



# 1-year outcomes for lung transplantation recipients with non-alcoholic fatty liver disease

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Shareable abstract (@ERSpublications)

In this single-centre, retrospective analysis of lung transplant recipients, we identified that mild-moderate non-alcoholic fatty liver disease is associated with acceptable perioperative and 1-year outcomes <https://bit.ly/36WNzhi>

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## Abstract

Advanced hepatic fibrosis and cirrhosis are absolute contraindications to lung transplantation. [1] However, whether fatty liver disease with mild-moderate fibrosis contributes to increased adverse outcomes post-lung transplantation remains unknown.

We present a retrospective analysis of patients transplanted at Brigham and Women's Hospital between 2015 and 2017 to identify whether patients with mild-moderate non-alcoholic fatty liver disease (NAFLD) experience increased short-term complications compared to patients with normal liver architecture. Patients with advanced (F3-F4) fibrosis and/or cirrhosis were considered non-suitable transplant candidates, *a priori*. This study was powered for a difference in index hospital-free days within the first 30 days of 25% ( $\alpha=0.05$ ,  $\beta=0.8$ ). Secondary outcomes included index intensive care unit (ICU)-free days within the first 10 days post-transplant, perioperative blood product transfusion, incidence of index hospitalisation arrhythmias and delirium, need for insulin on discharge post-transplant, tacrolimus dose required to maintain a trough of 8–12 ng·mL<sup>-1</sup> at index hospital discharge, and 1-year post-transplant incidence of insulin-dependent diabetes, acute kidney injury, acute cellular rejection, unplanned hospital readmissions and infection.

150 patients underwent lung transplantation between 2015 and 2017 and were included in the analysis; of these patients 40 (27%) had evidence of NAFLD. Median index hospital-free days for patients with NAFLD were non-inferior to those without (16 days, IQR 10.5–19.5 *versus* 12 days, IQR 0–18.0,  $p=0.03$ ). Regarding secondary outcomes, both index hospitalisation and 1-year outcomes were non-inferior between patients with NAFLD and those with normal liver architecture.

This study demonstrates that mild-moderate severity NAFLD may not be a contraindication to lung transplantation.

## Introduction

Beginning in 2015, lung transplant candidates at Brigham and Women's Hospital (BWH) with risk factors for liver disease underwent in-depth, stepwise evaluation to better characterise and risk-stratify patients for severe liver disease. This protocol was instituted after experiencing several episodes of fulminant hepatic failure post-transplant in patients without previously known liver disease based on standard serologic assessment of liver function tests, albumin and coagulation studies. The intent of the new protocol was to obtain a basic assessment of liver architecture in all lung transplant candidates *via* ultrasonography, while more carefully screening for liver abnormalities in patients with known risk factors. Our protocol identified



a large percentage of patients with mild–moderate liver disease. While cirrhosis and advanced hepatic fibrosis are accepted contraindications to lung transplantation, whether mild–moderate fatty liver disease contributes to untoward outcomes post-lung transplantation is unknown [1]. This question is of increasing importance given the wide prevalence of non-alcoholic fatty liver disease (NAFLD) in the general population. NAFLD currently afflicts 20–40% of the worldwide population [2]. NAFLD, defined as replacement of >5% of the liver with fat in the absence of other causes of hepatic inflammation (viral disease, >20 g alcohol use per day, drug toxicity and autoimmune disease), is a risk factor for non-alcoholic steatohepatitis (NASH), fibrosis, cirrhosis and hepatocellular carcinoma [2].

NAFLD is also associated with a multitude of extrahepatic comorbidities, including hypertension, hyperlipidaemia, diabetes, atrial fibrillation, coronary artery disease, venous thromboembolism, infection, weakness and chronic kidney disease [2, 3–8]. NAFLD is more than just correlative to these comorbidities; rather, evidence suggests that the upregulated proinflammatory process induced by NAFLD is causative. For example, NAFLD promotes insulin resistance by disrupting long-chain fatty acid digestion and creating intermediates that downregulate metabolic pathways such as Akt/mTORC2 [2, 9, 10]. Moreover, NAFLD causes an accelerated decline in renal function by augmenting intrarenal proinflammatory pathways including connective tissue, epidermal and platelet-derived growth factors (CTGF, EGF, PDGF) to promote glomerulosclerosis and tubular atrophy [10, 11]. NAFLD contributes to vascular disease by upregulating oxidative stress pathways, with subsequent upregulation of tumour necrosis factor- $\alpha$  and interleukin-6 pathways, activation of coagulation cascades, inhibition of fibrinolysis, increased vascular tone and resultant intimal thickening [10–12]. Finally, NAFLD can promote sarcopenia *via* insulin resistance and resultant myosteatosis, protein catabolism and myostatin-induced proteolysis [13].

