Original Article

Outcome in patients with cystic fibrosis liver disease

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Abstract

Background: Liver disease is an important complication in CF.
Aims: To determine if CFLD is a risk factor for mortality in CF, and which baseline characteristics predict all-cause mortality.
Methods: Irish children with CFLD, and their age and gender matched controls were enrolled at baseline and reviewed after 10 years to determine which characteristics predict mortality.
Results: 72/84 (85.71%) participants were followed, (mean age Cases 21.71 yrs SD 6.5, CF controls 23.62 SD 5.6, 22 (61%) males), with no difference in duration of follow-up. Nineteen participants (26.4%) died, 38.9% (14/36) with CFLD and 13.89% (5/36) CF controls (Odds Ratio (OR) 3.94 95% CI:1.23–12.56 p = 0.005). In logistic regression, liver disease (OR 4.28 95% CI 1.07–17.16) female gender (OR 12.25 95% CI 2.37–63.24), reduced pulmonary function, (OR 5.11 95% CI 1.09–23.81) were each independent risk factors for mortality in CF.
Conclusions: Liver disease is an independent risk factor for mortality in CF.
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Keywords: Cystic fibrosis liver disease; Mortality; Outcome; Nutrition; Female gender

Cystic fibrosis (CF) is a multi-organ disease due to mutations in the *CFTR* gene (cystic fibrosis transmembrane conductance regulator) leading to defective clearance of secretions from epithelial surfaces [1–5]. While pulmonary disease still remains the main cause of morbidity and mortality in CF, understanding the consequences of other manifestations of CF such as liver disease is of increasing importance if we are to further improve the outcome for patients.

The diagnosis of CFLD is not straightforward and the lack of a gold standard for the diagnosis has hampered our understanding of CFLD [2–6]. Many children with CF will develop evidence of liver abnormalities including raised liver enzymes, abnormalities on liver ultrasonography or hepatomegaly [2–5]. However, less than 10% of children with CF have clinically significant liver disease with portal hypertension [2,4]. The lack of a consistent definition of CFLD has led to significant disparities in the reported

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prevalence and outcome for CFLD [4]. The CF Foundation has proposed a classification of CFLD which separates cirrhosis with or without portal hypertension from other forms of liver disease such as raised aminotransferases and hepatic steatosis, and the use of this classification may help improve our understanding of CFLD [4].

A number of reports have suggested that liver disease is not a risk factor for mortality in CF [7–9]. However, many of these studies lack an adequate control group with which to compare outcome. Liver disease, even in the presence of portal hypertension is not considered a contraindication to lung transplantation in CF [10,11], and the outcome following lung transplantation is not reported to be compromised by the presence of liver disease [12]. Nevertheless, there is emerging evidence, which supports the hypothesis that liver disease may be a poor prognostic factor in CF [13–15]

In a national study of CFLD we have shown that children with clinically significant CFLD are shorter and lighter than their age and gender matched controls and have worse pulmonary function [16]. At a 7-year follow-up, while there was no difference in mortality between CF participants and CF controls, there was evidence that participants with CFLD had a more severe phenotype, with reduced nutritional parameters, poorer lung function and a greater rate of decline in Forced expiratory volume in 1 sec (FEV$_1$) compared to controls [15]. In the present study we continue to follow this cohort 10 years after they participated in the baseline study to examine differences in all cause mortality between participants with CFLD and CF controls with no evidence of liver disease and to identify risk factors for mortality [17].

1. Methods

Persons with CF who participated in the baseline study in 1999–2000 [16] and in the 7 year follow-up [15] were invited to participate in a review at 10-years. At baseline cases were defined as any child aged between 5 and 18 years with CF (confirmed by sweat chloride), who had liver disease with portal hypertension. Portal hypertension was defined clinically (splenomegaly/ hypersplensim), or ultrasonographically splenomegaly (increased compared with body-size-appropriate values,) varices, ascites, reversal of portal vein flow or endoscopically. Controls were children with CF who had no biochemical, ultrasonographic or clinical evidence of liver disease. At baseline CF controls were pair-matched for age and sex with CFLD participants.

