients and adjusted for age, sex, serum creatinine, need for dialysis before transplant, post-transplant dialysis, length of stay, LAS, functional status, height, BMI, diabetes, ethnic category, pCO_2, serum bilirubin, waitlist time, oxygen requirement, FEV1, single- versus double-lung transplant, diagnostic grouping, mean pulmonary artery pressure, time from admission to transplant, pretransplant lung perfusion, ECMO at 72 hours post-transplant, MV at 48 hours post-transplant, sex mismatch, ischemic time, donor age, donor sex, donor ethnic category, donor height, donor BMI, donor pO_2, pulmonary infection in the donor, donor cause of death, donor mechanism, donor smoking history, donor drug and alcohol use history, extended criteria donor, and transplant center volume. The proportional hazards assumption was tested by plotting scaled Schoenfeld residuals with respect to time with no obvious violations.

Missing data. To minimize bias introduced by selectively excluding recipients with missing data, random forests imputation was used.[13] No variable included in the analysis was missing more than 10% with the majority of missing variables <1%. No exposure or outcome variables were missing; all missing variables were covariates. The proportion of missing data by year was found to decrease over time in the overall cohort but not in the MV group (Figure E3); 30-day mortality did not vary between those with and without missing data in the MV group (OR, 0.62, 95% confidence interval [CI], 0.24-1.45).

Population AF. To quantify the impact of a specific risk factor on mortality, as has been done in other studies in the lung transplant population,[14,15] we calculated the population AF for the impact of mechanical ventilation on 30-day mortality for the early group as well as for the modern group. In this scenario, AF is interpreted as the proportion of mortality risk attributable to mechanical ventilation. Stated differently, in the same population with no other changes, the AF would be the proportion of mortality

TABLE 1. Mechanically ventilated recipient characteristics and their donors: comparing early with modern groups

Mechanically ventilated characteristics	Early (n = 462), median	IQR or %	Modern (n = 424), median	IQR or %	*P* value	z score
Recipient						
Age, y	56.0	41.0, 63.0	57.0	41.0, 64.0	.44	–0.15
Sex, male, n, %	264	57	236	56	.71	0.54
BMI, kg/m^2	24.5	19.9, 28.5	24.3	20.3, 28.1	.91	1.33
Height, cm	170.2	162.6, 176.8	167.6	162.6, 175.4	.13	–1.13
FEV1, % predicted	33.0	21.0, 54.0	31.0	19.0, 47.0	.01	–2.22
pCO_2, mm Hg	52.9	41.4, 68.5	55.0	43.0, 69.0	.27	–0.60
Creatinine, mg/dL	0.7	0.6, 1.0	0.6	0.5, 0.9	<.01	–3.93
Total bilirubin, mg/dL	0.5	0.3, 0.7	0.4	0.3, 0.7	.14	–1.06
Lung Allocation Score	61.3	39.5, 88.3	83.8	58.4, 90.5	<.01	–6.64
Waitlist time, d	32.5	9.0, 128.5	24.0	7.0, 97.2	.02	–2.02
Diabetes mellitus, n, %	110	24	122	29	.11	–1.20
Hospital length of stay, d	28.0	18.0, 48.2	25.0	16.0, 44.0	.07	–1.51
Days from admission to transplant	1.0	0.0, 12.8	11.0	1.0, 22.0	<.01	–8.20
Transplant type (double), n, %	379	82	359	85	.34	–0.42
Pretransplant lung perfusion, n, %	0	0	17	4	<.01	–4.05
Post-transplant dialysis, n, %	48	10	50	12	.26	–0.63
Post-transplant ECMO > 72 h, n, %	5	1	9	2	<.01	–15.45
Post-transplant ventilation >48 h, n, %	276	60	297	70	<.01	–2.93
Mean PA pressure, mm Hg	n	%	n	%	.98	1.96
≥30	242	62	235	62		
>30-40	97	25	88	23		
>40-50	33	8	33	9		
>50-60	15	4	17	5		
>60	5	1	4	1		
Diagnostic category	n	%	n	%	.06	–1.52
Obstructive lung disease	119	26	82	19		
Pulmonary arterial hypertension	12	3	6	1		
Suppurative lung disease	95	21	95	22		
Fibrotic lung disease	236	51	241	57		
Functional status	n	%	n	%	<.01	–8.02
Moribund	8	2	2	0		
Very sick	87	19	91	21		
Severely disabled	143	31	219	52		
Disabled	26	6	38	9		
Requires considerable assistance	20	4	22	5		
Requires occasional assistance	29	6	17	4		
Unable to carry on normal activity	25	5	5	1		
Some symptoms of disease	70	15	17	4		
Minor symptoms of disease	31	7	9	2		
No evidence of disease	20	4	4	1		
Center volume	n	%	n	%	<.01	–2.75
≤20 transplants/y	86	19	102	24		
21-34 transplants/year	195	42	133	31		
≥35 transplants/y	181	39	189	45		
Cause of death	n	%	n	%	.03	–1.89
Graft failure	18	7	13	9		
Infection	15	6	9	7		
Cardiovascular	40	15	20	14		
Pulmonary	7	3	7	5		
Primary graft dysfunction	4	1	3	2		
Hemorrhage	34	13	20	14		
Malignancy	33	12	10	7		
Other	44	16	39	28		

(Continued)

TABLE 1. Continued

Mechanically ventilated characteristics	Early (n = 462), median	IQR or %	Modern (n = 424), median	IQR or %	*P* value	z score
Donor						
Age, y	33.0	22.0, 48.0	33.0	23.0, 48.0	.46	–0.09
Sex, male, n, %	251	54	233	55	.91	1.31
Sex mismatch, n, %	151	33	153	36	.32	–0.47
BMI, kg/m^2	24.5	21.6, 27.9	25.8	22.6, 30.0	<.01	–3.85
Height, cm	170.2	165.0, 177.8	170.2	162.6, 178.0	.42	–0.19
Last pO_2, mm Hg	400.0	201.5, 495.5	422.0	281.5, 493.0	.20	–0.84
Ischemic time, h	5.4	4.4, 6.5	5.4	4.3, 6.5	.95	1.63
Pulmonary infection, n, %	176	38	260	61	<.01	–6.74
ECD donor, n, %	54	12	45	11	.69	0.49
Cause of death	n	%	n	%	.04	–1.73
Anoxia	54	12	80	19		
Cerebrovascular/stroke	194	42	157	37		
Head trauma	190	41	171	40		
CNS tumor	3	1	2	0		
Drug use	n	%	n	%		
Cigarette use (>20 pack y)	69	15	35	8	.01	–2.42
Heavy alcohol use (2+ drinks/day)	65	14	57	13	.74	0.66
Cocaine use (ever)	48	10	47	11	.34	–0.40
Other drug use, nonintravenous	134	29	165	39	.01	–2.51

Comparing early (May 4, 2005, to May 3, 2011) with modern (May 4, 2011, to April 4, 2018) groups of unmatched mechanically ventilated lung transplant recipients and their donors (expressed as median and IQR or n and % as appropriate). *IQR*, Interquartile range; *BMI*, body mass index; *FEV1*, forced expiratory volume in 1 second; *pCO_2*, partial pressure of carbon dioxide; *ECMO*, extracorporeal membrane oxygenation; *PA*, pulmonary artery; *pO_2*, partial pressure of oxygen; *ECD*, extended criteria donor including delayed cardiac death; *CNS*, central nervous system.

risk that could be eliminated if no recipients were on mechanical ventilation. This is calculated by the difference between the overall average mortality risk of the entire population (MV and NMV) and the average mortality risk of the unexposed (NMV) expressed as a fraction of the overall average mortality risk (MV and NMV).[16] These calculations were completed on matched recipients and adjusted for center volume.

