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ORIGINAL ARTICLE

Lung function decline is mitigated following liver transplantation in people with cystic fibrosis: A retrospective cohort study

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Abstract

There is paucity of literature on the health outcomes following liver transplantation (LT) in people with cystic fibrosis (pwCF). We aim to evaluate changes in lung function following LT in pwCF. We performed a retrospective cohort study of pwCF who underwent LT between 1987 and 2019 in the United States and Canada. Simultaneous lung-liver transplants and individuals who had lung transplant prior to LT were excluded. We analyzed pre-LT and post-LT percent predicted forced expiratory volume in 1 second, body mass index, rates of pulmonary exacerbation, and post-LT overall survival. A total of 402 LT recipients were included. The median age of transplant was 14.9 years and 69.7% of the transplants were performed in children less than 18 years old. The rate of decline in percent predicted forced expiratory volume in 1 second was attenuated after LT from −2.2% to −0.7% predicted per year with a difference of 1.5% predicted per year (95% CI, 0.8, 2.2; $p < 0.001$). Following LT, the rate of decline in body mass index was reduced, and there were fewer pulmonary exacerbations (0.6 pre vs. 0.4 post; rate ratio 0.7, $p < 0.01$). The median survival time post-transplant was 13.9 years and the overall probability of survival at 5 years was 77.6%. Those with higher lung function pre-LT had a lower risk of death post-LT, and those with genotypes other than F508 deletion had worse survival. LT in pwCF occurs most often in children and adolescents and is associated with a slower rate of decline in lung function and nutritional status, and a reduction in pulmonary exacerbations.

Abbreviations: BMI, body mass index; CF, cystic fibrosis; CFLD, cystic fibrosis-related liver disease; CFRD, cystic fibrosis-related diabetes; CFTR, cystic fibrosis transmembrane conductance regulator; HRSA, Health Resources and Services Administration; IQR, interquartile range; LT, liver transplantation; LTFU, lost to follow-up; OPTN, Organ Procurement and Transplantation Network; PH, proportional hazards; ppFEV1, percent of predicted forced expiratory volume in 1 second; pwCF, people with cystic fibrosis; UNOS, United Network for Organ Sharing.

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INTRODUCTION

Cystic fibrosis (CF) is a progressive multisystem disorder that is caused by pathogenic variants in the CF transmembrane conductance regulator (CFTR) gene.[1] Although lung involvement in CF is the main cause of morbidity and mortality, CF-related liver disease (CFLD) occurs in ~10% of the population and is the third leading cause of death in people with cystic fibrosis (pwCF).[2] CFLD usually develops during childhood and may progress to portal hypertension, decompensated liver cirrhosis, and liver failure, ultimately requiring liver transplant.

Liver transplant for CFLD has been a treatment option for over 3 decades; the first orthotopic transplant in a person with CF was conducted in 1987[3] and since then, outcomes have improved. In 2006, Melzi et al[4] reported 1- and 5-year survival rates of 85%–90% and 64%–85%, respectively, across 27 European CF and transplant centers.

Liver transplant recipients with underlying CF continue to have CF-related lung disease, chronic infection, and pancreatic insufficiency. Immunosuppression increases susceptibility to infections and can worsen chronic infections. Published data on the impact of liver transplantation for CFLD on lung function and nutritional status show somewhat varied results. An early small retrospective study that included 29 pediatric and adult pwCF suggested that lung function improved by 5.9% up to 6 months following liver transplant compared to CF patients without liver transplantation.[4,5] However, another single cohort study examined 18 adults with CF and found that percent of predicted forced expiratory volume in 1 second ($ppFEV_1$) decreased from a mean of 60% pretransplant to 48% 2 years following liver transplant ($p < 0.01$).[6] A more recent study showed stability in lung function up to 18 months following liver transplant with a decline noted after 24 months compared to pre-liver transplant values.[7] The previously published literature is restricted by small sample sizes limiting generalizability, short follow-up time, and the use of pre- and post-lung function study designs.

The primary objective of this study was to quantify rate of change in lung function per year after receiving a liver transplant in pwCF. Secondary end points included rate of change in body mass index (BMI) per year, pulmonary exacerbation rates pre- and post-liver transplant, as well as contemporary survival outcomes, changes in transplant rates, and age at transplant over time.