Exclusions and losses to follow-up at 10 years were as follows: 5 cases of CFLD were excluded because they had not been reviewed by a paediatric hepatologist at baseline; it was determined on re-examination of their baseline data that their radiological or clinical assessment was not adequate to support a diagnosis of portal hypertension [15]. Participants were not matched for FEV$_1$ at baseline, and there were no a priori exclusion criteria based on pulmonary function tests at baseline. An FEV$_1$ of less than 30% predicts mortality within 2 years. On this basis, 3 controls with an FEV$_1$ < 30% at baseline were excluded from follow-up [15].

To review the validity of the baseline findings, the data was re-analysed without the 8 participants (5 cases and 3 controls) excluded from the follow-up data. Exclusion of this group of participants did not alter the findings of the baseline study.

In this follow-up study we used data collected at baseline in 1999–2000 to examine risk factors for mortality after 10 years follow-up. This included baseline pulmonary function tests (FEV$_1$ Z scores (Standard Deviation Scores)) anthropometric data with skin fold measurements, clinical biochemistry, and gender and liver disease. Baseline data for height, weight, and body mass index were expressed as centiles and Z scores using the Centre for Disease Control (CDC) 2000 reference data [18]. Upper arm circumference and skin fold thickness measurements were calculated as described previously [15,16]. FEV$_1$ was recorded as absolute values and the reference range described by Stanojevic et al. [19] (www.growinglungs.org.uk) was used to calculate centiles and Z scores of FEV$_1$ per cent predicted based on age height and gender, because Z scores allow a more accurate comparison of pulmonary function across a range of ages [19,20].

2. Ethical approval

This study was approved by all hospital Research Ethics Committees providing care for study participants, with the guidance that eligible participants should not undertake any extra investigations or hospital visits. Consent was obtained from participants and/or their parents.

3. Statistical analysis

The baseline study used a paired analysis design to compare patients with and without CFLD [16]. Losses to follow-up, exclusions and deaths required un-pairing of the data at follow-up. The end point for the comparison of the two groups was death or transplant (liver or lung) referred to as mortality. Transplant was classified as mortality because in the absence of a transplant the outcome was death.

Results are presented as median and interquartile range, as most of the data showed a degree of skewness. Wilcoxon Log-Rank tests were used to compare groups, and chi-square tests for differences in proportions. Multiple logistic regression was used to examine the simultaneous effect of several different explanatory variables on risk of death in CF. To avoid any linearity assumptions in the final logistic regression model FEV$_1$ Z score and BMI Z score were dicotomised into an FEV$_1$ Z score of <-2 SD below the mean compared to an FEV$_1$ Z score of ≥ -2 SD below the mean; a BMI Z score <-1 SD below the mean, and a Z score ≥ -1 SD below the mean. Significance was set at the 5% level. Data was analysed using Epi-Info (CDC, Atlanta USA).

