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The Association of Post–Lung Transplant Pulmonary Embolism With the Development of Chronic Lung Allograft Dysfunction

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Background. Pulmonary embolism (PE) is a rare yet serious postoperative complication for lung transplant recipients (LTRs). The association between timing and severity of PE and the development of chronic allograft lung dysfunction (CLAD) has not been described. **Methods.** A single-center, retrospective cohort analysis of first LTRs included bilateral or single lung transplants and excluded multiorgan transplants and retransplants. PEs were confirmed by computed tomography angiography or ventilation/perfusion (VQ) scans. Infarctions were confirmed on computed tomography angiography by a trained physician. The PE severity was defined by the Pulmonary Embolism Severity Index (PESI) score, a 30-d post-PE mortality risk calculator, and stratified by low I and II (0–85), intermediate III and IV (85–125), and high V (>125). PE and PESI were analyzed in the outcomes of overall survival, graft failure, and chronic lung allograft dysfunction (CLAD). **Results.** We identified 57 of 928 patients (6.14%) who had at least 1 PE in the LTR cohort with a median follow-up of 1623 d. In the subset with PE, the median PESI score was 85 (75.8–96.5). Most of the PESI scores (32/56 available) were in the low-risk category. In the CLAD analysis, there were 49 LTRs who had a PE and 16 LTRs (33%) had infarction. When treating PE as time-dependent and adjusting for covariates, PE was significantly associated with death (hazard ratio [HR] 1.8; 95% confidence interval [CI], 1.3-2.5), as well as increased risk of graft failure, defined as retransplant, CLAD, or death (HR 1.8; 95% CI, 1.3-2.5), and CLAD (HR 1.7; 95% CI, 1.2-2.4). Infarction was not associated with CLAD or death. The PESI risk category was not a significant predictor of death or CLAD. **Conclusions.** PE is associated with decreased survival and increased hazard of developing CLAD. PESI score was not a reliable predictor of CLAD or death in this lung transplant cohort.

(*Transplantation Direct* 2024;10: e1572; doi: 10.1097/TXD.0000000000001572.)

Lung transplantation has become a highly effective treatment for patients with end-stage lung disease to increase lifespan and quality of life.[1] Yet, lung transplantation is a major surgery that carries a myriad of early as well as long-term complications. Early postoperative outcomes are limited mainly by primary graft dysfunction, acute rejection (AR), pulmonary effusions, acute kidney injury, and bronchial stenosis, whereas long-term complications can range from lymphoproliferative disorders to recurrent infections from atypical bacterial and fungal pathogens because of chronic immune suppression.[2-4] Graft failure, which leads to mortality or the need for retransplant, can be caused by any of these early or long-term complications, such as severe AR, infections, or primary graft dysfunction. However, chronic lung allograft dysfunction (CLAD), a diagnosis of sustained decreased lung function without known etiology, remains the limiting burden to improving long-term graft survival in lung transplant recipients (LTRs).[5,6]

Pulmonary embolism (PE) is a rare yet serious postoperative complication for LTRs. The reported incidence of PE

Received 14 June 2023. Revision received 19 October 2023.

Accepted 27 October 2023.

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Notation of prior abstract publication/presentation: Early versions of this project were presented as abstracts and poster presentations at American Thoracic Society 2020 and CHEST 2016.

J.C.M. participated in research design, obtained institutional review board approval, collected most data, participated in performance of research, wrote original article draft, and incorporated edits from other authors. C.X. performed data analysis for the study, contributed analytic tools, and contributed relevant portions of the article related to statistical methods. S.P. supervised and performed data analysis for the study, contributed analytic tools, and contributed relevant portions of the article related to statistical methods. M.D. assisted in a significant portion of data collection, research design, and helped to edit the article. C.W.F. assisted in a significant portion of data collection and helped to edit the article. T.D. and L.D.S. supervised the process of institutional review board submission, organized oversight for data collection, and provided mentorship throughout the process of data collection and article writing in addition to significant edits to the article.

