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An international/multicentre report on patients with cystic fibrosis (CF) over the age of 40 years

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Abstract

Background: The lifespan of patients with cystic fibrosis (CF) is increasing significantly. The objective of this international pilot study was to study the characteristics of these long-term survivors.
Methods: Four centres with large CF clinics from London (UK), Minneapolis (USA), Toronto (Canada) and Verona (Italy) identified 366 patients who had survived 40years and longer.
Results: At all centres males survived longer than females. There were more pancreatic sufficient patients in Verona (60%) and Toronto (40%) than in London (16%) and Minneapolis (21%). The percentage of ΔF508 homozygous patients varied between 47% in London and 45% in Minneapolis to only 26% in Toronto and 9% in Verona.

Average FEV_1 and BMI values of the surviving population appeared to stabilise after 40years of age. FEV_1 was on average 12% higher in patients who were pancreatic sufficient ($p > 0.0001$). There was no difference in survival between the centres. The overall median survival after the age of 40 was 13years. The estimated annual death rate was approximately 3.4% from the age of 40–60years.
Conclusions: Significant numbers of patients are now surviving to 40years or more, and it is hoped that an in-depth study of these patients may identify the factors contributing to longer survival.
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Keywords: Cystic fibrosis; Longevity

1. Introduction

The lifespan of patients with cystic fibrosis (CF) has been steadily increasing in all countries where it has been measured, and there are good epidemiological reasons for believing that this trend, which has been apparent for several decades, will continue even in the absence of novel treatments directed toward correcting the basic CF genetic and molecular defect(s) [1,2].

Death from CF during childhood is now a rarity in the UK and other industrialised countries, and well over 95% of CF children can expect to enter adult life, with a corresponding need for appropriate medical services [3].

Survival beyond the fourth decade presents new questions and potential problems which are still being formulated. The effects of CF on the aging process, and vice versa, are not known, apart from a preliminary international study of malignancy [4]. Other diseases with a prevalence closely linked to age, such as arterial

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disease, type 2 diabetes mellitus, osteoarthritis and Alzheimer disease, could in theory be more or less common in age-matched CF patients — who usually have, for example, low cholesterol levels but an increased risk of diabetes. Understanding the nature of such interaction between diseases could shed important light on the mechanisms and control of both CF and other conditions.

The International Study of Aging in Cystic Fibrosis was set up to address these and other issues, and to share the limited experience of caring for relatively elderly CF patients with other professionals [5]. A preliminary search among interested CF centres in 2003 identified more than 1800 patients who were still alive beyond the age of 40 [6]. It was further evident that the numbers of such patients would escalate rapidly over the next decade. The current actuarial mean survival in countries with well developed CF services being about 35–40years for both sexes combined, and increasing year on year [7]. Male and female patients in the United Kingdom who were alive in 2003 at the age of 30years, had an estimated mean expectation of dying by 52.7 and 49.4years respectively [7]. In the Canadian Patient Data Registry, the percentage of patients over age 40 has steadily doubled every 5years, from less than 0.2% in 1977 to 6.7% in 2002. At this rate, 20% of Canadian CF patients will be over 40years of age by 2010 [8]. Similar aging patterns are seen in other western countries.

As a starting point it was therefore decided to look at individuals over 40years of age in more detail, to try to identify the factors which had contributed to their better survival, whether genetic, socioeconomic or therapeutic, and to discover whether later complications of CF could be anticipated, and whether they would experience a relatively greater or lesser risk of common age-associated disorders. The experience of four large CF centres, two in Europe (London and Verona) and two in North America (Minneapolis and Toronto), has now been analysed. Data were obtained from existing medical records and are presented in this report, which provides baseline data for planned prospective and more detailed enquiries.

2. Methods

Four CF centres, Royal Brompton Hospital, London, Cystic Fibrosis Center, University of Minnesota, Minneapolis, USA, St Michael's Hospital, Toronto, Canada and CF Centre, Verona, Italy contributed to this study. Clinical data from CF patients in each centre who had reached 40years of age by 31/12/2004 was anonymised and submitted to Toronto for analysis (by MC). Patients were grouped as seen in 03/04, i.e. alive at the end of the study, or last seen before 2003/2004 — i.e. patients who had died over 40years of age prior to 2003/2004. The following data was collected:

- date of birth,
- sex,
- genotype,
- pancreatic sufficiency or insufficiency,
- sputum microbiology (when last seen in the 2003/2004 group)
- forced expiratory volume in one second (FEV_1)
- Body Mass Index (BMI).