Lung transplantation, and the related need for immunosuppression, is also associated with increased morbidity; allograft recipients have an increased incidence of diabetes, hypertension, hyperlipidaemia, atrial arrhythmias, skeletal muscle weakness and chronic kidney disease [14–17]. Whether the complications of lung transplantation are additive to, or perhaps synergistic with, that of the proinflammatory effects of NAFLD is unknown.

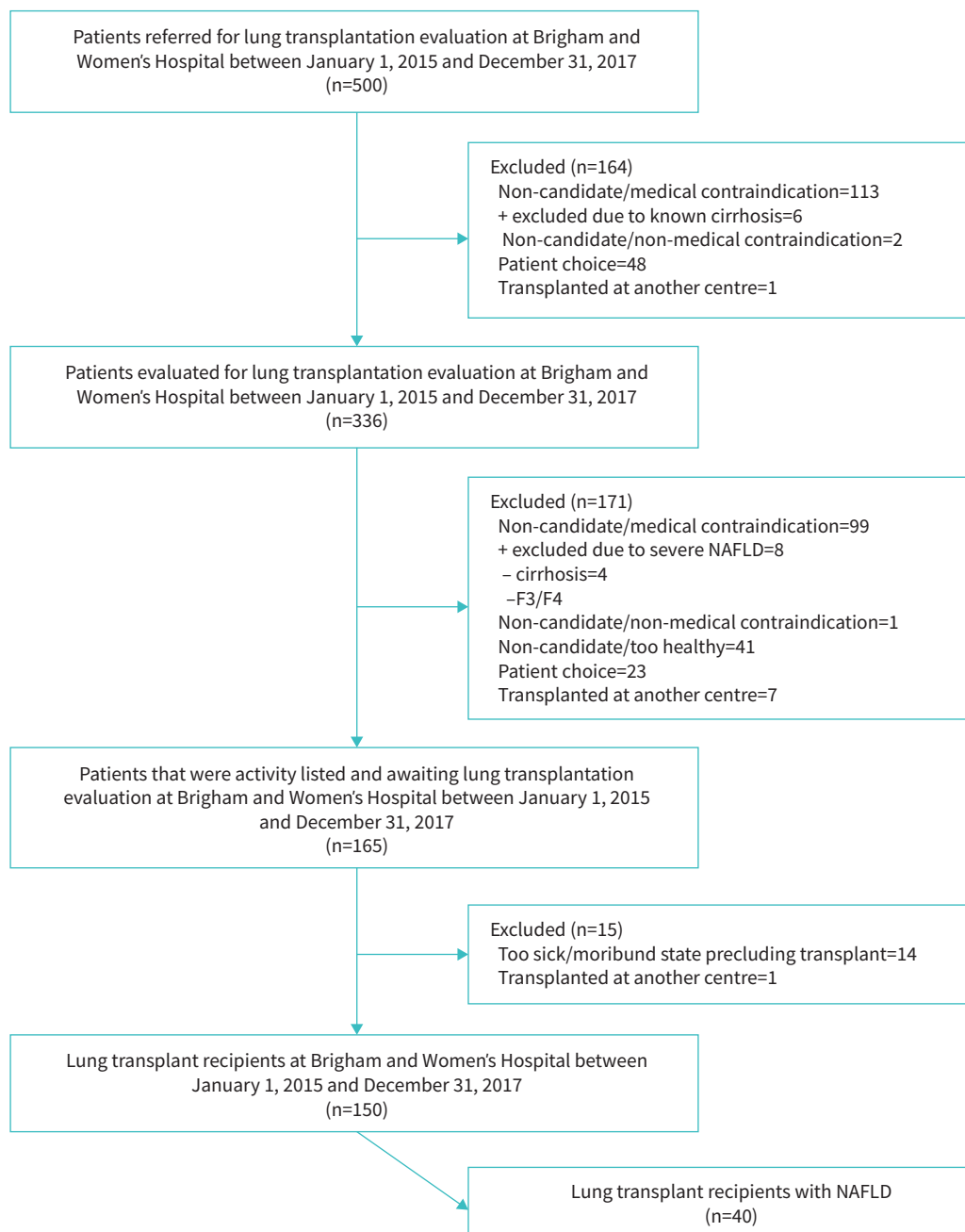
Given the association of hepatic steatosis with a proinflammatory state and its subsequent effect on cardiovascular disease, insulin resistance, kidney injury and infection, we hypothesised that lung allograft recipients with mild–moderate NAFLD would incur greater complications within the first-year post-transplantation. The primary outcome of this study is index hospital-free days within the first 30 days. Secondary outcomes include index intensive care unit (ICU)-free days, perioperative blood product transfusion, incidence of index hospitalisation arrhythmias and delirium, need for insulin on discharge post-transplant and tacrolimus dose required to maintain a goal trough of 8–12 ng·mL<sup>-1</sup> at hospital discharge post-transplant. Other secondary outcomes include incidence of insulin-dependent diabetes, acute kidney injury, acute cellular rejection, unplanned hospital readmissions and infection, all at 1 year post-transplant.