4. Results

At baseline there were 42 CFLD participants with CFLD who were pair matched for age and sex with 42 participants with CF but no evidence of liver disease (CF Controls). Seventy two (85.7%) of the original 84 participants were available for follow-up. Fig. 1 is a schematic representation of the outcome
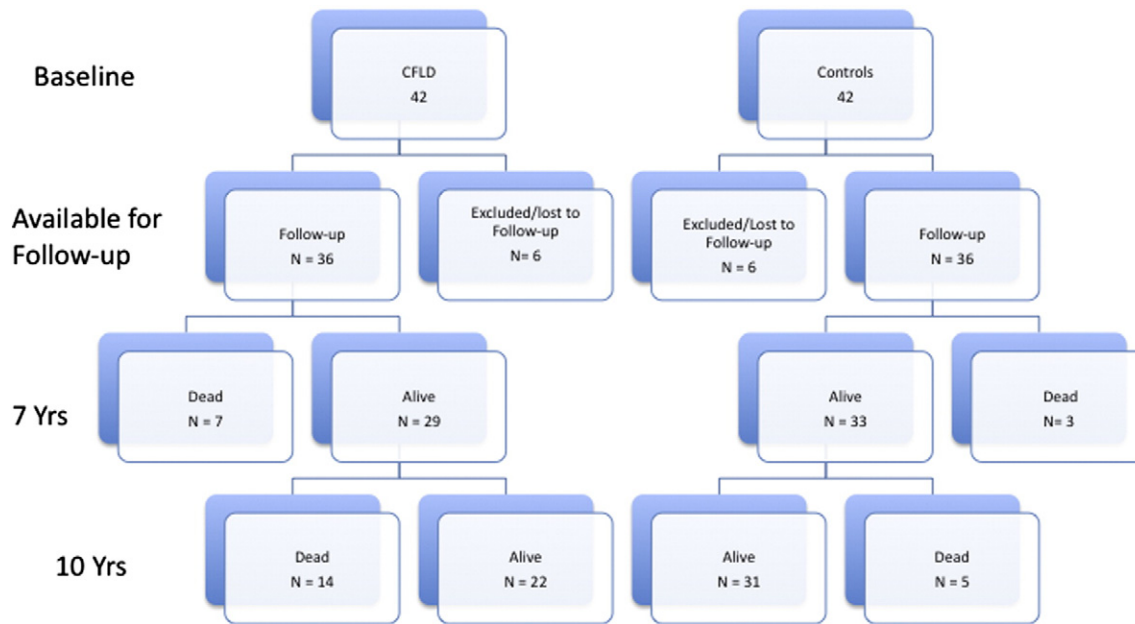
Fig. 1. Event tree diagram showing those who have died and those still alive with CFLD in comparison with age and gender matched controls with CF but no evidence of liver disease at two time points (7 and 10 years) after enrollment in the baseline study.

after 10 years of follow-up. Table 1 compares the baseline characteristics of those with CFLD and CF Controls, together with baseline characteristics of those who were alive (n = 53) and those who have died (n = 19) at follow-up. There was no difference in the age at baseline between participants with CFLD and CF controls (Table 1). However there was a statistically significant difference in the median age at follow-up between those who died and those who were alive at follow-up (Table 1).

5. Mortality in CFLD

At the 10-year follow-up, 19 (26.38%) of 72 participants had died or received an isolated organ transplant (liver = 2, lung = 2) (Fig. 2). Participants with CFLD had a significantly greater risk of mortality compared to CF controls with no evidence of liver disease (14/36 (38.9%) compared to 5/36, (13.9%); OR 3.94 95% CI 1.24–13.56 p = 0.01).

Table 1
Baseline characteristics of participants.

Variable	CFLD	CF controls	p	Dead	Alive	p
N	36	36		19	53	
Age at baseline (years)	13.9 (4.5)	14.0 (5.6)	0.67	14.1 (3.9)	13.9 (5.2)	0.7
[a]Age at follow-up (years)	21.7 (6.5)	23.6 (5.6)	0.19	19.8 (3.5)	24.3 (5.2)	0.001
Duration follow-up (years)	10.4 (2.6)	10.4 (0.1)	0.07	6.7 (3.7)	10.5 (0.1)	0.001
Age Diagnosis CF (Mths)	4.5 (22.5)	1.5 (5.5)	0.18	5.0 (22.5)	2.0 (9.5)	0.4
Birth weight (kg)	3.5 (0.6)	3.1 (1.4)	0.19	3.3 (0.6)	3.4 (1.1)	0.3
Height [b]Z score	−0.9 (1.8)	−0.8 (1.8)	0.25	−1.1 (1.2)	−0.9 (2.1)	0.4
Weight Z score	−0.9 (2.0)	−0.6 (3.1)	0.19	−1.1 (1.6)	−0.8 (0.7)	0.07
[c]BMI Z score	−0.2 (0.7)	−0.2 (0.9)	0.73	−0.8 (1.5)	−0.2 (0.8)	0.04
[d]FEV$_1$ Z score	−2.2 (2.5)	−1.5 (4.3)	0.05	−3.6 (2.6)	−1.7 (2.1)	0.001
Albumin	40.0 (5.0)	41.0 (5.00)	0.02	38.0 (8.00)	41.0 (5.0)	0.003
Platelets	143.5 (138)	311.0 (97)	0.01	153.0 (285)	269.0 (128)	0.55
[e,f]UAFA <25th centile (n%)	19 (54.3)	11 (33.3)	0.08	12 (66.7)	18 (36.0)	0.02
Male (n%)	22 (61)	22 (61)	0.5	7 (36.8)	37 (69.8)	0.01

Baseline characteristics of participants with CFLD and CF controls (Column 2–4) and baseline characteristics of those who have died or are alive after 10 years follow-up.

