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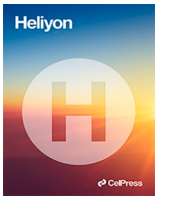

Research article

Metabolic complications in lung transplantation for cystic fibrosis - A case control study

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ABSTRACT

Background: Metabolic complications post-lung transplant are poorly understood and little is known about how these complications differ between patients with or without cystic fibrosis (pwCF and pwoCF). This study compared post-lung transplant outcomes between pwCF and pwoCF relating to survival and incidence of diabetes, dyslipidaemia, hypertension, and renal impairment.

Methods: A retrospective (2004–2017) case-control study involving 90 pwCF and 90 pwoCF (age, sex and year of transplant matched) was conducted. Demographic variables, pre/post-transplant metabolic diseases, blood investigations and medications were extracted. Descriptive statistics were used to describe the cohort. Mann-Whitney U and Chi-squared tests were used to analyse morbidity and mortality data. Regression analyses were used to identity independent variables that impacted clinical outcomes. Kaplan Meier analysis with log-rank testing was used to compare survival.

Results: PwCF were younger, had lower BMIs, and were less likely to have pre-transplant extra-corporeal membrane oxygenation (ECMO) use. A total of 37 pwCF and 41 pwoCF died ($p = 0.65$) during the period of observation with no differences in survival. Adjusting for covariates of age, sex and BMI via multiple logistic regression, CF status was associated with a dramatic increased risk of new-onset diabetes post-transplant (adjusted odds ratio 28.7; 95 % CI, 28.76 to 108.7). No other differences in adjusted risk were found.

Conclusions: As pwCF had a greater adjusted risk of developing new post-transplant diabetes and experienced metabolic complications at similar rates as pwoCF, the findings highlight the need for rigorous monitoring of pwCF for possible metabolic complications post-transplant.

1. Background

Cystic fibrosis (CF) is an autosomal recessive genetic disorder of the cystic fibrosis transmembrane conductance regulator with more than 2000 unique mutations described to date [1]. Survival of patients with CF (pwCF) was historically limited to childhood, though in recent decades, life expectancy has dramatically increased due in part to advances in medical care and nutritional supports resulting in the current median life expectancy of 57.3 years in Canada [2]. It is expected that with the introduction of highly effective modulator therapy (HEMT), life expectancy will continue to rise [3]. As the indication for modulators are based on patient genetics,

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not all are eligible for HEMT. Consequently, in individuals with CF who are ineligible or do not respond to HEMT, progressive irreversible respiratory insufficiency remains a possibility, resulting in a need for lung transplantation [4]. Lung transplant can significantly improve life expectancy for individuals with end-stage lung disease [5]. However, assessing the likelihood of survival post-transplant for pwCF is complex, and there are often significant complications such as allograft failure, infection, and metabolic diseases [4].

Over half of solid organ transplant recipients experience metabolic complications, and those with pre-existing metabolic disease may experience worsening of their disease post-transplant [6]. Metabolic complications may impact both graft and patient survival, and may lead to increased risk of cardiovascular and cancer-associated mortality [6]. In a study of over 3000 patients, CF diagnosis was found to be a risk factor for post-transplant diabetes mellitus [7]. However, there is little research regarding other metabolic complications of individuals post-transplant with CF relative to patients without CF (pwoCF). PwCF may be at increased risk of developing complications of metabolic disorders, such as hypertension, dyslipidemia, atherosclerosis and cardiovascular diseases in part due to life-long exposure to systemic inflammation [8]. Consequently, we hypothesize that pwCF will experience relatively more metabolic diseases compared to pwoCF after adjusting for confounding variables. The objectives of this study were to compare post-transplant survival and rates of diabetes, dyslipidaemia, hypertension, chronic kidney disease complications between pwCF and pwoCF.

2. Methods

2.1. Study design and population

The study is a retrospective case-control study of PwCF and pwoCF transplanted 2004–2017 at the University of Alberta hospital (Edmonton, Canada) with 1:1 matching to patients transplanted for non-CF diagnoses. PwCF and pwoCF were matched based on age, sex-at-birth, and year of transplantation. Patients were first matched by sex, then each group was ranked in order of age, and paired by each decade of life to minimize the age difference between matching pairs. Finally, year of transplantation was matched. The University of Alberta institutional review board approved this study (Pro00091643) (a waiver of consent granted by the ethics board).