The following events and complications were also recorded:

- lung transplantation
- diabetes
- major haemoptysis
- allergic bronchopulmonary aspergillosis
- portal hypertension
- pneumothorax.

The definitions of diabetes, major haemoptysis, allergic bronchopulmonary aspergillosis, portal hypertension and pneumothorax were centre-specific, in that these conditions were diagnosed as present by the patient's clinician and recorded as such in the case file.

Lung function and BMI were summarized in box plots at 5year intervals, using the measurement date nearest each individual's birthday. Repeated measures regression analysis was conducted using longitudinal measures on individual subjects to estimate average rates of change over time in FEV_1 and

Table 1
CF patients over 40 years of age (1979–2004) — basic demographics

	London	Minnesota	Toronto	Verona	Total
Last seen					
1979–2002	25	26	40	9	100
2003–2004	90	63	75	38	266
Total	115	89	115	47	366
Sex[a]					
Female	48 (41.7)	31 (34.8)	47 (40.9)	21 (44.7)	147
Male	67 (58.3)	58 (65.2)	68 (59.1)	26 (55.3)	219
N	115	89	115	47	366
Age at diagnosis[b]					
Adult ≥18 years	32 (27.8)	35 (39.8)	44 (38.3)	26 (63.4)	137
Child <18 years	83 (72.2)	53 (60.2)	71 (61.7)	15 (36.6)	222
N	115	88	115	41	359
Pancreatic status[b]					
Sufficient	19 (16.5)	19 (21.4)	50 (43.5)	28 (59.6)	116
Insufficient	96 (83.5)	70 (78.6)	65 (56.5)	19 (40.4)	250
N	115	89	115	47	366
Genotype[c]					
ΔF508/ΔF508	41 (42.7)	35 (45.4)	28 (26.2)	4 (8.7)	108
ΔF508/0	51 (53.1)	34 (44.2)	55 (52.3)	23 (50)	164
O/O	4 (4.2)	8 (10.4)	23 (21.5)	19 (41.3)	54
N	96	77	107	46	326
[d]*Symptoms at diagnosis*					
Chest only	41 (35.6)	3 (5.3)	41 (35.7)	16 (34)	101
Gut only	44 (38.2)	4 (7.0)	13 (11.3)	2 (4.2)	63
Both	13 (11.3)	2 (3.5)	51 (44.3)	5 (10.6)	71
Unknown	1 (0.8)	24 (42.1)	9 (7.8)	19 (12.8)	53
Family history	18 (15.7)	26 (45.6)	6 (5.2)	6 (12.8)	56
N	115	89	116	47	

No. (%) *N*=Number on whom data was available.
0=a recognised CF allele other than ΔF508.
[a] $p=0.0002$, Chi-square test (1*df*) of equal proportions for male and female.
[b] $p<0.001$, Chi-square test (3*df*) of equal proportions in the 4 sites.
[c] $p<0.001$, Chi-square test (6*df*) of equal proportions in the 4 sites.
[d] Some patients had more than one.

BMI. Chi-square statistic with 3 degrees of freedom was used to compare the proportion of patients reported with specific complications and the proportion positive for specific lung infections. Kaplan Meier survival curves after the age of 40years were computed, and compared using the log rank test. Significance was taken as $p < 0.05$.

3. Results

The numbers of patients who had died over the age of 40, and last seen in London, Minnesota, Toronto and Verona were 25, 36, 40 and 9 respectively, and patients seen in 2003–2005, (i.e. still alive), were 90, 63, 75 and 38. London, Minnesota, Toronto and Verona therefore contributed data for 115, 89, 115, and 47 patients respectively. This paper therefore reports on a total of 366 patients from the four centres. Not all data were available on all patients but this is indicated by *n* numbers in the tables.

There were no major differences in the analysis of patients seen in 2003–2004 when compared with the whole group who passed the age of 40years since 1979 (Table 1). Age distribution by site was similar with the median in the mid-40s and the oldest subjects in the 60s. There were group differences in percentage diagnosed as children ($p = 0.001$), most in London, (72%) least in Verona (36%), similar in Toronto (62%) and Minnesota (60%). The reason for diagnosis (Table 1) varied between sites. In London the most frequent features were respiratory and gastrointestinal symptoms, whereas in Minneapolis they were recorded as family history or unknown. In all centres more males had survived to 40years than females ($p = 0.0002$), and the sex ratio was not different between centres ($p = 0.7$). There were many more pancreatic sufficient patients (Table 1) in Verona (59.6%) and Toronto (40.5%) than in London and Minneapolis (16.5 and 21% respectively) ($p < 0.001$). The incidence of mutations ΔF508/ΔF508 varied significantly (Table 1), being