For all analyses, $P < .05$ was considered significant. All analyses were done using R (v3.6.1; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Between May 4, 2005, and April 4, 2018, a total of 24,003 recipients underwent lung transplantation in the United States (Figure 1). Of those, 998 recipients had previous lung transplants, 798 recipients were on ECMO at time of transplant, 630 were pediatric recipients, 355 were heart–lung transplant recipients, and 5 patients did not complete the transplant. These patients were excluded from the study. Of the remaining 21,375 recipients, 8477 were transplanted between May 4, 2005, and May 3, 2011, and 12,898 were transplanted between May 4, 2011, and April 4, 2018. From the entire cohort, 886 recipients were recorded as being on preoperative MV (4.1%), 462 of those in the early period and 424 recipients in the modern period.

MV Recipient and Donor Baseline Characteristics

Comparing early with modern groups. There were notable differences in the MV recipient and donor population when comparing the early to modern periods (Table 1). The modern group had lower FEV1%, lower serum creatinine, greater LAS, shorter waitlist time, longer time from admission to transplant, presence of pretransplant lung perfusion, greater post-transplant use of ECMO >72 hours and incidence of post-transplant ventilation >48 hours, decreased functional status, more transplants performed at greater-volume centers, and more often died of graft failure, infection, and pulmonary causes than the earlier group. Donors in the modern group had greater BMI, greater incidence of pulmonary infections, greater incidence of anoxia as cause of death, less donor cigarette use, and greater donor drug usage when compared with the earlier group.

Adjusted association of baseline characteristics with 30-day mortality. In testing baseline characteristics of the entire unmatched MV group, 3 variables were associated with 30-day mortality (Table 2); pCO_2, serum creatinine, and the need for post-transplant dialysis increased the odds of 30-day mortality. Notably, no association was found between 30-day mortality and recipient single- versus double-lung transplant, FEV1, LAS, O_2 requirement, ischemic time, need for post-transplant ECMO > 72 hours or post-transplant mechanical ventilation >48 hours, center volume, donor age, or using an extended-criteria donor.

Differences in Mortality Between Early and Modern Groups

MV group. We compared the adjusted hazard of death at 30 days, 4, and 14 months post-transplant, as well as 3 years,

TABLE 2. Mechanically ventilated recipients and their donors: baseline characteristics and 30-day mortality

Mechanically ventilated characteristics (n = 886)	OR (95% CI)	*P* value
Recipient		
Age	0.99 (0.96-1.02)	.32
Sex	1.12 (0.55-2.34)	.76
BMI	1.05 (0.98-1.12)	.20
Height	0.99 (0.95-1.04)	.74
FEV1	0.99 (0.97-1.01)	.34
pCO_2	1.02 (1.00-1.04)	.01
Creatinine	1.99 (1.21-3.20)	<.01
Total bilirubin	1.12 (0.68-1.51)	.54
Lung Allocation Score	0.99 (0.97-1.00)	.17
Waitlist time	1.00 (1.00-1.00)	.25
Mean PA pressure	1.02 (0.99-1.05)	.19
O_2 requirement	1.03 (0.98-1.08)	.22
Days from admission to transplant	1.00 (0.98-1.01)	.72
Transplant type	1.34 (0.58-2.95)	.48
Ischemic time	0.91 (0.74-1.10)	.35
Post-transplant dialysis	3.52 (1.17-6.99)	<.01
Post-transplant ECMO >72 h	1.01 (0.05-5.65)	.99
Post-transplant ventilation >48 h	0.99 (0.52-1.94)	.98
Center volume	0.99 (0.98-1.01)	.44
Donor		
Sex mismatch	0.70 (0.34-1.37)	.32
Age	1.00 (0.98-1.02)	.84
Sex	1.93 (0.87-4.34)	.11
BMI	0.97 (0.91-1.02)	.29
Height	1.01 (0.97-1.04)	.71
Pulmonary infection	0.55 (0.28-1.04)	.07
pO_2	1.00 (1.00-1.00)	.36
ECD donor	0.45 (0.10-1.34)	.21

Association of baseline characteristics of unmatched mechanically ventilated lung transplant recipients (May 4, 2005, to April 4, 2018) and their donors with 30-day mortality using multivariable logistic regression. Adjusted for age, sex, BMI, LAS, diagnosis, center volume, single vs double transplant, waitlist time, serum creatinine, pCO_2, FEV1, ischemic time, donor height, donor BMI. *OR*, Odds ratio; *CI*, confidence interval; *BMI*, body mass index; *FEV1*, forced expiratory volume; *pCO_2*, partial pressure of carbon dioxide; *PA*, pulmonary artery; *ECMO*, extracorporeal membrane oxygenation; *pO_2*, partial pressure of oxygen; *ECD*, extended-criteria donor including delayed cardiac death.

5 years, and overall, for the matched 424 MV recipients in each of the early and modern time periods. We found that MV recipients in the modern period had a 25-fold lower hazard of death than MV recipients in the early period at 30 days (hazard ratio [HR], 0.04; CI, 0.02-0.08), and 3-fold at 4 months (HR, 0.29; CI, 0.15-0.59), and near 2-fold at 14 months (HR, 0.59; CI, 0.38-0.92) (Figure 2, Table 3). Mortality at 3 and 5 years, as well as overall, was also lower in the modern group compared with the early group. A sensitivity analysis of survival to 6 months had similar results as survival to 4 months (HR, 0.34; CI, 0.19-0.62). When conditional survival was used (given survival to 4 months, what was the hazard of death up to 14 months in the early vs modern MV groups), the modern group had improvement in survival; however, this association did not achieve statistical significance (HR, 0.94; CI, 0.49-1.78). A sensitivity analysis performed for 14-month mortality given survival to 6 months had similar results. We investigated if recipient selection from the waitlist changed over time to potentially confound our results and found decreased odds of death on the waitlist for MV patients in the modern compared to early time periods (OR, 0.54; CI, 0-.41, 0.69) (Figure E4). Given concern that excluding patients receiving ECMO from our analysis and therefore not capturing sicker recipients in the modern cohort that failed MV and were transitioned to ECMO, we completed a sensitivity analysis including those recipients bridged on ECMO. This did not significantly change our results.

NMV group. We performed the same comparison in the NMV group, comparing the adjusted hazard of death for the matched 8015 NMV recipients in each of the early and modern time periods (Table 3). We found that NMV recipients in the modern period had a trend toward a lower hazard of death at 30 days than the NMV recipients in the early period (HR, 0.90; CI, 0.72-1.11), with a stronger association at 4 months (HR, 0.78; CI, 0.67-0.90), and 14 months (HR, 0.74; CI, 0.67-0.81), although these differences were not as profound as in the MV group. Three, 5-year, and overall mortality HRs were also decreased in the modern compared with the early groups.

