Lung transplantation in the elderly: Influence of age, comorbidities, underlying disease, and extended criteria donor lungs

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ABSTRACT

Objective: As large registries show an increased risk for lung transplant recipients aged 60 years or more, few single centers report favorable outcomes for carefully selected older recipients without providing essential details. The purpose of our study was to determine variables that influence survival in the elderly.

Methods: All adult bilateral first lung transplants between January 2000 and December 2014 were divided in 2 groups: those aged less than 60 years (N = 223) and those aged 60 years or more (N = 83). The Charlson-Deyo Index determined recipient comorbidities. The Oto Donor Score assessed donor lung quality.

Results: Recipients aged 60 years or more had a significant lower median survival compared with their younger counterparts (48 vs 112 months, respectively, $P < .001$). Recipient age was as an exponentially increasing univariate risk factor for mortality. By adjusting for variables in multivariate analysis, this trend was nonsignificant. The displacing variables were idiopathic pulmonary fibrosis (hazard ratio [HR], 1.5; 95% confidence interval [CI], 1.0-2.2), Charlson-Deyo Index 2 or greater (HR, 1.3; 95% CI, 1.0-1.8), systemic hypertension (HR, 1.7; 95% CI, 1.2-2.6), gastroesophageal reflux (HR, 1.9; 95% CI, 1.1-3.1), diverticulosis (HR, 1.7; 95% CI, 1.0-2.7), and an Oto Donor Score 8 or greater (HR, 1.5; 95% CI, 1.1-2.0). All of these risk factors were significantly more likely to occur in recipients aged 60 years or more, except for a tendency for high Charlson-Deyo Index.

Conclusions: The comorbidity profile, underlying disease, and donor lung quality appear to be more important than age in reducing long-term survival. Older age serves as a marker for a complex constellation of factors that might be considered the relative or absolute contraindication to lung transplantation rather than age, per se. (J Thorac Cardiovasc Surg 2017;154:2135-41)

Worse survival in the elderly due to several risk factors.

Central Message

Older age is not predominantly reducing long-term survival per se, but the complex constellation of factors that are often associated with it.

Perspective

Our study demonstrates that consideration of the comorbidity profile, the underlying disease, and the marginality of the donor lung are more important than age per se to optimize the outcome in elderly recipients. We recommend to further identify and specify these factors in this special group that is increasingly referred for transplantation.

See Editorial Commentary page 2142.

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Because of demographic changes, there is an increasing number of older patients undergoing lung transplantation (LTx). The number of LTx recipients aged 60 years or

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Abbreviations and Acronyms

CI	= confidence interval
Group<60	= recipients aged <60 years
Group60 ⁺	= recipients aged ≥60 years
HR	= hazard ratio
IPF	= interstitial pulmonary fibrosis
ISHLT	= International Society for Heart and Lung Transplantation
LTx	= lung transplantation
UNOS	= United Network for Organ Sharing

more increased worldwide from more than 20% in the year 2000 to more than 40% in 2012.¹

The early published guidelines of the International Society for Heart and Lung Transplantation (ISHLT) in 1998 suggested 60 years of age to be the upper age limit for bilateral LTx because of “a significantly worse survival rate” as shown in the ISHLT Registry.² On the basis of growing experience, the 2006 guidelines adapted the statement of age more than 65 years to be a “relative contraindication” for LTx resulting in “less optimal survival, likely due to comorbidities.”³ In 2015, no recommendation of a fixed upper age limit was given; however, it is stated “increasing age generally is associated with comorbid conditions that are either absolute or relative contraindications.”⁴

Although the current ISHLT⁵ and United Network for Organ Sharing (UNOS)⁶ registries continue to show a significantly increasing risk for LTx recipients aged 60 years or more, some single-center reports indicate that carefully selected older LTx candidates might have similar survival as younger recipients.⁷⁻¹⁰ However, appropriate selection criteria for these recipients are lacking. In this study, we identify variables that influence survival in the elderly by comparing recipients aged less than 60 years and 60 or more years.

