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TEMPORAL TRENDS IN HEALTHCARE RESOURCE USE AND ASSOCIATED COSTS OF PATIENTS WITH CYSTIC FIBROSIS

Running head: Evolution of costs of care for cystic fibrosis

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Author contributions

All authors participated in the research and in the preparation of the manuscript.

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Abstract (250 words)

Background: Better insights into the natural course of cystic fibrosis (CF) have led to treatment approaches that have improved pulmonary health and increased the life expectancy of affected individuals. This study evaluated how the combination of modified demographics and changes in CF management impacted resource consumption and the cost of care.

Methods: Medical records of CF patients from 2006 to 2016 in the French CF Registry were linked to their corresponding claims data (SNDS). Medications, medical visits, procedures, hospitalisations, and indirect costs were annualized by calendar year from 2006 to 2017.

Results: Of the 7,671 patients included in the French CF Registry, 6,187 patients (80.7%) were linked to the SNDS (51.9% male, mean age=24.7 years). The average cost per patient was €14,174 in 2006, €21,920 in 2011 and €44,585 in 2017. Costs associated with hospital stays increased from €3,843 per patient in 2006 to €6,741 in 2017. In 2017, the mean cost per CF patient was allocated as follows: 72% for medications (of which 51% for modulator therapies), 15% for hospital stays, 7% for medical visits, 3% for indirect costs, 2% for medical devices, 1% for outpatient medical procedures.

Conclusion: There was a strong increase in the mean annual cost per CF patient between 2006 and 2017, mostly due to the cost of therapy after the introduction of cystic fibrosis transmembrane conductance regulator (CFTR) modulators. The combination of an increase in the number of CF patients – particularly adult patients – and an increase in the annual cost per patient led to a substantial increase in the total cost of CF disease care for the health systems.

Keywords: cystic fibrosis; healthcare resource use; costs; observational study

Abbreviations²

² BMI Body mass index; CF Cystic fibrosis; CFTR Cystic fibrosis transmembrane conductance regulator; FEV Forced expiratory volume; HCRU Healthcare resource use; ICD International classification of diseases; IQR Interquartile range; NHS National Health System; SD Standard deviation; SNDS *Système National des Données de Santé* – national system of health data.

Introduction

Cystic fibrosis (CF) is an autosomal recessive genetic disease caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene [1]. CFTR protein dysfunction induces a multisystem disease including respiratory manifestations and pancreatic, liver and gastrointestinal diseases. The prognosis remains dominated by the pulmonary manifestations leading to respiratory exacerbations and lung function decline [1]. During recent decades, the prognosis of CF patients has dramatically improved following progress in symptomatic and multidisciplinary care based on international standards of care, the implementation of new-born screening programmes, the early treatment of pulmonary disease, and the prevention of malnutrition [2, 3]. Intensified symptomatic care provided by specialised teams has led to improved survival but also to a higher treatment burden [4]. Recently, mutation-specific small molecules targeting defective CFTR, referred to as CFTR modulators, have been developed to correct CFTR dysfunction, improve lung function and nutritional status and reduce the frequency of pulmonary exacerbations [5, 6]. Ivacaftor was the first CFTR modulator to be approved (in 2012 for patients aged ≥ 6 years), and now indicated for patients aged 6 months and above and weighing at least 5 kg who have one of the following mutations in the CFTR gene: R117H, G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N and S549R.

In 2015, the lumacaftor/ivacaftor co-therapy was approved for F508del-homozygous patients aged ≥ 12 years and has been extended for F508del homozygous patients aged ≥ 2 years since 2020.

Costs related to CF care have increased over time following the implementation of new therapies and the increased life expectancy of adult patients [7]. The most recent studies estimating the direct cost of CF in France date from the period from 2001 to 2004 [7-9]. There is a need for an updated medico-economic evaluation of CF care to analyse the combined impact of evolving standards of care and modified demographics on medical resource consumption and costs following the introduction of highly effective CFTR modulators. The 'Système National des Données de Santé' (SNDS, the French National Health Data System) lists all reimbursed outpatient and inpatient medical resources used (claims data) by 98.8% of the French population covered by the national health system [10]. As a result of the fully centralised health system in France, this resource provides a unique opportunity to study health expenditures over the course of 10 years. Such exhaustive real-life data, complemented by the clinical data from the French Cystic Fibrosis Registry, provide a reliable assessment of the burden of CF care. This paper reports the

analyses of the 10-year changes in healthcare resource use (HCRU) and associated costs in the context of the demographic changes observed over the same decade.

