The prevalence, clinical status and genotype of cystic fibrosis patients living in Cuba using national registry data

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Abstract

Background: We aimed to establish a national cystic fibrosis (CF) registry for Cuba, a developing country.

Methods: Regional centres that deliver care for all CF patients provided information for a national database.

Findings: The prevalence of CF in Cuba is 26.3 cases per 1,000,000 population. The median age at diagnosis is 2 years, and the median age of the total population was 15 years. Of those aged 16 years or older, the prevalence of *Pseudomonas aeruginosa* infection was 46%, the prevalence of *Staphylococcus aureus* infection was 36%, and 80% of individuals were receiving oral azithromycin. The commonest gene mutation was F508del which was observed in 50% of patients.

Interpretation: These data demonstrate that it is possible to establish a national CF registry in a developing country such as Cuba. This provides baseline data to permit evaluation of health care delivery enable the spread of good clinical practice nationally.

Highlights

- **These data demonstrate the establishment of a national cystic fibrosis registry in Cuba, a developing country**
- **The data provide a summary of the prevalence of disease, demographics, microbiology and genotype of all individuals with a diagnosis of cystic fibrosis who live in Cuba**

Introduction

Cystic fibrosis (CF) is a disease in which large gains in survival have been observed over the past five decades [1, 2] as a consequence of medical advances [3]. supported by the introduction of national registries [4-7] that have collected data on clinical status and facilitated dissemination of good practice. This has aided health care planning and permitted epidemiological studies on risk factors [8][9, 10], thus improving future care. A recent review has identified that developing CF patient registries in Latin American countries has potential to improve clinical outcomes [11].

Cuba is a Caribbean country that is well recognised for the quality of its medical care and collection of health service data [12], despite a persisting economic embargo from the USA [13]. A registry of all patients with a known diagnosis of cystic fibrosis was established in Cuba in 2015, and has been used to present a summary of the prevalence of disease and a description of the population with CF living in this country along with demographic and clinical parameters.

Methods

Data collection

The Cuban Cystic Fibrosis registry was established by the national association of cystic fibrosis doctors in conjunction with the Cuban Institute of Hygiene Epidemiology and Microbiology and the data were collected in 2015 during routine clinic visits. Data were collected on demographic, anthropomorphic, most recent Forced Expiratory Volume in one second (FEV_1), Forced Vital capacity (FVC), Shwachman score [14]**,** most recent microbiological results in clinical records, genotype, and current treatment regimen stratified by below or above the age 16 years (age of transferring to adult care in Cuba). The Cuban CF registry is a healthcare improvement database designed to audit and improve clinical care for patients, and no ethical approval was required for this evaluation and summary of these data.

Data analysis

The data were extracted of all patients who provided data in 2015 and imported into Stata (v13, Texas). Age stratified z scores for BMI were generated using 2007 WHO reference data and predicted lung function calculated using Global Lung Initiative data [15]. Estimates of the Cuban population collected in 2016 [16] were used to generate prevalence data.

Results

There were 296 patients entered onto the national registry of cystic fibrosis for Cuba, of whom 181 (61%) were male. The median age was 15 years (interquartile range of 7 to 24 years) and the distribution of current age is presented in Figure 1a. The median age at diagnosis was 2 years

(interquartile range of 1 to 7 years) and this distribution is presented in Figure 1b. Lung function data were available in 57 adults, who had a mean FEV_1 value of 2.10 L (standard deviation sd 0.86). The mean BMI for adults aged 16 years or more was 21.43 kg/m^2 (sd 4.23).

The most recent microbiological data were available for 251 (85%) patients. Of those aged 16 years or over, there was a prevalence of any *Pseudomonas aeruginosa* infection of 46% and mucoid *Pseudomonas aeruginosa* infection of 28%. The other infections are presented in Table 3. For patients aged 16 years or more, there was a median of 2 pulmonary exacerbation in the preceding 12 months (range 0 to 6). For those aged 16 or over, 133 (80%) were receiving azithromycin, 28 (41%) enteral feeding and 73 (51%) pancreatic supplements.

Data were available on genotype for 238 (80%) of individuals. The commonest gene defect was F508del which was observed in 119 (50%) of patients, of whom 32 (13%) were homozygous for this gene. In 79 (33%) individuals no gene was identified.

The prevalence of cystic fibrosis in Cuba was 26.3 cases per 1 million population Regionally, the prevalence varied and was 25.7, 27.2 and 26.4 cases per 1 million population in the Western, Central and Eastern regions respectively with no differences between the three regions (p=0.93, chi-squared test).