## Methods

Permission to perform this retrospective analysis was obtained from the institutional review board at BWH prior to collecting data from the electronic record. Patients aged >18 years who underwent lung transplantation evaluation at BWH between January 1, 2015 and December 31, 2017 were included; a total of 150 patients met inclusion criteria and were transplanted (figure 1). As part of the routine assessment, all patients underwent a screening abdominal ultrasound. Patients with risk factors for hepatic dysfunction underwent more detailed assessment of liver fibrosis (see figures 2 and 3). We decided *a priori* that severe fibrosis (F3–F4) and cirrhosis were absolute contraindications to lung transplantation. Post-lung transplantation care at BWH was per the usual protocol and has been previously published [18].

## Diagnosis of NAFLD

Abdominal ultrasound was performed in all lung transplant candidates, per our standard evaluation protocol. In patients with risk factors for hepatic disease (see figure 2), we performed an additional diagnostic algorithm. Our hepatology colleagues provided guidance regarding which additional series of noninvasive testing was necessary to exclude significant fibrosis/cirrhosis in order to obviate the need for liver biopsy (figure 3). Selected noninvasive diagnostic studies included hepatic transient elastography (FibroScan®, Echosens SA, Paris, France), serum biomarker profiling (FibroSure, LabCorp, Burlington, NC, USA) and cross-sectional imaging (with computed tomography (CT) or magnetic resonance imaging (MRI)). The evaluation to exclude advanced NAFLD is based upon pragmatic expert opinion, as even within the hepatology field, “a validated, widely accepted procedure for the diagnosis and monitoring of NAFLD does not yet exist” [19]. Nevertheless, noninvasive studies are useful for excluding advanced



**FIGURE 1** Flow chart of patients included in the analysis. NAFLD: non-alcoholic fatty liver disease.

disease (F3 or F4 disease on the Metavir scoring system) [20–22]. For example, ultrasound has a sensitivity ~85% and specificity ~95% to detect moderate steatosis [21]. Hepatic transient elastography (FibroScan®), which utilises applied mechanical excitation to detect tissue elasticity, is well validated in patients with chronic hepatitis B and C, alcoholic liver disease and NAFLD, with a negative predictive value of 97% for advanced fibrosis [19, 23–26]. Hepatic transient elastography (FibroScan®) results were correlated to histologic Metavir scores as follows: <2 kPa=F0, 2–7 kPa=F0–F1, 7.5–10 kPa=F2, 10–14 kPa=F3, >14 kPa=F4 [26]. The FibroSure test is a panel of six serologic markers (ALT, GGT, total bilirubin, haptoglobin, apolipoprotein A1 and  $\alpha$ -2 microglobulin) to assess liver scarring and correlates with biopsy ~75% of the time in patients with hepatitis B, hepatitis C, alcoholic liver disease and NAFLD [27–29]. FibroSure results were classified as 0–0.21=F0, 0.21–0.27=F0–F1, 0.27–0.31=F1, 0.31–0.48=F1–F2, 0.48–0.58=F2, 0.58–0.72=F3, 0.72–0.74=F3–F4, >0.75=F4 [29]. In cases of discordance between FibroScan and FibroSure results, or where a diagnosis of advanced fibrosis was equivocal, cross-sectional imaging and/or

- a) Known liver disease, including non-alcoholic fatty liver disease
- b) Abnormal liver function tests
- c) Abnormal liver imaging on screening abdominal ultrasonography
- d) Systemic disease that can potentially involve the liver
- e) Known telomeropathy
- f) Exposure to hepatitis B or hepatitis C
- g) Chronic or heavy alcohol used (>7 drinks/week for females, >14 drinks/week for males)
- h) Other conditions that predispose to hepatopathy (e.g. right heart failure)

**FIGURE 2** Indications to undergo protocolised evaluation of liver function.

liver biopsy were used as the arbiter of hepatic fibrosis severity. Notably, multidetector CT can detect  $\geq$ F2 with a sensitivity of 70–80% and a specificity  $\sim$ 85% [30–32]. While magnetic resonance imaging is the preferred mode of cross-sectional imaging, it is not always feasible in patients with end-stage lung disease who have marginal gas-exchange [32, 33].