Table 2
CF patients over 40 years of age (1979–2004) — major events and complications

	London	Minnesota	Toronto	Verona	Total
Lung transplantation	22 (19.1)	10 (11.2)	21 (18.3)	1 (2.1)	54
	N=115	*N*=89	*N*=115	*N*=47	*N*=366
Diabetes	32 (27.8)	19 (21.4)	39 (35.3)	10 (21.3)	100
	N=115	*N*=89	*N*=115	*N*=47	*N*=366
Major haemoptysis	19 (16.5)	2 (2.2)	8 (7.0)	11 (23.4)	40
	N=115	*N*=89	*N*=115	*N*=47	*N*=366
Allergic bronchopulmonary aspergillosis	13 (11.3)	3 (3.4)	NA	7 (14.9)	23
	N=115	*N*=89	NA	*N*=47	*N*=251
Portal hypertension	5 (4.3)	0 (0)	9 (7.9)	0 (0)	29
	N=115	*N*=89	*N*=115	*N*=47	*N*=366
Pneumothorax	15 (13.0)	4 (4.5)	3 (2.6)	4 (8.5)	26
	N=115	*N*=89	*N*=115	*N*=47	*N*=366
Lung function: FEV_1 mean (SD)	53 (27)	55 (28)	58 (24)	55 (31)	55 (27)
	N=115	*N*=89	*N*=115	*N*=47	*N*=366
Nutrition: BMI mean (SD)	22 (3.3)	24 (3.2)	24 (3.6)	22 (3.0)	23 (4.0)
	N=103	*N*=63	*N*=82	*N*=35	*N*=283

No. (%) *N*=number on whom data was available. NA=not available.

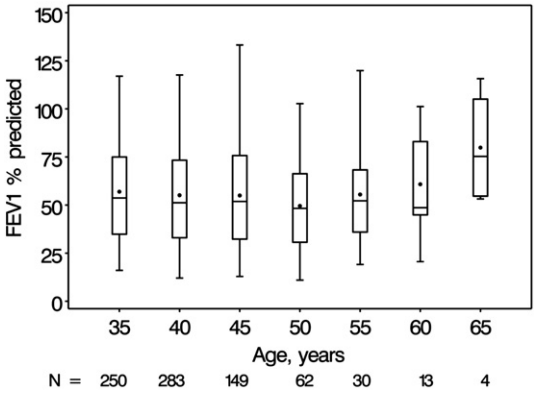

Fig. 1. CF patients over 40 years (2003–2004 data) showing FEV_1 at 5 yearly intervals.

42.7% in London, 45.4% in Minneapolis but only 26.2% in Toronto and 8.7% in Verona ($p < 0.001$). Mean lung function and BMI for those who were observed at age 40 was remarkably similar across centres. Not all patients were observed at age 40 since some were diagnosed later or transferred from another centre.

More lung transplants were carried out in London and Toronto than in the other centres (Table 2, $p = 0.02$). The incidence of CF-related diabetes was not significantly different in the 4 centres ($p = 0.13$). Major haemoptysis was seen more frequently in London and Verona ($p = 0.002$). Allergic bronchopulmonary aspergillosis (Table 2) was higher in Verona and London than in Minneapolis ($p = 0.05$) but data were not available for Toronto. Portal hypertension was more frequent in Toronto than London, and unexplainably not seen in Minnesota and Verona (Table 2). Pneumothorax was more commonly seen in London (13%) than elsewhere (Table 2) ($p = 0.01$). Only London had survival data on post-pneumothorax survival which was a mean of 122 months.

3.1. Microbiology (2003–2004 group)

Information on pathogens isolated from the sputum was available for 259 patients for the last year of study. London,

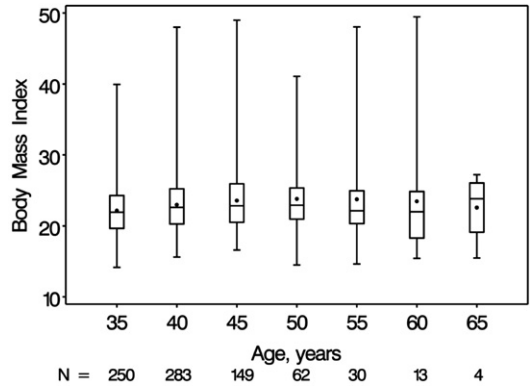

Fig. 2. CF patients over 40 years (2003–2004 data) showing BMI at 5 yearly intervals.

