The Brazilian Cystic Fibrosis Patient Registry

2014

GRUPO BRASILEIRO DE ESTUDOS DE FIBROSE CÍSTICA

2014 ANNUAL REPORT

To all the people interested in cystic fibrosis:

The Brazilian Cystic Fibrosis Patient Registry (REBRAFC) contains demographic data on the diagnosis and treatment of patients with cystic fibrosis (CF) in Brazil, which is aimed at improving attention to the disease in our country. This is the sixth year the report has been published, with increasing participation of colleagues and centers operating in Brazil. There is still much to do for Brazilian patients, who lack access to diagnostic and therapeutic resources in various regions of the country. The continuity and solidity of REBRAFC is of particular importance in this scenario, as it is the main documented feature of the real situation of Brazilian patients and their evolution over the years, showing, therefore, how CF is being diagnosed and treated in the country.

We believe that this initiative can contribute to changes in the government's agenda and result in better health care for individuals with CF in Brazil.

About Cystic Fibrosis and The Brazilian Cystic Fibrosis Study Group.:

Cystic fibrosis (CF) is an autosomal recessive disease with multisystemic involvement (respiratory, gastrointestinal, hepatic, and genitourinary systems). It is a complex, progressive, and potentially lethal disease but still scarcely known in Brazil, despite the existence of some specialized centers and professionals dedicated to studying it and taking care of patients for many years. Treatment is also complex and involves high-cost medications, of which some are funded by the Ministry of Health and others are funded by the State Health Departments, so access to medicines is not uniform in the country.

The Brazilian Cystic Fibrosis Study Groups (GBEFC) is a nonprofit organization composed of healthcare professionals working in the area, established on November 5, 2003. Among the activities of the GBEFC are the dissemination of research, staff training and aiding in the development of CF treatment centers in the country, organizing scientific meetings about the disease (five editions of the Brazilian CF Congress), working with the Ministry of Health for defining a national protocol of CF care, and implementation of newborn screening in the remaining Brazilian states.

The GBEFC maintains an Internet site (www.gbefc.org.br) that provides information on cystic fibrosis. This report and previous ones (2009, 2010, 2011, 2012, and 2013) are available for free download in Portuguese and English versions.

EXECUTIVE COMMITTEE OF THE BRAZILIAN CYSTIC FIBROSIS REGISTRY:

Dr. Luiz Vicente Ribeiro Ferreira da Silva Filho

- Executive Coordinatorof the REBRAFC
- Assistant Professor at the Pediatric Pulmonology Unit, Instituto da Criança (HCFMUSP)
- Researcher at the Research and Learning Institute of Hospital Israelita Albert Einstein, São Paulo, SP

Dr. Francisco José Caldeira Reis

- Former Presidentof the Brazilian Cystic Fibrosis Study Group
- Professor of Pediatrics at the Federal University of Minas Gerais (UFMG)
- Pediatric Pulmonologist trained at Prof. Victor Chernick's Service, University of Manitoba, Children's Hospital of Winnipeg, Manitoba, Canada
- Advisor of the Hospital Infantil João Paulo II, Rede FHEMIG, Belo Horizonte, MG

Prof. Dr. Paulo José Cauduro Maróstica

- Full Professor, Department of Pediatrics, UFRGS
- Coordinator of the GP in Health of Children and Adolescents, UFRGS
- Head of the Pediatric Pulmonology Unit, Hospital de Clínicas de Porto Alegre, RS

Dr. Rodrigo Abensur Athanazio

- Assistant Physician of the Pulmonology Department at the Instituto do Coração (InCor) of Hospital das Clínicas da FMUSP

Dra. Neiva Damaceno

- Assistant Professor at the Pediatric Pulmonology Group of the Faculty of Medical Sciences of Santa Casa de São Paulo
- Former Presidentof the Brazilian Cystic Fibrosis Study Group (GBEFC)

Adilson Yuuji Hira

- Engineer
- Laboratory of Integrated Systems, Escola Politécnica of the University of São Paulo (USP)

Angela Tavares Paes

- Statistician Federal University of São Paulo (UNIFESP)
- Doctorate from the Institute of Mathematics and Statistics, University of São Paulo (IME-USP)
- Applied Statistics Sector, Pro-Rectory of Graduate Studies and Research, Federal University of São Paulo

REBRAFC HIGHLIGHTS IN 2014

1. A total of **3,511 patients were registered**, of whom 3,327 (94.7%) had some annual follow-up data (some spirometry and/or anthropometry data).
2. **More than 50% of patients already had at least 3 years of follow-up (2,043 patients, 58.2%).**
3. In the country, **166 new** cases were diagnosed, and **newborn screening accounted for about 70% of new diagnoses**. The median age of diagnosis of the patients, however, is still 1.19 years.
4. The median age of Brazilian patients was 11.5 years, and about 25% of patients were 18 years or older.
5. **Brazil still had <50% of patients with genetic research results.**
6. Of patients with genetic study, about a quarter were homozygous for the F508del mutation.
7. Thirty-five percent of patients aged up to 5 years had *Pseudomonas aeruginosa* identification in respiratory secretion samples. This proportion reached 62% of patients aged between 25 and 35 years.
8. The proportion of the total of patients with identification of **mucoid** strains of *P. aeruginosa* in respiratory secretion samples was 20% and is falling every year (in 2009, this figure was 31%).
9. Many of the Brazilian patients with CF had poor nutritional status (body mass index [BMI] below the 50th percentile), a proportion that increases in adolescence.
10. Of the Brazilian patients with CF, 81% used pancreatic enzymes, but only 63% used nutritional supplements.
11. Cumulatively, patients with CF were identified at **11,368 outpatient appointments** and were hospitalized for 14,896 days in 2014.
12. About **a third of patients between 6 and 17 years old** already had moderate and severe changes in pulmonary function.
13. Twenty-four patients with CF underwent lung transplantation in Brazil in 2014.
14. Forty-six patients died in 2014, the leading cause being of respiratory origin. The mean age of death was 19.8 years.

1. INTRODUCTION

This report describes data from the Brazilian Cystic Fibrosis Patient Registry (REBRAFC), which contains information on the demographic, diagnostic, and treatment aspects of patients with cystic fibrosis in Brazil. It presents data of patients with follow-up during 2014 and included in the registry in 2015. By the time the database for analysis was generated, 3,511 patients had been registered in the database, of whom 3,327 (94.7%) had some follow-up registered.

The numbers of records and follow-ups have been increasing, as shown in Figure 1. The number of new registered cases also draws attention, as it was considerably higher than in those in previous years. In 2015, 587 new records were noted, a quite expressive number if compared with those in the last 3 years (255 records in 2014, 487 records in 2013, and 384 records in 2012). Another interesting fact is that more than half of the patients (2,043, 58.2%) had at least 3 years of follow-up (Table 1). These results evidence the improvement in the quality of data and the continuity of the work by REBRAFC.

Figure 1

Growth in the numbers of records and follow-up between 2009 and 2014.

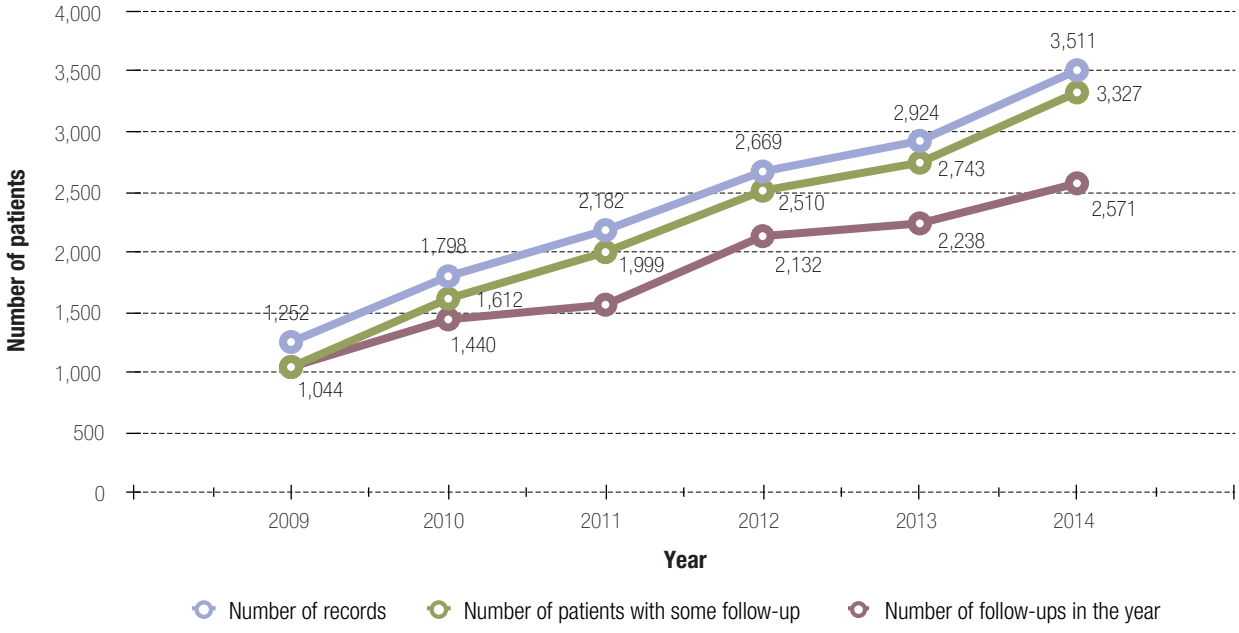


Table 1

Distribution of patients according to follow-up time

Follow-up time	N	%	Accumulated %
6 years	457	13.0	13.0
5 years	507	14.4	27.5
4 years	506	14.4	41.9
3 years	573	16.3	58.2
2 years	569	16.2	74.4
1 years	715	20.4	94.8
No follow-up	184	5.2	100.0
Total	**3,511**	**100**	

n = number of patients.

For describing personal and diagnostic data, all the registered patients (n = 3,511) were considered. For analyzing follow-up data, only data from 2014 (inserted in 2015) were considered, adding up to 2,571 patients.

2. DEMOGRAPHIC DATA

Table 2

Distribution of the patients according to birth state, 2014.

Birth state	n	%
São Paulo	956	27.2
Minas Gerais	400	11.4
Bahia	388	11.1
Rio Grande do Sul	379	10.8
Rio de Janeiro	219	6.2
Paraná	189	5.4
Santa Catarina	173	4.9
Pará	124	3.5
Espirito Santo	115	3.3
Ceará	101	2.9
Pernambuco	75	2.1
Distrito Federal	62	1.8
Goiás	56	1.6
Mato Grosso	48	1.4
Mato Grosso do Sul	34	1.0

Birth state	n	%
Alagoas	29	0.8
Rio Grande do Norte	24	0.7
Paraíba	16	0.5
Maranhão	12	0.3
Tocantins	10	0.3
Piauí	8	0.2
Rondônia	8	0.2
Amazonas	6	0.2
Sergipe	6	0.2
Acre	3	0.1
Amapá	3	0.1
Roraima	1	0.03
Não informado	66	1.9
Total	**3,511**	**100**

n = number of patients.

Figure 2

Distribution of the patients according to birth region, 2014.

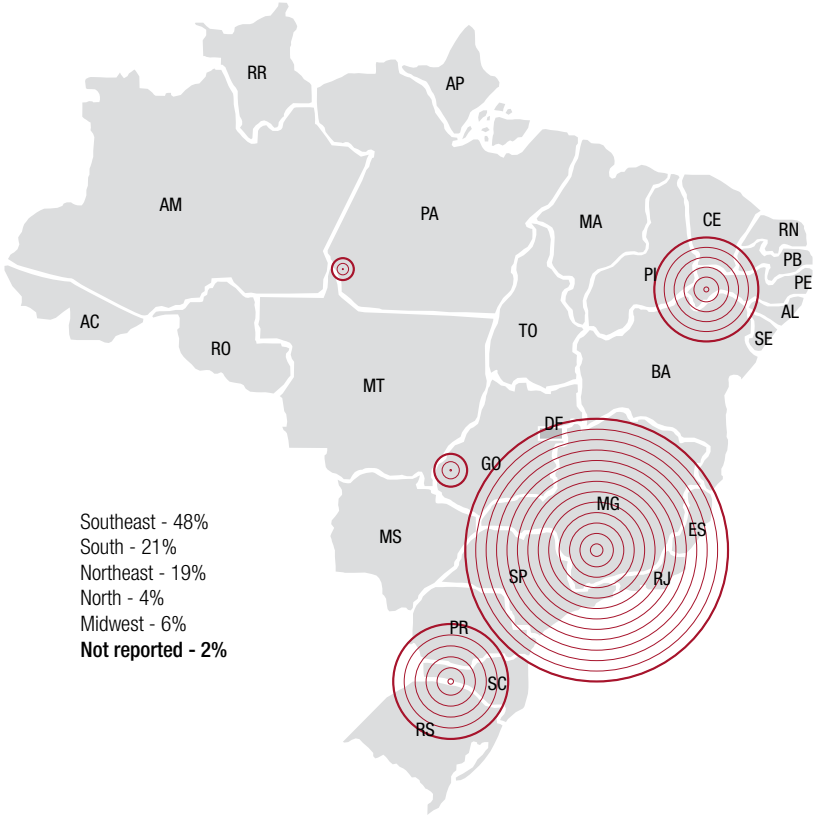


Table 3 shows the distribution of the patients according to the state of the care center in which they were registered. The increase in the participation of centers from the Midwest and some states in the North and Northeast compared with the previous year drew some attention. It is interesting to note that in addition to the greater participation of care centers and improvement in the quality of the data registered, some decentralization can be observed, with a reduction in the proportion of cases from the South and Southeast, and an increase in cases registered in the Midwest, North, and Northeast (Figure 3).