PATIENTS AND METHODS

We performed a retrospective cohort study in all recipients who underwent bilateral LTx from January 2000 to December 2014, with a survival follow-up of November 8, 2016. Pediatric recipients and retransplants were excluded. Patients were divided into 2 groups based on age at transplantation: Group<60: aged less than 60 years (N = 223), Group60⁺: aged 60 years or more (N = 83), for an optimal illustration of our sample size in regard to comparison with already published studies and consensus articles. We used electronic medical records to extract preoperative, intraoperative, and postoperative parameters for every individual recipient. Each postoperative event was observed for 3 months. Recipient cause of death also was evaluated. The corresponding donor data were retrieved using electronic donor records.

Definition of Charlson-Deyo Index and Oto Donor Score

Pretransplant recipient comorbidities were collected mainly on the basis of relative contraindications from ISHLT guidelines published in 2006³ and

2015.⁴ To estimate the impact of multiple recipient pretransplant comorbidities, the age-independent Charlson-Deyo Index¹¹ was used. This index considers 19 comorbid conditions (ranging from 1 to 6 points), of which 1 point was always reserved by the chronic pulmonary disease in each of our recipients.

Oto Donor Score¹² was used to estimate the quality of donor lungs, including 5 extended donor criteria based on the recent ISHLT Consensus Report¹³: age, smoking history, chest x-ray, secretion in bronchoscopy, and pulmonary arterial oxygen tension/fraction of inspired oxygen ratio.

Statistical Analysis

Statistical analysis was performed with R 3.3.2 (R Core Team, 2016), IBM SPSS Statistics 23.0 (IBM Corp, 2015, Armonk, NY), and Stata 13.1 (Stata-Corp LP, College Station, Tex). Categorical variables were compared by chi-square test or Fisher exact test for expected frequencies less than 5. Continuous variables were analyzed by the Mann-Whitney test. Survival was calculated by the Kaplan-Meier method and compared with log-rank test. Cox regression was used to assess risk factors for mortality. First, every variable was checked with a univariate (enter) model. Variables with a *P* value less than .2¹⁴ were tested in a multivariable stepwise backward Cox regression model. The number of factors introduced into the final multivariable model was calculated by considering sample size and number of occurring deaths.¹⁵ To confirm that variables show a stable significance, they had to be frequent in number. Linear regression was used to test collinearity between variables. A variance inflation factor greater than 5 and a tolerance less than 0.2 was defined as indicating a collinearity problem. Separate univariate and generalized additive (gam) Cox regressions for mortality with flexible smoothing in the R-package mgcv¹⁶ were conducted to analyze the effect of recipient age as a continuous variable on mortality. The local research ethics review committee approved the study (KEK-ZH-Nr.2013-0624).

RESULTS

Pretransplant recipient and donor characteristics are presented in Table 1. Interstitial pulmonary fibrosis (IPF) and emphysema were the 2 frequent underlying diseases in Group60⁺, whereas it was cystic fibrosis in Group<60.

Recipients in Group60⁺ significantly more often had 2 or more comorbidities in general (53% vs 31%) and diverticulosis, gastroesophageal reflux, systemic hypertension, peripheral vascular disease, postinterventional coronary diseases, and transient cerebrovascular incident in particular. The Charlson-Deyo Index¹¹ also showed a non-significant trend of more comorbidities in the older group.

A significantly higher number of recipients in Group60⁺ received grafts that did not satisfy 2 or more of the 5 ideal donor criteria according to the ISHLT document.¹³ This is in line with the derived Oto Donor Score,¹² which also showed a significantly higher amount of more extended donor grafts in Group60⁺.

As shown in Table 2, intensive care unit stay was significantly longer in Group60⁺, whereas days of intubation and intraoperative extracorporeal membrane oxygenation use were comparable. A cytomegalovirus high-risk constellation (recipient: negative, donor: positive) was significantly more frequent in Group60⁺, affecting more than half of the recipients. Postoperative atrial fibrillation, abdominal complications, and delirium occurred more significantly in Group60⁺.