METHODS

Data collection and sources

In this retrospective cohort study, data from pwCF who underwent liver transplantation between 1987 and 2019 were included. This study used data from the Organ Procurement and Transplantation Network (OPTN). The OPTN data system includes data on all donor, waitlisted candidates, and transplant recipients in the United States, submitted by the members of the OPTN. The Health Resources and Services Administration (HRSA), US Department of Health and Human Services provides oversight to the activities of the OPTN contractor. Data from US CF Foundation Patient Registry supplemented with data from OPTN following probabilistic linkage using the LinkPlus software were used for this study. Data from the Canadian CF Registry were harmonized and included. Further details on the linkage process have been published elsewhere.[8,9] All individuals consented to have their data submitted to CF registries and used for research purposes. Simultaneous lung-liver transplants and cases in which a lung transplant prior to liver transplantation were excluded given our focus on the impact of liver transplantation on lung disease. This study was approved by the Research Ethics Board at St. Michael's Hospital, Toronto, Ontario (Research Ethics Board # 14-148), Seattle Children's Hospital (Institutional Research Board # 15294), and University of Washington (Institutional Research Board # STUDY00002270). All research was conducted in accordance with both the Declarations of Helsinki and Istanbul.

Study variables

Measured lung function values were standardized to $ppFEV_1$ (using the Global Lung Function Initiative reference equations[10]). BMI *z*-score was calculated using World Health Organization growth curves for ages 0–2 and Centers for Disease Control and Prevention growth curves for ages 2–19.[11,12] Individuals aged 20 years and older were assumed to be 20 to calculate centiles for people of all ages. BMI was classified as underweight if the patient has a BMI *z*-score of <-1.17 for children aged under 19 years at the time of measurement or a BMI <18.5 kg/m^2 for those 19 years or older, and overweight if the BMI *z*-score is 1.04 or higher or BMI > 24.9 kg/m^2 for adults. For descriptive purposes, the clinical measures in closest visit either in the year of, but prior to, liver transplant were reported. For analysis of decline in $ppFEV_1$ or BMI, the first stable clinical measurement of each annual review year pre- and post-liver transplant up to 5 years prior to and up to 5 years post-liver transplant was used. For individuals who received a lung transplant following a liver transplant, all clinical measurements post-lung transplant were excluded from these analyses. Pulmonary exacerbations were defined as worsening pulmonary symptoms that required hospitalization or initiation of home i.v. antibiotics. Pulmonary exacerbation rates were calculated in the year prior to and 1 year following liver

transplant, excluding the year of liver transplant. Because pulmonary exacerbations were not robustly captured in the registries prior to 2003, we restricted the analysis on rates of exacerbations to 2004 onward to allow for a 1-year lookback period. Microbiology was defined as ever/never growth of *Pseudomonas aeruginosa (P. aeruginosa)*, *Burkholderia cepacia* complex (*B. cepacia* complex) on respiratory cultures at some point within the 5 years prior to transplant date. As recorded in the registry, race was categorized into White and non-White. Genotype was defined as the presence of either homozygous or heterozygous F508del, or other CF-causing mutations. CF-related diabetes (CFRD) was recorded as being present or absent in each year in adjusted models. However, for descriptive purposes, we present prevalence of CFRD in the pretransplant period. The use of CFTR modulators was classified as ever being used during the study period. Lost to follow-up rate was defined as those patients who were alive but whose most recent report year in the registry was 2016 or earlier. Graft failure was defined as either death from a liver or gastrointestinal cause, needing a second liver transplant, or documented graft status as failed in OPTN's data.

Statistical methods

Continuous variables were summarized using median and interquartile range while categorical variables were summarized by frequency and proportion. A segmented regression analysis and Davies test was used to determine if there was a change point in the proportion of transplants done over time. A simple linear regression was used to estimate the trend over time.

To compare the rate of change in $ppFEV_1$ or BMI *z*-score post-liver transplant compared to pretransplant, a piecewise linear mixed-effects model was used with a random intercept and random slope term, with a cut point at the time of liver transplant. For the lung function and BMI change analyses, individuals were limited to an equal number of measurements pre- and post-liver transplant (eg, if only 2 years of $ppFEV_1$ data post-transplant were available, only 2 years of pretransplant $ppFEV_1$ data were included). A mixed-effects Poisson regression model was used to compare the pulmonary exacerbation rates in the 2 periods. Adjusted complete case analyses included sex, baseline $ppFEV_1$ (or BMI *z*-score, depending on the model), CFRD, *B. cepacia* complex, *P. aeruginosa*, and year of transplant.