Data is presented as median with interquartile range or proportion.

 [a] Age at follow-up in those who have died is age at death.
 [b] Z Score = Standard deviation score.
 [c] BMI = body mass index.
 [d] FEV$_1$ = forced expiratory volume in 1 sec.
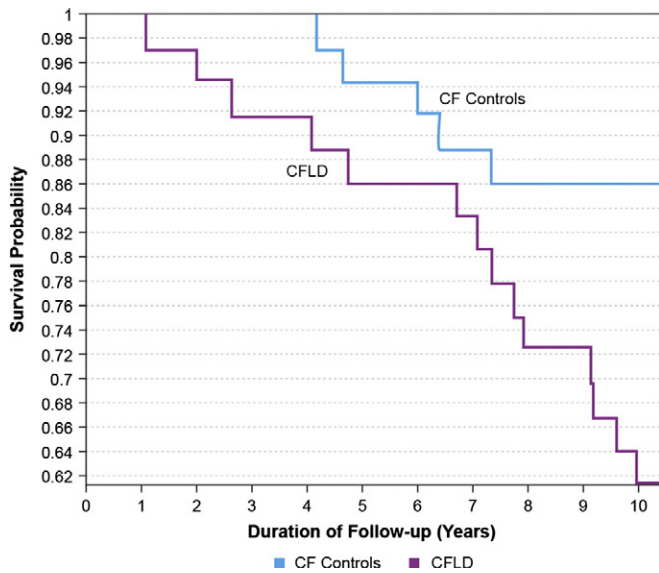 [e] UAFA = upper arm fat mass.

Fig. 2. Kaplan Meier Plot showing the probability of survival in CF participants with liver disease (CFLD Red Line) compared to CF Controls with no evidence of liver disease (CF Controls Blue Line) (Log Rank Test p = 0.02).

While 22/36 (61%) participants were male, 9/14 (64.28%) of those who died with CFLD were female compared to 5 males (Adjusted OR 5.77 95% CI 1.33–28.24 p = 0.015) Table 2. Of the 5 controls who died 3 were female and 2 were male.

6. Risk factors for mortality

Participants who died or received a transplant (n = 19) during the 10 year follow-up period had statistically significant reduced measurements at baseline for BMI, UAFA and pulmonary function compared to those who were still alive (n = 53) (Table 1). Differences in albumin but not platelet count were also apparent at baseline between those alive and those who died over the subsequent 10 years.

In an exploratory logistic regression model nutritional parameters (BMI, height, weight, skin fold measurements) pulmonary function and serum albumin and platelet count were entered as continuous variables, while gender and liver disease were binary variables (data not shown). In the final model pulmonary function was dichotomised into those with milder disease (FEV$_1$ % predicted Z score ≥-2 SD below the mean) and those with moderate to severe disease (FEV$_1$ % predicted Z score <-2 SD below the mean) at baseline. BMI was dichotomised as normal BMI Z score ≥-1 SD below the mean, or low BMI Z score as <-1 SD below the mean. Liver disease with portal hypertension, female gender, and moderate to severe lung disease (FEV$_1$ Z score of <-2 SD below the mean) were all independent risk factor for mortality in CF (Table 2). In this model a low BMI (BMI Z score of <-1 SD below the mean) almost reached statistical significance (OR 6.47 95% CI 0.96–43.26 p = 0.054).

7. Cause of death in participants with CFLD

Of the 14 participants with CFLD who died or received a transplant (n = 2), 7 (50%) died from pulmonary causes, while 7 (50%) died from hepatic causes. There were no differences in baseline data between those individuals with CFLD who died and those who were still alive (data not shown).