Table 3

Distribution of the patients according to the state of the care center, 2014.

State of the care center	n (%)
São Paulo	1,020 (29.1%)
Rio Grande do Sul	412 (11.7%)
Bahia	391 (11.1%)
Minas Gerais	391 (11.1%)
Rio de Janeiro	217 (6.2%)
Paraná	205 (5.8%)
Santa Catarina	154 (4.4%)
Pará	127 (3.6%)
Espírito Santo	120 (3.4%)
Ceará	105 (3.0%)

State of the care center	n (%)
Distrito Federal	103 (2.9%)
Pernambuco	72 (2.1%)
Goiás	52 (1.5%)
Mato Grosso	39 (1.1%)
Alagoas	30 (0.9%)
Mato Grosso do Sul	26 (0.7%)
Rio Grande do Norte	24 (0.7%)
Paraíba	12 (0.3%)
Maranhão	11 (0.3%)
Total of patients	**3,511 (100%)**

n = number of patients.

Figure 3

Distribution of the patients according to the state of the care center, 2013 and 2014.

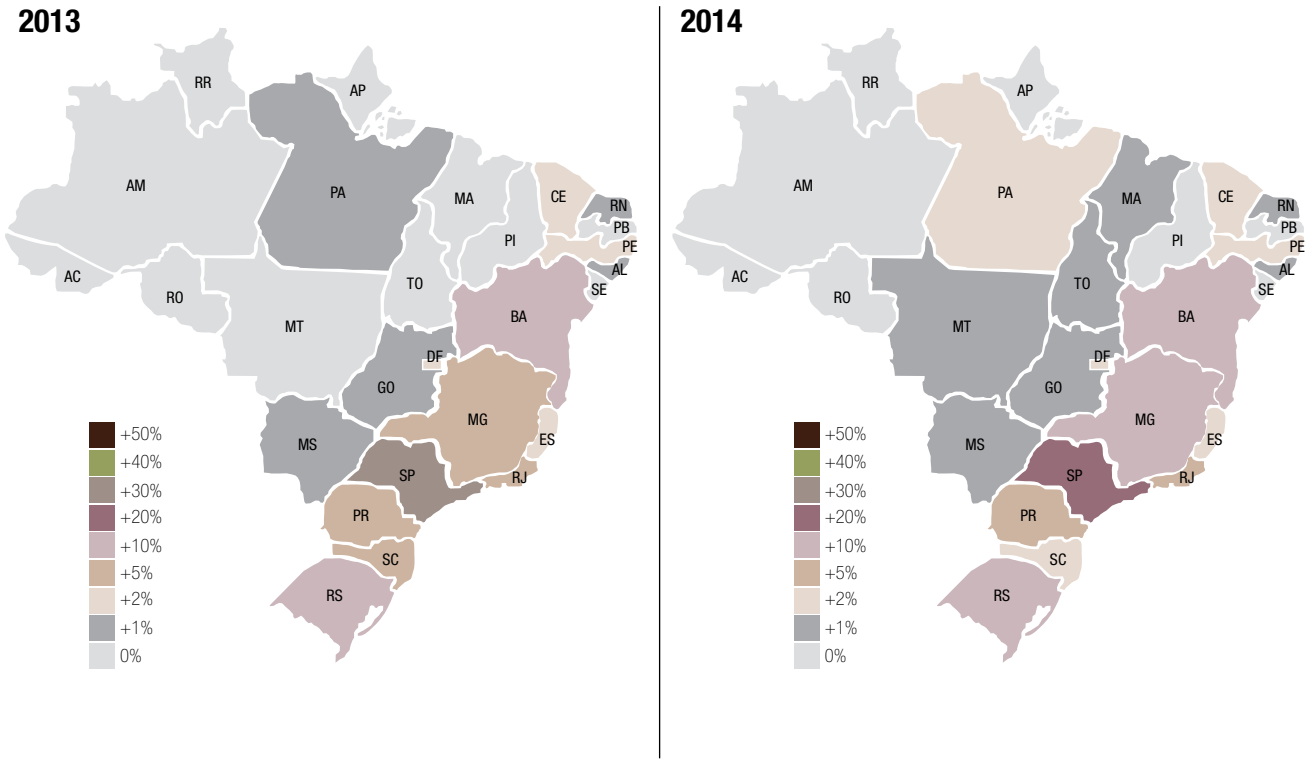


Table 4

Distribution of the patients according to sex and ethnic group, 2014.

Sex	n (%)
Male	1,545 (52.8%)
Female	1,379 (47.2%)
Total of patients	**2,924 (100%)**

Ethnic group	n (%)
White	2,028 (69.4%)
Mulato	698 (23.9%)
Black	188 (6.4%)
Asian	7 (0.2%)
Native	3 (0.1%)
Total of patients	**2,924 (100%)**

n = number of patients.

Table 5

Distribution of the patients according to current age (last spirometry/anthropometry), 2014.

Age (years)	
Mean (standard deviation)	13.67 (11.24)
Median (p25-p75)	11.52 (5.81 – 17.93)
Total of patients	**3,166**
Patients who died	**129**
Patients with no spirometry/anthropometry	**216**

n=number of patients; p25 = percentil 25, p75=percentil 75.

Figure 4

Distribution of the patients according to current age (last spirometry/anthropometry), 2014.

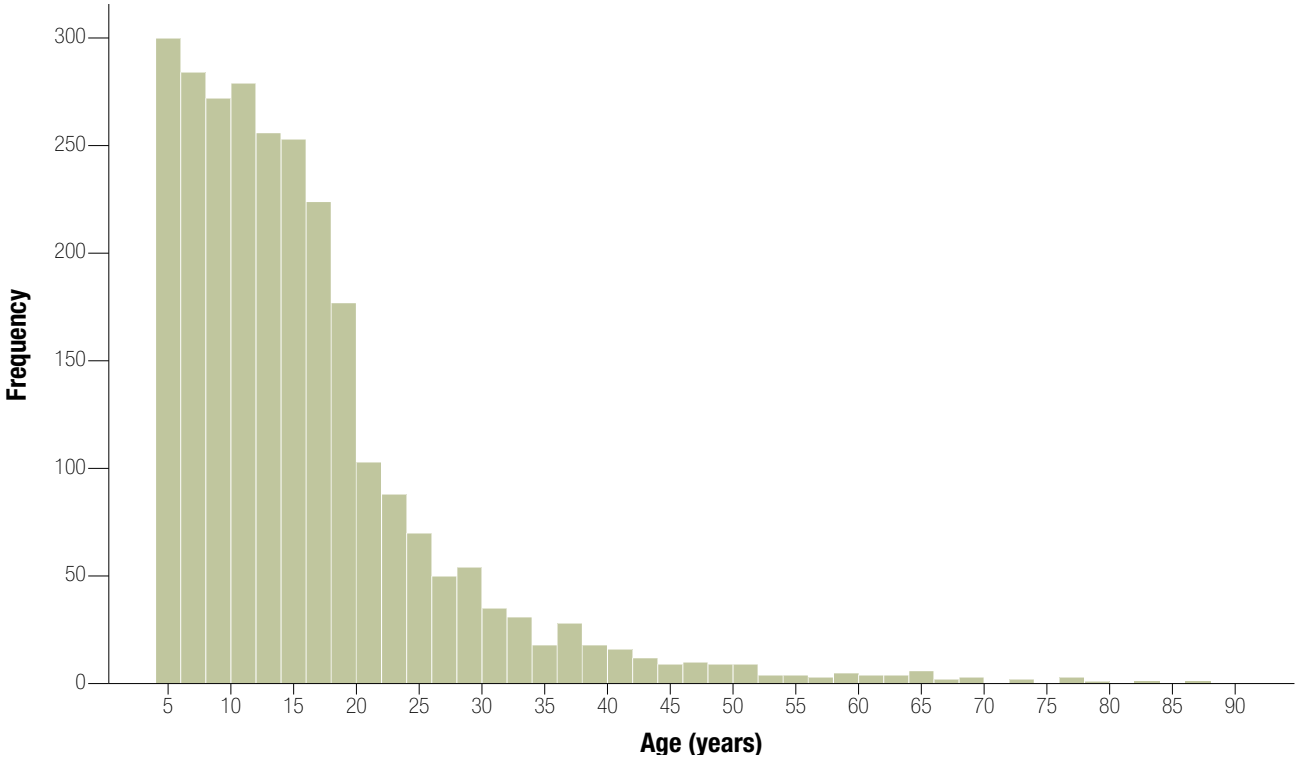


Figure 5

Distribution of the patients according to current age (last spirometry/anthropometry), 2014.

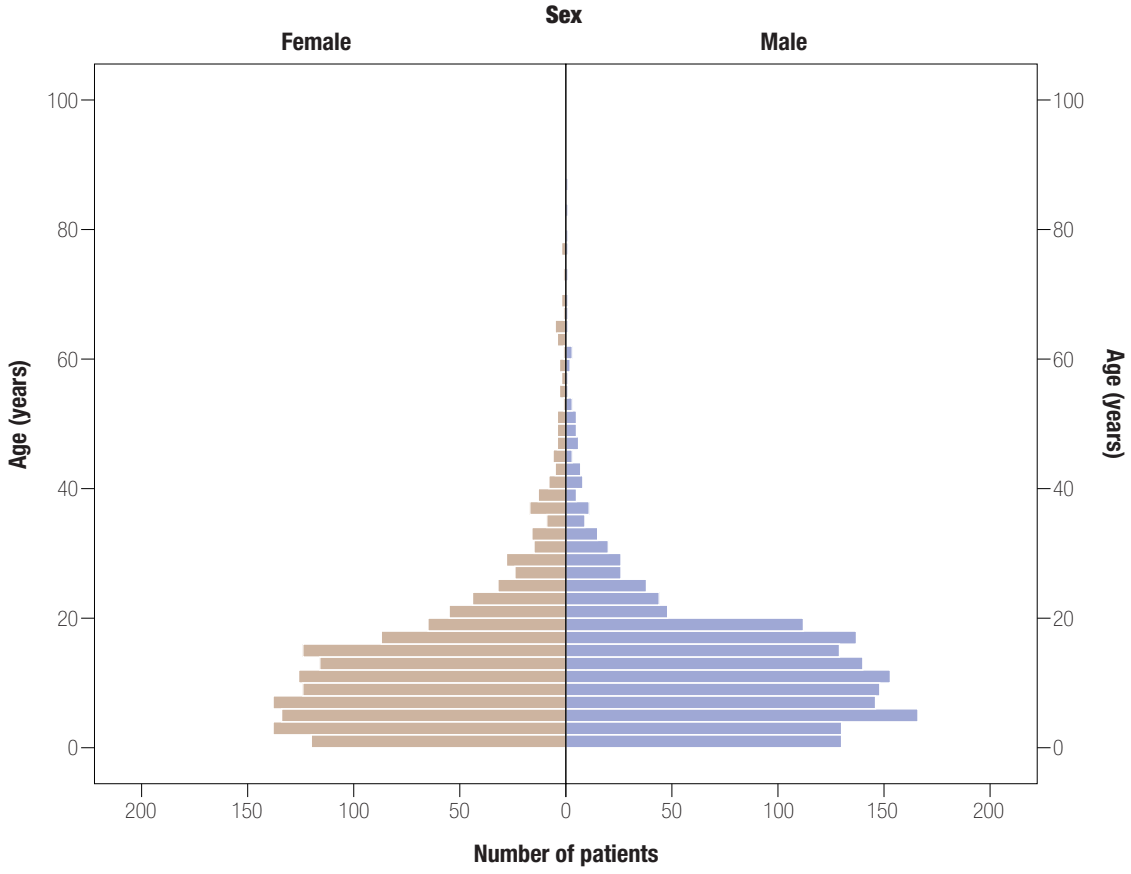


Table 5

Distribution of the patients according to current age group, 2014.

Age group (years)	N (%)
Up to 5	666 (21.0%)
> 5 to 10	709 (22.4%)
>10 to 15	676 (21.4%)
>15 to 20	512 (16.2%)
>20 to 25	230 (7.3%)
>25 to 30	135 (4.3%)
>30 to 35	75 (2.4%)
>35 to 40	55 (1.7%)
>40 to 45	35 (1.1%)
>45 to 50	21 (0.7%)
>50 years	52 (1.6%)
Total of patients	**3,166 (100%)**
Patients with no information	**216**

Age group (pediatric – adult)	n (%)
<18 years	2,386 (75.4%)
≥18 years	780 (24.6%)
Total of patients	**3,166 (100%)**
Patients with no information	**216**

n = number of patients

Note: Patients do not have information either because they were not followed up or because they did not undergo spirometry/anthropometry. In the current age analysis, deaths were not considered (n = 129).

Figure 6

Evolution of current age from 2009 to 2014. Values are expressed as medians.