Survival time after liver transplant was calculated in years as the time from the date of first liver transplant to December 31 of the last year of known follow-up, the date of death, or the date of lung transplant, whichever comes first. The Kaplan-Meier method was used to calculate the median survival time as well as the probability of overall survival post-liver transplant at 1, 3, and 5 years, by lung function, and time period. A Cox Proportional Hazards model was used to compare the risk of death between those with $ppFEV_1$ <70% and equal to or >70% based on the median $ppFEV_1$ value, liver transplant year ($\leq$2003 and >2003) and by sex. The $ppFEV_1$ threshold of 70% aligns with OPTN guidance on prioritization.[13] The last recorded lung function measurement before liver transplant was used to classify individuals into lung function categories. To compare transplant year cohorts, the survival data were censored at 6 years because 6 years represents the median follow-up time for patients who received a liver transplant after 2004. Patients who received a transplant between 2014 and 2019 were excluded to ensure all patients could be followed for at least 6 years.

Sensitivity analyses

A sensitivity analysis for all outcomes was performed whereby individuals who were ever on CFTR modulators were excluded. A sensitivity analysis for lung function and BMI outcomes was performed by time periods (1987–2003 and 2004–2019).

All analyses were conducted using the open-source software R version 4.0.3. All *p*-values are 2 sided and assessed at $p < 0.05$ unless otherwise stated.

RESULTS

Study population and baseline characteristics

A total of 402 liver transplant recipients were included after exclusions (Figure 1). Baseline demographic and clinical characteristics are detailed in Table 1. Around two-thirds of liver transplant recipients were male. The median age of transplant was 14.9 years (interquartile

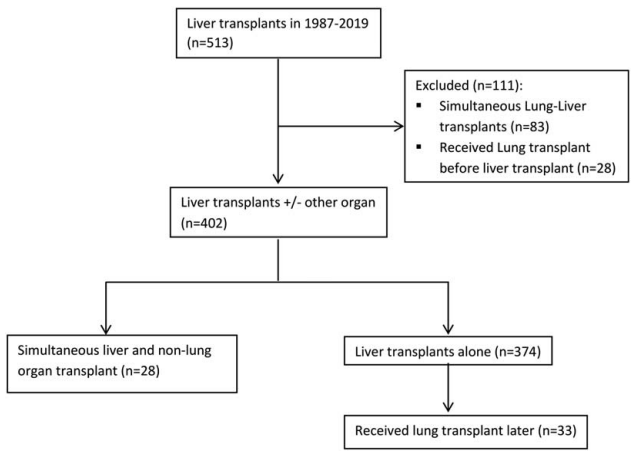

FIGURE 1 Flow diagram of cohort creation.

TABLE 1 Clinical and demographic characteristics of liver transplant recipients at baseline (pretransplant)[a]

Variable	Categories	Frequency
Overall	N	402
Country	Canada	31 (7.7)
	United States	371 (92.3)
Sex	Female	156 (38.8)
	Male	246 (61.2)
Race	Non-White	23 (5.7)
	White	379 (94.3)
Age at transplant (y)	Median (IQR)	14.9 (10.2–19)
Pediatric (< 18 y) transplants		280 (69.7)
Pancreatic status	Insufficient	391 (97.3)
CFRD (pretransplant)	No	225 (56)
	Yes	164 (40.8)
	Missing	13 (3.2)
Genotype	Homozygous F508	205 (51)
	Heterozygous F508	106 (26.4)
	Other	90 (22.4)
	Missing	< 5
Liver transplant with other simultaneous nonlung organ transplant[b]	—	28 (6.9)
Donor type	Cadaveric	290 (72.1)
	Living	55 (13.7)
	Unknown	57 (14.2)
$ppFEV_1$	Median (IQR)	70.1 (53.6–82.7)
(N = 367)[c]	Missing	27 (7.4)
	> 70%	170 (46.3)
	40–70%	140 (38.1)
	< 40% predicted	30 (8.2)
BMI categories	Adequate weight	239 (59.5)
	Overweight	31 (7.7)
	Underweight	91 (22.6)
	Missing	41 (10.2)
Pseudomonas aeruginosa	—	303 (75.4)
Burkholderia cepacia complex	—	8 (2)
CFTR modulators (ever)	Any	86 (21.4)
	Ivacaftor	6 (1.5)
	Lumacaftor-ivacaftor	35 (8.7)
	Tezacaftor-ivacaftor	41 (10.2)
	Elexacaftor-tezacaftor-ivacaftor	39 (9.7)
Lung transplant following liver transplant	—	33 (8.2)
Vital status	Alive	210 (52.2)
	LTFU[d]	16 (7.6)
	Deceased	192 (47.8)

