Incidence and Outcomes of Post-lymphoproliferative Disorder in Lung Transplant Recipients. Analysis of the ISHLT Registry

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ABSTRACT

PURPOSE

Post-transplant lymphoproliferative disorder (PTLD) is a rare but life-threatening complication following solid organ transplant. Its incidence varies depending on the organ transplanted with rates described as high as 8% following lung transplantation. In this study, we assessed the incidence and outcomes of lung transplant recipients who developed PTLD using the International Society of Heart and Lung Transplant (ISHLT) Transplant Registry in order to better understand the clinical characteristics and the impact of PTLD in this population.

METHODS

All adult primary lung transplants performed between 2000 and June 2015 were included. Kaplan – Meier analysis was used to assess cumulative incidence of PTLD and a time dependent variable Cox proportional hazards model was utilized to assess the association between post-transplant survival and the occurrence of post-transplant PTLD.

RESULTS

The ISHLT registry identified 44,532 adult primary lung transplants during the study period. Considering only recipients transplanted at centers reporting PTLD complications to the ISHLT registry, there were 19,939 eligible lung transplants for this analysis. Median age at time of transplant was similar between lung transplant recipients with or without PTLD (56 years-old vs 57 years-old, respectively). Similarly, there was no difference in percentage of bilateral versus single lung transplants between recipients with or without PTLD. Of those who developed PTLD, 50% of cases occurred within 12 months following lung transplantation. The cumulative incidence of PTLD was 1.6% (95% CI = 1.5%, 1.8%) during the first year and 4.4% (95% CI= 3.9%, 5.0%) at 10 years after lung transplant. Considering the development of PTLD as a time-dependent indicator in our survival model, there was a 3-fold increase risk of death after PTLD diagnosis (95% CI = 2.73, 3.36; p-value < 0.001) compared to lung transplant recipients who did not develop PTLD.

CONCLUSION

Our study suggests that PTLD is relatively rare complication after lung transplant. However it is associated with high risk of mortality. Therefore, identifying risk factors for predicting the development of PTLD following lung transplantation could help in defining specific surveillance strategies as well as tailored therapeutic approaches.

OBJECTIVES

Aim 1: Describe the incidence of post-transplant lymphoproliferative disorder (PTLD), timing after transplant and clinical characteristics of lung transplant patients affected by PTLD.

Aim 2: Identify specific clinical risk factors associated with the development of PTLD.

		Cohort	TXP Pts with PTLD	TXP Pts with no PTLD
KESULIS		N= 19309	N=454	N= 18855
	Age (median, IQR)	57.0 (47.0, 63.0)	58.0 (45.2, 62.0)	57.0 (47.0, 63.0)
Table 1. Overall study demographics	BMI (median, IQR)	24.8 (21.0, 28.2)	24.6 (20.6, 28.0)	24.8 (21.1, 28.2)
	Female, n (%)	8320 (56.9%)	173 (61.9%)	8147 (56.8%)
	Bilateral Lung Transplant, n (%)	12297 (63.7%)	301 (66.3%)	11996 (63.6%)
	Death in follow up, n (%)	9539 (49.4%)	340 (74.9%)	9199 (48.8%)

Fig.2 KM curve illustrating the cumulative incidence of PTLD after lung transplant



Aim 3: Examine the impact of PTLD on the overall survival of lung transplant patients.

METHODS

We analyzed the International Society of Heart and Lung Transplantation (ISHLT) registry for all primary adult lung transplant performed between January 2006 and June 2015 with at least 1-year follow-up data. Inclusion criteria figure 1.

Among all patients in the analysis cohort, the Kaplan Meier (KM) method was used to obtain estimates of the cumulative event probability of PTLD as function of time. To describe the relationship between PTLD and death post-transplant, a KM curve for subjects with and without PTLD was overlaid. Univariable and multivariable Cox proportional hazards models were used to analyze time to PTLD as a function of patient characteristics prior to transplant. Similarly, an extended Cox regression model for time to all-cause death as a function of PTLD was developed. Statistical

significance was considered if p < 0.05.