Repeating these analyses but including recipients bridged with ECMO provided similar survival analysis results. We also confirmed that time (year of transplant) was associated with survival (HR, 0.99; CI, 0.98-1.0; $P = .01$).

Modern Group Comparisons Between MV and NMV Recipients

Baseline characteristics. As expected, there were multiple differences between NMV and MV recipients in the modern period (Table 4). Compared with NMV recipients, MV recipients were younger, more often female, had lower BMI, greater pCO_2, lower creatinine, greater LAS, shorter waitlist times, greater incidence of diabetes, longer hospital length of stay, longer times from admission to transplant, more often received a double-lung transplant, less often underwent pre-transplant lung perfusion, more often required post-transplant dialysis, more often required post-transplant ECMO for >72 hours and post-transplant ventilation for >48 hours, had greater mean pulmonary artery pressures, different diagnoses, lower functional status, were more often transplanted at a high-volume center, and more often died of infectious, cardiovascular, and pulmonary causes. Compared with NMV donors, donors in the MV group were more often female, shorter, had longer graft ischemic times, and more often died of cerebrovascular causes.

Adjusted hazard of death. Compared with NMV recipients, MV recipients in the modern period had

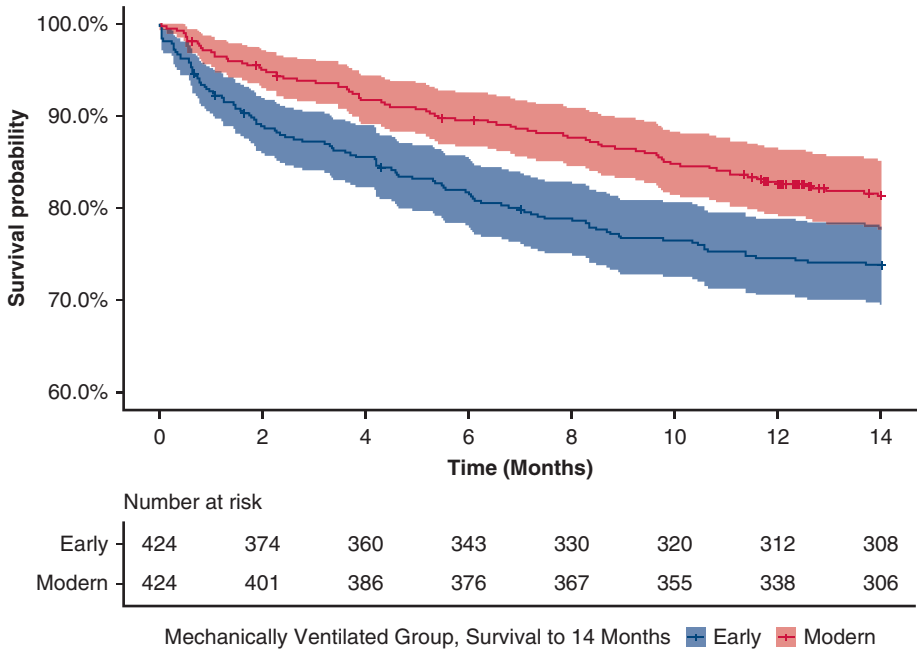


FIGURE 2. Kaplan–Meier survival curves demonstrating survival to 14 months post-transplant for propensity score–matched mechanically ventilated lung transplant recipients comparing early (May 4, 2005, to May 3, 2011) to modern (May 4, 2011, to April 4, 2018) time periods.

increased mortality at 30 days' post-transplant (9.53; CI, 4.57-19.86) (Table 5). This increased hazard of death did not carry through to subsequent time periods.

TABLE 3. Mechanically ventilated recipients: comparing modern with early groups

Mortality time period	HR (95% CI)	*P* value
Mechanically ventilated recipients		
30 d	0.04 (0.02-0.08)	<.001
4 mo	0.29 (0.15-0.59)	.001
14 mo	0.59 (0.38-0.92)	.018
3 y	0.71 (0.51-1.00)	.049
5 y	0.71 (0.53-0.95)	.020
Overall	0.97 (0.55-0.94)	.016
Nonmechanically ventilated recipients		
30 d	0.90 (0.72-1.11)	.316
4 mo	0.78 (0.67-0.90)	.001
14 mo	0.74 (0.67-0.81)	<.001
3 y	0.80 (0.75-0.86)	<.001
5 y	0.86 (0.81-0.91)	<.001
Overall	0.90 (0.85-0.95)	<.001

Comparing modern (May 4, 2011, to April 4, 2018) with early (May 4, 2005, to May 3, 2011) propensity score–matched mechanically ventilated (n = 424 vs 424) and nonmechanically ventilated (n = 8015 vs 8015) recipients using Cox regression analysis. Adjusted for age, sex, serum creatinine, need for dialysis before transplant, post-transplant dialysis, length of stay, Lung Allocation Score, functional status, height, body mass index, diabetes, ethnic category, pCO_2, serum bilirubin, waitlist time, oxygen requirement, forced expiratory volume, single- vs double-lung transplant, diagnostic grouping, mean pulmonary artery pressure, time from admission to transplant, pretransplant lung perfusion, extracorporeal membrane oxygenation at 72 h post-transplant, mechanical ventilation at 48 h post-transplant, sex mismatch, ischemic time, donor age, donor sex, donor ethnic category, donor height, donor body mass index, donor pO_2, pulmonary infection in the donor, donor cause of death, donor mechanism, donor smoking history, donor drug and alcohol use history, extended-criteria donor, and transplant center volume. *HR*, Hazard ratio; *CI*, confidence interval.

Impact of MV on Survival

To quantify the impact of MV on survival, we calculated the population AF of MV on 30-day mortality for each of the matched early and modern groups. This concept is explained in more detail in the methods section. In the early group, the AF was calculated as 5.7% (CI, 2.2%-9.2%) whereas in the modern group, the AF was lower (0.6%, CI, –2.4% to 3.7%). This finding underscores the reduced impact of MV as a risk factor for mortality at 30 days in the modern group.

DISCUSSION

In this retrospective analysis of a national registry, we sought to determine whether outcomes for MV recipients have improved over time, what baseline characteristics of MV recipients are associated with 30-day mortality, and to compare outcomes of MV versus NMV recipients in the modern era (Video 1). We found that survival has improved over time for lung transplant recipients, most markedly in those who require preoperative invasive MV. Using propensity score–matched recipients and multivariable modeling, we found a reduction in adjusted hazard of death at multiple time points post-transplant in the modern MV group when compared with the early MV group (Figure 3). When examining baseline characteristics in the MV group, we found that recipient pCO_2, serum creatinine, and post-transplant dialysis were associated with increased 30-day mortality. Furthermore, regarding the quantifiable risk of mechanical ventilation, we found a reduced population AF of 30-day mortality risk from

TABLE 4. Modern group characteristics: comparing nonmechanically ventilated with mechanically ventilated recipients and their donors