Material and Methods

Study design and data sources

Two study designs were used: a repeated cross-sectional design to study HCRU and related costs per calendar year and a historical cohort for the analyses of HCRU and costs over the follow-up period. This study involved patients recorded in the French CF Registry for whom linkage with the SNDS could be achieved. In the absence of direct identifiers, the linkage was performed using other information common to the two databases by a probabilistic method. It means that for each patient of the registry, a patient from the SNDS database was identified, based on the same sex, same month and year of birth, and same region of residence, and then based on other variables as dates of spirometry, transplant and sweat tests. To measure the quality of the linkage and to validate it, a sensitivity analysis based on an alternative method was performed.

The French CF Registry collects data on all CF patients followed at CF care centres. Available information includes the diagnosis, medical monitoring, prescribed therapy, and anthropometric, respiratory, and bacteriological data [11]. In the SNDS, the following anonymized data are prospectively recorded for all patients living in France and covered by the national health insurance: 1) patient characteristics such as age, sex, and medical diagnoses [International Classification of Diseases – 10th revision (ICD-10) codes] for severe and expensive chronic diseases for which health insurance provides full coverage [Chronic Disease status], region of residence, and date of death; 2) primary care, namely, detailed reimbursements for drugs with prescribing and dispensing dates, the corresponding codes for primary care and consultations with specialists, medical procedures, biological tests, medical devices and reimbursed care provided by non-medical health professionals; and 3) hospitalisations at all French public and private hospitals (PMSI data), such as discharge diagnoses [ICD-10 codes], main procedures performed during hospitalisation, dates of discharge, lengths of stay, outpatient visits to hospital, and medicines and/or medical devices included in a specific expansive list of products [10].

Study population

Patients with CF identified in the French CF Registry between 2006 and 2016 were selected. Data for each patient were linked to the SNDS over the 2006-2017 period.

Patients were followed-up during the period between the index date (i.e., date of diagnosis in the registry if it occurred between 2006 and 2016 or from 01/01/2006 when the date of diagnosis or sweat test was prior to 2006) and the end of follow-up, as defined by the occurrence of one of the following events, whichever occurred first: death, loss to follow-up (date of last information recorded in the SNDS prior to a 24-month period without any reimbursement), or the end of the study period (31/12/2017).

Statistical methods

Socio-demographic characteristics and clinical data were described with descriptive statistics as follows: for quantitative variables, the sample size (N), mean, standard deviation, median, and interquartile range (IQR) are reported, and for qualitative and ordinal variables, the sample size (N) and the frequency are reported.

Comorbidities were identified in two different ways: chronic disease status or specific therapies. Clinical characteristics such as forced expiratory volume (FEV-1) and body mass index (BMI) were assessed during the last year of follow-up.

HCRU related to CF included CFTR modulators, other CF treatments (e.g., inhaled RhDNase, inhaled antibiotics, oral and intravenous antibiotics, pancreatic enzymes, vitamins, antidiabetic treatments), visits to healthcare professionals, medical procedures and devices, hospitalisations, emergency room visits, transport and sick leave compensation. HCRU was characterised by the number of users and the number of dispensed units.

All related costs were calculated from a National Health Service perspective, that is, the actual costs reimbursed by the National Health System. The computations were carried out per calendar year. HCRU and related costs were also analysed by age group.

The statistical analysis was performed with SAS Enterprise Guide® (SAS Institute, North Carolina), version 7.13.

Ethics

This observational study was conducted using anonymized data after approval by the French Institute for Health Data (approval n°217, on December 1, 2016) and the National Informatics and Liberty Committee (approval n° DE-2018-001, on March 12, 2018).

Results

Study population and follow-up

This study considered 7,671 patients included in the French CF Registry. Probabilistic linkage with the claims database could be performed for 6,187 (80.7%) patients. The median duration of follow-up was 12 years (interquartile range: 9.9 - 12). Follow-up was censored due to death for 460 (7.4%) patients, and 44 patients (0.7%) were lost to follow-up, but most patients (91.9%) were followed until the end of the study period.

Patient characteristics

The study population included a slight majority of men (51.9%), and the mean age at diagnosis or at the date of the sweat test was 4.2 years (\pm 10.2). Table 1 shows that 43.1% of the population had the F508del/F508del genotype, while 41.1% had the F508del/others genotype. During the last year of follow-up, the median FEV-1 was 82.0%, and the median BMI was 19.3 kg/m² (Table 1). Male and female patients had similar clinical characteristics (data not shown).