Discussion

The establishment of a national registry of cystic fibrosis in Cuba has allowed the first estimates of the prevalence of this disease in this country and provides a summary of the current clinical status of this population.

One of the strengths of this analysis is that it has taken advantage of the national network of cystic fibrosis centres that provide multidisciplinary care to all individuals with a diagnosis of CF living in the country. Hence, all patients who have a diagnosis of CF are reported to the registry and will have been included in the analysis. As Cuba is an island with secure borders, it is likely that all individuals with a diagnosis of CF in this country will be registered with the national healthcare system rather than receive treatment elsewhere.

The prevalence of individuals with a diagnosis of CF in Cuba is 26 per 1 million population, compared to 74 per 1 000 000 in the European Union and 80 per 1 000 000 population in the United States [17]. There are a number of possible explanations for the lower prevalence of

patients with a diagnosis of CF in Cuba compared to elsewhere. These include systemic under-diagnosis of CF across the island, that this is a true difference as a consequence of the different populations having different frequencies of the genotypes that cause CF disease [18] and hence differential phenotypic severities or simply the relatively young demographic structure of the Cuban cystic fibrosis population as a consequence of decreased survival compared to more affluent countries with more therapeutic possibilities. Filho *et al* [11] have highlighted the suboptimal access to a variety of effective interventions that individuals with cystic fibrosis living in Latin America experience, and these concerns apply to the Cuba health system as well.

Inevitably, participants are those with a known diagnosis of CF and hence it is difficult to know what is the burden of undiagnosed disease nationally. This is a very important issue, as any individual with untreated CF can be expected to fail to thrive as a child and experience premature mortality compared to those who receive optimal treatment. The relatively similar prevalences of CF across Cuba with a highest value of 27.2 per 1 000 000 population in the Central region and a lowest value of 25.7 per 1 000 000 population in the Western region make a regional bias in underdiagnosis less likely, but do not preclude the possibility of undiagnosed cases across the country as a whole.

These data also demonstrate that the median age at diagnosis of the total population with a diagnosis of CF is 2 years, reflecting the time taken for the patient to present to the attention of the medical services and for the clinical diagnosis of CF to become apparent. Population-based screening of new-born infants for CF is currently being introduced to Cuba and we will be able to monitor its effectiveness using the future registry data.

The benefits of developing national registries for CF are multiple [19], although to date they have been largely available in developed countries. These data demonstrate that it is possible to establish a national CF registry in the context of a developing country. This permits intra-national and international comparisons of the Cuban CF data from an epidemiological perspective, while also using these data to drive forward the care of CF patients living on the island.

Author Contributions

The study was designed by all the authors. F R-C and R S-M collected the data. The analysis was by R S-M and AF. All authors contributed to data interpretation, data presentation and writing of the manuscript. All authors approved the final version of the manuscript.

Declarations of Interest

There are no conflicts of interest.

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Table 1. Description of demographics of population of individuals with diagnosis of cystic fibrosis living in Cuba

	Age < 16 years	Age 16+ years	Total population
Total	154 (52)	142 (48)	296
Male sex (%) N=94	92 (60)	89 (63)	181 (61)
Skin colour, (%) White Mixed Black	 99 (73) 33 (24) 4 (3) N=136	 81 (67) 34 (28) 5 (4) N=120	 180 (70) 67 (26) 9 (4) N=256
Mean weight, Kg (sd)	-	58.3 (13.6) N=118	-
Mean height, m (sd)	-	1.64 (0.09) N=118	-
Mean Body mass index, kg/m^2 (sd)	-	21.43 (4.23) N=118	-
Body mass index Z score by age	-0.38 (1.58) N=127		
Receive social security support (%)	30 (19)	30 (21)	60 (20)
Relationship status (%) Single Married/cohabiting Divorced	 - - -	 74 (67) 35 (32) 2 (2) N=111	 - - -
In paid work (%) N=88	-	60 (68)	-
Education (%) Primary school Secondary school Pre-university University	 - - - -	 3 (3) 29 (28) 54 (53) 16 (16) N=102	 - - - -
Mean FEV_1 (sd) N=57	-	2.10 (0.86)	-
%predicted FEV_1 (sd) N=57		58.6 (21.1)	
Mean FVC (sd) N=57	-	3.06 (1.03)	-
%predicted FVC (sd) N=57		71.6 (20.0)	
Mean FEV_1 / FVC N=57	-	0.69 (0.15)	-

All available data has been presented
- = meaningful data not available
FEV_1 = Forced expiratory volume on one second
FVC = Forced Vital Capacity

Table 2. Description of clinical details, microbiology and treatment of individuals with diagnosis of cystic fibrosis living in Cuba