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The authors declare no funding or conflicts of interest.

ISSN: 2373-8731

DOI: 10.1097/TXD.0000000000001572

after lung transplant varies widely from around 1% to 15%.[7] Importantly, the risk of PE is reported as a long-term risk, most likely due to the extended disability and limited mobility experienced by LTR contributing to a hypercoagulable state and, as such, is a sustained risk beyond the early postoperative period.[2,8,9] Previous studies have focused on describing the incidence and risk factors of venous thromboembolic events, as well as specifically PE, after lung transplantation and their associations with decreased survival.[7,9-14] Notably, pulmonary infarction has been described in a case of increased mortality, highlighting the amplified risk of such an event possibly because of a lack of collateral bronchial artery anastomoses to adequately perfuse the transplanted lungs.[15] To date, although literature provides single-center perspectives on survival analyses after venous thromboembolic events, the association between timing and severity of PE and the subsequent development of CLAD have not been previously described. The Pulmonary Embolism Severity Index (PESI) is a measurement tool to risk stratify clinically significant PE and subsequently calculate the risk of 30-d mortality at the time of PE diagnosis.[16] However, PESI use has not been reported in lung transplant cohort studies. Thus, we sought to identify whether PE and the PESI risk categorization are associated with CLAD, graft failure, and overall survival in a lung transplant cohort with an extended follow-up period.

MATERIALS AND METHODS

We performed a single-center, retrospective cohort analysis of first-time LTRs from May 2005 to August 2015 with follow-up through October 31, 2018. We included both bilateral orthotopic lung transplant and single orthotopic lung transplant, whereas multiorgan transplants and retransplants were excluded. PE was confirmed by computed tomography angiography (CTA) and/or ventilation and perfusion (VQ) scans. It is not standard practice at this center to assess PE in the donor. If there is a clinical concern, a CTA would be requested, and if a significant donor PE is found, the organ is excluded from transplantation. Infarction was confirmed on CTA by a physician observing partial filling defects or eccentric wedge-shaped artifacts. PESI was used to score each PE event and individually stratify the clinical risk. PESI clinical risk was categorized as low (0–85), intermediate (86–125), and high risk (>125).[16] CLAD was defined by the International Society of Heart and Lung Transplantation guidelines as a sustained decline in posttransplant FEV_1 <80% of the average of the highest 2 posttransplant FEV_1 measurements with no concurrent comorbidities.[6] For this analysis, we included both definite and probable CLAD in the CLAD outcome. Inclusion criteria to be eligible for CLAD analysis were survival of at least 90 d and completion of at least 5 posttransplant pulmonary function tests. Graft failure was defined as the earliest date of death, retransplant, or CLAD at any time point after the first transplant.

We operated under institutional guidelines for retrospective studies at Duke University Medical Center and conducted our study under the approved institutional review board Pro00105273. We conducted the statistical analysis under R version 4.0.2 with "coxph" function in the "survival" package.[17] This article adheres to the applicable Consolidated Standards of Reporting Trails guidelines.

Survival and Graft Failure Analyses

Time-varying PE Cox model: time from PE to outcome (death, graft failure) was modeled using a Cox proportional hazards model. Patients who did not have the event are administratively censored on October 31, 2018. PE was considered as a time-varying variable. We fit an unadjusted (no covariates) model and an adjusted covariates model. Covariates included sex (binary), race (categorical), transplant age (continuous), transplant type (categorical), diagnosis group (categorical), length of hospital stay (continuous), ECMO at candidate listing (categorical), and ECMO at transplant (categorical). All further adjusted models use these same covariates previously listed, unless otherwise stated.

PESI score model: time from PE to event (death, graft failure) was modeled using a Cox proportional hazards model. We fit an unadjusted (no covariates) model, an adjusted covariates model, and an adjusted covariates model plus an infarction variable model.