### Statistical analysis

The sample size of this retrospective analysis was calculated with regard to a primary outcome of index hospital-free days within the initial 30 days post-transplant. We performed a power calculation based on the median hospital length of stay in our cohort of 18 days (IQR 11–25). We identified a sample size of 150 subjects to detect a 25% increase in hospital-free days in the NAFLD cohort, with  $\alpha=0.05$  and  $\beta=0.2$ , understanding that the rate of NAFLD in the general population is  $\sim$ 20%.

Statistical analysis was performed using STATA version 15.1 (StatCorp LLC, College Station, TX, USA). For all results, p-values  $\leq 0.05$  were considered significant. Differences in baseline demographic data were assessed using Fisher's exact test for binary data, Pearson's chi-square test for categorical variables and Wilcoxon's rank sum tests for continuous data, as none of the continuous variables were normally distributed.

We performed univariate analyses using Fisher's exact test to assess for a relationship between NAFLD and binary outcomes; continuous variables were dichotomised above and below the median for these analyses. Multivariate logistic regression analyses were then performed, including covariates that were significant on univariate assessment at  $p < 0.1$ .

### Definitions

We utilised the following definitions when identifying outcomes: 1) delirium = critical care nursing diagnosis and documentation using the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) clinical tool and/or administration of therapy for agitation [34]; 2) hypertension = need for left ventricular afterload-reducing medications in the post-transplant setting; 3) diabetes = need for insulin therapy (haemoglobin A1c% is not routinely checked in the tertiary setting at BWH); 4) acute cellular rejection = any pathologic finding of  $\geq$ A1 or  $\geq$ B1R rejection by the International Society for Heart and Lung Transplantation (ISHLT) criteria [35]; 5) infection = suspected or documented infection necessitating

- a) Assessment of hepatitis B and hepatitis C serologies and abdominal ultrasound in all candidates
- b) In patients with increased risk factors for hepatic disease: FibroSure score AND/OR Hepatic transient elastography (FibroScan)
- c) Confirmatory cross-sectional liver imaging (with CT and MRI), as needed
- d) Hepatology consultation for consideration of liver biopsy if liver disease suspected despite a negative noninvasive evaluation

**FIGURE 3** Evaluation of liver architecture in lung transplant candidates. CT: computed tomography; MRI: magnetic resonance imaging.

hospitalisation; and 6) kidney function was estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula for glomerular filtration rate [36].

## Results

### Patient recruitment

During the inclusion period, 500 patients were referred to BWH for lung transplantation consideration, of which 336 patients underwent the formal evaluation process. In this cohort 232 patients (69%) met criteria for undergoing more detailed evaluation for hepatic disease (figures 2 and 3). Twenty-one patients (9%) required liver biopsy. Notably, 8 out of 232 patients (3.4%) were deemed non-viable lung transplant candidates due to F3/F4 fibrosis or cirrhosis. Six out of the eight patients were diagnosed with advanced fibrosis *via* liver biopsy and the other two with cross-sectional imaging (CT and MRI, respectively; see figure 1). Ultimately 150 patients underwent lung transplantation at BWH during the 2015–2017 time period, of which 40 patients had mild–moderate NAFLD.