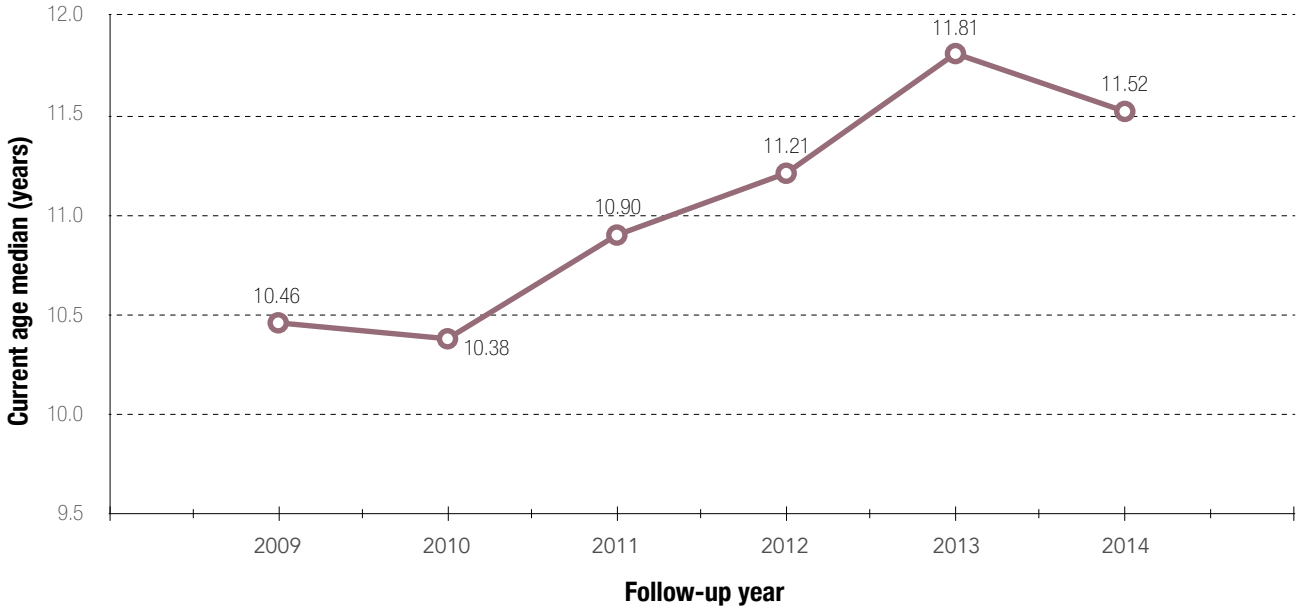
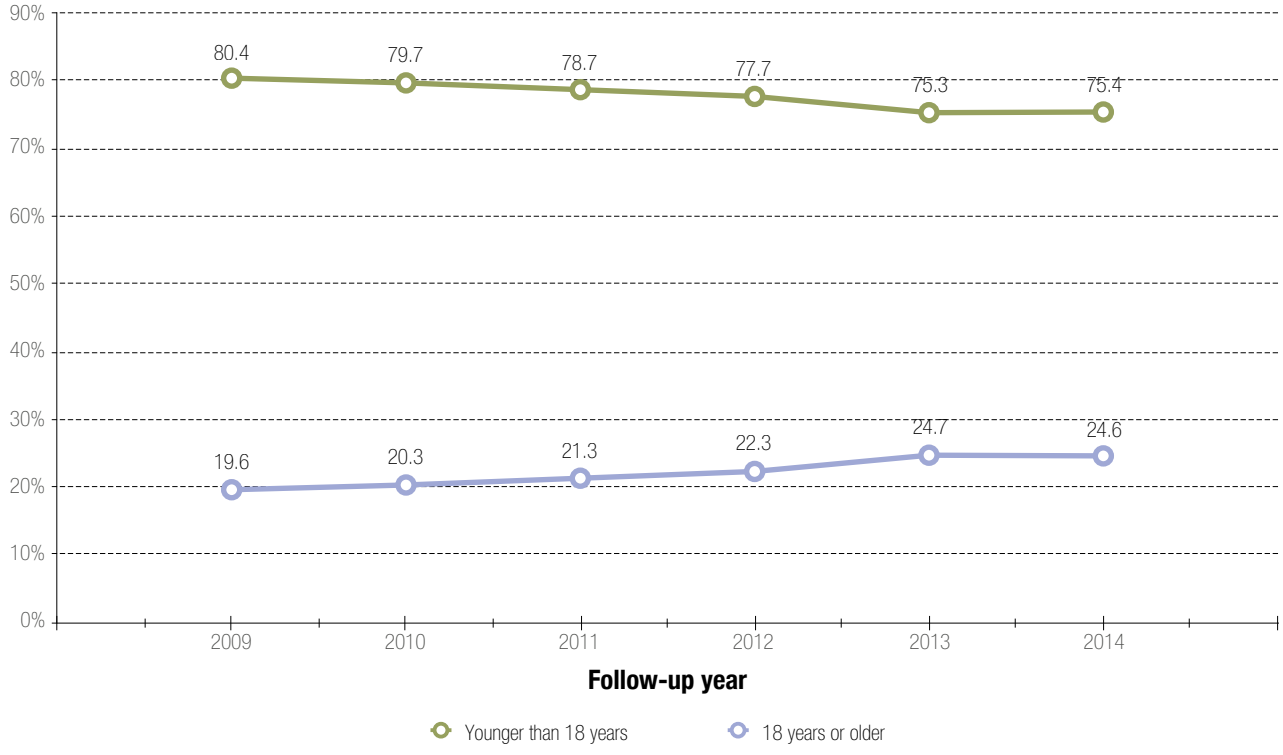


Figure 7

Distribution of the patients according to pediatric age group from 2009 to 2014.



3. DIAGNOSTIC DATA

Table 6

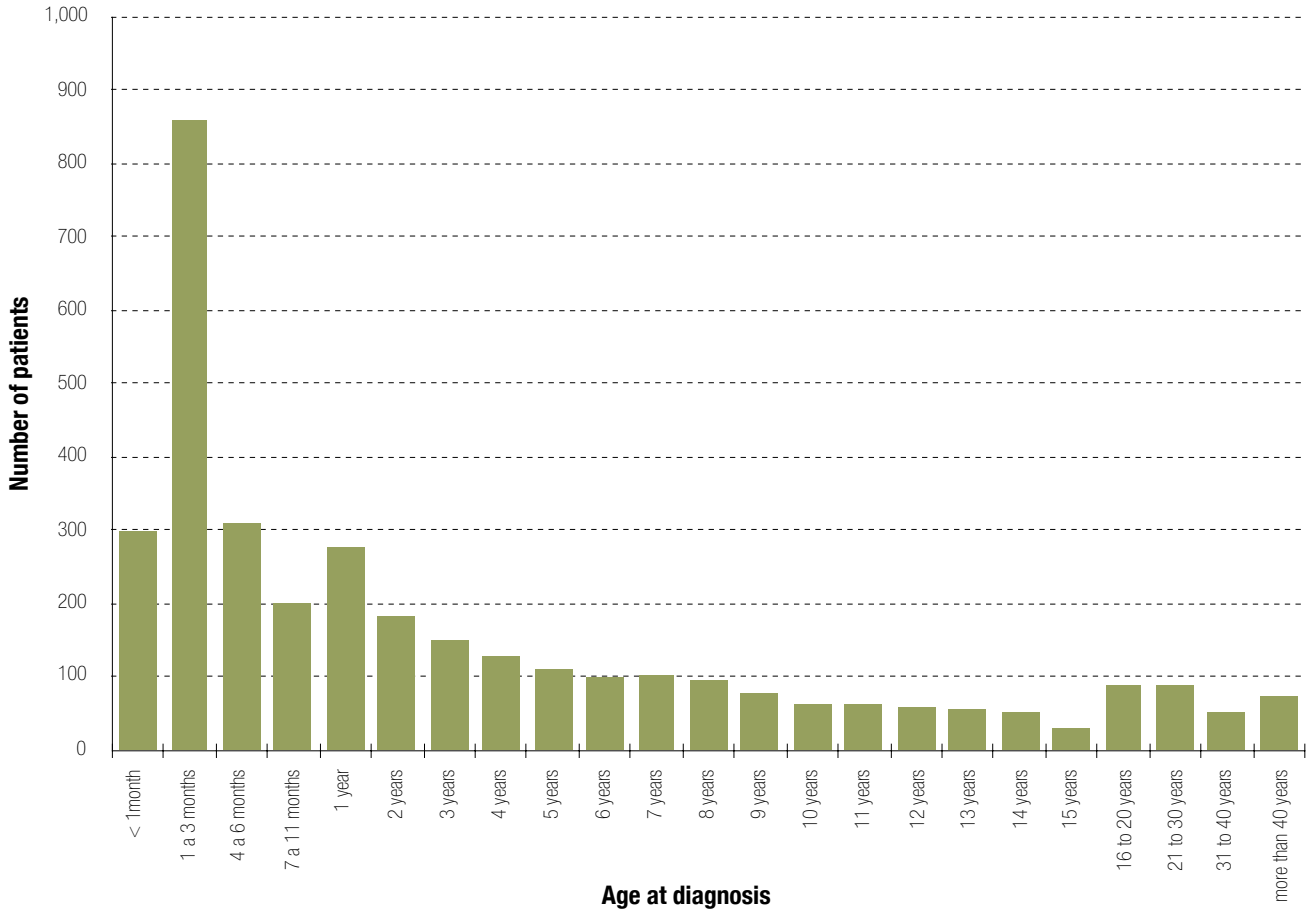
Description of the patients according to age at diagnosis.

Age (years)	
Mean (standard deviation)	5.55 (9.94)
Median (p25-p75)	1.19 (0.21 – 7.08)
Total of patients	**3,504**
Patients with no information*	**7**

n, number of patients; p25, 25th percentile; p75, 75th percentile.
Birthdates/diagnosis incorrectly filled.

Figure 8

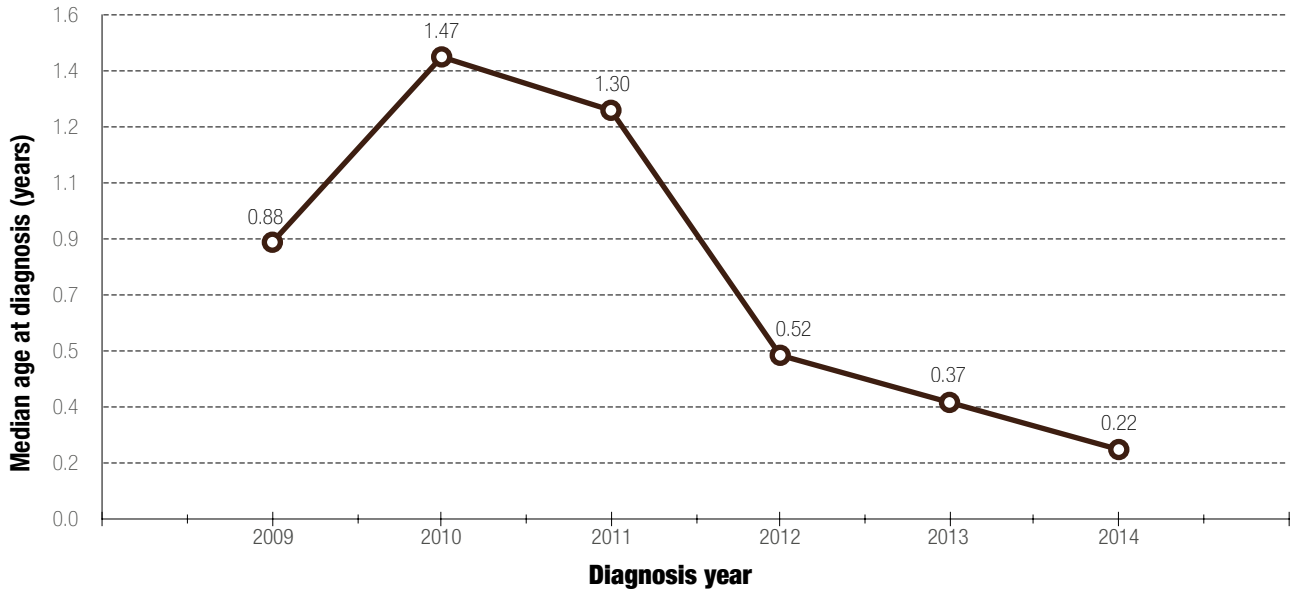
Distribution of Patients according to age at diagnosis, 2014.



To assess whether the age at diagnosis has decreased over the years, a statistical analysis was performed by using analysis of variance with log-transformed data and nonparametric Kruskal-Wallis test with multiple comparisons. This analysis considered only cases diagnosed between 2009 and 2014. The results obtained show that the age at diagnosis in cases diagnosed in 2014 was significantly younger than that in cases diagnosed between 2009 and 2011 ($p < 0.01$; Figure 9).

Figure 9

Variation in age at diagnosis over the years. Values are presented as medians.



Observation: In the chart shown in Figure 9, the diagnosis year (extracted from the diagnostic data) is used instead of the follow-up year.

Table 7

Distribution of the patients according to conditions for diagnosis, 2014

Conditions for diagnosis	n (%)
Persistent respiratory symptoms	2,137 (60.9%)
Growth deficit/malnutrition	1,372 (39.1%)
Steatorrhea or malabsorption	1,243 (35.4%)
Newborn screening (IRT)	1,032 (29.4%)
Family history	286 (8.1%)
Clinical or surgical meconium ileus	268 (7.6%)
Sinus disease and/or nasal polyp	209 (6.0%)
Metabolic disorder	198 (5.6%)
Edema/anemia	131 (3.7%)
Rectal prolapse	32 (0.9%)
Prolonged jaundice	35 (1.0%)
Infertility	16 (0.5%)
Others	188 (5.4%)
Unknown condition	87 (2.5%)
Total number of patients	**3.511 (100%)**

Table 8

Description of the patients according to sweat test results.