CLAD Analyses

To be included in the CLAD analysis, patients had to meet a 90-d postoperative survival landmark. That is, patients were excluded if death, graft failure, or retransplant preceded 90 d after transplant for any reason.

Time-varying PE Cox model: time from PE to CLAD was modeled using a Cox proportional hazards model. Patients who did not have the event were administratively censored on October 31, 2018. PE was considered a time-varying variable. We fit an unadjusted (no covariates) model and an adjusted model with the previously described covariates.

PESI score model: time from PE to time to CLAD/death was modeled using a Cox proportional hazards model. We fit an unadjusted (no covariates) model, an adjusted covariates model, and an adjusted covariates model plus an infarction variable model.

Time-varying PE with infarction model: due to a competing risk, time to combined outcome (CLAD/death) was modeled using a Cox proportional hazards model. Patients who did not have the event are administratively censored on October 31, 2018. PE with infarction was a time-varying variable. We fit an unadjusted (no covariates) model and an adjusted covariates model.

To assess the validity of the proportional hazards assumption, we used a weighted residuals test in all adjusted models.[18] If covariates violated the proportional hazards assumption, we used a time-varying coefficient approach to allow the hazard ratio (HR) to vary over time.[19]

RESULTS

Patient Characteristics

The cohort included 928 LTRs during the study period with a median age of 60.0 y (49.0–67.0) at the time of first transplant. Seven hundred thirteen LTRs (76.8%) received a bilateral orthotopic lung transplant and 572 LTRs (61.6%) identified as men. Of those within the cohort who were considered eligible for CLAD (N = 869), 326 (39.0%) developed CLAD within the study period. Further demographics are noted in Table 1.

In the cohort, 57 patients (6.14%) developed at least 1 PE after their first lung transplant during the follow-up period (median 1623 d). The median time from transplant to PE

TABLE 1.

Demographic and clinical characteristics in the overall study cohort, then as stratified by confirmed PE

Characteristics	Entire cohort (N = 928)	PE cohort[a] (N = 57)
Age at transplant, y	60 (49–67)	62 (56–66)
Male	572 (62%)	39 (68%)
Race		
Black	74 (8%)	4 (7%)
White	835 (90%)	53 (93%)
Other	19 (2%)	0 (0%)
Median follow-up, d	1623 (712–2594)	993 (313–2142)
Native lung disease[b]		
COPD	238 (26%)	11 (19%)
Vascular	22 (2%)	2 (4%)
Cystic	134 (14%)	6 (11%)
Restrictive	534 (58%)	38 (66%)
Transplant type		
Bilateral lung	713 (77%)	35 (61%)
Single lung	215 (23%)	22 (39%)
ECMO (at time of transplant)	24 (2.6%)	1 (2%)
Length of stay, d	15 (10–26)	16 (10–38)
CLAD[c]		
Eligible for Analysis	869 (94%)	48 (84%)
Events	326 (38%)	24 (42%)

Continuous variables presented as median (IQR); categorical variables presented as frequency (proportion).

[a]PE defined as a confirmed artifact on CTA and/or VQ scan mismatch.

[b]As according to American Thoracic Society/ European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association criteria.

[c]To be eligible for CLAD evaluation, patients must have at least 90 d of follow-up and at least 5 PFTs measured; Summary measures reported among patients eligible for CLAD evaluation.

CI, confidence interval; CLAD, chronic lung allograft dysfunction; COPD, chronic obstructive pulmonary disease; CTA, computed tomography angiography; ECMO, extracorporeal membrane oxygenation; HR, hazard ratio; IQR, interquartile range; PE, pulmonary embolism; PFTs, pulmonary function tests; VQ scan, ventilation/perfusion scan.

diagnosis was 74 d (21–189). Of the patients with PE, 42 (73.7%) occurred within the first 180 d posttransplant. In the CLAD model, there were 49 eligible LTRs with a PE event and 16 (33%) had an infarction. In the PE cohort, the median PESI score was 85 (75.8–96.5). Most of the PESI scores (32/56 available) were stratified into the low-risk category (0–85).