[a]Values are N (%) unless otherwise specified.
[b]These included liver plus intestines, kidney, pancreas, and other organ transplants.
[c]Excludes 35 patients aged <6 years at time of clinical measurement.
[d]Lost to follow-up was defined as those patients who were alive but whose most recent report year in the registry was 2016 or earlier.
Abbreviations: BMI, body mass index; CFRD, cystic fibrosis-related diabetes; CFTR, cystic fibrosis transmembrane conductance regulator; IQR, interquartile range; LTFU, lost to follow-up; $ppFEV_1$, percentage of predicted forced expiratory volume in 1 second.

range 10.2–19) and 69.7% of the transplants were done in children less than 18 years of age. The majority of donors were cadaveric with 13.7% living donors.

A segmented regression analysis determined a change point to have occurred in the year 1996. Since 1996, the percentage of liver transplants (number of liver transplants/total patients in the year) over time has steadily and significantly decreased down from 0.07% in 1996 to 0.03% in 2019 ($p < 0.001$).

Changes in lung function

Median lung function prior to liver transplant was 70.1% predicted (interquartile range 53.6–82.7). Ninety-six percent of individuals had $ppFEV_1$ measurements within 1 year of, but prior to, the liver transplant. The difference between the rate of decline in $ppFEV_1$ pre- and post-liver transplant in the unadjusted model was 2.2% predicted per year (95% CI, 1.4, 2.9; $p < 0.001$). After adjusting for confounders, this difference was slightly attenuated to 1.5% predicted per year (95% CI, 0.8, 2.2; $p < 0.001$), which represents a 69% relative reduction in the rate of decline in lung function (Figure 2, Table 2).

Nutritional status

Almost 23% of liver transplant recipients were classified as underweight (22.6%) prior to the transplant. The difference between the rate of decline in BMI z-score pre- and post-liver transplant in the unadjusted model was 0.06 per year (95% CI, 0.02, 0.09; $p < 0.001$). Once adjusted for potential confounding factors, the difference in rate of change in BMI z-score pre- and post-liver transplant was 0.03 per year, which was not statistically significant (95% CI, −0.003, 0.06; $p = 0.07$) (Figure 3).

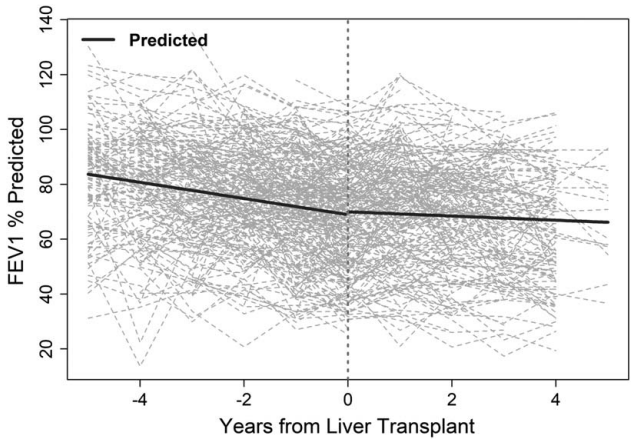

FIGURE 2 Change in rate of decline of $ppFEV_1$ pre- and post-liver transplant (N = 288). Abbreviation: $ppFEV_1$, percentage of predicted forced expiratory volume in 1 second.