2.2. Measures

A retrospective chart review was undertaken from the lung transplant program database as well as the electronic medical record systems used by the lung transplant and the CF care teams (E-clinician). Sex at birth, age, body mass index (BMI) at the time of transplant, and extracorporeal membrane oxygenation (ECMO)/ventilator use pre-lung transplantation was collected for demographic characterization of the study population. Pre- and post-transplantation comorbidities (including hypertension, diabetes, dyslipidaemia, renal dysfunction), standard of care blood investigations (including lipid profile, creatinine and HbA1c) and medication lists were extracted from the charts. See Appendix A for definitions of metabolic complications and measurements.

2.3. Sensitivity analysis

Up to 50 % of the data was missing around dyslipidemia and its treatment in our database; up to 35 % of data on hypertension diagnosis or treatment was missing; and 8 % of data on renal impairment diagnosis or treatment was missing. Sensitivity analysis was conducted by repeating the exploratory and multivariate analyses after removal of patients with missing data.

2.4. Statistical analyses

Continuous variables were reported using summary statistics (means and standard deviation), and categorical variables were reported using counts and percentages. Descriptive statistics were used to describe the cohorts. Mann-Whitney U and Chi squared tests were used to analyse morbidity data. The long-rank test was used for comparison of the Kaplan-Meier survival curves to determine mortality outcome. Multiple logistical regression was used to identify independent variables that contributed to metabolic outcomes. Age, sex and BMI were considered as co-variates in the modelling. $P < 0.05$ was considered significant. Analyses were performed using Prism 9.0 (GraphPad Software, Boston, Massachusetts, USA, www.graphpad.com).

Table 1
Cohort demographics and baseline pretransplant characteristics.

	Total (n = 180)	pwCF (n = 90)	pwoCF (n = 90)	p-value
Age at transplant in y, mean (SD)	37.3 (12.96)	30.8 (10.81)	43.9 (11.57)	≤0.01
Female, n (%)	98 (54.4 %)	49 (54.4 %)	49 (54.4 %)	>0.99
BMI at transplant in kg/m^2, mean (SD)	22.3 (4.9)	19.7 (3.2)	24.9 (4.9)	<0.01
ECMO pre-transplant, n (%)	12 (6.7)	4 (4.4)	8 (8.9)	0.04

PwCF patients with cystic fibrosis; pwoCF patients without cystic fibrosis; SD standard deviation; BMI body mass index; ECMO extracorporeal membrane oxygenation.

3. Results

3.1. Cohort characteristics

A total of 90 pwCF received a lung transplant at the University of Alberta hospital over the time period January 1st, 2004 to December 31st, 2017. We matched these cases based on age, sex at birth, and year of transplant to 90 pwoCF controls for a sample size of 180 subjects total. The indication for lung transplantation for pwoCF is listed in Supplemental Table 1. Follow-up was complete to June 2019. Table 1 demonstrates the cohort demographics and baseline characteristics. Despite attempts at matching, significant differences in the age remained between the CF and non-CF cohorts. PwCF had a significantly lower BMI compared to pwoCF given that CF is a malabsorptive condition. There was more ECMO use pre-transplant in the pwoCF cohort. Pre-transplant, a total of 10 individuals were intubated (5 with CF; 5 non-CF), 5 had a tracheostomy (2 pwCF; 3 pwoCF), and 15 received non-invasive ventilation (10 pwCF; 5 pwoCF).

3.2. Survival

37 pwCF and 41 pwoCF died during the study period ($p = 0.65$). Kaplan-Meier survival curves demonstrate similar post-transplant survival between the two cohorts that were not significantly different ($p > 0.05$; hazard ratio = 0.92; 95 % confidence interval: 0.58, 1.44; Fig. 1).