PE and Overall Survival

In an unadjusted analysis, there was an association with worse survival in LTR with a PE event (HR 1.97; 95% confidence interval [CI], 1.42-2.72). In a multivariate analysis adjusted for age at transplant, type of transplant, native lung disease, race, length of stay, and ECMO at time of transplant, LTRs with a PE had a significantly higher risk of death (HR 1.79; 95% CI, 1.29-2.49) as compared with those without a PE. When we assessed the time-invariant PESI score with time to death, we did not identify an association between the PESI score and time to death (Table 2). Furthermore, after we risk stratified PESI scores by low (0–85), intermediate (86–125), and high (>125) risk, there was no difference between PESI risks and time to death (Table 2).

PE and Graft Survival

Among the 928 LTRs, 50 (5.4%) developed PE after the first transplant and before the onset of graft failure. In an unadjusted model, time-varying PE had a positive association with increased hazard of graft failure (HR 1.91; 95% CI, 1.38-2.64). After adjusting for covariates, PE maintained a positive association with an increased risk of graft failure (HR 1.77; 95% CI, 1.28-2.46). In unadjusted models as well as adjusted models, PESI score was not associated with graft failure (Table 3). Interestingly, risk stratified PESI scores did not have an association with the risk of graft failure in unadjusted models (Table 3).

TABLE 2.

Association between PESI and time to death (N = 56)

Variable	Unadjusted, HR (95% CI)	Adjusted for covariates, HR (95% CI)
PESI	1.01 (0.997-1.02)	1.01 (0.99-1.03)
PESI stratified		
Low (32 patients)	Ref	Ref
Intermediate (21 patients)	1.79 (0.93-3.46)	1.28 (0.57-2.86)
High (3 patients)	1.43 (0.33-6.18)	1.69 (0.34-8.35)
PESI stratified		

CI, confidence interval; HR, hazard ratio; PESI, Pulmonary Embolism Severity Index.

PE and CLAD Analysis

Of the 928 first-time LTRs, 869 (94%) were eligible to be included in the CLAD analysis. Furthermore, of the 869 CLAD-eligible LTRs, 49 (5.6%) developed a PE. Of these, 48 patients (98%) developed a PE before the onset of CLAD and were included in the models. The median time from PE diagnosis to confirmed CLAD diagnosis was 643 d (175–1395). In the unadjusted model, PE had a positive association with an increased hazard of CLAD (HR 1.83; 95% CI, 1.32-2.55). After adjusting for covariates in the time-varying Cox model, PE sustained an increased risk for developing CLAD (HR 1.69; 95% CI, 1.21-2.36). Length of stay showed evidence of violating the proportional hazards assumption in the PE to CLAD combined outcome model; therefore, the coefficient for length of stay is time-varying in the final model (Table 4). PE maintained a similar statistically significant association between PE and CLAD/death after this adjustment. Moreover, PE within 180 d was associated with a similar increased hazard for a combined outcome (HR 1.77; 95% CI, 1.23-2.55), whereas PE after 180 d did not show a significant signal (Table 5). All other covariates in all other adjusted models did not show evidence of violating the proportional hazards assumption.

Interestingly, when assessing the association between PESI and CLAD-free survival (time to CLAD/death), there was no significant difference in the unadjusted model (Table 6), yet a marginal statistical significance in the adjusted covariates

TABLE 3.

Association between PESI and time to graft failure (N = 49)

Variable	Unadjusted, HR (95% CI)	Adjusted for covariates, HR (95% CI)
PESI	1.01 (0.997-1.02)	1.01 (0.997-1.03)
PESI stratified		
Low (26 patients)	Ref	Ref
Intermediate (20 patients)	1.93 (0.97-3.83)	1.80 (0.78-4.14)
High (3 patients)	2.34 (0.67-8.23)	3.45 (0.81-14.69)

CI, confidence interval; HR, hazard ratio; PESI, Pulmonary Embolism Severity Index.