### NAFLD diagnosis

NAFLD was identified in 40 out of 150 (27%) of our cohort by one or more screening modalities. Abdominal ultrasound detected abnormal liver architecture in 35 out of 40 patients in our cohort with NAFLD (sensitivity = 87.5%). The remaining five patients with normal abdominal ultrasound results were diagnosed *via* FibroScan and/or FibroSure testing; these patients underwent advanced testing due to short telomere syndrome, history of abnormal transaminases on serologic testing, history of hepatitis C and history of alcohol abuse. Nine of the 40 patients (23%) with NAFLD had steatosis without fibrosis, as diagnosed by ultrasound, FibroScan, FibroSure cross-sectional imaging and/or liver biopsy. Thirty-one (77.5%) patients who were ultimately diagnosed with NAFLD underwent transient elastography (FibroScan) testing. FibroScan was non-diagnostic in 3 out of 31 patients (9.7%). FibroScan testing showed F0–F1, F2, F3 and F4 hepatic fibrosis in 24 (60%), 2 (5%), 1 (2.5%) and 1 (2.5%) patient(s), respectively, among the NAFLD cohort. The two patients diagnosed with F3 and F4 disease *via* FibroScan underwent liver biopsies that were not suggestive of advanced fibrosis and were ultimately transplanted. FibroSure testing was performed in 17 out of 40 patients and was non-diagnostic in one of those patients (5.8%). FibroSure testing showed F0, F1–F2, F2, F3 and F4 disease in 6, 5, 3, 1 and 1 patient(s), respectively. The two patients with advanced fibrosis underwent cross-sectional imaging and/or liver biopsy, which were not felt to be consistent with advanced fibrosis (see table 1), and the patients were ultimately transplanted. Eleven of the 40 patients underwent both FibroScan and FibroSure testing. The results were concordant in eight patients, with each test showing  $\geq$ F2 fibrosis; this is similar to findings in other patient populations, such as those with hepatitis C virus [37]. In two of the three cases where FibroScan and FibroSure did not agree, liver biopsy was performed, and results were more concordant with FibroScan findings. CT imaging was performed in 10 patients, 8 of whom had FibroScan or FibroSure testing; CT imaging was performed in instances where patients could not tolerate MRI due to the severity of hypoxaemia. CT imaging was concordant with FibroSure and FibroScan results in 9/10 instances.

### Baseline characteristics

NAFLD was significantly associated with body mass index (median and interquartile range body mass index (BMI) for patients with NAFLD 29.1 (26.7–31.1) *versus* 25.5 (22.7–28.9) for those without,  $p=0.0004$ ) and end-stage lung disease diagnosis, with a higher rate of interstitial lung disease in patients with NAFLD (see table 2,  $p=0.019$ ). There was no correlation between NAFLD and lung allocation score, 6-min walk distance or allograft ischaemic time (see table 2). There was a trend towards significant association between NAFLD and pre-transplant incidence of hyperlipidaemia (53% *versus* 35%,  $p=0.059$ ) and age (63.4 (55.7–66.9) *versus* 58.8 (48.9–65.9) years,  $p=0.062$ ).

### Univariate analysis

NAFLD had no adverse effect on post-transplant outcomes, as seen on univariate analyses (table 3). There was no significant difference in blood product transfusion rate, delirium, requisite tacrolimus dosing, diabetes, atrial fibrillation, venous thromboembolism, acute cellular rejection, infectious complications requiring hospitalisation or incidence of cytomegalovirus (CMV) viraemia observed between groups. Of the 6 patients with NAFLD that developed CMV viraemia post-transplant, only 2 were of high-risk serostatus (CMV D<sup>+</sup>/R<sup>-</sup>); in patients without NAFLD, 7 of the 19 instances of CMV viraemia were in patients that were CMV mismatched. Interestingly, NAFLD was associated with improved number of hospital-free days within the first 30 days following transplantation (median 16 days, IQR 10.5–19.5 *versus* median 12 days, IQR 0–18.0,  $p=0.03$ ). Finally, at 1 year post-transplant, patients with NAFLD had greater preservation in renal function; the median decline in baseline GFR

TABLE 1 Identification and distribution of hepatic fibrosis grade among transplant recipients with non-alcoholic fatty liver disease