3.3. Metabolic complications

Metabolic complications including diabetes, dyslipidemia, hypertension and chronic kidney disease were examined pre- and post-transplant (Table 2). There were statistically more patients with diabetes prior to (Type I; $p = 0.018$, Type II; $p = 0.017$) and new-onset post-transplantation in the pwCF compared to the pwoCF cohort ($p < 0.01$). There were no differences in cases of dyslipidemia prior to transplantation ($p = 0.14$) but there were a greater number of new diagnoses (incident cases) of dyslipidemia post-transplantation in the pwoCF compared to pwCF group ($p < 0.0001$). However, 40–50 % of the data was missing around dyslipidemia and its treatment in our database. Sensitivity analysis was conducted after removal of patients with missing data and the difference between the cohorts were further strengthened. With regards to hypertension, more pwoCF had hypertension pre-transplantation compared to pwCF ($p = 0.03$) but there were no differences in new-onset (incident) hypertension post-transplant between the two groups ($p = 0.83$). Roughly 30–35 % of data on hypertension diagnosis or treatment was missing. Sensitivity analysis was conducted after removal of patients with missing data which did not significantly change the outcome. Finally, there were higher rates of post-transplant incident chronic renal impairment in pwoCF compared to pwCF ($p = 0.004$). There were no cases of renal insufficiency pre-transplant in either cohort. Roughly 8 % of data on renal impairment diagnosis or treatment was missing. Sensitivity analysis was conducted after removal of patients with missing data which did not significantly change the outcome.

Multivariable logistic regression models were used to analyse the relationship between CF status and new-onset metabolic complications adjusting for residual differences in age, sex, BMI and CF status (Table 3). After adjusting for confounders, age and BMI were found to be independent risk factors for the development of diabetes. Strikingly, CF status was a very strong risk factor for new-onset diabetes post-transplant (odds ratio: 28.8; 95 % CI, 28.76,108.7). As expected, increasing age is a risk factor for development of dyslipidemia and hypertension post-transplant. CF status was not a significant risk factor of the development of post-transplant dyslipidemia, chronic kidney disease or hypertension.

4. Discussion

This case-controlled study included 90 pwCF who received a lung transplant from 2004 to 2017, matched by age, sex-at-birth and year of transplant with 90 pwoCF who received a lung transplant to compare mortality and metabolic complications post-transplant. Our findings here demonstrate that other metabolic complications are equally common regardless of CF status with new-onset diabetes

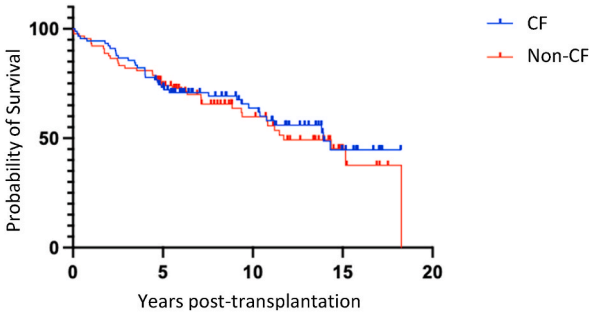

Fig. 1. Post-transplant survival of patients with and without CF.

Table 2
Metabolic complications pre and post lung transplant.

	Total (n = 180)	pwCF (n = 90)	pwoCF (n = 90)	p-value
Diabetes[a]				
Pre-Tx Type I, n (%)	9/180 (5.0)	8/90 (8.9)	1/90 (1.1)	0.018
Pre-Tx Type II/CF related, n (%)	15/180 (8.3)	12/90 (13.3)	3/90 (3.3)	0.017
Post-Tx New diagnosis, n (%)	92/145 (63.4)	61/72 (84.7)	31/73 (42.5)	<0.01
Dyslipidemia[b]				
Pre-Tx, n (%)	5/99 (5.1)	4/46 (8.7)	1/53 (1.9)	0.14
Post-Tx New diagnosis, n (%)	34/86 (39.5)	7/40 (17.5)	27/46 (58.7)	<0.0001
Hypertension[c]				
Pre-Tx, n (%)	9/124 (7.3)	1/61 (1.6)	7/63 (11.1)	0.03
Post-Tx New diagnosis, n (%)	98/117 (83.8 %)	49/59 (83.1 %)	49/58 (84.5)	0.83
Chronic kidney disease[d]				
Post-Tx New diagnosis, n (%)	117/166 (70.5 %)	53/87 (60.9)	64/79 (81.0)	0.004

pwCF patients with cystic fibrosis; pwoCF patients without cystic fibrosis; LTx lung transplantation.
[a] 20 % of data reported on diabetes post-transplant was missing.
[b] 40 and 50 % of data reported on dyslipidaemia was missing pre-transplant and post-transplant, respectively.
[c] 30 and 35 % of data reported on hypertension was missing pre-transplant and post-transplant, respectively.
[d] There were no instances of chronic kidney disease pre-transplant. 8 % of data reported on renal impairment was missing post-transplant.