Modern group characteristics	NMV (n = 12,474), median	IQR or %	MV (n = 424), median	IQR or %	*P* value
Recipient					
Age, y	61.0	53.0, 66.0	57.0	41.0, 64.0	<.01
Sex, male, n, %	7496	60	236	56	<.01
BMI, kg/m^2	25.7	22.0, 28.8	24.3	20.3, 28.1	<.01
Height, cm	170.2	162.6, 177.8	167.6	162.6, 175.4	<.01
FEV1, % predicted	36.0	22.0, 54.0	31.0	19.0, 47.0	<.01
pCO_2, mm Hg	45.0	39.0, 53.0	55.0	43.0, 69.0	<.01
Creatinine, mg/dL	0.8	0.7, 1.0	0.6	0.5, 0.9	<.01
Total bilirubin, mg/dL	0.4	0.3, 0.6	0.4	0.3, 0.7	.34
Lung Allocation Score	40.2	34.9, 49.9	83.8	58.4, 90.5	<.01
Waitlist time, d	62.0	19.0, 184.0	24.0	7.0, 97.2	<.01
Diabetes mellitus, n, %	2298	19	122	29	<.01
Hospital length of stay, d	16.0	11.0, 26.0	25.0	16.0, 44.0	<.01
Days from admission to transplant	1.0	0.0, 1.0	11.0	1.0, 22.0	<.01
Transplant type (double), n, %	8633	69	359	85	<.01
Pretransplant lung perfusion, n, %	826	7	17	4	.01
Post-transplant dialysis, n, %	701	6	50	12	<.01
Post-transplant ECMO >72 h, n, %	190	2	9	2	<.01
Post-transplant ventilation >48 h, n, %	4022	32	297	70	<.01
Mean PA pressure, mm Hg	n	%	n	%	<.01
≥30	8625	72	235	62	
>30-40	2120	18	88	23	
>40-50	705	6	33	9	
>50-60	295	2	17	5	
>60	199	2	4	1	
Diagnostic category	n	%	n	%	<.01
Obstructive lung disease	3716	30	82	19	
Pulmonary arterial hypertension	428	3	6	1	
Suppurative lung disease	1300	10	95	22	
Fibrotic lung disease	7030	56	241	57	
Functional status	n	%	n	%	<.01
Moribund	82	1	2	0	
Very sick	126	1	91	21	
Severely disabled	828	7	219	52	
Disabled	741	6	38	9	
Requires considerable assistance	3187	26	22	5	
Requires occasional assistance	1919	15	17	4	
Unable to carry on normal activity	3268	26	5	1	
Some symptoms of disease	1866	15	17	4	
Minor symptoms of disease	394	3	9	2	
No evidence of disease	50	0	4	1	
Center volume	n	%	n	%	<.11
≤20 transplants/y	2482	20	102	24	
21-34 transplants/y	4047	32	133	31	
≥35 transplants/y	5945	48	189	45	
Cause of death	n	%	n	%	.20
Graft failure	302	9	13	9	
Infection	121	4	9	7	
Cardiovascular	616	19	29	14	
Pulmonary	74	2	7	5	
Primary graft dysfunction	62	2	3	2	
Hemorrhage	377	12	14	10	
Malignancy	284	9	10	7	
Other	802	25	39	28	

(Continued)

TABLE 4. Continued

Modern group characteristics	NMV (n = 12,474), median	IQR or %	MV (n = 424), median	IQR or %	*P* value
Donor					
Age, y	33	23.0, 47.0	33.0	23.0, 48.0	.44
Sex, male, n, %	7620	61	233	55	.01
Sex mismatch, n, %	3952	32	153	36	.06
BMI, kg/m^2	25.4	22.5, 29.0	25.8	22.6, 30.0	.09
Height, cm	172.7	165.0, 180.0	170.2	162.6, 178.0	<.01
Last pO_2, mm Hg	415.0	277.6, 485.0	422.0	281.5, 493.0	.35
Ischemic time, h	5.0	4.0, 6.1	5.4	4.3, 6.5	<.01
Pulmonary infection, n, %	8248	66	260	61	.05
ECD donor, n, %	1470	12	45	11	.51
Cause of death	n	%	n	%	.03
Anoxia	2886	23	80	19	
Cerebrovascular/stroke	3861	31	157	37	
Head trauma	5390	43	171	40	
CNS tumor	59	0	2	0	
Drug use	n	%	n	%	
Cigarette use (>20 pack y)	940	8	35	8	.50
Heavy alcohol use (2+ drinks/d)	1841	15	57	13	.85
Cocaine use (ever)	1838	15	47	11	.21
Other drug use, nonintravenous	5348	43	165	39	.43

Comparing baseline characteristics of unmatched nonmechanically ventilated lung transplant recipients (NMV) and mechanically ventilated recipients (MV) in the modern group (May 4, 2011, to April 4, 2018) (expressed as median and interquartile range (IQR) or n and % as appropriate). *NMV*, Nonmechanically ventilated; *IQR*, interquartile range; *MV*, mechanically ventilated; *BMI*, body mass index; *FEV1*, forced expiratory volume; *pCO_2*, partial pressure of carbon dioxide; *ECMO*, extracorporeal membrane oxygenation; *PA*, pulmonary artery; *pO_2*, partial pressure of oxygen; *ECD*, extended-criteria donor including delayed cardiac death; *CNS*, central nervous system.

mechanical ventilation in the modern group compared to the earlier group. However, we also found that MV recipients still have a greater risk of death than NMV recipients in the modern time period.

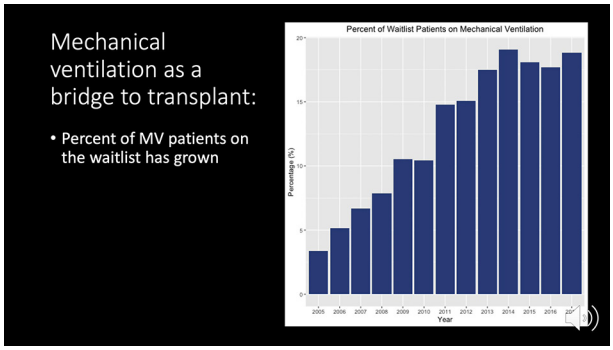
In this era well after the implementation of the LAS, it is clear that we are transplanting sicker patients than we were previously.[7] As evidenced in our study, modern MV recipients have lower FEV1, greater LAS, shorter waitlist times, are admitted to the hospital days before receiving their transplant, and are more often to receive extended postoperative ECMO or MV support than their earlier counterparts. Despite this, survival of the MV recipient has improved. Our finding of a lower population AF in the modern group compared to the early group suggests that the negative impact of MV on 30-day mortality has decreased over time, and that our perioperative care of these patients has improved.