	Chloride (mEq/l)	Mass (mg)	Conductivity (mmol/l)
Mean (standard deviation)	89.50 (26.43)	147.37 (78.53)	103.9 (19.3)
Median (p25–p75)	90.15 (70.5-105.5)	135.00 (100-186)	105.5 (96-116)
Total number of patients	**2,999**	**2,123**	**384**

n, number of patients; p25, 25th percentile; p75, 75th percentile.
For chloride and mass, the average of two measurements was considered.

Table 9

Diagnosis by newborn screening with immunoreactive trypsinogen (IRT).

IRT dosage (ng/ml)	1st dosage	2nd dosage
Mean (standard deviation)	206.5 (118.8)	204.2 (128.3)
Median (p25-p75)	180.5 (125-258)	174.0 (116-249)
Total number of patients	**904**	**718**

Table 10

Other diagnostic tests reported

	n (%)
Measurement of nasal potential difference	100 (2.8%)
Rectal biopsy	73 (2.1%)
Total number of patients	**3,511 (100%)**

n=number of patients

Table 11

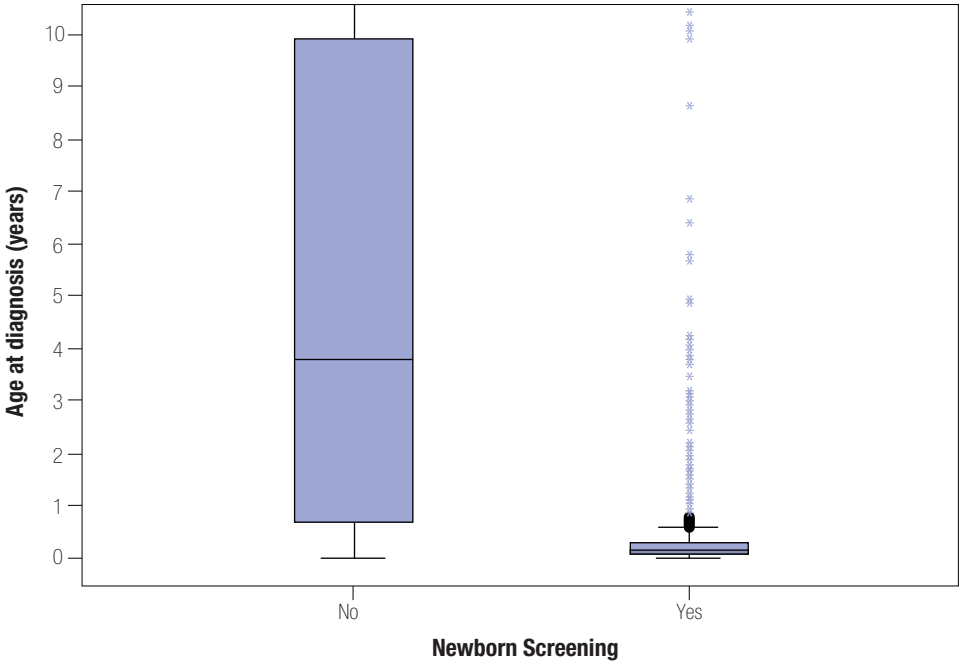
Description of the patients according to age at diagnosis and whether or not newborn. screening was performed

	Newborn Screening		
Age at diagnosis (years)	**No**	**Yes**	**Total**
Mean (standard deviation)	7.70 (11.13)	0.41 (1.10)	5.55 (9.94)
Median (p25–p75)	3.82 (0.73-9.95)	0.14 (0.09-0.29)	1.19 (0.21 – 7.08)
Total number of patients	**2.473**	**1.031**	**3.504**
Patients with no information	**6**	**1**	**7**

p25, 25th percentile; p75, 75th percentile.

Figure 10

Distribution of the patients according to age at diagnosis and whether or not newborn screening was performed, 2014.

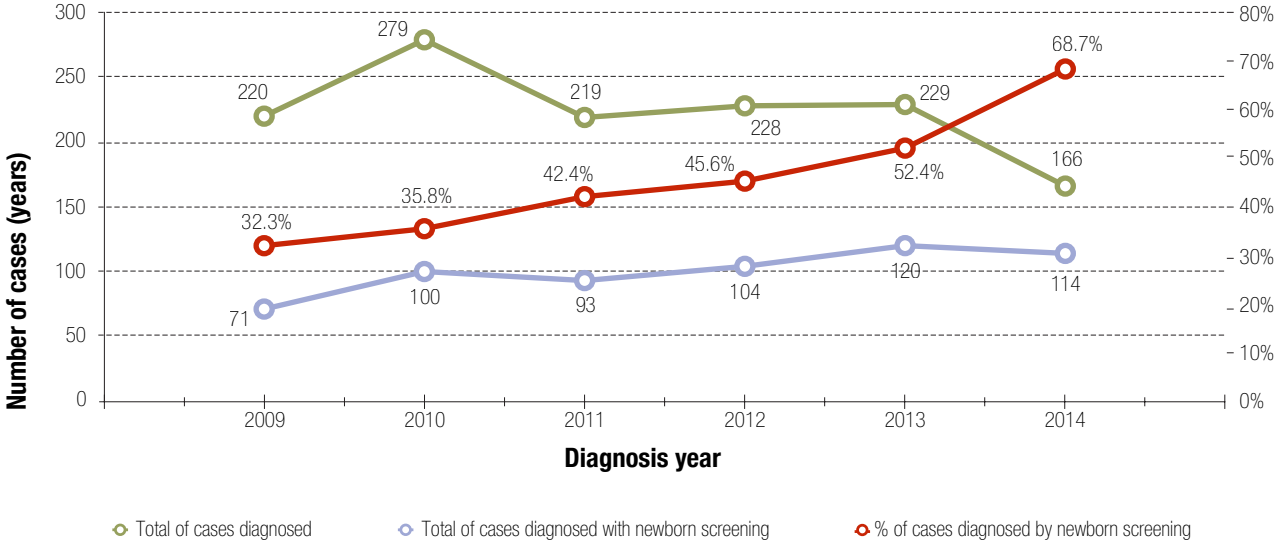


When comparing age at diagnosis between the groups, it was found to be significantly younger among those who underwent newborn screening (Student t test with log-transformed data and nonparametric Mann-Whitney test, both with $p < 0.001$).

The increasing contribution of newborn screening to the diagnosis of cystic fibrosis in Brazil can be seen in Figure 11. From 2009 to 2014, 1,341 cases of cystic fibrosis were diagnosed, of which 602 (44.9%) were diagnosed through newborn screening. The increasing percentage of cases diagnosed through newborn screening every year is noticeable, reaching almost 70% of all cases diagnosed in 2014.

Figure 11

Diagnosis by newborn screening from 2009 to 2014.



4. GENETIC DATA

The genetic data contained in this report should be interpreted with caution because of the lack of consistency in the conduction of genetic tests for CF in Brazil. Some centers only conduct research for the DeltaF508 mutation, while others research on mutation panels or sequencing of the CFTR gene.

Table 12

Description of the patients according to cystic fibrosis genetic study results.

Genotype performed	n (%)
No	1,907 (54.3%)
Yes	1,604 (45.7%)
Total number of patients	**3,511 (100%)**

Amount of mutations identified	n (%)
None	283 (17.6%)
One	498 (31.0%)
Two	823 (51.3%)
Total of patients with genotype	**1,604 (100%)**

Genotype – description	n (%)
DF508/DF508	403 (25.1%)
DF508/Other	269 (16.8%)
DF508/ Unidentified	446 (27.8%)
Other/Other	108 (6.7%)
Other/ Unidentified	95 (5.9%)
Unidentified / Unidentified	283 (17.6%)
Total of patients with genotype	**1,604 (100%)**

Figure 12

Distribution of the patients according to genetic study results (n = 1,604), 2014.

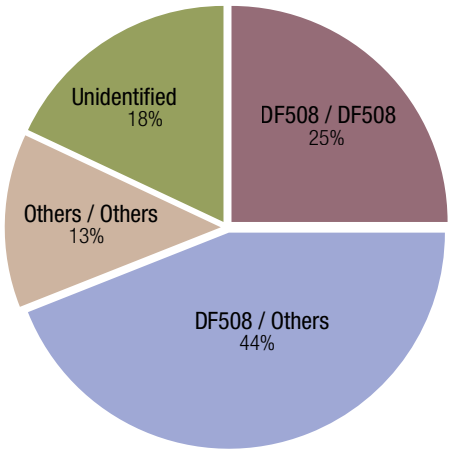


Table 13

Description of the mutations identified (1604 patients, 3208 alleles), 2014.

Mutation	Frequency	% according to the total of alleles
F508del	1523	47.48%
G542X	139	4.33%
3120+1G>A	38	1.18%
R334W	36	1.12%
R1162X	32	1.00%
G85E	31	0.97%
N1303K	26	0.81%
W1282X	16	0.50%
S4X	12	0.37%
S549R	11	0.34%
3849+10kbC>T	11	0.34%
R1066C	9	0.28%
R553X	9	0.28%
2183AA>G	8	0.25%
G551D	8	0.25%
1717-1G>A	7	0.22%
711+1G>T	6	0.19%
Y1092X	6	0.19%
1078delT	5	0.16%
1812-1G>A	5	0.16%
D1152H	5	0.16%
I507del	4	0.12%
L206W	4	0.12%
P205S	3	0.09%
S549N	3	0.09%
3272-26A>G	3	0.09%
2789+5G>A	2	0.06%
A561E	2	0.06%
R347P	2	0.06%

Mutation	Frequency	% according to the total of alleles
2789+5G>A	2	0.06%
3659delC	2	0.06%
M1101K	2	0.06%
R1158X	2	0.06%
R75Q	2	0.06%
1341+1G>A	1	0.03%
1898+1G>A	1	0.03%
2184delA	1	0.03%
2184insA	1	0.03%
3121-1G>A	1	0.03%
3132delTG	1	0.03%
711+1G>T	1	0.03%
711+5G>A	1	0.03%
991del5	1	0.03%
A559T	1	0.03%
c.2051-2052del AAinsG	1	0.03%
4382delA	1	0.03%
G576A	1	0.03%
D579G	1	0.03%
E585X	1	0.03%
2307insA	1	0.03%
L997F	1	0.03%
2347delG	1	0.03%
Q220X	1	0.03%
R347P	1	0.03%
R347H	1	0.03%
R851X	1	0.03%
W1089X	1	0.03%

OBS: The table lists only the mutations recorded in the CFTR2 database, excluding non-pathogenic polymorphisms or dependent on combinations with pathogenic mutations to result in protein dysfunction.

FOLLOW-UP DATA

For describing the **follow-up data**, only the year 2014 was considered (n = 2,571).

5. ANTHROPOMETRIC DATA

Anthropometric data were obtained on the day of the pulmonary function test or the last visit of the year, in situations in which the pulmonary function test was not performed.

In the calculations of the percentiles and Z scores of the anthropometric data, the data from the *Centers for Disease Control and Prevention* (CDC), USA (available in http://www.cdc.gov/growthcharts/), were used as reference.

Table14

Description of the patients according to anthropometric data.

WEIGHT (kg)	NCHS percentile	Z score
Mean (standard deviation)	33.96 (29.80)	-0.68 (1.26)
Median (p25;p75)	26.00 (7;56)	-0.63 (-1.47; 0.15)
Total number of patients	**1,968**	**1,968**

HEIGHT (cm)	NCHS percentile	Z score
Mean (standard deviation)	33.94 (28.87)	-0.63 (1.15)
Median (p25, p75)	26.00 (8; 55)	-0.63 (-1.38; 0.13)
Total number of patients	**1,967**	**1,967**

BMI (kg/m2)	Absolute Value (18-year-old patients or older)	NCHS percentile (patients younger than 18 years old)
Mean	21.33 (3.74)	43.42 (32.06)
Median (p25;p75)	20.80 (18.80;23.23)	41.00 (13; 71)
Total number of patients	**568**	**1,377**

p25, 25th percentile; p75, 75th percentile.

By analyzing the nutritional parameters according to age, the percentiles and Z scores of the anthropometric measures tended to decrease over the years in patients younger than 18 years (Figures 13 and 14). The strong association between nutrition and disease severity is evidenced by the worsening of nutritional parameters and pulmonary function (see below).

On the other hand, in the adult patients, BMI tended to increase with age (Figure 15). This finding may result from a survival bias in the adult population, as patients with more-severe disease progress to premature death and the remaining patients have milder disease and better nutritional status, with a higher concentration of atypical cases.

Figure 13

Evolution of the median percentiles of weight, height, and BMI from (20 to 50 years years), 2014.