Minnesota, Toronto and Verona recorded *Pseudomonas aeruginosa* 77.8%; 70.7%; 46.7% and 55.6% respectively ($p = 0.0002$); *Staphylococcus aureus* 57.8%; 20.7%; 22.7% and 61.1% respectively ($p < 0.0001$); *Haemophilus influenza* 18.9%; 0%; 10.7%, 22.2% respectively ($p = 0.002$), *Burkholderia cepacia* 6.7%; 1.7%; 22.7% and 5.6% respectively ($p = 0.0002$); *Stenotrophomonas maltophilia* 1.1%; 1.7%; 9.3% and 22.2% respectively ($p < 0.0001$); *Aspergillus fumigatus* 2.2%, 36.2%, 30,7% and 0% respectively ($p < 0.0001$); *Mycobacterium tuberculosis* was only isolated from one patient in London, none was recorded at the other centres.

3.2. Lung function

FEV_1 is shown in Fig. 1 plotted at 5year intervals, and shows that the distribution of lung function values are remarkably similar at ages 40 to 55, with slightly higher values at aged 60 and 65 reflecting a very small number of survivors. FEV_1 was on the average 12% predicted higher in the pancreatic sufficient than the insufficient patients ($p < 0.0001$). The average values of FEV_1 were higher in Verona but there was no significant difference in FEV_1 across site or age group when pancreatic insufficiency/sufficiency was included in the repeated measures regression model. FEV_1 was consistently 3% predicted lower in females compared with males but this was not statistically significant ($p = 0.11$). In repeated measures analysis restricted to ages 35–55years there was a consistent negative effect over time that did not differ across centres, reflecting a rate of change in FEV_1 of − 0.4% predicted/year ($p = 0.02$). This reflects the average longitudinal rate of decline in individuals, but through mortality selection the average FEV_1 in box plots appeared constant across the ages.

3.3. Body Mass Index (BMI)

The average BMI values (Fig. 2) were 22–23 at all ages with a small inter-quartile range up to the age of 55years, i.e. the majority of patients having a healthy BMI in the 19–25 range. Toronto and Minnesota had higher BMI than London and Verona ($p = 0.0001$). Female BMI was on the average 1.3 points lower than males ($p < 0.001$) and pancreatic sufficient patients had a BMI on average 2.6 points higher than PI patients. Unlike FEV_1 there was no longitudinal decline in BMI, in the analysis of repeated measures. In fact there was a significant average increase in BMI of 0.1 units/year ($p = 0.001$), indicating that long time adult survivors have well-maintained or improved nutritional status as they get older.

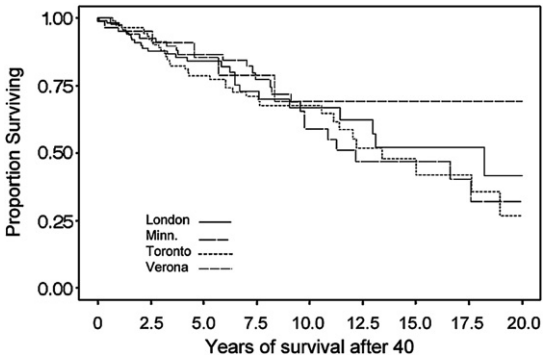

Fig. 3. All patients over 40 years of age, survival from the age of 40 years.

3.4. Survival

There was no significant difference between the survival curves of the four centres (log rank test $p = 0.8$). The overall median survival after the age of 40 was 13years, i.e. to 53years of age, and the survival curves were quite linear (Fig. 3). Survival analysis for the combined four centres gave an estimated death rate of approximately 3.4%/annum from the age of 40–60years (based on the estimated 32% survival) and 68% mortality by the age of 60years.

4. Discussion

Patients with CF are surviving longer. We have reported on detailed records of 366 who have survived to more than 40years. More males than females survived in all four centres. In London the patients were diagnosed younger, and in Verona older. This may be because in Verona there were more patients with pancreatic sufficiency (which is known to be associated with late diagnosis) [9], whereas symptoms of malabsorption are a common method of presentation leading to diagnosis in childhood. A higher proportion of CF patients in Southern Europe are pancreatic sufficient, and the high incidence of pancreatic sufficiency in Toronto (40%) may reflect the large number of immigrants from Mediterranean countries, particularly Italy. In contrast, Minneapolis, with a population largely derived from Northern Europe, is genetically and clinically much more similar to London.