Patient	Screening indication	US abdomen result	FibroScan result kPa	FibroScan fibrosis grade	FibroSure result	FibroSure fibrosis grade	CT abdomen result	MRI abdomen result	Liver biopsy result
1	ABN US	Steatosis	—	—	—	—	Steatosis	—	—
2	ABN US	Steatosis	—	—	—	—	—	Steatosis	—
3	ABN US	Steatosis	—	—	—	—	Mild steatosis	—	—
4	ABN US	Steatosis	5.1	F0–F1	0.52	F2	—	—	Steatosis
5	ABN US	Steatosis	4.2	F0–F1	0.54	F2	—	—	—
6	Short telomere	Normal	4.9	F0–F1	—	—	—	—	—
7	ABN US	Steatosis	6.9	F0–F1	0.33	F1–F2	—	—	—
8	ABN US	Steatosis	3.9	F0–F1	NR	—	—	—	—
9	ABN US	Steatosis	—	—	0.54	F2	—	—	—
10	ABN US	Steatosis	—	—	—	—	—	—	—
11	ABN US	Steatosis	5.4	F0–F1	—	—	Normal	—	—
12	ABN US	Steatosis	—	—	0.14	F0	—	—	—
13	ABN US	Steatosis	—	—	0.32	F1–F2	Normal	—	—
14	ABN US	Steatosis	4.9	F0–F1	—	—	—	—	—
15	Short telomere/ ethanol abuse	Normal	5.5	F0–F1	—	—	Normal	—	—
16	ABN US	Steatosis	4.4	F0–F1	—	—	—	—	—
17	ABN US	Steatosis	NR	—	0.12	F0	—	—	—
18	ABN US	Steatosis	7.1	F1	0.18	F0	Normal	—	—
19	ABN LFTs	Normal	44.3	F4	0.69	F3	—	Normal	Mild fibrosis
20	ABN LFTs	Normal	5.1	F0–F1	—	—	—	—	—
21	ABN US	Steatosis	6.2	F0–F1	—	—	—	—	—
22	ABN US	Steatosis	7.7	F2	—	—	—	—	—
23	ABN US	Steatosis	6.1	F0–F1	—	—	Normal	—	—
24	HCV	Normal	NR	—	0.86	F4	—	Normal	—
25	ABN US	Steatosis	4.8	F0–F1	0.19	F0	Normal	—	—
26	ABN US	Steatosis	7	F0–F1	0.39	F1–F2	—	—	—
27	ABN US	Steatosis	5.4	F0–F1	—	—	—	—	—
28	ABN US	Steatosis	4.9	F0–F1	—	—	—	—	—
29	ABN US	Steatosis	2.3	F0–F1	—	—	—	—	—
30	ABN US	Steatosis	—	—	—	—	—	Steatosis	—
31	ABN US	Steatosis	6.8	F0–F1	—	—	—	—	—
32	ABN US	Steatosis	4.2	F0–F1	—	—	—	—	—
33	ABN US	Steatosis	4.5	F0–F1	—	—	—	—	—
34	ABN US	Steatosis	—	—	—	—	—	Steatosis	—
35	ABN US	Steatosis	3.5	F0–F1	—	—	—	—	—
36	ABN US	Steatosis	NR	—	—	—	—	—	Mild steatosis
37	ABN US	Steatosis	10.1	F3	0.1	F0	Normal	—	Mild fibrosis
38	ABN US	Steatosis	6.8	F0–F1	0.47	F1–F2	Normal	—	—
39	ABN US	Steatosis	3.6	F0–F1	0.17	F0	Normal	—	—
40	ABN US	Steatosis	4.4	F0–F1	0.46	F1–F2	Normal	—	—

CT: computed tomography; MRI: magnetic resonance imaging; ABN US: abnormal ultrasound; ABN LFTs: abnormal liver function tests; HCV: hepatitis C virus.

was 48% (IQR 33–57%) for patients with NAFLD versus 58% (IQR 42–68%) for those without (CKD-EPI formula,  $p=0.03$ ).

#### Multivariate logistic regression analysis

We adjusted for age, BMI, presence of pre-transplant hyperlipidaemia and lung allocation score disease diagnosis group, as these were all found to be significantly associated with NAFLD at a  $p<0.10$ . We evaluated outcomes that were either significant on univariate analysis or were clinically relevant. On multivariate analysis, there was a trend towards increased need for platelet transfusion during the peri-transplant surgery period in patients with NAFLD (OR= 2.23,  $p= 0.06$ ); there were no associations between NAFLD and other forms of blood product transfusion needs. Patients with NAFLD experienced increased hospital-free days within the first 30 days post-transplant (OR= 3.34, 95% CI 0.50–6.19,  $p=0.02$ ). The relationship between NAFLD and improved renal function seen on univariate analysis was no longer significant after adjusting for the above confounders. See table 4 for further details.