TABLE 1. Pretransplant recipient and donor characteristics

Recipient characteristics			
Variable	Group<60	Group60 ⁺	P value
N	223	83	
Age, y, median (range)	44 (18-59)	63 (60-70)	
Male gender	115 (51.6%)	50 (60.2%)	.2
Diagnosis			
CF	92 (41.3%)	0	<.001
Emphysema	61 (27.4%)	33 (39.8%)	.04
IPF	36 (16.1%)	35 (42.2%)	<.001
IPAH	14 (6.3%)	3 (3.6%)	.6
Other	20 (9.0%)	12 (14.5%)	
mPAP >25 mm Hg	131 (58.7%)	50 (60.2%)	.8
Waitlist time (d), median (range)	175 (0-1175)	155 (2-914)	.5
Comorbidities in Charlson-Deyo Index			
Postinterventional coronary disease	11 (4.9%)	13 (15.7%)	.002
Congestive heart failure	20 (9.0%)	7 (8.4%)	.9
Peripheral vascular disease	3 (1.3%)	5 (6.0%)	.02
Diabetes mellitus			
No end-organ damage	44 (19.7%)	7 (8.4%)	.02
End-organ damage	1 (0.4%)	0	.5
Mild liver disease	13 (5.8%)	5 (6.0%)	.9
Renal impairment	8 (3.6%)	7 (8.4%)	.1
Transient cerebrovascular incident	0	2 (2.4%)	.02
Other comorbidities			
BMI ≥30 kg/m ²	16 (7.2%)	6 (7.2%)	.9
Systemic hypertension	27 (12.1%)	27 (32.5%)	<.001
Osteoporosis	53 (23.8%)	24 (28.9%)	.4
Diverticulosis	12 (5.4%)	24 (28.9%)	<.001
Gastroesophageal reflux	12 (5.4%)	13 (15.7%)	.004
Critical situation (eg, MV, ECMO, ICU)	26 (11.7%)	3 (3.6%)	.05
Accumulated number of comorbidities (of 14 factors above) median (range)	1 (0-5)	2 (0-5)	<.001
≥1	155 (69.5%)	67 (80.7%)	.05
≥2	70 (31.4%)	44 (53.0%)	.001
≥3	18 (8.1%)	21 (25.3%)	<.001
Charlson-Deyo Index median (range)	1 (1-5)	1 (1-5)	.2
≥2	85 (38.1)	37 (44.6)	.3
≥3	23 (10.3)	12 (14.5)	.3
Donor characteristics			
No. of extended donor criteria, median (range)	1 (0-4)	2 (0-5)	.03
≥2	91 (40.8%)	47 (56.6%)	.01
≥3	26 (11.7%)	17 (20.5%)	.05
Oto Donor Score median (range)	6 (0-12)	7 (0-13)	.003
≥8	74 (33.2%)	41 (49.4%)	.01
≥9	49 (22.0%)	32 (38.6%)	.003

CF, Cystic fibrosis; IPF, idiopathic pulmonary fibrosis; IPAH, idiopathic pulmonary arterial hypertension; mPAP, mean pulmonary artery pressure; BMI, body mass index; MV, mechanical ventilation; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit.

During the study period, a total of 167 recipients died: 109 (49%) and 58 (70%) in Group<60 and Group60⁺, respectively. Table 3 shows the causes of death. Infections leading to sepsis or multiorgan failure were the most common factors in both groups. Death due to cardiac failure tended to be higher in Group60⁺.

Short-term survival was comparable between Group<60 and Group60⁺ (2-year survival ± standard error 80.7% ± 2.6% vs 73.5% ± 4.8%, respectively), whereas long-term survival showed a significant disadvantage for recipients aged 60 years or more (log-rank $P < .001$) (Figure 1). Median follow up was 9.3 years