All of the CF controls died from pulmonary complications of CF. The controls with CF who died in this study (n = 5) had much worse pulmonary function at baseline (median FEV$_1$ % predicted Z score -4.48 SD IQR 1.69) compared to controls (n = 31) who were still alive (median FEV$_1$ % predicted Z Score -1.46 SD IQR 3.56 p = 0.001) and were shorter and lighter than the controls who were still alive, suggesting that the controls with CF who had died at follow-up were much sicker at baseline compared to those who survived.

8. Comparison of those alive at 10 years

Twenty-two participants with CFLD were alive after 10 years. Fifteen (68.18%) had clinical and radiological evidence of liver disease with portal hypertension and hypersplenism at follow-up. Of the 8 participants who were classified as "indeterminate" liver disease at the 7 year follow-up because they had no definite clinical evidence of portal hypertension, 6 remain "indeterminate." One of the 8 has died from pulmonary complications, and one developed portal hypertension with varices. The participant who has developed portal hypertension at 10 years was less than 10 years of age at baseline.

Of those who were still alive at 10 years there was no difference in height, weight, or BMI between participants with CFLD and CF controls. However, 11/22 (50%) of participants with CFLD had cystic fibrosis related diabetes mellitus (CFRDM)

Table 2
Multiple logistic regression of the risk factors for mortality in CF.

Variable		Outcome dead n	Outcome alive n	Odds ratio*	95% CI	Adjusted odds ratio	95% CI	p
Liver disease	Yes	14	22	3.9	1.2–12.6	4.3	1.1–17.2	0.04
	No	5	31					
Gender	Female	12	16	3.9	1.3–11.9	12.2	2.4–63.2	0.01
	Male	7	37					
FEV$_1$ Z score	<-2 SD	15	23	4.8	1.4–18.8	5.1	1.1–23.8	0.04
		4	30					
BMI Z score	<-1SD	7	7	3.7	1.1–13.4	6.5	0.96–43.3	0.054
		12	46					
Age at baseline						1.1	0.8–1.3	0.4

Univariate (*unadjusted odds ratio) and multivariate logistic regression analysis of the risk factors for mortality in participants with cystic fibrosis.

requiring insulin therapy, compared to 6/31 (19.4%) CF controls (OR 4.04 95% CI 1.19–14.71 p = 0.02). At baseline only 3 participants with CFLD had evidence of impaired glucose tolerance and one CF control, and none of the 4 was receiving insulin at baseline.

9. Discussion

The outcome for individuals with CF has dramatically improved over the last 20 years due to advances in the diagnosis and management of CF particularly with the introduction of newborn screening. While pulmonary complications remain the main cause of morbidity and mortality in CF it is now important to consider non-pulmonary complications of CF, such as liver disease, to determine if survival can be further improved. We have shown that CFLD represents a worse phenotype in CF [15]. Having now followed the original pair-matched cohort for 10 years we show that CFLD with portal hypertension is an independent risk factor for mortality in CF. Participants in this study with CFLD have almost 3 times the risk of death compared to controls with CF but no evidence of liver disease in this study. In keeping with previous clinical and research evidence [21–27] we also found that female gender and poor pulmonary function were independent risk factors for mortality in this study population.

While poor nutrition is a significant risk factor for mortality in CF, a BMI Z score <−1 SD failed to reach statistical significance in this model (Table 2). However, BMI centile may not reflect accurately the nutritional status in individuals with portal hypertension as an enlarged spleen or possible ascites may inflate the BMI measurement.