TABLE 2 Baseline demographics of transplant recipients

	Transplant candidates January 1, 2015 to December 31, 2017			HR	p-value
	All patients	Patients with NAFLD	Patients without NAFLD		
Subjects n	150	40	110		
Age years (median/interquartile range)		63.4 (55.7–66.9)	58.8 (48.9–65.9)	1.87	0.06
Female	65 (43)	13 (33)	52 (47)		0.14
BMI (median/interquartile range)		29.1 (26.7–31.1)	25.5 (22.7–28.9)	3.53	< 0.01
Underlying diagnosis					0.02
<b>Obstructive</b>	46 (31)	8 (20)	38 (35)		
Emphysema		7	21		
A1AT-deficiency		1	6		
Bronchiectasis		0	6		
Bronchiolitis		0	5		
<b>Pulmonary vascular</b>	5 (3)	0	5 (5)		
<b>Cystic fibrosis</b>	17 (11)	2 (5)	15 (14)		
<b>Interstitial lung disease</b>	82 (55)	30 (75)	52 (47)		
IPF		17	29		
NSIP		2	1		
HP		1	2		
PF		7	17		
BOOP/COP		2	1		
Sarcoid		1	1		
LAM		0	1		
Lung allocation score (median/interquartile range)		38.2 (34.6–45.6)	38.6 (33.5–51.9)	−0.45	0.66
Pre-transplant 6-min walk distance feet (median/interquartile range)		808 (713–1146)	859 (659–1122)	−0.24	0.81
Pre-transplant diabetes	29 (19)	7 (18)	22 (20)		0.82
Pre-transplant hypertension	72 (65)	22 (55)	50 (46)		0.36
Pre-transplant hyperlipidaemia	59 (41)	21 (53)	38 (35)		0.06
Allograft ischaemic time minutes (median/interquartile range)		257 (224–316)	261 (208–317)	−0.12	0.90
CMV serologic mismatch (D <sup>+</sup> /R <sup>−</sup> )	44 (29)	13 (33)	31 (28)		0.69

Data expressed as n (%) unless otherwise indicated. NAFLD: non-alcoholic fatty liver disease; BMI: body mass index; IPF: idiopathic pulmonary fibrosis; NSIP: nonspecific interstitial pneumonia; HP: hypersensitivity pneumonitis; PF: pulmonary fibrosis; BOOP/COP: bronchiolitis obliterans organising pneumonia/cryptogenic organising pneumonia; LAM: lymphangioleiomyomatosis; CMV: cytomegalovirus.

## Discussion

Our results show that lung allograft recipients with NAFLD with mild–moderate fibrosis have non-inferior 1-year post-transplant outcomes, compared to patients without NAFLD. NAFLD does not seem to contribute to increased morbidity, despite the association with significant comorbidities in the general population, including hypertension, diabetes, atrial fibrillation and chronic kidney disease. This finding is important given the wide prevalence of hepatic steatosis and fibrosis. It may be that proinflammatory signalling that contributes to the pathogenesis of NAFLD is less significant than the effects of alloimmunity and immunosuppression.

The correlation between NAFLD and index hospital-free days in this study cannot be readily explained. We do not believe that NAFLD would confer any benefits related to perioperative recovery post-transplant. We demonstrate that NAFLD is not associated with inferior outcomes post-transplant.

Our study has several strengths. One is the generalizability of our population to that of most lung transplant centres, based on similar baseline demographics reported in other studies and registries [38]. Another strength is the multimodal approach to characterising fatty liver disease in our patient population. This is particularly important given the lack of an agreed upon gold standard for diagnosing NAFLD.

Our study also has several limitations. First, is the retrospective, single-centre design. Second, our study suffers from a lack of global consensus for diagnosing NAFLD. We did utilise abdominal ultrasound testing in all patients, which is the currently accepted initial mode of evaluation, though this may have missed detection of mild disease in some patients [26]. This is why we utilised other testing modalities for liver disease in patients with risk factors. Advanced testing was guided by hepatology expertise and patient

TABLE 3 One-year outcomes in lung transplant recipients with NAFLD

Outcome (within 1 year post-transplantation unless otherwise specified)	Patients with NAFLD	Patients without NAFLD	p-value
ICU-free days within 10 days post-transplant (median, IQR)	5.0 (2.0–6.0)	3.0 (0–6.0)	0.27
Hospital-free days within 30 days post-transplant (median, IQR)	16.0 (10.5–19.5)	12.0 (0–18.0)	0.03
<b>Transfusion (within 3 days post-transplant)</b>			
Packed red blood cells >2 units	11/40 (28)	47/110 (43)	0.13
Fresh frozen plasma >2 units	17/40 (43)	39/110 (36)	0.45
Platelets (any)	21/40 (53)	46/110 (42)	0.27
Cryoprecipitate (any)	10/40 (25)	19/110 (17)	0.35
<b>Atrial fibrillation during index hospitalisation</b>	21/40 (53)	46/108 (42)	0.35
<b>Delirium during index hospitalisation</b>	16/40 (40)	55/108 (51)	0.27
<b>Daily tacrolimus dose required to maintain a goal trough of 8–12 ng/mL prior to index hospitalisation discharge mg (median, IQR)</b>	6.0 (4.0–8.5)	8.0 (5.0–10.0)	0.66
<b>Venous thromboembolism within initial 12 months<sup>#</sup></b>	16/38 (42)	44/103 (43)	1.00
<b>Acute cellular rejection event (any grade, within initial 12 months)<sup>#</sup></b>	18/38 (47)	41/102 (40)	0.45
<b>Need for insulin at time of discharge from index hospitalisation</b>	29/40 (73)	70/104 (67)	0.77
<b>Need for insulin within initial 12 months<sup>#</sup></b>	16/38 (42)	31/102 (30)	0.23
<b>% decline of pre-transplant glomerular filtration rate (CKD-EPI) at 12 months<sup>#</sup></b>	48 (33–57)	58 (42–68)	0.03
<b>Unplanned re-hospitalisations within initial 12 months post-transplant<sup>#</sup></b>	2.0 (1.0–3.0)	2.0 (1.0–3.0)	0.43
<b>CMV viraemia (viral load &gt;137 copies) incidence within initial 12 months post-transplant</b>	6/40 (15)	19/110 (17)	0.74
<b>Hospitalisation for infection during initial 12 months post-transplant<sup>#</sup></b>	20/38 (53)	43/102 (42)	0.34