Management of critically ill patients has changed over the last decade. Emphasis has been placed on early mobilization,[9,17] preoperative mobilization while on ECMO,[10]

TABLE 5. Mechanically ventilated versus nonmechanically ventilated recipients in the modern group

Mortality time period	HR (95% CI)	*P* value
30 d	9.53 (4.57-19.86)	<.01
4 mo	1.09 (0.61-1.94)	.77
14 mo	0.88 (0.62-1.23)	.45
3 y	1.01 (0.77-1.31)	.97
5 y	1.01 (0.79-1.28)	.95
Overall	1.06 (0.84-1.34)	.60

Comparing propensity score–matched mechanically ventilated lung transplant recipients with nonmechanically ventilated recipients in the modern group (May 4, 2011, to April 4, 2018) using Cox regression analysis. Adjusted for age, sex, serum creatinine, need for dialysis before transplant, post-transplant dialysis, length of stay, lung allocation score, functional status, height, body mass index, diabetes, ethnic category, pCO_2, serum bilirubin, waitlist time, oxygen requirement, forced expiratory volume, single- vs double-lung transplant, diagnostic grouping, mean pulmonary artery pressure, time from admission to transplant, pretransplant lung perfusion, extracorporeal membrane oxygenation at 72 hours post-transplant, mechanical ventilation at 48 hours post-transplant, sex mismatch, ischemic time, donor age, donor gender, donor ethnic category, donor height, donor body mass index, donor pO_2, pulmonary infection in the donor, donor cause of death, donor mechanism, donor smoking history, donor drug and alcohol use history, extended-criteria donor, and transplant center volume. *HR*, Hazard ratio; *CI*, confidence interval.



VIDEO 1. This video walks viewers through the main structure of our study on outcomes of mechanically ventilated lung transplant recipients and presents the pertinent results. The 3 main aims of the study are discussed. Tables 1-3, and 5 are reviewed, as are Figures 1 and 2. Video available at: https://www.jtcvs.org/article/S0022-5223(20)30519-5/fulltext.

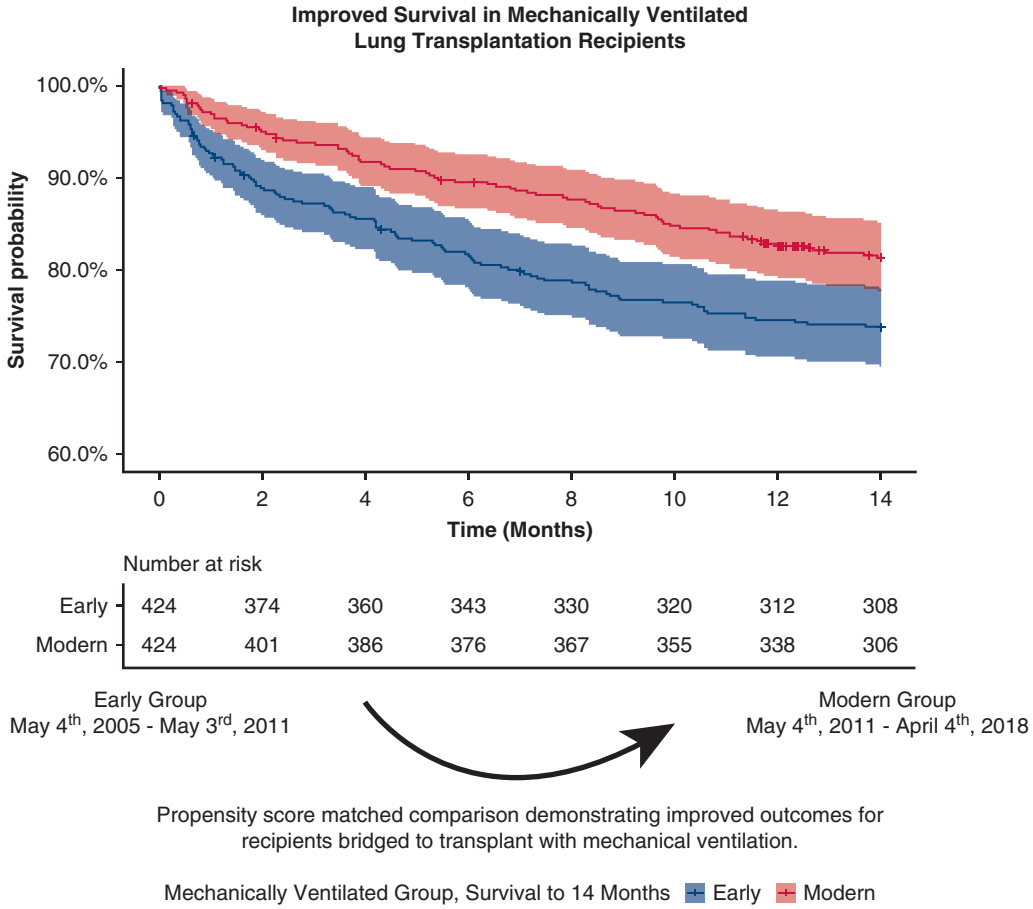


FIGURE 3. Using a national registry, we compared hazard of death for propensity score–matched mechanically ventilated recipients who underwent lung transplantation from May 4, 2005, to May 3, 2011 (early group) to May 4, 2011, to April 4, 2018 (modern group) and found improved survival in the modern group compared with the early group at multiple time points post-transplant. We quantified the impact of mechanical ventilation on survival using population-attributable fractions and found a reduction in the late compared to the early group. This improvement in recipient survival may reflect improvements in recipient perioperative management over time.

low tidal volume ventilation with limited fraction of inspired oxygen,[5] and noninvasive positive pressure ventilation.[18] Evolving treatments for ischemia–reperfusion injury, such as inhaled nitric oxide, may also play a role,[19] as may the benefits of minimizing patient sedation.[20]

Consistent with our findings, recent data suggest that outcomes in this cohort of patients with MV are not as dismal as once believed.[1,21] With improvement in patient management, the proportion of candidates bridged to transplant on MV, ECMO, or both has grown.[5,7] A recent study showed how the use of ECMO as a bridge to transplant has grown in recent years to even surpass the use of MV as a bridging strategy.[22] Other work demonstrated the improved outcomes of those recipients bridged on both MV and ECMO compared with MV alone, suggesting the potential advantage of more liberal bridging strategies to transplantation.[7] This shift, in combination with implementation of the LAS system and urgency-driven allocation, has led to increased transplantation in this population.[5] Thus, increases in center volume and experience have probably contributed to improved recipient outcomes. Our findings support this hypothesis, given the increased proportion of MV recipients transplanted at a high-volume center in the modern era.

Despite the improved survival seen in MV recipients, our study found that the 30-day mortality of MV recipients remains greater than NMV recipients. This is consistent with multiple previous studies confirming the association between recipient preoperative MV and mortality in lung transplantation.[1,4,21] The MV recipient represents a sicker patient population, and worse outcomes than those with a less severe progression of their disease are not surprising.[23] It has been suggested that this decrease in survival is most pronounced early after transplantation.[4] This is consistent with our finding of a strikingly increased hazard of death at 30 days post-transplant with no difference in odds of mortality between groups as we moved to longer time points. This supports the possibility that progression in early perioperative management plays a key role in the improvement of postoperative mortality in this patient population.

Our analysis has limitations. Despite using a large national dataset, the lack of granularity in the data prevented examining specific donor and recipient characteristics that would have been helpful. This lack of detail limited our ability to define the specific cause of the improved mortality seen in our study and may explain why studies conducted outside of the OPTN database do not see the differences in outcome that we found between MV and NMV recipients.[7] We therefore cannot rule out unmeasured confounders. The finding that any MV recipients were classified with minor to no symptoms of disease at time of transplant (Tables 1 and 4) suggests errors in the data collection. In addition, changes made to the LAS system on February 19, 2015, occurred during the study period and may have changed scores for multiple patients. For example, the addition of total bilirubin to the LAS would increase the LAS of candidates with pulmonary vascular disease, increasing their likelihood of transplantation in the later study period. Furthermore, an emergency action change to lung allocation policy was implemented on November 25, 2017 by the OPTN to more broadly share available lungs, increasing the mean LAS of transplanted patients.[24] This resulted in an increase in the overall death rate and a decrease in the overall transplant rate, although this varied by LAS and diagnosis group. These changes may have increased the estimated mortality risk in our later group. However, the effect was likely small, given that our study period ended soon thereafter on April 4, 2018.