Pulmonary exacerbations

Following liver transplant, there was a reduction in pulmonary exacerbations requiring hospitalization or home i.v. antibiotics (0.6 pre vs. 0.4 post; rate ratio 0.7, 95% CI, 0.5, 0.9, $p = 0.003$) after adjusting for potential confounding factors.

Survival outcomes

Median survival time after transplant was 13.9 years (95% CI, 12.1, 16.6) (Figure 4A). The probability of survival at 1, 3, and 5 years was 88.7% (95% CI, 85.6, 91.8), 82.8% (95% CI, 79.1, 86.7), and 77.6% (95% CI, 73.4, 82), respectively. Individuals with "other" genotypes had worse survival compared to either homozygous or heterozygous F508 (data not shown). There was no statistical difference in survival post-liver transplant between males and females (data not shown). There was a lower risk of death in those transplanted more recently (2004–2019) compared to those transplanted between 1987 and 2003 (HR 0.4, 95% CI, 0.2, 0.6; $p < 0.001$) (Figure 4B). The 1-, 3-, and 5-year survival for people transplanted before 2004 were 81.9%, 74.4%, and 67.8%, respectively, compared to 93.6%, 90.4%, and 87% for people transplanted after 2004. The 1-, 3-, and 5-year survival for people with pretransplant $ppFEV_1 < 70\%$ were 83.8%, 74.6%, and 66.7%, respectively, compared to 94.1%, 92.7%, and 89.8% for people with $ppFEV_1 \geq 70\%$ (Figure 4C). After adjusting for sex, age at transplant, year of transplant, genotype, nutritional status, CFRD, *P. aeruginosa* infection, and year of transplant, those with $ppFEV_1 \geq 70\%$ had a lower risk of death (HR 0.4, 95% CI, 0.3, 0.6; $p < 0.001$).

Following liver transplant, 50% of the people had graft failure over the entire study period. When assessing graft status by time periods, 67.3% of those who were transplanted in the period 1987–2003 had graft failure compared to 34.5% in the latter time period (2004–2019).

Sensitivity analyses

The changes seen in $ppFEV_1$ and BMI *z*-score were essentially unchanged after excluding people who were on CFTR modulator therapies (Supplemental Table S1, http://links.lww.com/LVT/A470 and Table S2). The magnitude of the risk reduction in pulmonary exacerbations was also unchanged; however, the *p*-value was borderline significant given the smaller sample size once people with modulators were excluded (Supplemental Table S3, http://links.lww.com/LVT/A470). Overall, survival estimates post-liver transplant were slightly lower once people on modulators were excluded from the analysis (Supplemental Figures S1–S3, http://links.lww.com/LVT/A470). A second sensitivity analysis by time periods assessing changes in ppFEV1 decline or BMI *z*-score changes pre- and post-liver transplant between the periods 1987–2003 and 2004–2019 were unchanged from the main analysis (Supplemental Tables S1, http://links.lww.com/LVT/A470 and S2).

DISCUSSION

In this large study of clinical outcomes post-liver transplant for CFLD, we show that extrahepatic organ function improved following transplant. Despite the theoretical risk of progression of chronic pulmonary infection following liver transplant and the associated

TABLE 2 Changes in $ppFEV_1$ pre- and post-liver transplant

	Intercept pre	Intercept post	Slope pre	Slope post	% change in slope
Univariate model	69 (66.6, 71.4)	70 (67.9, 72.1)	−2.9 (−3.5, −2.4)	−0.8 (−1.3, −0.2)	74
Multivariable model[a]	72.9 (70.2, 75.6)	73.6 (71.1, 76.1)	−2.2 (−2.8, −1.7)	−0.7 (−1.3, −0.1)	69

[a]Adjusted for sex, age at transplant, genotype, baseline $ppFEV_1$, BMI *z*-score, CFRD, *Pseudomonas aeruginosa, Burkholderia cepacia* complex, and year of transplant.
Abbreviation: $ppFEV_1$, percentage of predicted forced expiratory volume in 1 second.