	Age < 16 years	Age 16+ years	Total population
Median Shwachman score (range)	85 (45 to 100) N=135	80 (0 to 98) N=117	85 (0 to 100) N=252
Pancreatic insufficiency (%)	92 (60)	59 (42)	151 (51)
Most recent sputum culture			
Microbiological data available (%)	135 (88)	116 (82)	251 (85)
Staph. aureus infection (%)	44 (33)	42 (36)	86 (34)
Methicillin Resistant *Staph. aureus* infection (%)	10 (7)	5(4)	15 (6)
Burkholderia cepacia infection (%)	0 (0)	2 (2)	2 (1)
Pseudomonas aeruginosa infection (%)	93 (69)	54 (47)	147 (59)
Mucoid *Pseudomonas aeruginosa* infection (%)	27 (20)	33 (28)	60 (24)
Median pulmonary exacerbations* in past year (range)	2 (0 to 10) N=132	2 (0 to 6) N=112	2 (0 to 10) N=244
Median hospital admissions in past year (range)	1 (0 to 10) N=114	0 (0 to 5) N=103	1 (0 to 10) N=217
Any admission in past year	89 (78) N=114	50 (49) N=103	139 (64) N=217
Treatment			
Oxygen (%)	15 (10)	11 (8)	26 (9)
Physiotherapy (%)	120 (78)	103 (73)	223 (75)
Bronchodilators (%) N=229	116 (99)	112 (100)	228 (100)
Nebulised saline (%) N=229	62 (53)	43 (38)	105 (46)
Nebulised antibiotics (%) N=229	71 (61)	58 (52)	129 (56)
Azithromycin (%)	120 (78)	113 (80)	233 (78)
Inhaled steroids (%) N=184	15 (18)	22 (22)	37 (20)
Pancreatic supplements (%)	114 (74)	73 (51)	187 (63)
Vitamin A supplements (%) N=257	121 (87)	114 (97)	235 (91)
Vitamin C supplements (%) N=257	129 (93)	113 (96)	242 (94)
Vitamin E supplements (%) N=257	139 (100)	115 (97)	254 (99)
Oral nutritional supplements	108 (70)	69 (49)	177 (60)
Enteral feeding (%) N=177	35 (32)	28 (41)	63 (36)

* pulmonary exacerbation was defined by clinicians

Figure 1a. Histogram of age of patients with diagnosis of cystic fibrosis in Cuba