	All CF patients	CF patients < 18 years old	CF patients \geq 18 years old
	N = 6 187	N = 2 115	N = 4 072
Genetic mutations			
F508del/F508del	2 664 (43.1%)	929 (43.9%)	1 735 (42.6%)
F508del/others	2 373 (38.4%)	801 (37.9%)	1 572 (38.6%)
F508del/Gating	166 (2.7%)	72 (3.4%)	94 (2.3%)
Gating/other	79 (1.3%)	25 (1.2%)	54 (1.3%)
others	801 (12.9%)	279 (13.2%)	522 (12.8%)
NA	104 (1.7%)	9 (0.4%)	95 (2.3%)
History of pseudomonas infection			
Yes	4 775 (77.2%)	1 477 (69.8%)	3 298 (81.0%)
NA	648 (10.5%)	177 (8.4%)	471 (11.6%)
FEV-1 (% predicted) in the last year of follow-up*			

Mean (SD)	78.0 (27.7)	95.2 (21.6)	69.7 (26.4)
Median (Q1-Q3)	82.0 (58.0 - 99.0)	98.0 (84.0 - 109.0)	71.7 (49.0 - 90.0)
Min - Max	8.3 - 200.0	8.3 - 152.0	9.0 - 200.0
<hr/>			
FEV-1 (% predicted) in the last year of follow-up (in classes)*			
NA	576 (9.3%)	289 (13.7%)	287 (7.0%)
<40	656 (10.6%)	42 (2.0%)	614 (15.1%)
40-90	2 837 (45.9%)	598 (28.3%)	2 239 (55.0%)
>90	2 118 (34.2%)	1 186 (56.1%)	932 (22.9%)
<hr/>			
BMI in the last year of follow-up*			
Mean (std)	19.6 (3.6)	17.2 (2.7)	20.9 (3.3)
Median (Q1-Q3)	19.3 (17.0 - 21.6)	16.7 (15.3 - 18.6)	20.6 (18.7 - 22.6)
Min - Max	9.0 - 42.2	9.0 - 34.3	12.0 - 42.2
<hr/>			
Death	460 (7.4%)		-
<hr/>			
Lung transplantation	866 (14.0%)		-

NA: not available; SD: standard deviation; FEV-1: forced expiratory volume in 1 second; BMI: body mass index; * If the variable was not available in the last year of follow-up, the closest variable was considered.

TABLE 1 Clinical characteristics of the overall study population (n= 6 187) and of paediatric and adult patients

During follow-up, 14.0% of the patients had a lung transplant, and 10.4% of the female patients aged 15 to 40 years had one or more pregnancies. Regarding comorbidities, 35.3% of the patients were treated for diabetes; 19.3% received anti-osteoporotic treatment; 9.5% were suffering from severe kidney disease, as indicated by hospital diagnoses; and 4.1% had cancer, as identified by hospital diagnoses. The percentage of patients treated for anxiety or depression was 44.4% (data not shown).

Figure 1 shows the comparability of our study population with the CF Registry in terms of deaths, transplants and the populations older than 6 years.