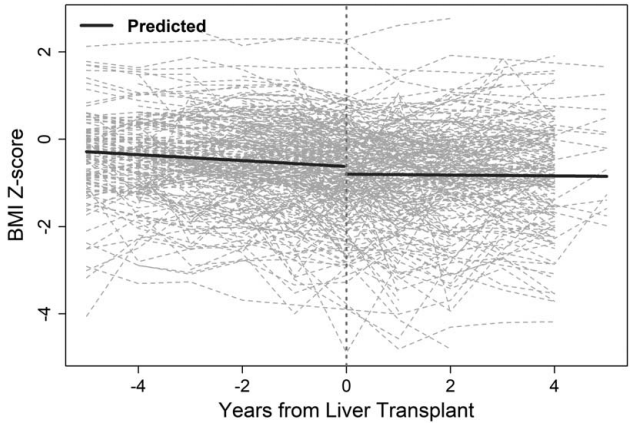

FIGURE 3 BMI *z*-score pre- and post-liver transplant (N = 301). Abbreviation: BMI, body mass index.

immunosuppressive therapies, pwCF who underwent liver transplantation had fewer pulmonary exacerbations with attenuation of the rate of lung function decline up to 5 years post-transplant. Furthermore, survival following liver transplantation in CF has improved over time likely due to improved surgical techniques and increased experience managing these patients pre- and post-transplant. Median survival time following transplantation for CFLD approached 14 years; however, individuals going into liver transplant with lower lung function were at higher risk of death even after adjusting for markers of disease severity thus the health status of these individuals should be optimized prior to transplant and followed closely after the surgery.

Although several studies have used predata and postdata to investigate the impact of liver transplant on lung function and BMI, only 2 studies specifically examined the rate of decline in lung function following liver transplant. Miller et al[14] analyzed data from 168 adult and pediatric liver transplant recipients matched to 840 corresponding matched individuals without liver transplant using US CF Foundation Patient Registry data from 1989 to 2007. Interestingly, they found that in the 3 years prior to liver transplant, the liver transplant group had stable lung function over time (rate of change in ppFEV$_1$ was 0.1% ± 0.4%/y). Following liver transplant, they reported a decline in lung function of −1.4% ± 0.4%/y. This is in contrast with our paper which showed a decline in lung function prior to liver transplant which was attenuated following liver transplant after adjusting for demographic and clinical factors. Furthermore, the rate of decline after liver transplant in our study was less than what was