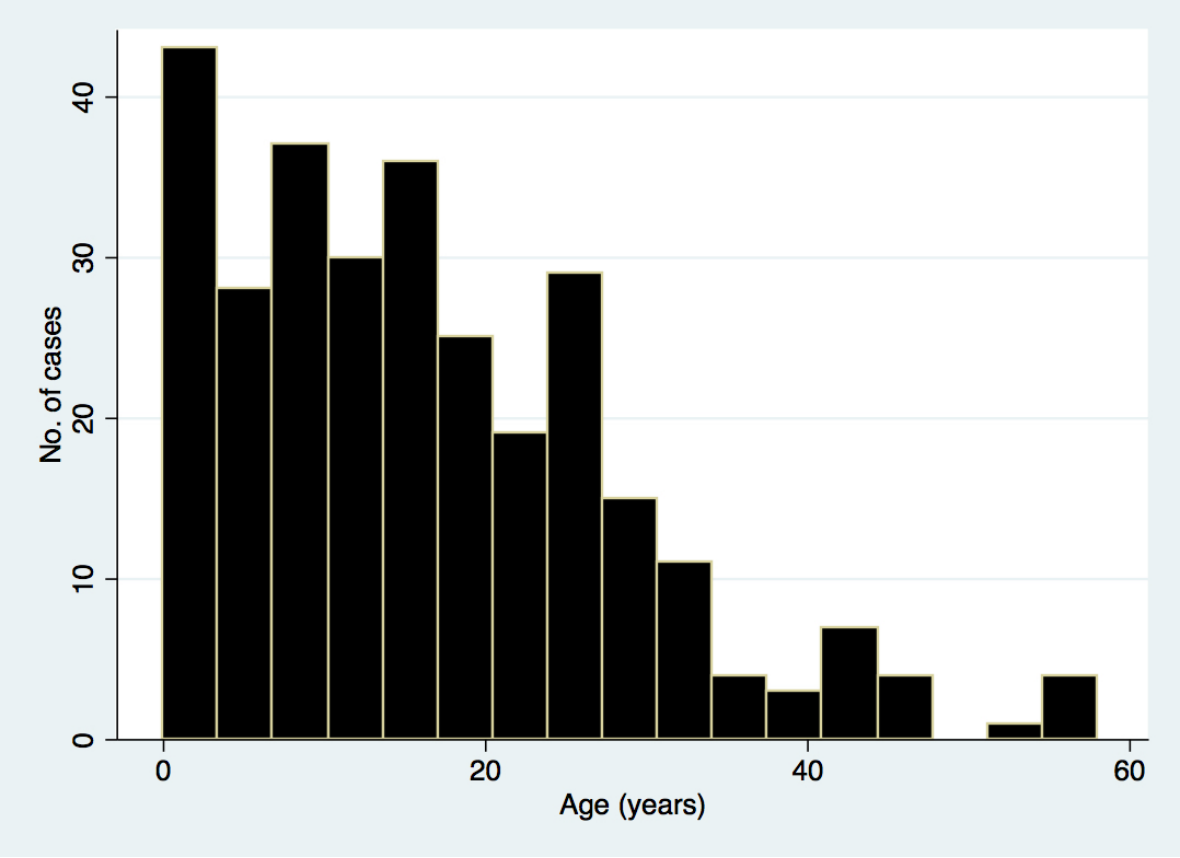
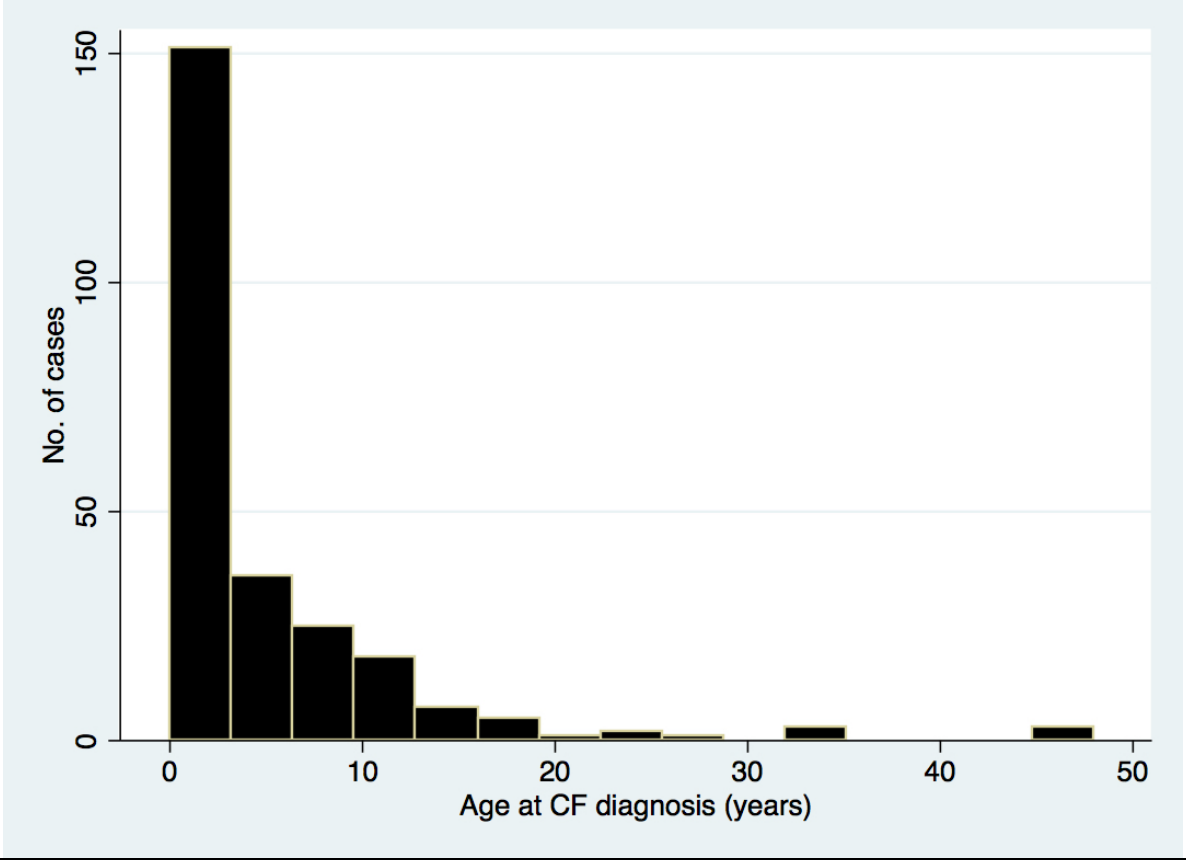


Figure 1b. Histogram of age at diagnosis of patients with diagnosis of cystic fibrosis in Cuba*



*Data available on 252 individuals