Table 3
Logistic regression models of the risk factors associated with new onset post-transplantation metabolic outcomes.

	Odds Ratio	95 % confidence interval
Diabetes		
Age	**1.05**	**1.00–1.09**
Female sex	1.11	0.50–2.49
BMI	**1.10**	**1.00–1.23**
CF status	**28.76**	**9.05–108.70**
Dyslipidemia		
Age	**1.12**	**1.06–1.21**
Female sex	2.22	0.72–7.50
BMI	0.90	0.78–1.04
CF status	0.31	0.09–1.06
Hypertension		
Age	**1.05**	**1.00–1.11**
Female sex	0.95	0.33–2.62
BMI	0.91	0.79–1.05
CF status	1.01	0.26–3.84
Chronic kidney disease		
Age	1.02	0.98–1.06
Female sex	1.01	0.50–2.03
BMI	1.02	0.93–1.14
CF status	1.92	0.83–4.56

BMI = body mass index; CF = cystic fibrosis.

being particularly common in pwCF, suggesting that while pwCF are on average younger, they are equally at risk for development of metabolic complications, possibly leading to similar survival rates post-lung transplant.

Despite matching, pwCF were significantly younger and had lower BMI. PwCF were also less likely to have received ECMO prior to transplantation, which suggests that pwCF were less acutely sick compared to pwoCF immediately pre-transplant. Previous literature has demonstrated that pwCF undergoing transplant have a better median survival than pwoCF, largely related to younger age, less tobacco smoking, and fewer comorbidities [9]. The lack of difference in mortality between the pwCF and pwoCF cohorts in our study suggests that despite statistical differences in some baseline characteristics between the cohorts, the matching may have been sufficient to balance these confounders for mortality. Consequently, the control cohort was reasonably selected for comparison.

Metabolic complications post-lung transplant are common [10]. However, there has been little work on understanding the differences in these outcomes in pwCF compared to pwoCF, particularly with confounding variables considered. Diabetes in particular is a common post-transplant complication given the chronic steroid and diabetogenic medication exposures [6]. These factors further exacerbate glycaemic control in those with pre-existing diabetes and can result in de novo post-transplant diabetes. Metabolic complications may impact long-term survival of transplant recipients, with pre-existing diabetes and post-transplant diabetes having shown to increase the risk of death by 65 % and 90 % respectively [11,12]. In contrast, a study evaluating one and five year survival rates for 123 pwCF post-transplant found a trend towards better survival for individuals that had (insulin-treated) diabetes than those without [13]. This may be attributed to the fact that glycaemic control is strongly correlated with survival post-lung transplant [14]. Given CF-related diabetes mellitus occurs in up to half of adults with CF as a result of CF pancreatic endocrine dysfunction, which

contributes to poorer outcomes, diabetes is an importance consideration for clinical management of pwCF pre/post-transplant [4]. This underlying vulnerability for dysglycemia in pwCF reflects the high prevalence of diabetes both pre and new onset post-transplant for pwCF. Previous research estimates that in general, lung transplant recipients pre-transplant have a 13 % pre-transplant rate of diabetes, that can increase to 20–40 % post-transplant [6,15]. In another single centre study, it was noted that of the 77 lung transplant recipients studied, pwCF were strikingly more likely to have pre-transplant diabetes (63 %) than pwoCF (6 %) and both groups experienced 60 % incidence of new onset post-transplant diabetes [16]. In contrast, Hackman and colleagues demonstrated a greater post-transplant prevalence of diabetes in patients with bronchiectasis (CF or non-CF) compared to those with restrictive or obstructive lung disease (68 % vs 43 % and 43 %) though the majority of pwCF in their study had pre-transplant diabetes as well [17]. Ye and colleagues focused on new incident cases of post-transplant diabetes and found similarly that CF status is a risk factor [7]. Consequently, it is controversial what the true incidence of new-onset diabetes is post-transplant for pwCF and pwoCF. Our study is consistent with published literature, finding that general pre-transplant prevalence of diabetes was 13.3 % where pwCF were more likely to have diabetes pre-transplant (22.2 %) compared to pwoCF (4.4 %). 63.4 % of all patients post-transplant developed new onset diabetes (Table 2). Additionally, after adjusting for the confounders of sex, age and BMI, pwCF were dramatically more likely to have new-onset diabetes post-transplant, firmly identifying that CF status is a strong risk factor for the development of diabetes post-transplant.