TABLE 2. Perioperative and postoperative recipient characteristics

Variable	Group<60	Group60 ⁺	P value
N	223	83	
Perioperative characteristics			
ECMO use	105 (47.1)	41 (49.4)	.7
CMV high-risk constellation	86 (38.1%)	47 (56.6%)	.004
ICU stay d, median (range)	3 (1-163)	5 (1-147)	.001
Intubation d, median (range)	1 (0-163)	1 (0-147)	.4
Complications within 3 mo			
Graft failure within 30 d	6 (2.7%)	2 (2.4%)	1.0
Critical illness	17 (7.6%)	9 (10.8%)	.4
polyneuropathy/myopathy			
Cerebrovascular accident	7 (3.1%)	3 (3.6%)	1.0
Atrial fibrillation	43 (19.3%)	33 (39.8%)	<.001
Dialysis	27 (12.1%)	11 (13.3%)	.8
Abdominal complication	20 (9.0%)	15 (18.1%)	.03
Phrenic nerve injury	5 (2.2%)	1 (1.2%)	1.0
MOF	6 (2.7%)	4 (4.8%)	.5
ARDS	10 (4.5%)	2 (2.4%)	.5
Hemothorax	40 (17.9%)	13 (15.7%)	.6
Primary graft dysfunction	22 (9.9%)	12 (14.5%)	.3
Reintubation	21 (9.4%)	10 (12.0%)	.6
Postoperative tracheotomy	45 (20.2%)	22 (26.5%)	.2
Intrathoracic reoperation	61 (27.4%)	25 (30.1%)	.6
Delirium	9 (4.0%)	14 (16.9%)	<.001
Post-transplant infections within 3 mo			
Bacterial	73 (32.7%)	32 (38.6%)	.3
Lung infection	56 (25.1%)	25 (30.1%)	.4
Organism bacteremia	20 (9.0%)	8 (9.6%)	.9
Sepsis	9 (4.0%)	5 (6.0%)	.5
<i>Clostridium difficile</i> diarrhea	10 (4.5%)	1 (1.2%)	.3
Fungal	52 (23.3%)	15 (18.2%)	.3
Viral	15 (6.7%)	7 (8.4%)	.6
CMV reactivation	5 (2.2%)	1 (1.2%)	1.0

ECMO, Extracorporeal membrane oxygenation; CMV, cytomegalovirus; ICU, intensive care unit; MOF, multiorgan failure; ARDS, acute respiratory distress syndrome.

(95% confidence interval, 8.3-10.4) in Group<60 and 4.0 years (95% confidence interval, 2.9-5.1) in Group60⁺. No recipients were lost to follow-up.

Recipient age was revealed as an exponentially increasing univariate risk factor for mortality ($P < .001$) (Figure 2, A), with a duplication of the risk between 60 and 70 years of age.

By adjusting for variables and by smoothing the nonlinear effect of recipient age on mortality in multivariate analysis ($P = .2$) (Table 4), the risk trend of increasing recipient age was nonsignificant (Figure 2, B). The displacing variables are listed in Table 4. Among underlying lung diseases, IPF was found to be a risk factor for mortality. Charlson-Deyo Index of 2 or greater was as a risk factor, indicating a potential risk for a recipient with a single underlying comorbidity, because 1 point was always assessing the underlying lung disease. However, these

TABLE 3. Cause of recipient death

	Group<60	Group60 ⁺	P value
N	109/223 (48.9%)	58/83 (69.9%)	
Infection leading to sepsis/MOF	37 (33.9%)	19 (32.8%)	.9
Cardiac failure	3 (2.8%)	6 (10.3%)	.04
Renal failure	2 (1.8%)	1 (1.7%)	
Hemorrhagic shock	3 (2.8%)	3 (5.2%)	
Intracranial bleeding	3 (2.8%)	3 (5.2%)	
Malignancy	15 (13.8%)	9 (15.5%)	.8
Graft failure	34 (31.2%)	14 (24.1%)	.3
Bowel perforation	9 (8.3%)	2 (3.5%)	.2
Other	1 (0.9%)	0	
Not available	1 (0.9%)	1 (1.7%)	
BOS at death	40 (36.7%)	16 (27.6%)	.3
Unknown	6 (5.5%)	6 (10.3%)	

MOF, Multiorgan failure; BOS, bronchiolitis obliterans syndrome.

underlying comorbidities were not frequent and stable enough to become independent multivariate risk factors. Among other comorbidities, systemic hypertension, diverticulosis, and gastroesophageal reflux were independent risk factors, without association with the Charlson-Deyo Index. Extended donor lungs started to be a risk at an Oto Donor Score of 8 or greater. No collinearity was observed among all variables in the multivariate model.

DISCUSSION

This study demonstrates that older age is not per se predominantly reducing long-term survival after LTx, but a complex constellation of factors that are more often associated with advanced age, namely, the comorbidity profile, underlying disease, and extended donor lungs.

FIGURE 1. Kaplan-Meier survival analysis showing a significant difference between the 2 groups. Group <60, recipients aged less than 60 years (N = 223); Group60⁺, recipients aged 60 years or more (N = 83). CI, Confidence interval.