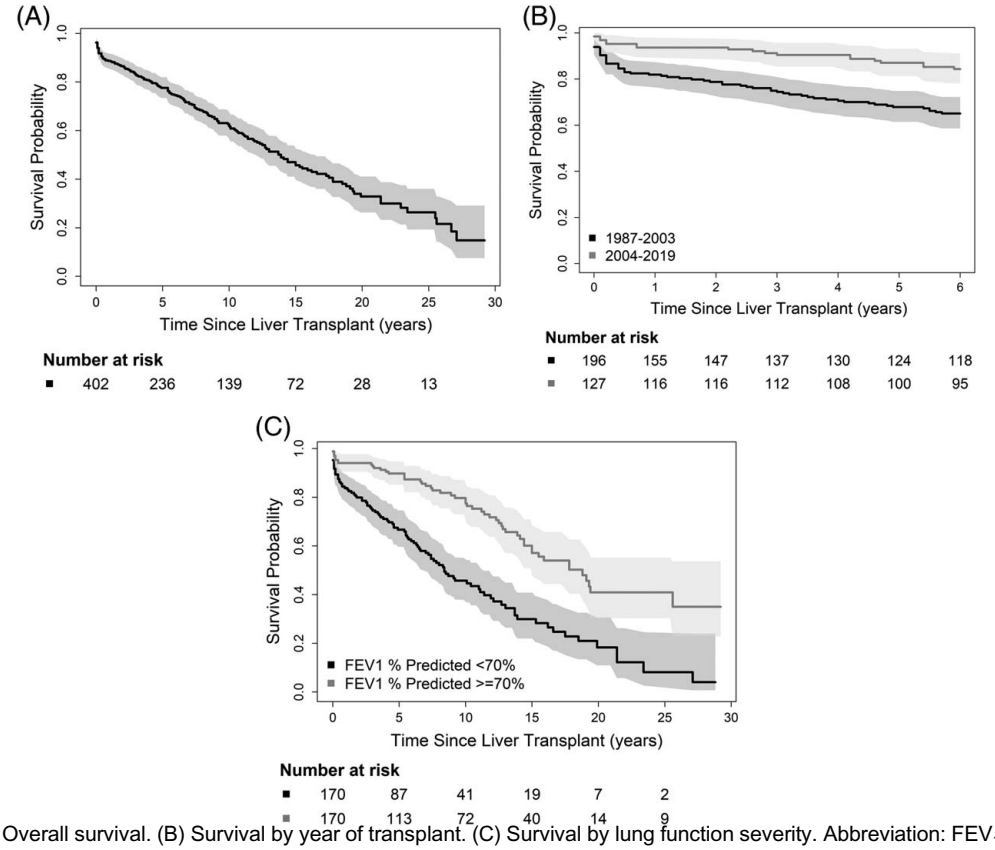

FIGURE 4 (A) Overall survival. (B) Survival by year of transplant. (C) Survival by lung function severity. Abbreviation: FEV$_1$, forced expiratory volume in 1 second.

reported by Miller and colleagues. This may be explained by the different time periods and analytic approaches used in the studies. In the same year, Dowman et al[15] published a single-center study of 63 liver transplant recipients (36 adults, 27 children). Outcomes in their CF cohort were compared with those reported in the literature for nontransplanted people with CF. In the adult cohort, the mean annual decline in $ppFEV_1$ was −0.7% up to 4 years post-transplant (which was similar to our results) compared to a reported decline of 3% for pwCF without liver transplant. In the pediatric cohort, the pretransplant *z*-score for $ppFEV_1$ was −1.4, which improved to −1.1 at 6 months although this change was not statistically significant. Further, a reduction in i.v. antibiotics courses for pulmonary exacerbations was reported post-transplant (3.9/y pretransplant to 1.5/y at year 1 and 1.1/y at 5 y) is consistent with a lower exacerbation rate seen in our study. Using data pre- and post-liver transplant, studies have shown significant improvements in mean BMI between the pretransplant period and the post-transplant period,[6,15] while Flemming et al[7] showed no significant change in BMI post-liver transplant. Our study also showed a trend toward improvements in nutritional status following liver transplant compared to pretransplant values although after adjustment, this was not statistically significant. However, it should be noted that BMI is a suboptimal marker for nutritional status in advanced liver disease. Prior to liver transplant, the degree of malnutrition, as represented by BMI, is probably masked by significant fluid retention increasing body weight. This may have contributed to an underestimation of the change in BMI seen in our study after liver transplant. A more robust marker to nutritional status is needed using anthropomorphic measurements such as fat-free muscle mass; however, we were limited by the data available within the CF registries.

Although the prevalence of CFLD is slowly increasing, our study highlighted the steady decrease in the percentage of liver transplants over time.[16] This decline is due to several reasons. As the optimal timing of listing has been unclear given CFLD's unique natural course compared to other chronic liver diseases, liver transplantations in the 1990s and 2000s were performed early in pwCF before the development of end-stage liver disease.[4,5,17] Another reason may be related to continued advances in CF care with resultant lung function and nutritional improvements, which are important clinical parameters used by OPTN to prioritize CF liver transplant candidates.[13,18]

Our study has notable limitations that must be acknowledged. The CFF Patient Registry data were probabilistically linked to OPTN; therefore, there is a potential for mismatches to have occurred despite using multiple identifiers in the linkage. However, we used a match score of 10 or greater, which has been used in previously published literature to minimize false matches while maximizing true matches. Additionally, there is a potential for residual confounding by factors unavailable in the registries or inadvertently excluded from our models, which could otherwise explain the change in health outcomes before and after liver transplantation. Although CFTR modulator therapy could impact the outcomes in our study, the conclusions were unchanged after excluding those people who started on modulator therapy at some point in the study window suggesting the improvements seen were independent of modulator therapies. The magnitude of the reduction in pulmonary exacerbations was robust; however, the *p*-value was borderline, which was most likely due to the reduction in the sample size after the exclusions. Further targeted research is needed to evaluate the impact of modulators on the liver transplant population in future studies. Due to limitations in our data set, we were unable to perform a robust time to graft failure analysis. The OPTN data set indicates graft failure as a binary outcome (Y/N) with no reference to the timing. A significant proportion of the outcomes for graft failure (92/203, 45%) were obtained using this binary variable thus were missing a date, which is necessary for a time-to-event analysis. We recognize that the 50% graft failure rate presented in this manuscript may falsely give the impression that liver transplants have poor outcomes but this must be interpreted in the context of our study, which included individuals over 3 decades. Furthermore, we see that the graft failure rate when presented in two time periods shows a lower graft failure rate in the most recent time window (2004–2019) giving perhaps a better representation of outcomes post-liver transplant.