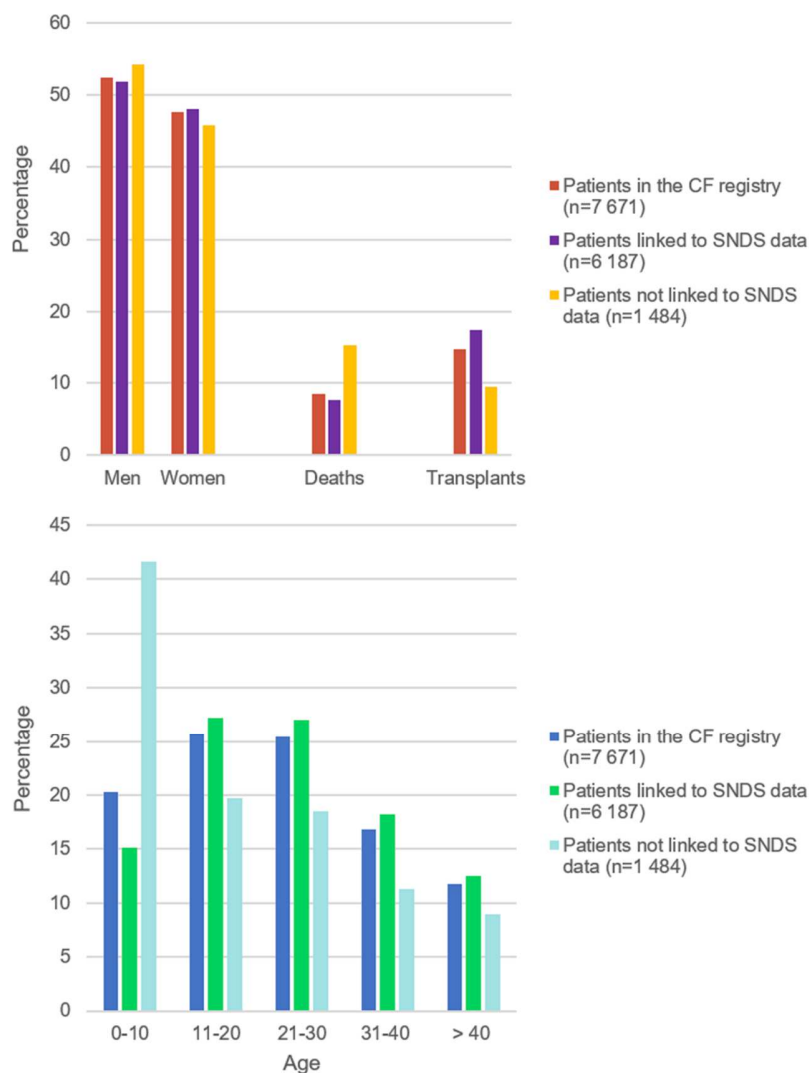


FIGURE 1 Description of patients in the French Cystic Fibrosis Registry linked or not linked to the SNDS data, in terms of gender, age, deaths and transplants.

HCRU and costs

In a cohort of 4,602 patients with a mean age of 17.5 years, the mean total cost per patient was €14,174 in 2006. In 2011, this cost increased to €21,920 per patient (5,334 patients, mean age=20 years). In 2017, the mean total cost was €44,585 per patient (5,680 patients; mean age=24.2 years). The costs of hospital stays increased from €3,843 per patient in 2006 to €6,741 in 2017. The costs of medical visits were stable, increasing from €2,974 per patient in 2006 to €3,660 in 2013 before decreasing to €3,284 in 2017. The costs of CFTR modulator therapies increased from €286 in 2014 to €22,829 in 2017, while the costs of other medications increased from €5,707 per patient in 2006 to €9,195 in 2017 (Figure 2 and e-Table 1).