While there is conflicting evidence on the outcome for individuals with CFLD and portal hypertension it is becoming clearer that those with clinically significant liver disease represent a worse phenotype in CF with reduced survival [13–15]. Most studies to date, which have examined the outcome for patients with CFLD have only considered liver-related deaths. However we know from the literature that those with CFLD who survive into adulthood have a relatively stable disease with few deaths due to liver complications [8–10]. It is important to consider all cause mortality and to include paediatric as well as adult patients. The numbers in this study are relatively small but it comprises a national cohort of well-characterised participants with CFLD and their age and sex matched controls, thereby minimising potential biases associated with single centre studies, such as differences due to clinical practice or referral patterns. The follow-up period spanned the transition into adult care, and the inclusion of all cause mortality, rather than mortality from hepatic causes alone is important because not all individuals with CFLD will die from hepatic causes [14]. Age and gender are significant risk factors for mortality in CF and therefore choosing an appropriate comparison group is essential in understanding the outcome for CFLD. In this study participants were matched at baseline for age and gender.

It is likely that our calculations underestimate the increased mortality risk for those with CFLD. While this study was strengthened by the inclusion of an appropriate age and sex matched control group, an unintentional limitation arose from the necessity to enrol participants during a routine hospital visit. This was a condition of the Research Ethics Committees' approval which stipulated that attendance over and above that necessary for usual care was not permitted. Therefore, it is likely that the controls in our study were not fully representative of the normal paediatric CF population in Ireland as they were likely to be sicker and require more frequent hospital visits than average. It is now clear that there were substantial differences in pulmonary function and BMI at baseline between those control patients who subsequently died and controls who were still alive. In retrospect, it would also have been prudent to exclude controls with an FEV_1 in the moderate to severe range. However, despite having enrolled a relatively sicker control group of patients with CF, the mortality among those with CFLD was still 2.8 times greater after a relatively short (10 year) follow-up.

As stated previously the diagnosis of portal hypertension in CF liver disease is less than straight forward [2,4–6]. We excluded 5 participants in the CFLD group from follow-up because it was determined on re-examination of their data that there was inadequate clinical or radiological data to support a diagnosis of portal hypertension. Three controls were also excluded because their FEV_1 was less than 30% predicted at baseline. An FEV_1 of less than 30% is not compatible with long-term survival [24] and would bias an outcome or survival analysis in a long-term follow-up study. A further 3 participants were lost to follow-up (1 with CFLD, 2 controls). In order to evaluate the impact of the exclusions and losses to follow-up on our findings we re-analysed the data classifying exclusions and losses to follow-up among cases and controls as all dead or all alive. Regardless of categorisation, participants at baseline with CFLD have a worse outcome compared to controls with no evidence of CFLD.

Our data do not help address the important question of how to identify those at risk of progressive liver disease with a poorer outcome. While those with CFLD had worse pulmonary function and nutritional parameters at baseline, there were no factors which differentiated those who died with liver disease from those who survived with liver disease. Almost 25% of children who had clinical or radiological evidence of portal hypertension at baseline have not developed progressive liver disease as adults with their liver disease following a relatively benign course. However in the absence of invasive procedures such as liver biopsy or portal pressure measurements it is not possible to determine if these young adults have any degree of portal hypertension after 10 years of follow-up.

It is important to note the high proportion of CFLD participants with diabetes mellitus requiring insulin therapy compared to CF controls. At baseline no participant was receiving insulin therapy, although 3 participants with CFLD and 1 CF control had impaired glucose tolerance [16]. This cannot be explained by the change in the diagnostic criteria or management of CFRD since baseline, and it was unlikely that there was any difference in the diagnosis and management of CFRD between cases and controls in this national cohort. Prospective studies of liver disease in CF which carefully phenotype participants for both liver disease and diabetes are

required to determine the relative contribution of liver disease and diabetes to reduced life expectancy in CF.

In conclusion, liver disease is an independent risk factor for mortality in CF patients and females with liver disease may have a poorer outcome than males with liver disease. Further studies examining all cause mortality in CFLD are required to confirm these findings.

Abbreviations

CF   cystic fibrosis
CFLD   cystic fibrosis liver disease
CFRDM   cystic fibrosis related diabetes mellitus
FEV_1 forced expiratory volume in 1 sec
MUAC   mid upper arm circumference
OR   odds ratio
SD   standard deviation
UAFA   upper arm fat area
Z score standard deviation score
95% CI   95% confidence interval

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Conflict of interest disclosures

The authors have no conflict of interests.

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