CONCLUSIONS

In recent years, there have been significant improvements in survival from lung transplantation in recipients who were MV before transplant. Although our ability to care for those at greatest risk has improved, these recipients continue to lag behind in outcomes compared with the nonventilated population. The improved survival over time in the MV recipient population supports continuing to transplant this population and also strengthens the importance of ongoing research in MV recipient management.

Conflict of Interest Statement

Dr Singer discloses personal fees (scientific advisory board; Breathe Therapeutics). All other authors have nothing to disclose with regard to commercial support.

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Key Words: lung transplantation, mechanical ventilation, survival, perioperative care, modern era

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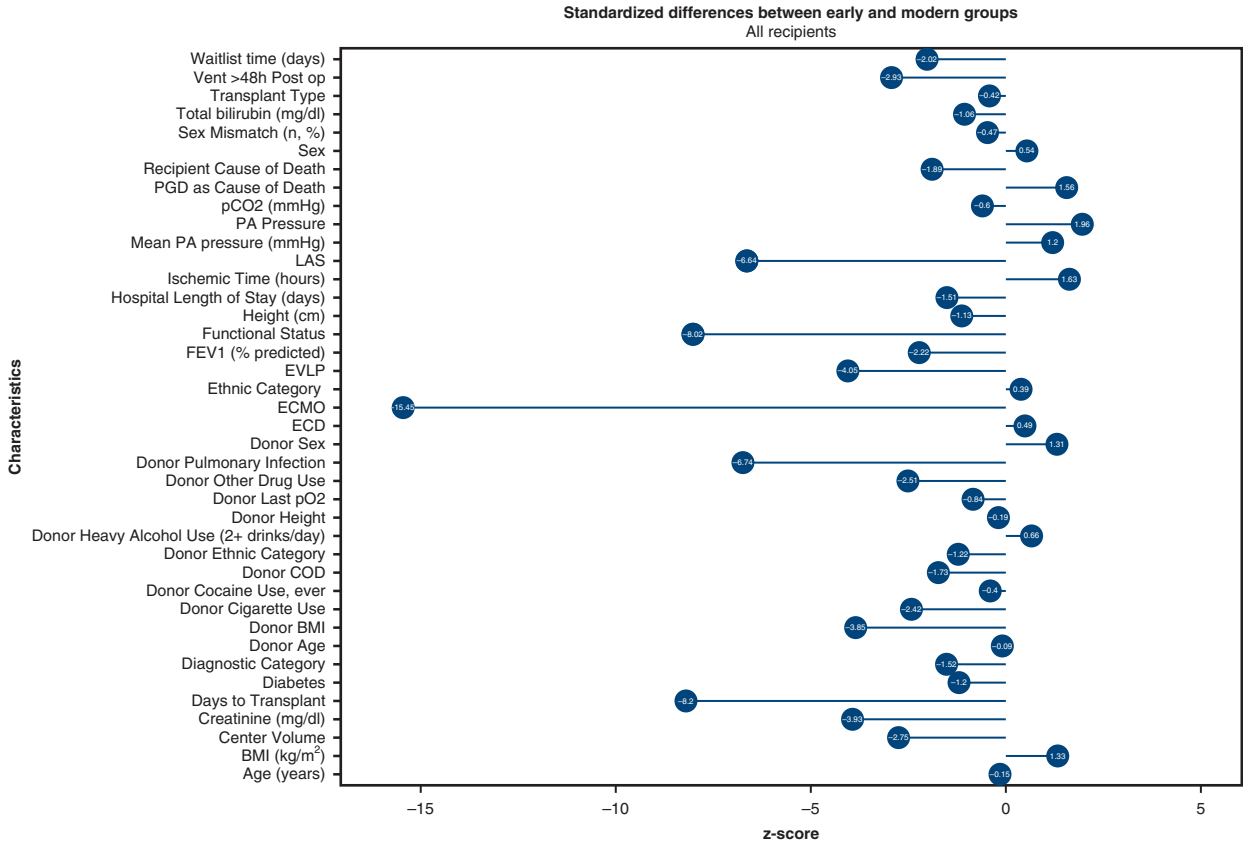

FIGURE E1. Diverging lollipop chart depicting z scores (standardized difference) between mechanically ventilated recipients unmatched between the early and modern time periods. The large values of the z scores emphasize the major differences between groups. *PGD*, Primary graft dysfunction; pCO_2, partial pressure of carbon dioxide; *PA*, pulmonary artery; *LAS*, lung allocation score; *FEV1*, forced expiratory volume in 1 second; *EVLP*, ex-vivo lung perfusion; *ECMO*, extracorporeal membrane oxygenation; *ECD*, extended criteria donor; pO_2, partial pressure of oxygen; *COD*, cause of death; *BMI*, body mass index.