FIGURE 2. A, Univariate penalized spline regression showing a significant risk for mortality for increasing recipient age ($P < .001$). B, Multivariable penalized spline regression showing a nonsignificant trend for recipient age ($P = .2$) after adjusting for IPF, Charlson-Deyo Index 2 or greater, diverticulosis, gastroesophageal reflux, and Oto Donor Score 8 or greater.

Although short-term survival was comparable between our age groups, long-term survival was significantly worse in older recipients. Moreover, we demonstrated an exponentially increasing risk for mortality for advancing recipient age, if no adjustment for the comorbidity profile, underlying disease, and quality of the donor lung was made. This clear disadvantageous outcome is comparable with the current ISHLT Registry^{1,5} and the UNOS Reports^{6,18} and was also supported by the Toronto Group¹⁷ and the UNOS report.¹⁸ In contrast, other single-center studies⁷⁻¹⁰ that used “carefully selected” older recipients demonstrated favorable intermediate and long-term outcomes (Table 5); however, these studies failed to list their detailed selection criteria for this success.

IPF generally is known to reduce post-transplant survival⁵ and revealed as a risk factor in our study as well. IPF was the predominant underlying disease in our older recipients, which was higher than in previous studies (Table 5).

Considering multiple comorbidities, more than half of our recipients aged 60 years or more had 2 or more comorbidities, which was remarkably more than in the

younger group. By accumulating comorbidities with the Charlson-Deyo Index,¹¹ recipients with a single underlying comorbidity were already at a significantly increased risk. Other studies that have focused on older age provided incomplete comorbidity data, which obviates a reasonable comparison.^{1,6-10,17} Among single-center studies with favorable outcomes in the elderly, the California Group⁸ reported that 1 comorbidity was tolerated in their group aged 65 years or more, which might be due to a stricter selection of candidates compared with our current series. The Toronto Group¹⁷ demonstrated a less favorable outcome in their 42 recipients aged more than 60 years; 4 cases of systemic hypertension were reported of, which 2 also had diabetes. Again, it appears that stricter selection criteria might have been applied compared with our series.

Among the comorbidities, systemic hypertension, diverticulosis, and gastroesophageal reflux were independent risk factors for mortality and each represented even a higher risk impact than the underlying diagnosis of IPF. Our older recipient group more often had all 3 of them.

Systemic hypertension as a pretransplant risk factor is remarkable, because it was only reported from a single study using UNOS Registry data in 821 recipients with pulmonary fibrosis.¹⁹ In another study on more than 8000 recipients, systemic hypertension was not a risk factor,²⁰ and ISHLT⁵ reports do not list it. A recent meta-analysis²¹ has shown that systemic hypertension was a risk factor for postoperative atrial arrhythmias and therefore had prognostic implications for length of hospital stay and overall survival. In our recipients aged less than 60 years and 60 years or more, 21% ($N = 9$) and 42% ($N = 14$) with systemic hypertension were affected by postoperative arrhythmias. In addition, pretransplant systemic hypertension might aggravate itself faster after transplant because of the side effect of immunosuppression treatment with calcineurin inhibitors than in previously healthy recipients and therefore leads to general organ damage earlier.

Acute diverticulitis is associated with a high mortality rate in immunosuppressed patients, and the rate of

TABLE 4. Multivariate analysis of risk factors for mortality

Variable	N	HR	95% CI	P value
Recipient age (smooth)	-	-	-	.2
IPF diagnosis	71	1.5	1.0-2.2	.04
Charlson-Deyo Index ≥ 2	122	1.3	1.0-1.8	.05
Systemic hypertension	54	1.7	1.2-2.6	.007
Diverticulosis	36	1.7	1.0-2.7	.03
Gastroesophageal reflux	25	1.9	1.1-3.1	.02
Oto Donor Score ≥ 8	115	1.5	1.1-2.0	.01

The following variables were no multivariate risk factors: emphysema diagnosis, idiopathic pulmonary arterial hypertension diagnosis, cytomegalovirus high-risk constellation, body mass index ≥ 30 kg/m², osteoporosis, all separate variables in the Charlson-Deyo Index, and critical situation (eg, mechanical ventilation, extracorporeal membrane oxygenation, and intensive care unit). HR, Hazard ratio; CI, confidence interval; IPF, idiopathic pulmonary fibrosis.