There was wide variation in the frequency of complications. In the case of allergic bronchopulmonary aspergillosis and portal hypertension there is difficulty in getting agreed criteria in different decades. We have therefore used a ‘clinical diagnosis’ by the clinician.

The prevalence of diabetes was highest in Toronto, but overall the range was from 21–35%. The reason for the increased risk of developing CF-associated diabetes in Toronto is not clear, but possible contributory factors may be the historical emphasis on a high-calorie diet in Toronto CF clinics, which is also reflected in the higher BMI [7]. There is good evidence that maintenance of good nutritional status in children with CF correlates positively with the clinical condition of CF adults [11], and with survival [10], but a higher risk of developing diabetes may be an unwanted consequence. Other explanations could be the higher incidence of post-transplant patients on immunosuppressants and because Toronto screens annually using OGTT. Other centres screened, but not all used this method.

The definition of major haemoptysis is imprecise, but it appears to be higher in London and Verona (16 and 23% respectively) compared with Minnesota and Toronto (2.2 and 7% respectively). Pneumothorax was more common in London at 13% than in the other centres. In two recent papers it has been reported to be associated with a poor prognosis and an increased risk of dying within 2years [12,13]. In the patients reported here,

average survival after an episode of pneumothorax was much better in London, 5 patients who have died survived between 60 and 320 months after their first pneumothorax, and a further 6 are still alive up to a median of 158 months.

Microbiology is only presented for the 2003–2004 period but there were striking differences which may represent geographical difference in prevalence. The higher rate of *B. cepacia* in Toronto is well known [14]. The lower rate of pseudomonas in Toronto may reflect a more frequent use of inhaled tobramycin, and some pseudomonas may have been replaced by *B. cepacia*.

The apparent stability of cross-sectional lung function and BMI after the age of 35years was striking, and this appears to be a new observation which applied to all centres. The mean longitudinal decline in FEV_1 of 0.4% predicted/year was small by any standards, and reflects a relative stability in these older patients. There was no evidence of longitudinal BMI decline, and average values indicated that these patients are able to maintain a healthy weight. Survival was similar between the four centres at 50years, in spite of an increased prevalence of *B. cepacia* in Toronto. Verona had less ΔF508/ΔF508 and less pancreatic insufficiency and may have a survival advantage at 60years. Based on the age-specific death rates in this study population, patients who reached 40years of age have a 50% chance of reaching 53years of age, and a 35% chance of reaching 60. Older patients aware of the study have found this observation encouraging, however, this contrasts with an earlier estimate, based on assumptions, of a 54% chance of survival to age 60years [6]. The improving outlook for each successive cohort of patients may in fact make the more favourable prediction more likely for patients who are currently approaching their 5th decade.

London, Minnesota and Toronto are lung transplant centres, so it is not surprising that they have a higher proportion of patients who had received transplanted lungs. Lung transplant rates are high in Toronto even though a large percentage of candidates are infected with *B. cepacia* which is associated with a reduced post-transplant survival [15].

These data provide a background for more detailed investigations. The crucial question is why do some patients survive longer than others? The available information indicates that it can only in part be related to the CFTR genotype: more than 40% of long survivors in London and Minnesota were homozygous for the "severe" ΔF508 mutation. The influence of modifier genes at other loci may be important [16]; for example, genes which modify inflammatory responses to infection [17,18].

The importance of non-genetic factors in determining the clinical severity of CF was highlighted by a recent report of a pair of genetically proven identical female twins. At the age of 40years their FEV_1 and body weights were strikingly different (88% v 29% predicted, and 66 v 55kg respectively), although the twin with the worse lung function had always had the lower body weight [19]. How important are social, economic and psychological factors [20], including adherence to therapeutic regimens? It is clear that the improved survival seen in the whole CF population maybe due in large measure to better medical care, but which components of that package of care have been most important? Most long survivors will have benefited from specialist centre care, which included frequent surveillance, intravenous antibiotics for exacerbation of pulmonary infection, lung clearance measures, inhaled antibiotics and nutritional advice and support. The importance of early childhood nutrition has been shown previously [10,11].

Mean life expectancy for CF children was less than 15years when these patients were born. Are we reporting individuals at the upper end of a multifactorial genetic spectrum of disease and longevity which has only become apparent because death from CF in early life has been largely eliminated, or are there identifiable environmental factors which could be reproduced? If the significant factors contributing to these patients' longevity can be identified, it may be possible to extend their benefits to the wider population of people with CF.

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