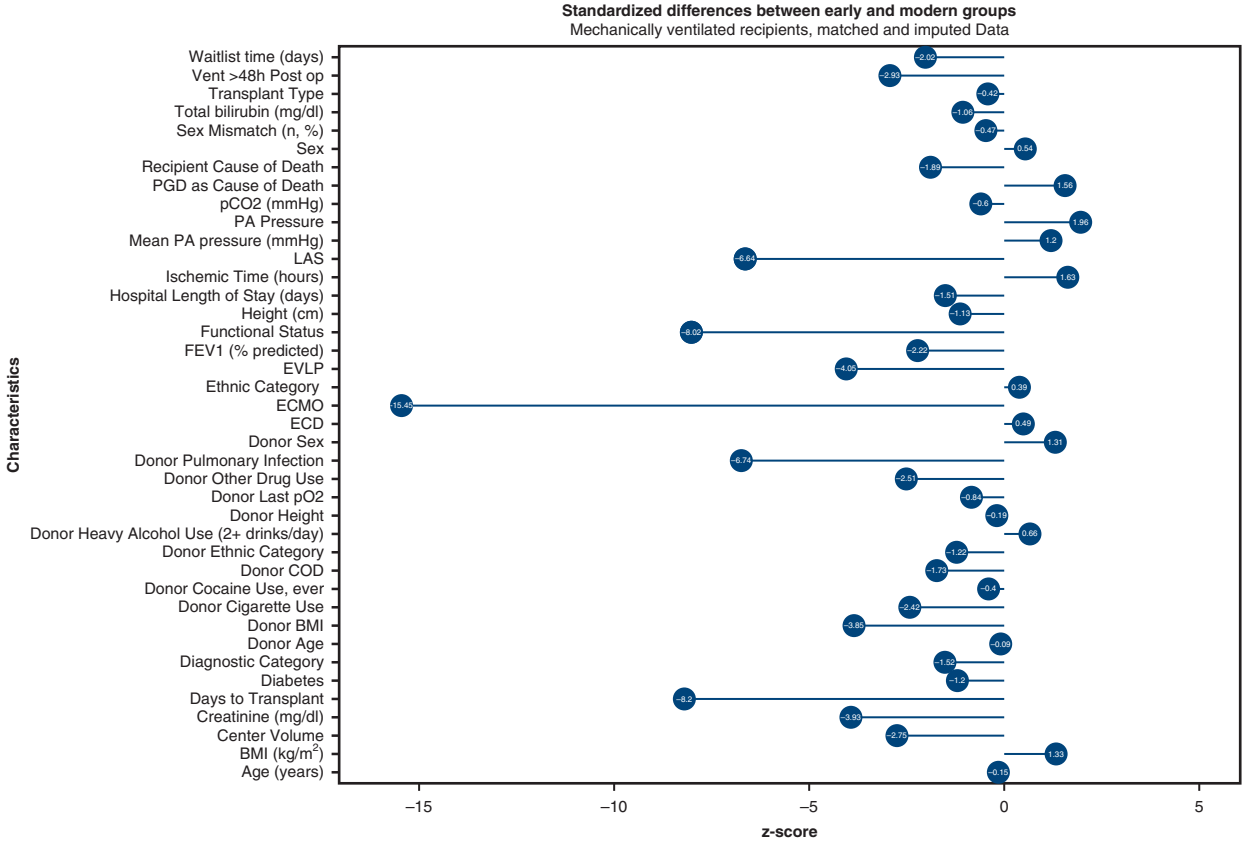

FIGURE E2. Diverging lollipop chart depicting z-scores (standardized difference) between mechanically ventilated recipients matched between the early and modern time periods. The large values of the z-scores emphasizes the persistent major differences between groups despite propensity score matching. *PGD*, Primary graft dysfunction; *pCO_2*, partial pressure of carbon dioxide; *PA*, pulmonary artery; *LAS*, lung allocation score; *FEV1*, forced expiratory volume in 1 second; *EVLP*, ex vivo lung perfusion; *ECMO*, extracorporeal membrane oxygenation; *ECD*, extended criteria donor; *pO_2*, partial pressure of oxygen; *COD*, cause of death; *BMI*, body mass index.

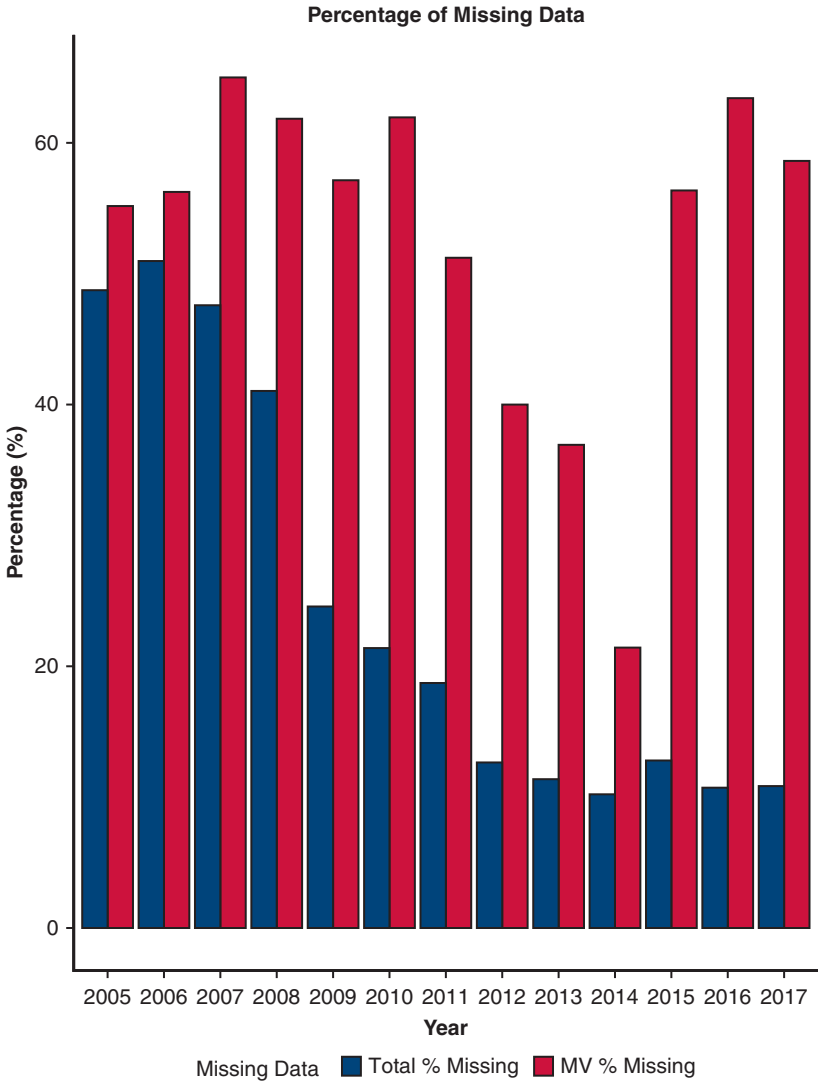

FIGURE E3. Bar plot depicting percentages of transplant recipients per year missing at least one variable. Note that this is different than the percentage of each variable that was missing. *Blue bars* indicate the total percentage of recipients missing at least one data point whereas *red bars* indicate the total percentage of mechanically ventilated recipients missing at least one data point. *MV*, Mechanically ventilated.