CONCLUSIONS

PTLD is a relatively rare event. The probability of PTLD occurring in the first 10 years after transplantation is 4.4% (95% CI = 3.9%, 5%), (fig.2)

Table 2. Univariable and multivariable Cox regression hazards for development

Univar HR	-	Multivar HR	
(95% CI)	р	(95% CI)	р
, <i>i</i>	< 0.001	<u> </u>	< 0.001
0.75		0.80	
(0.69, 0.82)		(0.71, 0.89)	
1.26		1.33	
(1.16, 1.38)		(1.20, 1.47)	
0.62		0.61	
(0.41, 0.94)		(0.40, 0.93)	
0.97	0.574	0.96	0.492
(0.88, 1.07)		(0.84, 1.09)	
0.77	0.006	0.81	0.060
(0.63, 0.93)		(0.65, 1.01)	
1.09	0.361	1.13	0.351
(0.90, 1.33)		(0.88, 1.45)	
1.03	0.373	0.99	0.758
(0.97, 1.08)		(0.93, 1.06)	
	< 0.001		0.003
1.19		1.59	
(0.69, 2.06)		(0.89, 2.82)	
1.81		1.56	
(1.39, 2.35)		(1.00, 2.44)	
1.47		1.58	
(1.19, 1.83)		(1.23, 2.01)	
0.38	< 0.001	0.39	< 0.001
(0.31, 0.45)		(0.32, 0.48)	
0.85	0.102	0.81	0.072
(0.70, 1.03)		(0.65, 1.02)	
	Univar HR (95% Cl) 0.75 (0.69, 0.82) 1.26 (1.16, 1.38) 0.62 (0.41, 0.94) 0.97 (0.88, 1.07) 0.77 (0.63, 0.93) 1.09 (0.90, 1.33) 1.03 (0.97, 1.08) 1.19 (0.69, 2.06) 1.81 (1.39, 2.35) 1.47 (1.19, 1.83) 0.38 (0.31, 0.45) 0.85 (0.70, 1.03)	Univar HR p (95% Cl) p < 0.001 0.75 $(0.69, 0.82)$ 1.26 $(1.16, 1.38)$ 0.62 $(0.41, 0.94)$ 0.97 0.574 $(0.88, 1.07)$ 0.77 0.006 $(0.63, 0.93)$ 1.09 0.361 $(0.90, 1.33)$ 1.03 0.373 $(0.97, 1.08)$ < 0.001 1.19 $(0.69, 2.06)$ 1.81 $(1.39, 2.35)$ 1.47 $(1.19, 1.83)$ 0.38 0.102 $(0.70, 1.03)$	Univar HRmultivar HR $(95\% Cl)$ p $(95\% Cl)$ < 0.001 < 0.001 0.75 0.80 $(0.69, 0.82)$ $(0.71, 0.89)$ 1.26 1.33 $(1.16, 1.38)$ $(1.20, 1.47)$ 0.62 0.61 $(0.41, 0.94)$ $(0.40, 0.93)$ 0.97 0.574 0.96 0.81 $(0.88, 1.07)$ $(0.84, 1.09)$ 0.77 0.006 0.81 0.361 1.09 0.361 1.09 0.361 1.03 0.373 0.99 0.99 $(0.97, 1.08)$ $(0.88, 1.45)$ 1.03 0.373 0.99 0.373 $0.99, 1.33$ $(0.89, 2.82)$ 1.19 1.59 $(0.69, 2.06)$ $(1.00, 2.44)$ 1.47 1.58 $(1.19, 1.83)$ $(1.23, 2.01)$ 0.38 < 0.001 0.39 0.39 $(0.31, 0.45)$ 0.102 0.85 0.102 $0.65, 1.02)$

- CF and restrictive disease were associated with a higher risk of PTLD relative to obstructive disease. While female recipients and recipients with positive EBV status were at lower risk of PTLD relative to male recipients and recipients with negative or unknown status (table 2)
- There was evidence of a non-linear relationship between recipient age and PTLD (Figure 3b). Between 45 and 65 years old, for every 5year increase in age, there is an increased HR of 1.3 for PTLD.
- PTLD is associated with a 3 (95% CI = 2.73,3.36; p < 0.001) times higher risk of death post-transplant (fig 3a)

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Fig.3a-b: A) KM curve illustrating all-cause mortality in the PTLD cohort (blue) vs Non-PTLD lung transplant recipients (black); B) Non linear relationship between Age and Development of PTLD