TABLE 5. Comparison of published Kaplan–Meier survival and idiopathic pulmonary fibrosis in the elderly

	Age, y	N	3 y (%)	5 y (%)	IPF %
Current series	60-65	61	59	41	41
	>65	22	68	32	58
ISHLT ¹	60-65	7342	-	46	-
	>65	2014	-	38	50
UNOS ¹⁸	60-69	6021	63	48	41
University of California ⁸	≥65	50	74	-	58*
University of Pittsburgh ⁹	60-65	43	63	-	23
	>65	78	69	-	55
University of Virginia ¹⁰	≥60	52	71	55	27
	≥65	16	91	91	
Mayo Clinic ⁷	≥60	42	-	47	37
University of Toronto ¹⁷	>60	42	-	37	36

IPF, Idiopathic pulmonary fibrosis; ISHLT, International Society for Heart and Lung Transplantation; UNOS, United Network for Organ Sharing. *All restrictive diseases.

developing acute diverticulitis is significantly higher than the baseline.²² At our center, we recently reported an overall rate of diverticulitis of 4.5% after LTx.²³ Progression of preexisting diverticulosis into diverticulitis has been shown to surpass this rate to up to 16%.²⁴

Gastroesophageal reflux has been found to be strongly associated with secondary aspiration contributing to chronic lung allograft dysfunction. However, causal proof is still pending.²⁵

Postinterventional coronary disease, congestive heart failure, peripheral vascular disease, diabetes mellitus, mild liver disease, and renal impairment were infrequent comorbidities in our series but reviled as a risk factor when combined in the Charlson-Deyo Index.

Postinterventional coronary artery disease was 16% more frequent in our older recipients along with a trend of more deaths due to cardiac failure. The Pittsburgh Group⁹ showed successful short-term survival in their patients aged 60 to 65 years and more than 65 years, of whom 12% and 26% had coronary artery disease, respectively. For mild to moderate coronary artery disease only, no affection of overall long-term outcome was found in 539 recipients at the Duke University.²⁶

Bacterial infection was the predominant cause of death in both age groups in our study. Previous studies have identified bacterial infections as the most common cause of death in older LTx recipients.^{8,9,17} On the other hand, others have not shown increased rates of post-LTx infections in older recipients¹⁰ or even a certain protection from infection.²⁰ Death from bronchiolitis obliterans syndrome was comparable with other studies.^{6,9,20}

In our study, significantly more extended criteria donor lungs were used in older recipients. We assessed the risk of donor lung quality with the Oto Donor Score¹² and found

a score of 8 or more points to be an independent risk factor. Half of the recipients in our older group were exposed to the risk of an 8-point or greater graft. Of note, other centers reported reduced outcome with an Oto Donor Score of 7 points¹² or less.²⁷ The impact of donor quality in older recipients has rarely been investigated. Only the California Group,⁸ which reported successful outcome in the elderly, showed that 46% of their recipients aged more than 65 years received extended criteria donor lungs compared with 28% in their younger group. However, the extended criteria of these grafts were not further specified, making a comparison impossible.

Study Limitations

Our study has several limitations. It is a retrospective, small-volume, single-center study over more than a decade. Although the Charlson-Deyo Index is widely used, it might not have expressed the exact strength of the broad spectrum of comorbidities in LTx recipients. Also, the Oto Donor Score considers just a few simple parameters and has not been tested in large cohorts.

CONCLUSIONS

Old recipient age has been considered a relative or absolute contraindication to LTx in part because of progressively poorer survival. However, it is uncertain whether older age is the predominant risk factor per se. This study reveals that the comorbidity profile, underlying disease, and donor lung selection seem to be more important than age in reducing survival. Older age then serves as a marker for a complex constellation of factors that reduce long-term survival after LTx. Some of these factors may be correctable, and others are immutable. It is the constellation of factors that might be considered the relative or absolute contraindication to LTx rather than any one of them, including age, per se. Because LTx in the elderly is an ongoing controversial ethical challenge, we encourage other centers to help further identify and specify factors to optimize outcome.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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