Data expressed as n (%) unless otherwise indicated. NAFLD: non-alcoholic fatty liver disease; ICU: intensive care unit; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; CMV: cytomegalovirus. <sup>#</sup>: for those surviving to the given outcome.

clinical status and was not intended to be formulaic. Rather a pragmatic, multimodal approach to excluding severe liver disease was adopted, given the clinical demands of scheduling FibroScan studies in sick patients and the need for timely lung transplant evaluation. Another limitation was the study size. While we did have sufficient power to assess differences in hospital-free days, we did not have sufficient power to assess other pertinent outcomes such as decline in renal function or incidence of acute cellular rejection. Finally, this analysis is limited to assessing outcomes of patients with NAFLD 1 year following transplantation; a longer follow-up period is likely needed to identify the negative impacts of NAFLD on extrahepatic comorbidities in lung transplant recipients, such as diabetes and cardiovascular disease.

TABLE 4 Multivariate analysis of 1-year outcomes in transplant recipients with non-alcoholic fatty liver disease (NAFLD) (adjusting for age, BMI, lung allocation score disease diagnosis group and pre-transplant hyperlipidaemia)

Outcome (within 1-year post-transplantation unless otherwise specified)	Odds ratio <sup>#</sup> (95% CI)	p-value
ICU-free days within 10 days post-transplant	0.71 (–0.39–1.79)	0.21
Hospital-free days within 30 days post-transplant	3.34 (0.50–6.19)	0.02
<b>Transfusion (within 3 days post-transplant)</b>		
Packed red blood cells >2 units	0.76 (0.32–1.79)	0.53
Fresh frozen plasma >2 units	1.63 (0.72–3.68)	0.24
Platelets (any)	2.23 (0.98–5.08)	0.06
Cryoprecipitate (any)	1.81 (0.71–4.58)	0.21
<b>Atrial fibrillation during index hospitalisation</b>	1.33 (0.58–3.02)	0.50
<b>Delirium during index hospitalisation</b>	0.59 (0.27–1.33)	0.20
<b>Venous thromboembolism within initial 12 months<sup>#</sup></b>	1.06 (0.48–2.35)	0.88
<b>Acute cellular rejection (any grade within initial 12 months)</b>	1.20 (0.55–2.66)	0.65
<b>Need for insulin (on index hospitalisation discharge)</b>	1.23 (0.51–2.96)	0.64
<b>Need for insulin within initial 12 months</b>	1.67 (0.72–3.88)	0.23
<b>Decline of pre-transplant glomerular filtration rate (CKD-EPI)</b>	–0.07 (–0.15–0.01)	0.07
<b>≥2 unplanned re-hospitalisations within initial 12 months</b>	1.18 (0.49–2.85)	0.72
<b>Hospitalisation for infection within initial 12 months</b>	1.44 (0.66–3.14)	0.36

ICU: intensive care unit; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration. <sup>#</sup>: an odds ratio value <1 denotes a decreased likelihood of occurrence in lung transplant recipients with NAFLD.



Notably, we chose to exclude patients with F3–F4 liver disease, *a priori*, to minimise perceived risks to this sub-population. Our current study provides justification to consider additional clinical studies assessing the safety of performing lung transplantation in patients with more advanced liver disease.

To our knowledge this is the first study to report on outcomes of lung transplant recipients with NAFLD with mild–moderate fibrosis. Based upon our findings, such patients should not be excluded from lung transplantation based upon their liver disease alone.

Conflict of interest: None declared.

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