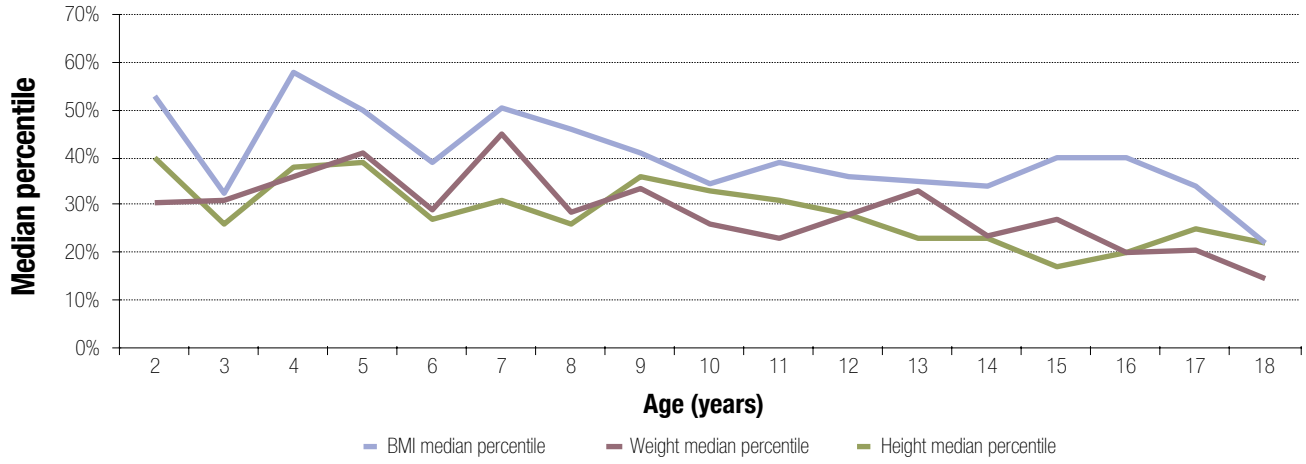


Figure 14

Evolution of weight and height Z scores according to age (from 2 to 18 years), 2014.

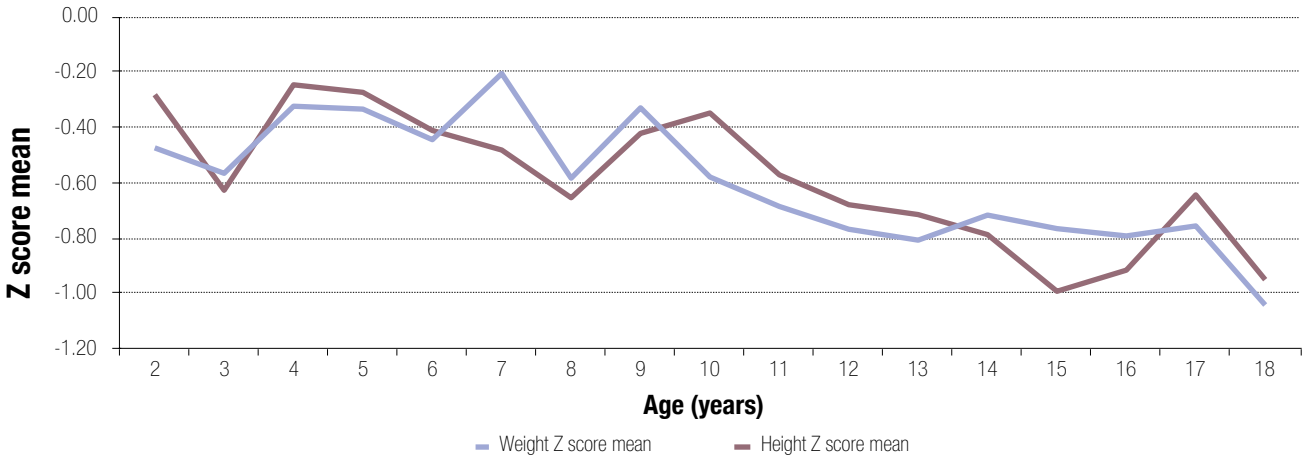
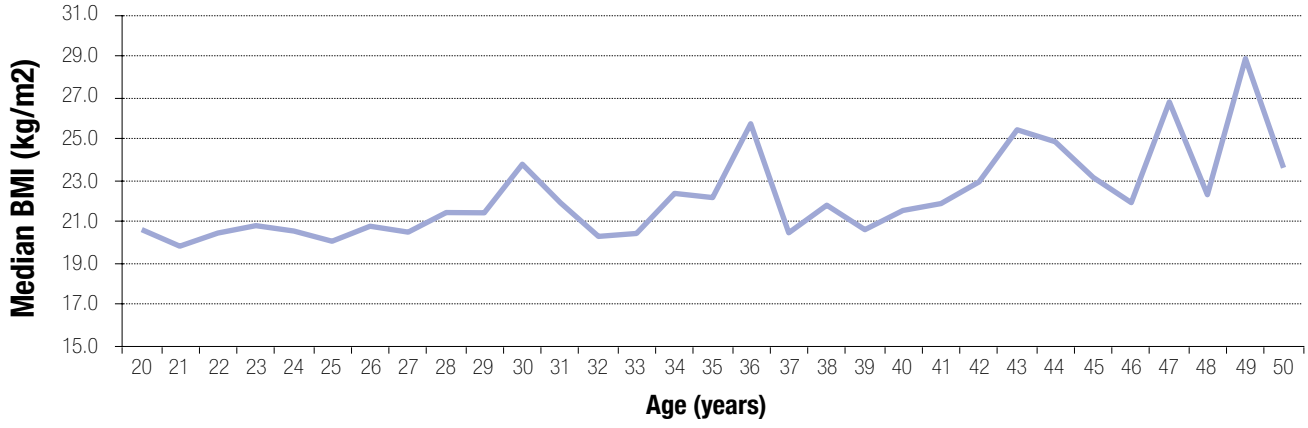


Figure 15

Evolution of body mass index (BMI) according to age (from 2 to 18 years), 2014.



6. PULMONARY FUNCTION DATA

Spirometry data are available for 1,322 patients (51.4%). For patients with more than one functional test in the year, the test data with the best values for pulmonary function were inserted. For the predicted values of pulmonary function, the publication by Stanojevic et al, Spirometry Centile Charts for Young Caucasian Children: The Asthma UK Collaborative Initiative. American Journal of Respiratory and Critical Care Medicine 2009, 180(6); 547-552, was used as a reference.

Table 15

Description of the patients according to pulmonary function data.

Z score – FVC	
Mean (standard deviation)	-1.54 (2.09)
Median (p25, p75)	-1.33 (-2.94; -0.16)
Total number of patients	**1,307**

FEV1-predicted Percentage	
Mean (standard deviation)	-2.13 (2.17)
Median (p25, p75)	-1.91 (-3.92; -0.51)
Total number of patients	**1,307**

FVC Predicted Percentage	
Mean (standard deviation)	82.21 (24.09)
Median (p25, p75)	84.28 (65.90; 98.18)
Total number of patients	**1,307**

FEV1/FVC	
Mean (standard deviation)	73.49 (27.27)
Median (p25, p75)	76.73 (52.06; 94.07)
Total number of patients	**1,307**

Z score – FEV1	
Mean (standard deviation)	0.76 (0.14)
Median (p25, p75)	0.79 (0.67; -0.87)
Total number of patients	**1,319**

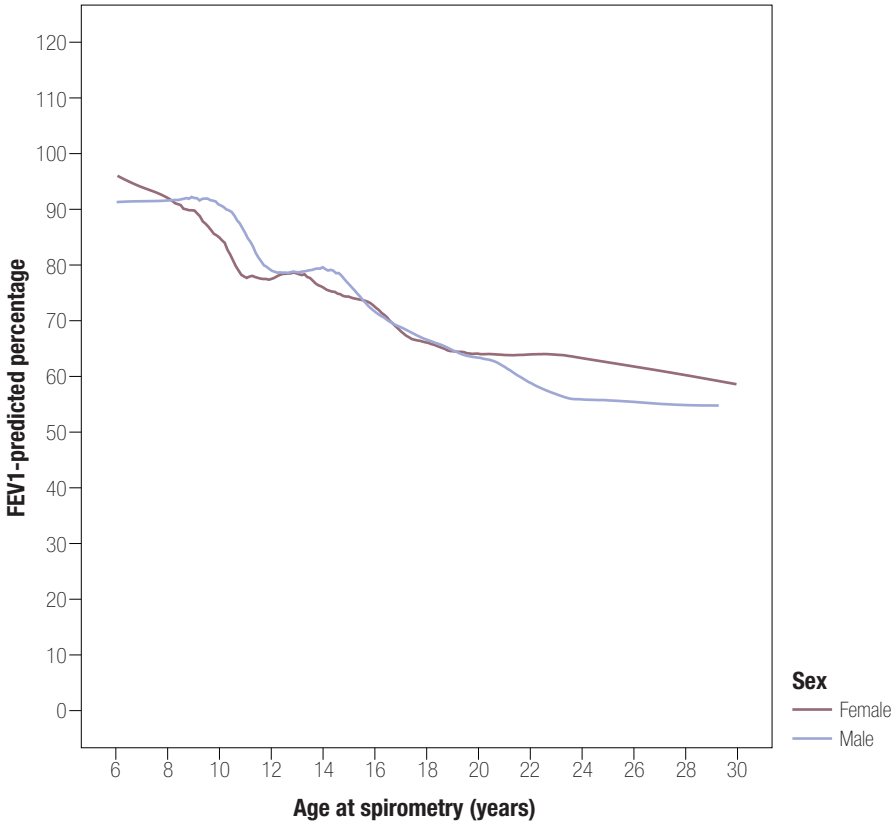
Z score – FEV1/FVC	
Mean (standard deviation)	-1.37 (1.63)
Median (p25, p75)	-1.35 (-2.65; -0.24)
Total number of patients	**1,307**

n=number of patients; p25, 25th percentile; p75, 75th percentile; FVC, forced vital capacity; FEV1, forced expiratory volume.

In the analysis of the data of pulmonary function according to age, forced expiratory volume (FEV1) values showed a progressive and sharp decrease with age, less evidently after 20 years old.

Figure 16

FEV1-predicted percentage according to age (from 6 to 30 years old), 2014.



These data can also be observed in Table 19 and Figure 17, which examine the distribution of patients according to age and degree of obstruction. A significant proportion of children and adolescents with functional changes already established. In the statistical analysis (chi-square test), a strong association was found between the degree of obstruction and age group ($p < 0.001$), demonstrating a progressive functional loss.

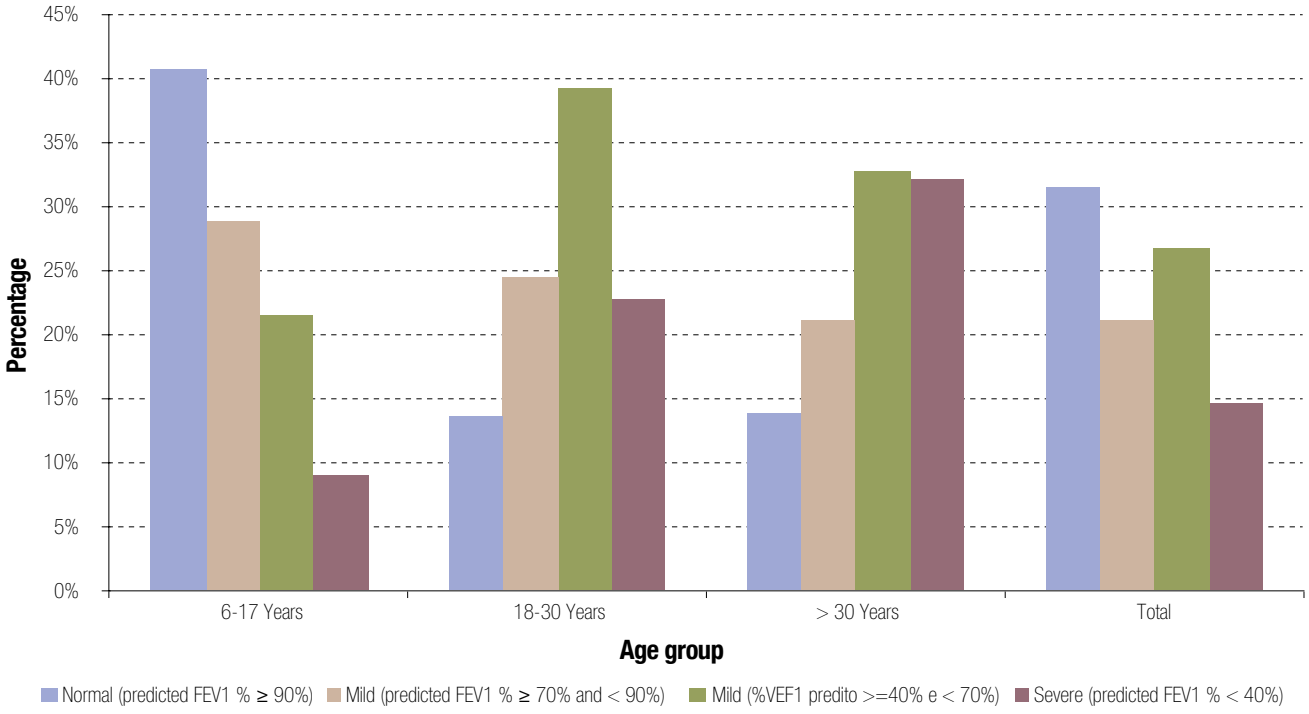
Table 16

Degree of obstruction according to age group, 2014.