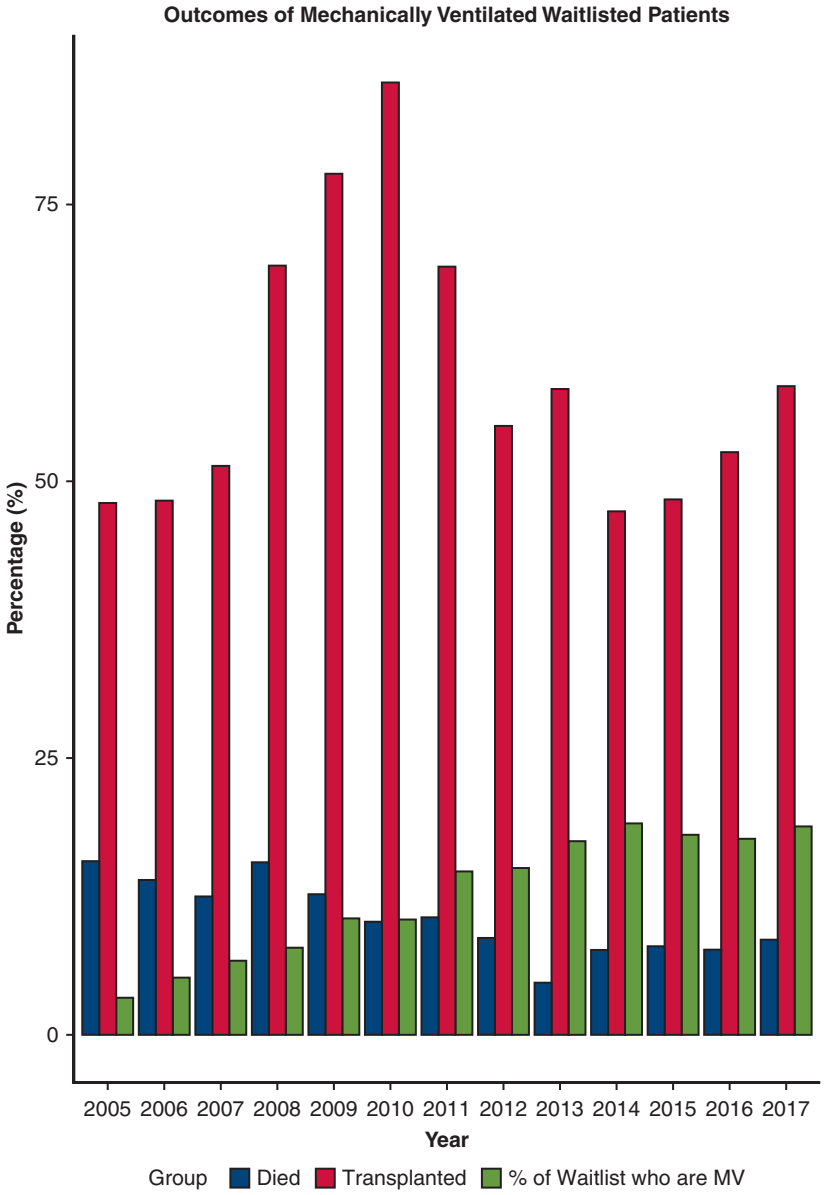

FIGURE E4. Bar plot depicting percentages of MV patients on the waitlist for lung transplantation. Although the percentage of MV patients on the waitlist has increased (*green bars*), the percentage of those MV patients that are transplanted has not (*red bars*). Furthermore, the percentage of MV patients on the waitlist that have died has decreased (*blue bars*). We used multivariable logistic regression to calculate the odds of death on the waitlist during the modern versus early time periods (odds ratio, 0.54; confidence interval, 0.41-0.69). Therefore, the odds of dying on the waitlist have decreased while the proportion of MV patients on the waitlist has increased. *MV*, Mechanically ventilated.

TABLE E1. Mechanically ventilated recipient characteristics and their donors: comparing early with modern groups

Mechanically ventilated characteristics	Early (n = 424), median	IQR or %	Modern (n = 424), median	IQR or %	*P* value	z score
Recipient						
Age, y	55.5	41.0, 63.0	57.0	41.0, 64.0	.35	–0.39
Sex, male, n, %	241	57	236	56	.78	0.78
BMI, kg/m^2	24.6	19.8, 28.5	24.3	162.6, 175.4	.12	–1.19
Height, cm	170.2	162.6, 177.8	167.6	162.6, 175.4	.12	–1.19
FEV1, % predicted	34.0	21.0, 55.0	32.0	19.8, 48.0	.02	–2.04
pCO_2, mm Hg	48.0	40.0, 60.4	53.0	42.0, 67.1	<.01	–3.74
Creatinine, mg/dL	0.8	0.6, 1.0	0.7	0.5, 0.9	<.01	–4.22
Total bilirubin, mg/dL	0.5	0.3, 0.7	0.4	0.3, 0.7	.10	–1.31
Lung Allocation Score	59.4	39.2, 87.6	83.8	58.4, 90.5	<.01	–7.12
Waitlist time, d	34.5	9.8, 133.0	24.0	7.0, 97.2	.01	–1.63
Diabetes mellitus, n, %	100	24	123	29	.09	–1.36
Hospital length of stay, d	28.0	18.0, 48.2	25.0	16.0, 44.0	.05	–1.63
Days from admission to transplant	1.0	0.0, 12.0	11.0	1.0, 22.0	<.01	–8.34
Transplant type (double), n, %	346	82	359	85	.27	–0.61
Pretransplant lung perfusion, n, %	0	0	17	4	<.01	–3.85
Post-transplant dialysis, n, %	41	10	50	12	.22	–0.78
Post-transplant ECMO >72 h, n, %	4	1	9	2	<.01	–15.01
Post-transplant ventilation >48 h, n, %	247	58	297	70	<.01	–3.32
Mean PA pressure, mm Hg	n	%	n	%	.98	2.11
≥30	270	64	269	63		
>30-40	97	23	95	22		
>40-50	37	9	36	8		
>50-60	15	4	18	4		
>60	5	1	6	1		
Diagnostic category	n	%	n	%	.05	–1.69
Obstructive lung disease	110	26	82	19		
Pulmonary arterial hypertension	12	3	6	1		
Suppurative lung disease	89	21	95	22		
Fibrotic lung disease	213	50	241	57		
Functional status	n	%	n	%	<.01	–8.74
Moribund	8	2	2	0		
Very sick	78	18	91	21		
Severely disabled	123	29	219	52		
Disabled	22	5	38	9		
Requires considerable assistance	18	4	22	5		
Requires occasional assistance	29	7	17	4		
Unable to carry on normal activity	25	6	5	1		
Some symptoms of disease	68	16	17	4		
Minor symptoms of disease	30	7	9	2		
No evidence of disease	20	5	4	1		
Center volume	n	%	n	%	.01	–2.39
≤20 transplants/y	83	20	102	24		
21-34 transplants/y	176	42	133	31		
≥35 transplants/y	165	39	189	45		
Donor						
Age, y	33.0	21.8, 47.0	33.0	23.0, 48.0	.23	–0.75
Sex, male, n, %	227	54	233	55	.73	0.61
Sex mismatch, n, %	140	33	153	36	.39	–0.29
BMI, kg/m^2	24.3	21.5, 27.5	25.8	22.6, 30.0	<.01	–4.44
Height, cm	170.2	165.0, 177.8	170.2	162.6, 178.0	.44	–0.16
Last pO_2, mm Hg	400.0	199.0, 498.2	422.2	281.8, 493.0	.23	–0.73
Ischemic time, h	5.3	4.3, 6.5	5.4	4.3, 6.5	.95	1.61
Pulmonary infection, n, %	143	34	260	61	<.01	–7.89

(Continued)

TABLE E1. Continued

Mechanically ventilated characteristics	Early (n = 424), median	IQR or %	Modern (n = 424), median	IQR or %	*P* value	z score
ECD donor, n, %	47	11	45	11	.91	1.35
Cause of death	n	%	n	%	.01	–2.22
Anoxia	45	11	80	19		
Cerebrovascular/stroke	181	43	157	37		
Head trauma	176	42	171	40		
CNS tumor	2	0	2	0		
Drug use	n	%	n	%		
Cigarette use (>20 pack y)	69	16	35	8	<.01	–2.93
Heavy alcohol use (2+ drinks/d)	59	14	57	13	.83	0.96
Cocaine use (ever)	44	10	47	11	.41	–0.22
Other drug use, nonintravenous	121	29	165	39	.01	–2.57

Comparing early (May 4, 2005, to May 3, 2011) to modern (May 4, 2011, to April 4, 2018) groups of propensity score matched mechanically ventilated lung transplant recipients and their donors (expressed as median and interquartile range (IQR) or n and % as appropriate). *IQR*, Interquartile range; *BMI*, body mass index; *FEV1*, forced expiratory volume; pCO_2, partial pressure of carbon dioxide; *ECMO*, extracorporeal membrane oxygenation; *PA*, pulmonary artery; pO_2, partial pressure of oxygen; *ECD*, extended criteria donor including delayed cardiac death; *CNS*, central nervous system.