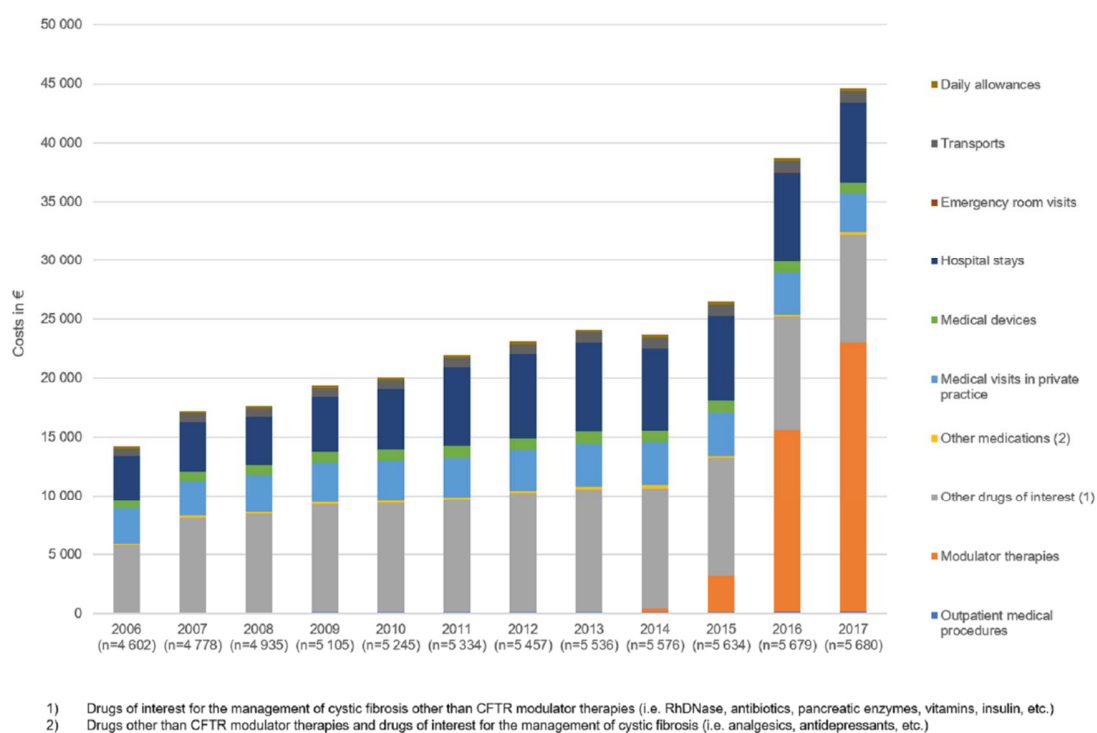


FIGURE 2 Mean cost in € per patient, type of expense, and calendar year

HCRU in 2017 is presented in Table 2: approximately one-half of the patients received azithromycin, more than one-third received inhaled antibiotics, and 45.4% received RhDNase. CFTR modulators were dispensed to 18.3% of the patients, and 14.2% received immunosuppressants (Table 2).

	Number of consumers (%)	Number of units among consumers	
		Mean number of dispensed units* (SD)	Median number of dispensed units* (Q1-Q3)
CFTR modulator therapies	1 042 (18.3%)	8.9 (4.3)	10.0 (5.0 - 12.0)
<i>Ivacaftor</i>	122 (2.1%)	10.7 (3.8)	12.0 (10.0 - 13.0)
<i>Ivacaftor/lumacaftor</i>	920 (16.2%)	8.7 (4.4)	10.0 (5.0 - 12.0)
Other CF treatments			
RhDNase	2 578 (45.4%)	6.2 (4.1)	6.0 (2.0 - 10.0)
Inhaled antibiotics	2 049 (36.1%)	18.7 (87.0)	5.0 (2.0 - 12.0)
Oral or intravenous antibiotics	4 982 (87.7%)	76.9 (151.0)	19.0 (8.0 - 67.0)
<i>Azithromycin</i>	2 634 (46.4%)	28.6 (19.5)	25.0 (12.0 - 45.0)
Pancreatic extracts	4 541 (79.9%)	45.5 (28.7)	41.0 (25.0 - 61.0)
Fat-soluble vitamins	4 980 (87.7%)	18.9 (15.7)	15.0 (7.0 - 26.0)
Ursodeoxycholic acid	1 610 (28.3%)	23.2 (18.8)	18.0 (10.0 - 33.0)
Antidiabetics			
<i>Oral antidiabetics</i>	159 (2.8%)	8.4 (7.0)	7.0 (3.0 - 12.0)
<i>Insulin</i>	1 027 (18.1%)	8.4 (7.6)	6.0 (3.0 - 11.0)
Anti-osteoporotics	273 (4.8%)	4.8 (3.6)	4.0 (2.0 - 7.0)
Other treatments			
Corticosteroids			
<i>Oral</i>	2 396 (42.2%)	7.8 (10.4)	3.0 (1.0 - 12.0)
<i>Inhaled</i>	555 (9.8%)	5.1 (6.6)	2.0 (1.0 - 6.0)
Antifungals			
<i>For oral use</i>	712 (12.5%)	2.4 (4.3)	1.0 (1.0 - 2.0)
<i>For systemic use</i>	925 (16.3%)	16.5 (18.0)	10.0 (4.0 - 23.0)
Proton pump inhibitors	2 841 (50.0%)	10.4 (7.6)	10.0 (4.0 - 13.0)
Psychotropic drugs			