	Age group			
Degree of obstruction	**6–17 years**	**18–30 years**	**>30 years**	**Total**
Normal (predicted FEV1 % ≥ 90%)	351 (40.7%)	42 (13.6%)	19 (13.9%)	412 (31.5%)
Normal/mild (predicted FEV1 % ≥ 70% and <90%)	248 (28.8%)	75 (244%)	29 (21.2%)	352 (26.9%)
Moderate (predicted FEV1 % ≥ 40% and <70%)	185 (21.5%)	121 (39.3%)	45 (32.8%)	351 (26.9%)
Severe (predicted FEV1 % < 40%)	78 (9.0%)	70 (22.7%)	44 (32.1%)	192 (14.7%)
Total number of patients	**862 (100%)**	**308 (100%)**	**137 (100%)**	**1,307 (100%)**

Figure 17

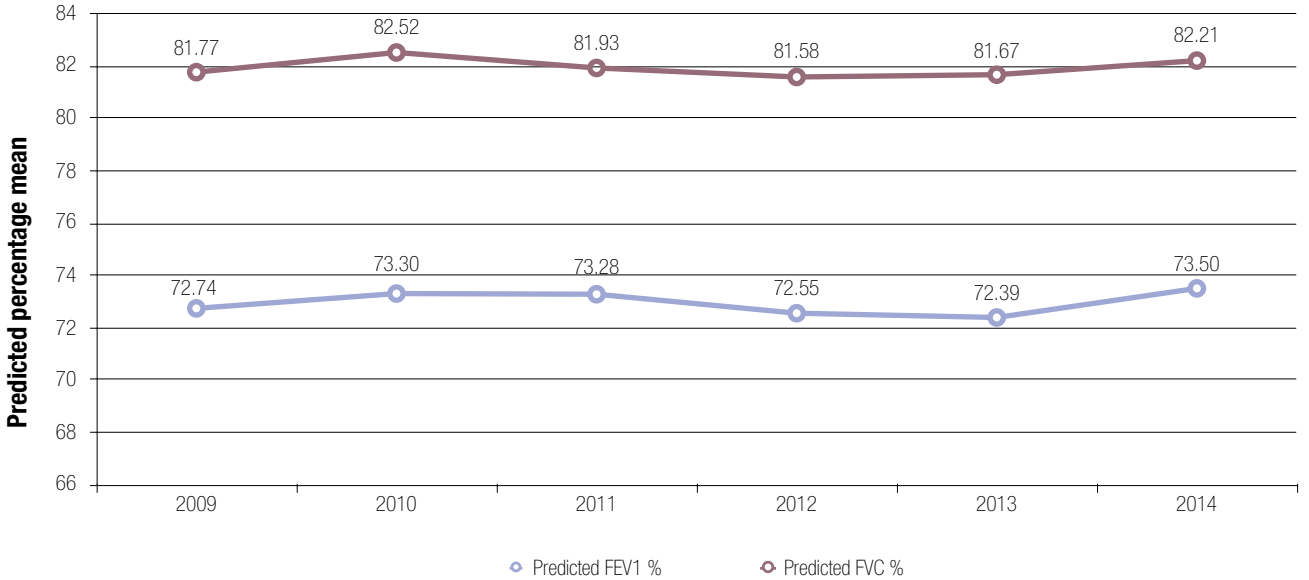
Distribution of the patients according to degree of obstruction according to the age group 2014.



By analyzing the evolution of pulmonary function over the years (2009–2014), we observed that the FEV1 and FVC values remain relatively unchanged over the period studied, with slight increases in the last year (Figure 18).

Figure 18

Variations in the percentages of the FVC- and FEV1-predicted values from 2009 to 2014.



Among the factors potentially associated with worsening of pulmonary function, nutrient levels and pulmonary function showed a relationship, both in pediatric patients (BMI percentile × FEV1 values) and adults (BMI × FEV1 value; Figures 19 and 20).

Figure 19

FEV1-predicted percentage according to BMI percentile in the patients aged 6 to 18 years, 2014.

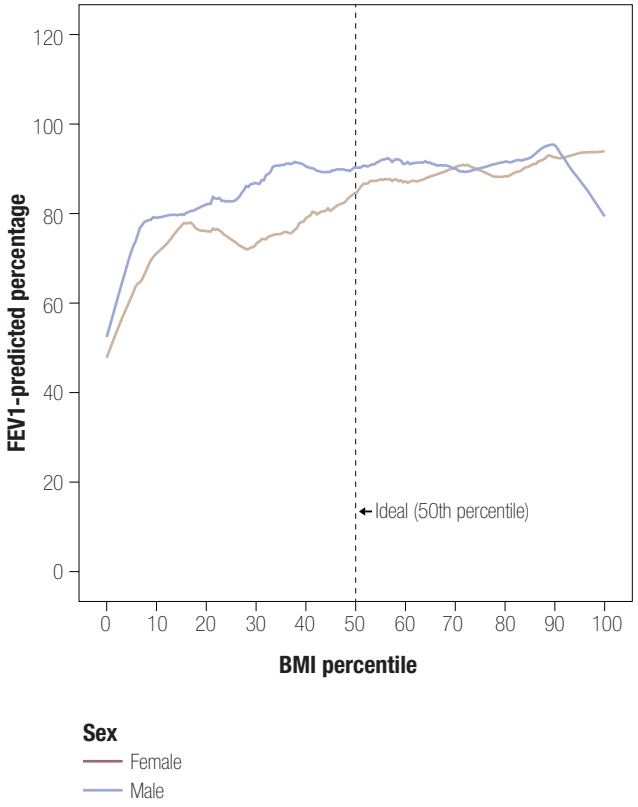
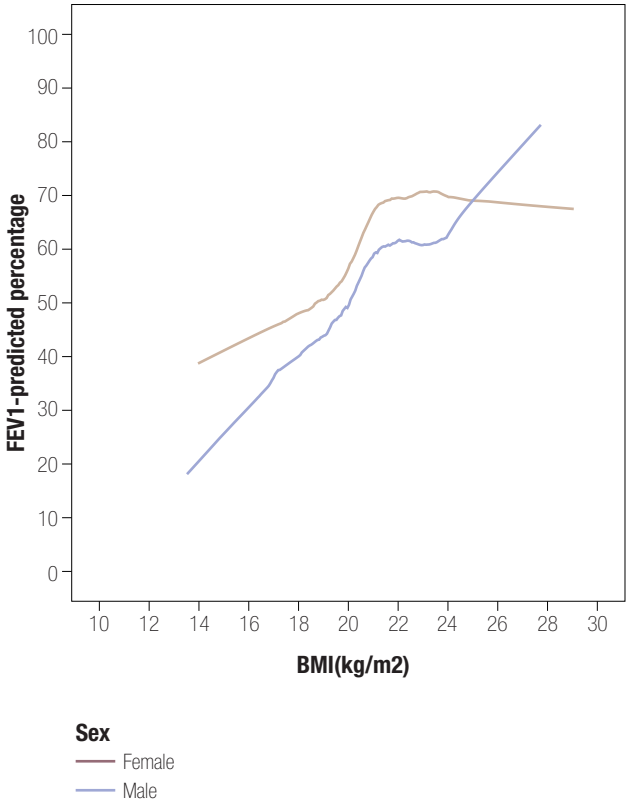


Figure 20

FEV1-predicted percentage according to BMI in patients aged 20 to 40 years old, 2014.



7. MICROBIOLOGIC DATA

Microbiological data refer to the identification of the pathogen in question at least once a year. As the processing techniques and culture of respiratory samples from patients with cystic fibrosis patients in Brazil have not been standardized yet, the data must be interpreted with caution.

Table 17

Description of the microorganisms identified.

Microorganisms identified	n	%
Oxacillin-sensitive Staphylococcus aureus	1,505	58.5%
Pseudomonas aeruginosa	1,081	42.0%
Non-mucoid Pseudomonas aeruginosa	712	27.7%
Mucoid Pseudomonas aeruginosa	524	20.4%
Burkholderia cepacia complex	231	9.0%
Haemophilus influenzae	229	8.9%
Oxacillin-resistant Staphylococcus aureus	215	8.4%
Stenotrophomonas maltophilia	112	4.4%
Klebsiella pneumoniae	137	5.3%
Candida species	137	5.3%
Achromobacter species	77	3.0%
Serratia species	73	2.8%
Aspergillus fumigatus	68	2.6%
Escherichia coli	66	2.6%
Other Pseudomonas	43	1.7%
Mycobacterium non-tuberculosis	12	0.5%
Mycobacterium tuberculosis	1	0.04%
Total number of patients	**2,571**	**100%**

Similarly to the mode observed in previous reports and international data, in the early years of life, a prevalence of colonization by oxacillin-sensitive Staphylococcus aureus is observed, gradually diminishing during adolescence (Table 18 and Figure 21). In parallel, there is a progressive increase in the identification of Pseudomonas aeruginosa, and this pathogen becomes the most frequent in the adult age group. The prevalence of oxacillin-resistant Staphylococcus aureus also increases over the years. It is interesting to notice the reduction in the identification of Burkholderia cepacia complex from the age of 35 years, which may represent the survival bias in milder cases, with a higher proportion of atypical forms of CF.

Table 18

Microorganisms identified according to age group.

	Microorganisms identified						
Age group (years)	*Oxacillin-sensitive S. aureus*	*Pseudomonas aeruginosa*	*Haemophilus influenzae*	*Burkholderia cepacia complex*	*Oxacillin-resistant S. aureus*	*Stenotrophomonas maltophilia*	n*
Up to 5	58.2%	35.6%	*11.8%*	*6.8%*	*7.5%*	*4.8%*	*584*
> 5 to 10	69.3%	36.4%	*11.4%*	*9.7%*	*7.4%*	*4.0%*	*580*
>10 *to* 15	64.1%	42.5%	*10.4%*	*9.7%*	*10.2%*	*6.5%*	*537*
>15 to 20	57.9%	46.3%	*7.2%*	*9.1%*	*9.1%*	*3.3%*	*361*
>20 to 25	43.9%	54.4%	*4.7%*	*9.9%*	*8.2%*	*4.1%*	*171*
>25 to 30	48.2%	61.8%	*0.9%*	*12.7%*	*11.8%*	*0.9%*	*110*
>30 to 35	50.0%	63.8%	*0.0%*	*13.8%*	*12.1%*	*3.4%*	*58*
>35 years	32.4%	45.4%	*1.9%*	*8.3%*	*4.6%*	*2.8%*	*108*

**Total: 2,509 patients (62 patients with no information about age))*

Figure 21

Prevalence of pathogens identified according to age group.

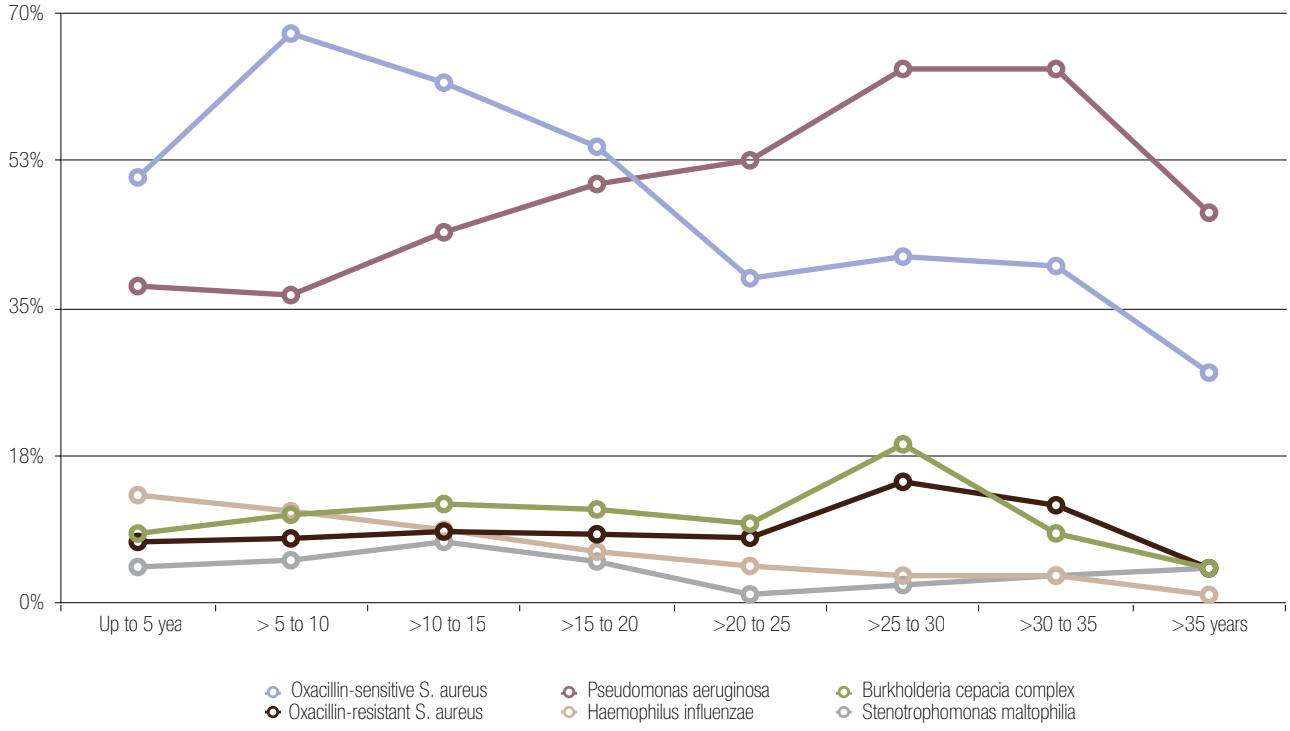
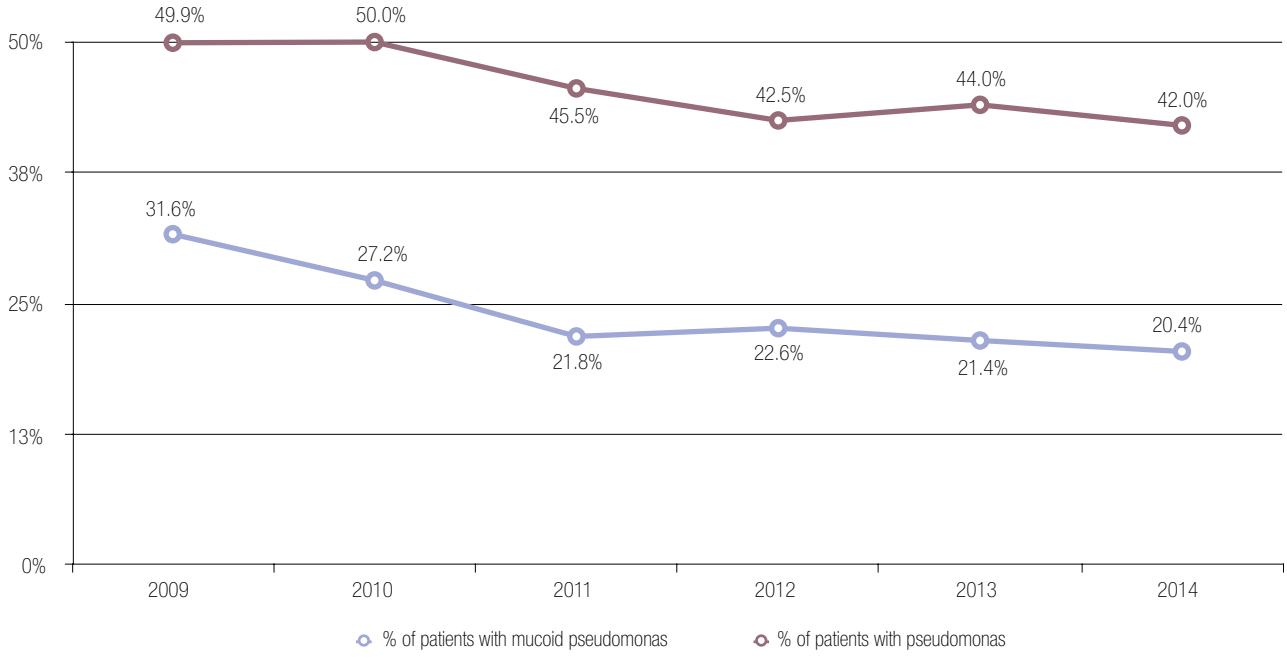