Dyslipidaemia is another important metabolic complication of lung transplantation, as hyperlipidaemia is associated with a faster decline in renal function post-transplant [18]. Prior studies have indicated a 6 % incidence of dyslipidaemia pre-transplant that increased to over 70 % post-transplant [6,15]. In this study, an increase in rates of dyslipidaemia was also seen, rising from 6 % pre-to 36 % post-transplant and we further add to the literature by finding that the risk of dyslipidaemia post-transplant is independent of CF status after adjusting for confounders. Thus, dyslipidaemia is a common complication that requires further attention for all patients post-transplant.

With regards to hypertension, in a cohort study of 67 patients that received a lung transplant, the rate of hypertension in general increased from 19.4 % to 70.1 % ($p < 0.01$) three years post-transplant [15]. Our study found similar results with hypertension identified in 6 % of all patients, increasing to over 60 % post-transplant and we additionally report no differences between the CF and non-CF groups, suggesting the importance of hypertension management in both cohorts post-transplant.

4.1. Limitations

The study relied on retrospective chart data, which, in some instances may be incomplete, likely due to inconsistencies in clinical data entry. We attempted to address this limitation with our sensitivity analysis, demonstrating that removal of the missing data did not impact the interpretation of the results. This study was also limited to a single centre and thus the sample size was relatively small and the results potentially at risk of incorporating center-specific effects. As such, a multi-center study would be beneficial to further validate these observations. Another limitation is due to the retrospective nature of the study, there was incomplete information on metabolically relevant intervention implementation, such as enteral or parenteral nutritional supplementation ever in life relative to transplantation, which could be more common in the CF cohort given gastrointestinal malabsorption uniquely associated with CF. Finally, as our study spanned from 2004 to 2017, clinical management pre/post lung transplantation and surgical techniques have evolved since 2004, which may contribute to improved survival and reduced complications with time. As our sample size was small, we could not perform a subgroup analysis to determine if the mortality and metabolic outcomes were different in more recent compared to remote data. Again, a larger multi-centred study would be able to overcome this limitation. Despite these challenges, this study adds to the understanding of post-lung transplant metabolic complications.

5. Conclusions

Our study demonstrated no substantial differences in post-lung transplant mortality for pwCF and pwoCF after cohort matching for age, sex and year of transplantation, suggesting that CF status is not an independent predictor of mortality. Metabolic complications such as diabetes, hypertension and dyslipidaemia appear to be important co-morbidities for both groups with pwCF having a greater independent risk of developing new post-transplant diabetes compared to pwoCF. Further research is needed to assess the impact of metabolic complications on long-term outcomes for CF and non-CF lung transplant recipients.

Compliance with ethics guidelines

This study was approved by the University of Alberta institutional review board, with the approval number Pro00091643. Informed consent was not required by this study because no participants were placed at risk as a result of the study, and a waiver of consent was applied.

Data availability

The data is not publicly available. Data may be made available upon reasonable request.

CRediT authorship contribution statement

Grace Lam: Conceptualization, Methodology, Formal Analysis, Writing - original draft. **Hima Patel:** Formal analysis, Data curation. **Heather Sharpe:** Writing – review & editing, Writing – original draft. **David Li:** Writing – review & editing, Data curation. **Kieran Halloran:** Writing – review & editing, Methodology, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Hima Patel reports financial support was provided by Northern Alberta Clinical Trials and Research Centre. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e30034.

Appendix A. Metabolic Complications Definitions

1. Renal dysfunction: as defined by creatinine criteria for CKD or need for permanent renal replacement therapy (dialysis or kidney transplant).
2. Blood pressure control: as defined by the need to initiate/escalate therapy by way of increased number or dose of anti-hypertensive (metoprolol, amlodipine, Ramipril, bisoprolol, labetalol, propranolol) pre- and post-lung transplantation.
3. Dyslipidaemia: as defined by the need to initiate lipid lowering agent(s) (atorvastatin, rosuvastatin) pre- and post-lung transplantation or by biochemical lipid profile.
4. Dysglycaemia: as defined by the need to initiate/escalate oral glycemic or insulin therapy by way of increased number of agents or dose of insulin pre- and post-lung transplantation, OR as defined by percentage change in HbA1c pre and post-transplant at 1 or 5 years.

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