In conclusion, our study shows that the trajectory of disease is favorably modified up to five years following liver transplantation in a large cohort of individuals with CF.

AUTHOR CONTRIBUTIONS

Anne L. Stephenson had full access to all of the data in the study and takes responsibility for the integrity of the data, the accuracy of the data analysis, and had final responsibility for the decision to submit for publication. Study concept and design: Anne L. Stephenson, Christopher H. Goss, Kathleen J. Ramos, Sanja Stanojevic, Bruce C. Marshall, Bradley S. Quon, Joshua S. Ostrenga, Albert Faro, Elizabeth A. Cromwell, Alexander Elbert. Acquisition and merging of data: Anne L. Stephenson, Jenna Sykes, Xiayi Ma, Kathleen J. Ramos, Joshua S. Ostrenga, Elizabeth A. Cromwell, Alexander Elbert. Analysis and interpretation of data: Anne L. Stephenson, Jenna Sykes, Xiayi Ma, Sanja Stanojevic, Christopher H. Goss, Bradley S. Quon, Bruce C. Marshall, Joshua S. Ostrenga, Elizabeth A. Cromwell, Albert Faro, Alexander Elbert. Drafting of the manuscript: Anne L. Stephenson, Faisal A. Albaiz.

Critical revision of the manuscript for important intellectual content: Anne L. Stephenson, Christopher H. Goss, Kathleen J. Ramos, Sanja Stanojevic, Bruce C. Marshall, Bradley S. Quon, Bruce C. Marshall, Joshua S. Ostrenga, Albert Faro, Elizabeth A. Cromwell, Alexander Elbert, Faisal A. Albaiz. Statistical analysis: Anne L. Stephenson, Xiayi Ma, Jenna Sykes, Sanja Stanojevic, Joshua S. Ostrenga, Elizabeth A. Cromwell. Obtained funding: Anne L. Stephenson, Sanja Stanojevic, Christopher H. Goss, Bradley S. Quon. Study supervision: Anne L. Stephenson.

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CONFLICTS OF INTEREST

Albert Faro has no personal disclosures. However, to advance drug development and a search for a cure, his employer, the Cystic Fibrosis Foundation (CFF), has contracts with several companies to help fund the development of potential treatments and/or cures for cystic fibrosis. Pursuant to these contracts, CFF may receive milestone-based payments, equity interests, royalties on the net sales of therapies, and/or other forms of consideration. The resulting revenue received by CFF is used in support of our mission. See "How Drugs Get on the Pipeline" on the CFF website for more information. Additionally, CFF may license CFF Patient Registry data to some companies to monitor drug safety as part of the U.S. Food and Drug Administration's required Phase 4 clinical trials process and to encourage research aimed at improving the care of people with CF while maintaining our obligation and commitment to protect the privacy of Registry participants. In connection with these licenses, and upon request, CFF may also assist company researchers in interpreting CFF Patient Registry data to aid in designing, analyzing, and interpreting real-world studies in CF.

Alexander Elbert reports no personal disclosures. However, the Cystic Fibrosis Foundation (CFF) has entered into therapeutic development award agreements and licensing agreements to assist with the development of CFTR modulators that may result in intellectual property rights, royalties and other fees provided to CFF by various pharmaceutical companies. These relationships have not influenced the content of this manuscript and are outside the submitted work. Anne L. Stephenson reports speaking fees from Vertex Pharmaceuticals Inc., advisory board fees from Horizon Therapeutics, and receives an annual stipend as Director of the Canadian CF Registry from Cystic Fibrosis Canada. None of these entities influenced the content of this manuscript and are all outside the submitted work. Christopher H. Goss reports funding sources that support other ongoing research; however, these sources of funding played no role in writing this manuscript or in the decision to submit for publication. Dr. Sanja Stanojevic consults for ndd Medical and Cheisi. She is on the speakers' bureau for Vyaire Medical. None of these relationships impacted the content of this manuscript. The remaining authors have no conflicts to report.

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