Figure 22

Percentage of patients with Pseudomonas aeruginosa from 2009 to 2014.



8. CLINICAL TREATMENT DATA

A total of 11,368 medical appointments were made in 2014, with a median of 4 medical appointments per patient/year.

Figure 23

Distribution of the patients according to the number of medical appointments performed in 2014.

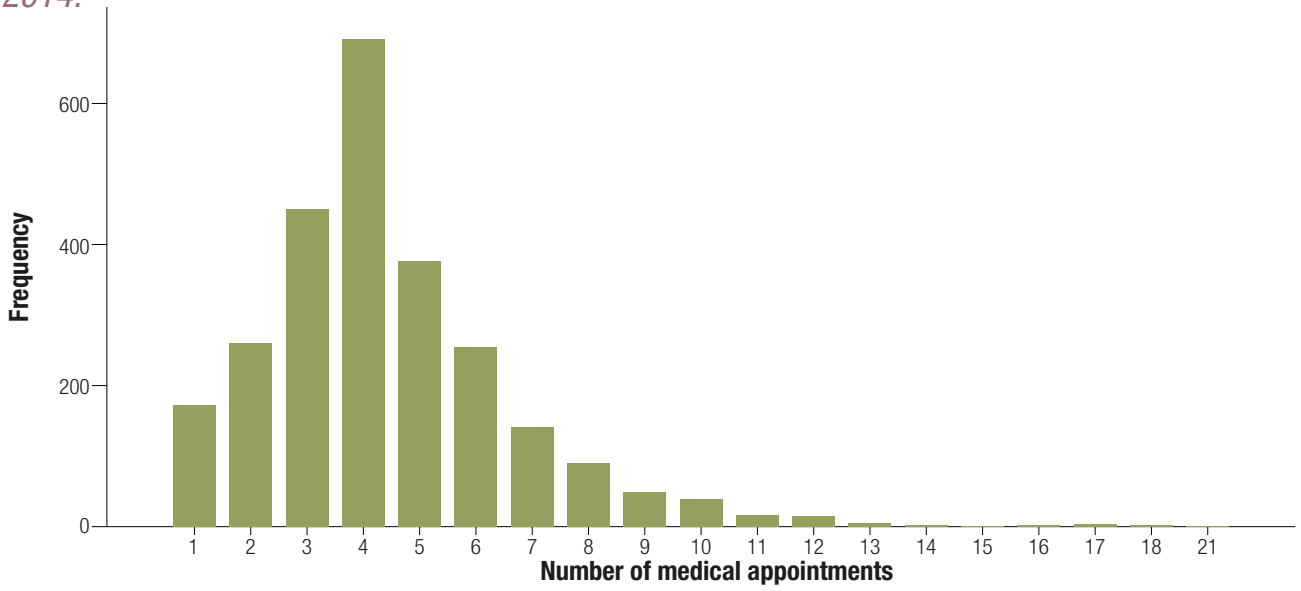


Table 19

Deaths.

Deaths	n (%)
No	2525 (98.2%)
Yes	46 (1.8%)
Causes of death*	
Respiratory failure	31
Septic shock/sepsis	8
Unknown origin – 6	
Abdominal septic shock (enterocolitis) – 1	
Septicemia due to *piercing* – 1	
Hemorrhagic shock (after lung transplantation)	2
Hypovolemic shock (dehydration)	1
Hematemesis	1
Acute myocardial infarction	1
Femur osteosarcoma	1
Unknown	1
Total of patients	**2,571 (100%)**

Age at death (years)	
Mean (standard deviation)	19.80 (10.15)
Median (p25–p75)	18.98 (14.21-25.65)
Minimum–maximum	0.27-41.64

Observation: In this report and in the previous ones, the percentage of deaths was calculated considering only the total of patients followed in the reference year. This estimate does not represent the survival of patients. It is worth highlighting that the most appropriate analysis of the deaths is the one using median survival curves.

Table 20

Shwachman-Kulczycki score: total score according to age group (up to 18 years, n = 1,636).

	Age group				
Total score	**Up to 5 years**	**> 5 to 10**	**>10 to 15**	**>15 to 18**	**Total**
Severe (≤40)	9 (1.8%)	9 (1.9%)	25 (5.4%)	12 (6.0%)	55 (3.4%)
Moderate (41–55)	17 (3.5%)	23 (4.8%)	56 (12.1%)	29 (14.4%)	125 (7.6%)
Mild (56–70)	48 (9.8%)	60 (12.4%)	90 (19.4%)	49 (24.4%)	247 (15.1%)
Good (71–85)	157 (32.1%)	197 (40.7%)	178 (38.4%)	79 (39.3%)	611 (37.3%)
Excellent (86–100)	258 (52.8%)	194 (40.1%)	114 (24.6%)	32 (15.9%)	598 (36.6%)
Total of patients	**489 (100%)**	**483 (100%)**	**463 (100%)**	**201 (100%)**	**1,636 (100%)**

Figure 24

Confidence intervals (95%) for the mean Shwachman-Kulczycki scores according to age group (up to 18 years, n = 1,636).

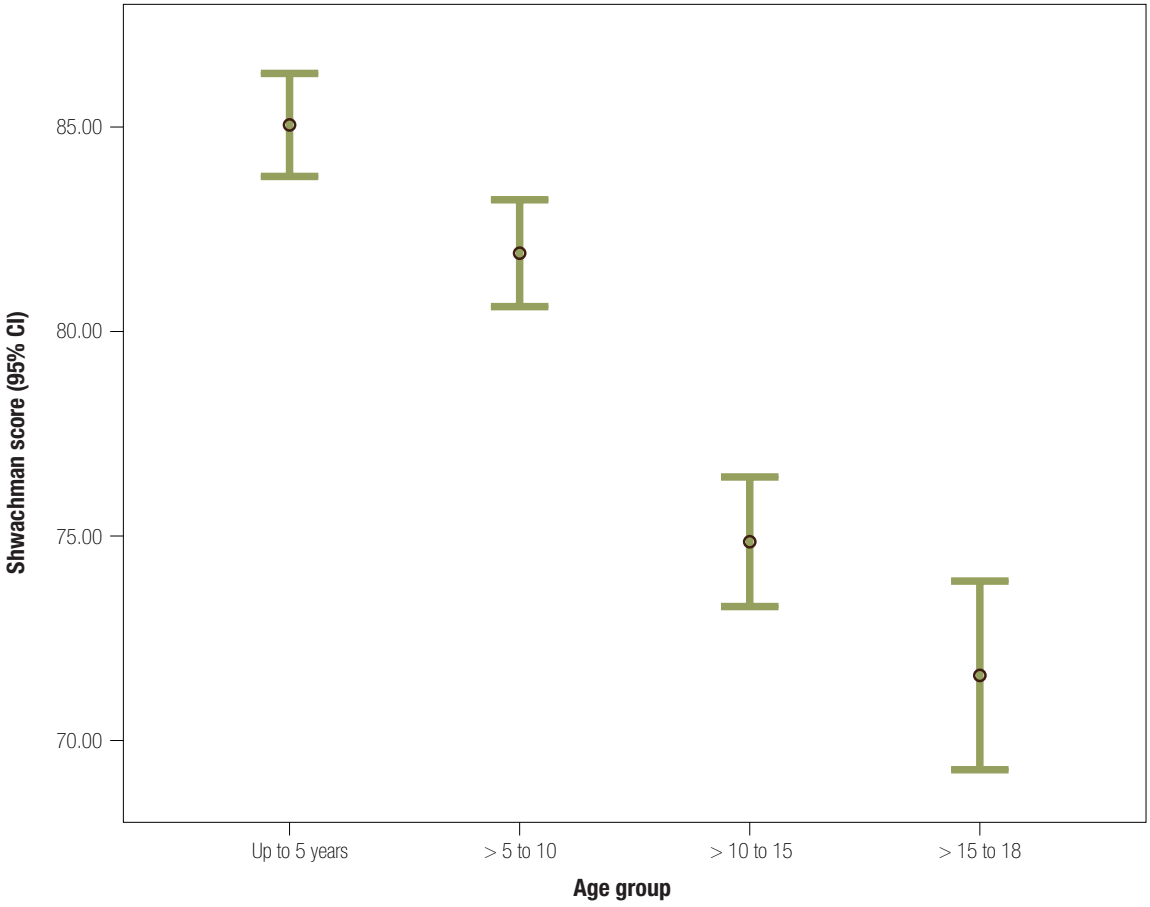


Table 21

Complications/comorbidities in the last year.

Complications/comorbidities in the last year	n (%)
Asthma	305 (11.9%)
Evidence of liver involvement	226 (8.8%)
Gastroesophageal reflux disease	145 (5.6%)
Diabetes	123 (4.8%)
Nasal polyposis	122 (4.7%)
Osteopenia/osteoporosis	107 (4.2%)
Hemoptysis	89 (3.5%)
Chronic atelectasis	49 (1.9%)
Pulmonary hypertension	32 (1.2%)
Cirrhosis with portal hypertension	26 (1.0%)
Cholelithiasis	25 (1.0%)
Allergic bronchopulmonary aspergillosis	22 (0.9%)
Distal intestinal obstruction syndrome	17 (0.7%)
Pancreatitis	13 (0.5%)
Pneumothorax	9 (0.4%)
Hematemesis	6 (0.2%)
Intestinal invagination	3 (0.1%)
Colonic stenosis	1 (0.04%)
Total number of patients	**2,571 (100%)**

n=number of patients.

Table 22

Transplants.

Transplants	n (%)
Lung transplant – corpse donor	24 (0.9%)
Liver transplant	1 (0.04%)
Total number of patients	**2,571 (100%)**

Table 23

Oxygen therapy.

Oxygen therapy	n (%)
No	2,479 (96.4%)
Yes	92 (3.6%)
Continuous	43 (1.7%)
Nocturnal	49 (1.9%)
Total of patients	**2,571 (100%)**

Table 24

Insulin

Use of insulin	n (%)
No	2,457 (95.6%)
Yes	114 (4.4%)
Total number of patients	**2,571 (100%)**

Table 25

Inhalants.