TABLE 4.

Association between time-varying PE (n = 48) and CLAD/death (N = 869)

Variable	Unadjusted, HR (95% CI)	Adjusted, HR (95% CI)	Time-transformed, HR (95% CI)
PE	1.83 (1.32-2.55)	1.69 (1.21-2.36)	1.66 (1.18-2.32)
PE and infarction			
No PE	Ref	Ref	
PE w/o infarction	1.88 (1.26-2.81)	1.79 (1.19-2.68)	
PE with infarction	1.74 (1.003-3.02)	1.52 (0.87-2.67)	

CI, confidence interval; CLAD, chronic lung allograft dysfunction; HR, hazard ratio; PE, pulmonary embolism.

TABLE 5.

Association between time-varying PE (n = 48) and time to CLAD/death (n = 869) with time-transformed LOS

Variable	HR (95% CI)
PE	
No PE	Ref
PE within 180 d	1.77 (1.23-2.55)
PE after 180 d	1.23 (0.55-2.77)

CI, confidence interval; CLAD, chronic lung allograft dysfunction; HR, hazard ratio; LOS, length of stay; PE, pulmonary embolism.

TABLE 6.

Association between PESI and CLAD/death (N = 48)

Variable	Unadjusted HR (95% CI)	Adjusted for covariates HR (95% CI)
PESI	1.01 (0.999-1.02)	1.02 (1.001-1.04)
PESI stratified		
Low (26 patients)	Ref	Ref
Intermediate (19 patients)	1.90 (0.94-3.81)	1.97 (0.86-4.52)
High (3 patients)	2.96 (0.83-10.53)	5.07 (1.16-22.28)

CI, confidence interval; CLAD, chronic lung allograft dysfunction; HR, hazard ratio; PESI, Pulmonary Embolism Severity Index.

analysis between PESI and time to CLAD and death was observed (HR 1.02; 95% CI, 1.001-1.04). Moreover, after risk stratifying the PE patients into low (n = 26), intermediate (n = 19), and high (n = 3) risk PESI scores, there was no association with combined CLAD-free survival (Table 6). Yet, there was a statistically significant association between high PESI and an increased hazard for combined outcome once adjusting for confounders (Table 6); however, there is a low sample size and high variability in the estimation of the HR.

PE With Infarction and CLAD Analysis

As a further exploratory analysis, we investigated how PEs with or without diagnosed infarction may affect the CLAD analyses and possibly serve as a risk stratification for CLAD risk. Interestingly, after stratifying the CLAD analysis PE cohort by those who had infarction (n = 16) versus no infarction (n = 33), we noted a consistently increased risk of CLAD in the PE cohort without infarction in both the unadjusted and adjusted models (HR 1.88; 95% CI, 1.26-2.81; HR 1.79; 95% CI, 1.19-2.68, respectively). Notably, the PE with infarction cohort only had a positive association with increased risk of CLAD/death in the unadjusted model (1.74; 95% CI, 1.003-3.02), but significance was not sustained for the infarction cohort after adjusting for covariates (Table 4).

DISCUSSION

Our results show that in a multivariate analysis LTRs who are diagnosed with a posttransplant PE have worse survival, as well as higher risks of graft failure and developing CLAD earlier than those without a PE event. Importantly, our analysis demonstrates that this effect is independent of other known contributors to poor outcomes after lung transplantation, such as transplant type and native lung disease. Interestingly, our study discovered that PESI was not a useful tool in predicting poor outcomes with no association with mortality or CLAD.

Previous studies have described increased mortality for patients who have PE after lung transplantation.[7,14] Yet, our study uniquely presents analysis within the context of a much larger cohort with an extended follow-up period while also building on these findings by additionally assessing the risk of CLAD and graft failure and whether the PESI score can be used as a risk stratification.