Bronchodilators	n (%)
Short-acting beta 2 agonist	848 (33.0%)
Long-acting beta 2 agonist	543 (21.1%)
Anticholinergic	94 (3.7%)

Antibiotics	n (%)
Inhalant tobramycin 300 mg	1,001 (38.9%)
Colomycin	432 (16.8%)
Amikacin	24 (0.9%)
Gentamicin	11 (0.4%)
Injectable tobramycin	16 (0.6%)
Vancomycin	8 (0.3%)
Aztreonam	4 (0.2%)
Others	47 (1.8%)

Mucolytics	n (%)
Alfadornase	1,846 (71.8%)
N-Acetylcysteine	100 (3.9%)

Salines	n (%)
0.9% saline	455 (17.7%)
3% hypertonic saline	107 (4.2%)
5% hypertonic saline	117 (4.6%)
7% hypertonic saline	508 (19.8%)
Total number of patients	**2,571 (100%)**

n=number of patients

Table 26

Oral medicines

	n (%)
Pancreatic enzymes	**2,073 (80.6%)**
<5,000 U/kg/day	617 (29.8%)
5,000–10,000 U/kg/day	1256 (60.6%)
>10,000 U/kg/day	180 (8.7%)
Unknown	20 (1.0%)
Nutritional supplements	**1,636 (63.6%)**
Oral	1,487 (90.9%)
Gastrostomy	61 (3.7%)
Gastric tube	19 (1.2%)
Unknown	69 (4.2%)
Azithromycin	960 (37.3%)
Proton pump inhibitors	609 (23.7%)
Ursodeoxycholic acid	504 (19.6%)
Corticosteroid	184 (7.2%)
H2 blockers	176 (6.8%)
Ibuprofen or other NSAIDs (arthropathy)	11 (0.4%)
Ibuprofen (pulmonary disease)	6 (0.2%)
Total number of patients	**2,571 (100%)**

n=number of patients.

**The percentages regarding the enzyme doses or type of supplement were calculated based on the subgroup(s) that used enzymes/supplements.*

Table 27

Pseudomonas aeruginosa eradication treatment

***P. aeruginosa* eradication treatment**	**n (%)**
Yes	583 (22.7%)
No	1.223 (47.6%)
Unknown	765 (29.8%)
Total number of patients	**2,571 (100%)**

Table 28

Intravenous treatments: hospitalizations.

Intravenous treatments	**n (%)**
Home care*	72 (12.4%)
Hospital care*	484 (83.3%)
Home and hospital care	25 (4.3%)
Total	581 (22.6%)
Total number of patients	**2,571 (100%)**

**Percentage in relation to the total number of patients in treatment*

Cycles/year	
Mean (standard deviation)	1.74 (1.22)
Median (p25–p75)	1 (1-2)
Total number of patients	**570**

Days/patient/year	
Mean (standard deviation)	26.04 (22.25)
Median (p25–p75)	15 (14-28)
Total number of patients	**572**

Catheter implanted	**n (%)**
No	2,534 (98.6%)
Yes	37 (1.4%)
Total number of patients	**2,571 (100%)**

Table 29

Intravenous antibiotics: days of hospitalization per year according to age group.

	Age group					
Days/year	**Up to 5 years**	**> 5 to 10**	**>10 to 15**	**>15 to 20**	**>20 years**	**Total**
Mean (SD)	21.7 (30.1)	22.0 (18.3)	26.2 (22.9)	28.4 (24.0)	29.1 (28.1)	*26.2 (25.5)*
Median (p25–p75)	14 (14-21)	14 (14-28)	15 (14-28)	19.5 (14-35)	20.0 (14-34)	*15 (14-29)*
Total number of patients	**129**	**86**	**127**	**104**	**114**	**560**

Table 30

Intravenous antibiotics: drugs used

Drugs used	n	(%)
Ceftazidime	358	13.9%
Amikacin	345	13.4%
Oxacillin	190	7.4%
Imipenem/meropenem	140	5.4%
Ciprofloxacin	121	4.7%
Sulfa-Trimethoprim	107	4.2%
Tobramycin	89	3.5%
Vancomycin	77	3.0%
Piperacillin/tazobactam	59	2.3%
Cefepime	59	2.3%
Gentamicin	25	1.0%
Linezolid	18	0.7%
Colomycin	12	0.5%
Cefuroxime	12	0.5%
Ticarcillin/piperacillin	8	0.3%
Aztreonam	8	0.3%
Chloramphenicol	1	0.04%
Others	47	1.8%
Total number of patients	**2,571**	**100%**

n=number of patients.

Table 31

Specific data of the adult population.

	Sex		
	Male	**Female**	**Total**
Azoospermia/hypospermia*	39 (12.8%)	-	39
Pregnancy	-	9 (3.4%)	9
Oral or injectable contraceptive	-	42 (15.7%)	42
Stable union	45 (14.8%)	85 (31.7%)	130 (22.7%)
Job	108 (35.5%)	82 (30.6%)	190 (33.2%)
Total number of patients aged ≥18 years	**304**	**268**	**572**

**Patients reporting investigation*

9. SURVIVAL

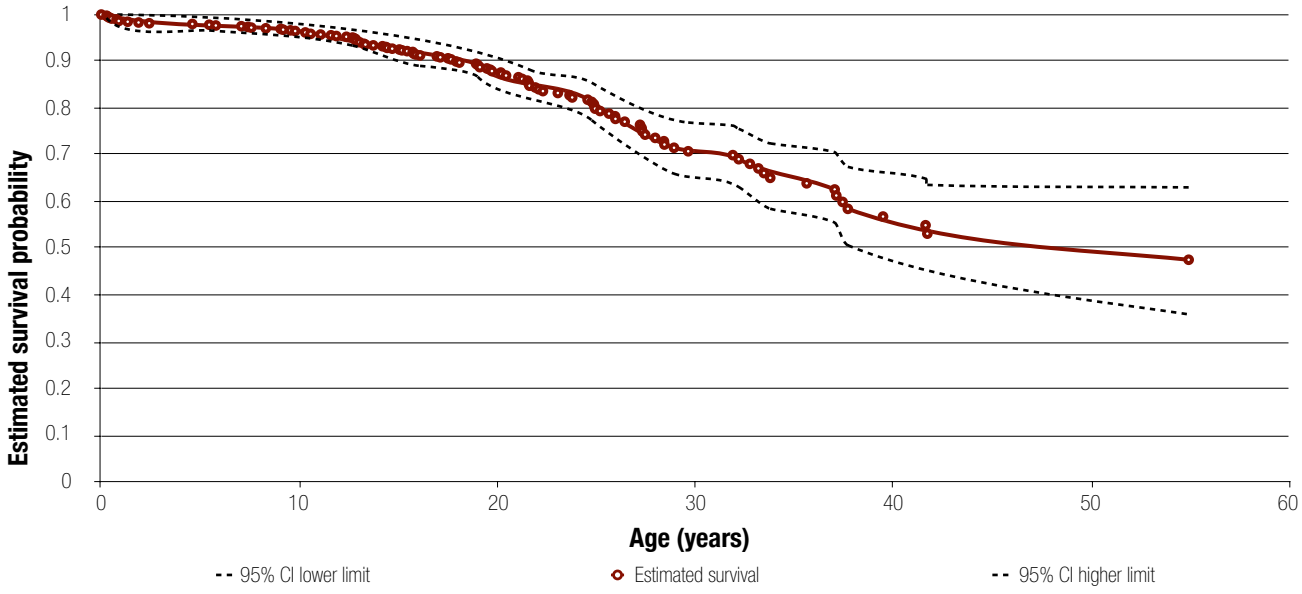
This is the first year we published our survival analysis where we used the available follow-up data. Deaths due to other causes (femur osteosarcoma, septicemia due to piercing, accidental death, unknown cause, acute myocardial infarction, and car accident) were excluded.

The same methodology used by the American organization *Cystic Fibrosis Foundation* (CFF) was adopted, using the same statistical analysis program. It should be noted that the survival curves only decreased in the ages at which deaths were observed. Given the small number of deaths registered in our platform, the curves of the Brazilian data show more apparent declines than the curves of the CFF, which has a substantially continuous decrease.

Between 2010 and 2014, 115 deaths by cystic fibrosis were recorded. Figure 26 shows the survival curve that considers all the patients observed in this period.

Figure 25

Survival curve by the Cox method: total number of patients from 2010 to 2014.



From the curve, an estimate of the median survival age, which is the age at which the survival rate (or estimated survival probability) reaches 50%, can be obtained. However, as the volume of Brazilian data is much smaller and the total follow-up time was still relatively short, the median survival estimate has poor accuracy. By observing the data obtained in this analysis, we found that the median survival was between 41.7 and 54.9 years, with a lower limit of 37.7 years (age when the confidence interval crosses the line of the 50% survival probability).

Acknowledgments:

This work would not be possible without the support of the pharmaceutical companies listed below, which ethically sponsored the initiative with enthusiasm, even without any perspective of privileged access to data or availability of marketing actions in the document.

- **Novartis Biociências S. A.**
- **Abbott Laboratórios do Brasil Ltda.**
- **Zambon Laboratórios Farmacêuticos Ltda.**
- **Multicare Pharmaceuticals**
- **Produtos Roche Químicos e Farmacêuticos S. A.**

We also thank all health-care professionals involved in the care of the patients with cystic fibrosis for their cooperation in this initiative, which we believe will bring great benefits to patients with cystic fibrosis in our country.

Centers that contributed to this report by providing the patients' follow-up data in 2014 (in alphabetical order for states):

Hospital	City	State	Responsible
Hospital Universitário Prof. Alberto Antunes – UFAL	Maceió	AL	Katharina Vidal de Medeiros Moura
Hospital Especializado Otavio Mangabeira	Salvador	BA	Maria Angélica Santana
Hospital Universitário Prof. Edgar Santos	Salvador	BA	Edna Lúcia Santos de Souza
Hospital Infantil Albert Sabin	Fortaleza	CE	Cláudia de Castro e Silva
Hospital da Criança de Brasília José Alencar	Brasília	DF	Luciana de Freitas Velloso Monte
Hospital de Base do Distrito Federal	Brasília	DF	Clarice Guimarães de Freitas
Hospital Infantil Nossa Senhora da Glória	Vitória	ES	Roberta de Cássia Melotti
Hospital Dr Dório Silva	Vitória	ES	Daniele Menezes Torres
Hospital das Clínicas da UFGO	Goiânia	GO	Lusmaia Damaceno Camargo Costa
APAE Anápolis	Anápolis	GO	Eliane Pereira dos Santos
Hospital Universitário Materno-Infantil de São Luis	São Luis	MA	Dra Denise Haidar
Hospital Infantil João Paulo II	Belo Horizonte	MG	Alberto Andrade Vergara
Hospital das Clínicas da UFMG	Belo Horizonte	MG	Dra Elizabet Vilar
Consultorio Francisco Reis	Belo Horizonte	MG	Francisco José Caldeira Reis
Hospital Julia Kubitschek	Belo Horizonte	MG	Marcelo de Fuccio
Hospital Universitário da UFJF	Juiz de Fora	MG	Marta Cristina Duarte
Hospital das Clinicas da UFMG - adultos	Belo Horizonte	MG	Marina Nishi
Hospital Universitario Maria Aparecida Pedrossian	Campo Grande	MS	Valéria Cristina de Ruchkys
Hospital Universitário João de Barros Barreto	Pará	PA	Valéria de Carvalho Martins
Hospital Universitario Lauro Wanderley	João Pessoa	PB	Constantino Cartaxo
Instituto Materno Infantil de Pernambuco	Recife	PE	Murilo Carlos Amorim de Britto
Hospital Pequeno Príncipe	Curitiba	PR	Paulo Kussek

Hospital	City	State	Responsible
Hospital das Clínicas da UFPR	Curitiba	PR	Carlos Antônio Riedi
Hospital das Clinicas da UFPR - Adultos	Curitiba	PR	Mariane Martynychen
Instituto Fernandes Figueira	Rio de Janeiro	RJ	Tania Wrobel Folescu
Hospital Universitário Pedro Ernesto - UERJ	Rio de Janeiro	RJ	Agnaldo J. Lopes
Hospital de Pediatria da Universidade do Rio Grande do Norte	Natal	RN	Vera Maria Dantas
Hospital de Clínicas de Porto Alegre - UFRGS	Porto Alegre	RS	Paulo Cauduro Maróstica
Hospital de Clínicas de Porto Alegre - Adultos	Porto Alegre	RS	Paulo de Tarso Roth Dalcin
Hospital São Lucas - PUCRS	Porto Alegre	RS	Leonardo Araújo Pinto
Santa Casa de Porto Alegre	Porto Alegre	RS	Gilberto Bueno Fischer
Hospital Santa Isabel	Blumenau	SC	Glaunir Maria Foletto
Hospital Infantil Joana de Gusmão	Florianópolis	SC	Norberto Ludwig Neto
Hospital Infantil Jeser Amarante Faria	Joinville	SC	Tiago Neves Veras e Rafaela C. Benvenutti da Costa
Hospital das Clínicas da UNESP	Botucatu	SP	Giesela Fleischer Ferrari
Hospital das Clínicas da UNICAMP (pediatria)	Campinas	SP	Antonio Fernando Ribeiro
Hospital das Clínicas da USP Ribeirão Preto	Ribeirão Preto	SP	Lidia Alice Gomes M. M. Torres
Hospital de Base Fac Med de SJ Rio Preto	São José do Rio Preto	SP	Katia Izabel de Oliveira
Irmandade da Santa Casa de Misericórdia de São Paulo	São Paulo	SP	Neiva Damaceno
Instituto da Criança do Hospital das Clínicas da FMUSP	São Paulo	SP	Joaquim Carlos Rodrigues
Hospital da UNIFESP	São Paulo	SP	Sonia Mayumi Chiba
Hospital das Clínicas da FMUSP	São Paulo	SP	Rafael Stelmach
Consultorio Fabiola Adde	São Paulo	SP	Fabíola Vilac Adde
Centro de Puericultura - CPAP	São Paulo	SP	Luiz Vicente Ribeiro F. da Silva Filho

GRUPO
BRASILEIRO DE
ESTUDOS DE
FIBROSE CÍSTICA

www.gbefc.org.br