To date, the observation that PE is associated with CLAD has not been described in prior literature and is a novel finding of our study. However, PE as a risk factor for CLAD has an unclear mechanism. It is possible that the PE event leads to a heightened inflammatory response that causes downstream cellular damage and an activated immune response, or the PE event contributes to the lack of collateral flow to the allograft that accelerates a decline in pulmonary function.[12] The higher incidence, as well as the specific association between PE within 180 d and CLAD/death, further highlights the increased awareness clinicians should maintain for diagnosing PE and minimizing CLAD and mortality risk. It is possible that some early PE in the postoperative period could be donor derived, and these would have been treated similarly based on clinical presentation. Moreover, this study did not assess the causes of PE in this population.

Interestingly, case studies have shown that PE with infarction may be associated with increased mortality.[15] However, our results yielded that, if anything, the absence of infarction was associated with increased death and CLAD in the adjusted, combined outcome models. It is possible that this reflects the difference in the management of PE. Although this study had higher numbers of infarctions compared with case reports, there was still a relatively low sample of PE with infarction. Our study clearly agrees with other studies along the lines that associations of pulmonary infarction and PE deserve more thorough investigation in future studies to discern infarction's role as a possible marker for mortality and CLAD development.[20]

Based on the evidence that PE is associated with both all-cause mortality and CLAD, we assessed whether PESI could provide any associations that clinicians use to help risk stratify PE. However, our data showed that raw PESI score did not show reliable associations with any of the measured outcomes nor PESI risk stratification. This could be because PESI, by definition, is assessing the risk of 30-d mortality of anyone presenting with a PE, whereas this analysis assessed all-cause mortality, graft failure, and CLAD, so factors that affect 30-d mortality in nontransplanted patients may intrinsically not have associations with these outcomes. Lack of predictive value of PESI could also be due to close post-transplant monitoring of LTRs. That is, LTRs who present with PE may receive higher levels of conservative care by the transplant program than a traditional patient presenting with PE; thus, LTRs with the same PESI scores may experience lower mortality than what is assumed within the scoring system. Kanade et al[10] found no increase in the risk of 30-d mortality in LTRs who had PE, which further confirms that PESI may not show an association with our measured outcomes.

Despite this being the largest study evaluating the association of PE with mortality and CLAD after lung transplantation, there are several limitations to this study. First, this initial study does not account for other known risk factors for CLAD, such as AR, infections, donor-specific antibodies, and HLA antibodies.[21] Our event rate limited the risk factors to include in the model. However, based on our findings, we would suggest that additional investigation of PE is warranted in future CLAD studies where there are larger event rates. Moreover, these investigations should assess the variations and abilities to treat PE within the early postoperative and how this may affect the onset of CLAD. Additionally, PE may be underdiagnosed after lung transplantation.[22,23] Reasons causing this underdiagnosis could be the lack of nerve innervations to the allograft, preventing some classic clinical presentations of PE (chest pain), as well as the reliance often on clinical suspicion for an imaging study to be ordered. Therefore, we may not be capturing the true incidence of PE in our study and thus may not have a completely precise representation of the risk of mortality or developing CLAD. Furthermore, we have the limitation of a single-center, retrospective study confined to 1 clinical environment. Future studies should assess multiple large academic transplant centers for improved power of analysis and include objective assessments of CLAD with a prospective design.

In conclusion, PE after lung transplant is associated with increased mortality, decreased graft survival, and earlier onset of CLAD. Clinicians should have an increased awareness for PE after lung transplant and should be alerted at diagnosis of PE as the allograft may be compromised, especially within the first 180 d. Future studies should address the mechanism behind PE association with CLAD and parse out the implications that infarction may play in risk. PESI score is not a reliable predictor of CLAD or death after PE in a lung transplant cohort.

ACKNOWLEDGMENTS

The authors would like to sincerely thank the Duke BERD Methods Core's for their support of this project, which was made possible (in part) by grant number UL1TR002553 from the National Center for Advancing Translational Sciences of the National Institutes of Health (NIH), and NIH Roadmap for Medical Research. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Center for Advancing Translational Sciences or NIH.

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