<i>Antidepressants</i>	412 (7.3%)	12.0 (11.6)	9.0 (3.0 - 17.0)
<i>Anxiolytics</i>	607 (10.7%)	6.1 (9.5)	2.0 (1.0 - 7.0)
Oral supplementation	1 017 (17.9%)	6.7 (7.2)	5.0 (2.0 - 9.0)
Immunosuppressants	809 (14.2%)	55.3 (22.2)	55.0 (41.0 - 69.0)
Ambulatory hospitalisations	4 901 (86.3%)	3.9 (6.5)	3.0 (2.0 - 5.0)
Conventional hospitalisations	1 968 (34.6%)	2.4 (2.3)	2.0 (1.0 - 3.0)
Visits to public hospital practitioners (all specialties)	4 000 (70.4%)	3.7 (3.1)	3.0 (1.0 - 5.0)
Medical devices	4 230 (74.5%)	50.6 (133.1)	18.0 (12.0 - 30.0)
<i>Oxygen therapy</i>	243 (4.3%)	33.6 (18.7)	37.0 (15.0 - 51.0)
<i>Assisted ventilation</i>	145 (2.6%)	36.9 (18.0)	44.0 (23.0 - 52.0)
<i>Aerosol delivery devices</i>	4 116 (72.5%)	19.1 (13.8)	16.0 (11.0 - 25.0)
<i>Enteral nutrition</i>	317 (5.6%)	377.4 (308.4)	338.0 (111.0 - 566.0)
<i>Parenteral nutrition</i>	111 (2.0%)	18.8 (31.6)	6.0 (1.0 - 23.0)
Transports	2 895 (51.0%)	12.1 (22.5)	6.0 (3.0 - 13.0)
Daily allowances (in nb of days)	674 (11.9%)	67.0 (93.5)	25.0 (10.0 - 81.0)

* mean number of units that were dispensed (i.e. prescribed, delivered and reimbursed) for the year 2017 among patients who received at least one reimbursement over the year.

TABLE 2 CF-specific healthcare resource use in 2017 (n= 5 680)

As a result, in 2017, the mean cost of care per patient was allocated as follows: 72% for medications (of which 51% for modulator therapies), 15% for hospital stays, 7% for medical visits, 3% for indirect costs, 2% for medical devices, and 1% for outpatient procedures (e-Figure 1).

Table 3 presents the annualized mean costs (in euros) (SD) per patient, per category of expense, and per age group over the follow-up period.

	7-11 years old (n=729)	12-18 years old (n=1 187)	19-30 years old (n=2 005)	>30 years old (n=1 884)
CFTR modulator therapies	1 848 (±11 095)	5 835 (±11 218)	3 606 (±9 989)	2835 (±9 070)
Other drugs of interest ⁽¹⁾	4 912 (±4 458)	8 631 (±7 103)	10 146 (±7 551)	10 154 (±7 896)
<i>RhDNase</i>	1 960 (±2 005)	3 243 (±2 737)	2 564 (±2 687)	1 767 (±2 811)
<i>Inhaled antibiotics</i>	1 537 (±2 354)	1 933 (±2 554)	1 975 (±2 505)	2 089 (±3 037)
<i>Oral or intravenous antibiotics</i>	442 (±999)	1 541 (±2 241)	2 678 (±2 956)	2 395 (±2 876)
<i>Pancreatic extracts</i>	534 (±365)	707 (±462)	718 (±529)	664 (±624)
<i>Fat-soluble vitamins</i>	44 (±47)	50 (±54)	47 (±50)	45 (±53)
<i>Oral corticosteroids</i>	3 (±4)	4 (±7)	8 (±14)	14 (±22)
<i>Analgesics</i>	5 (±4)	5 (±9)	21 (±176)	33 (±118)
<i>Bronchodilators</i>	123 (±381)	279 (±1 079)	363 (±1 355)	425 (±1 538)
Other drugs ⁽²⁾	94 (±290)	101 (±190)	177 (±415)	367 (±752)
Visits (in private practice)	3 734 (±2 259)	3 972 (±3 006)	3 651 (±4 163)	2 616 (±3 369)
Medical devices	746 (±1 273)	1 167 (±1 797)	1 058 (±1 487)	861 (±1 299)
Hospitalisations	3 854 (±5 436)	5 186 (±9 980)	8 074 (±11 409)	8 261 (±10 729)
Daily allowances	NA	0 (±4)	155 (±586)	603 (±1 345)
Transports	477 (±944)	792 (±1 808)	1 009 (±2 190)	996 (±1 839)
Total	15 771 (±15 254)	25 782 (±21 001)	28 024 (±21 630)	26 939 (±20 574)

(1) Drugs of interest for the management of cystic fibrosis other than CFTR modulator therapies

(2) Drugs other than CFTR modulator therapies and drugs of interest for the management of cystic fibrosis

Table 3 Annualized mean costs (in euros) (SD) per patient, per type, and per age group over the follow-up period

Discussion

The study relied on the successful linkage of 80.7% (N=6,187) of the patients included in the French CF Registry with the SNDS claims data. Over the follow-up period, the size of our cohort increased from 4,602 to 5,680, the mean age increased from 17.5 to 24 years and the mean cost per patient increased from €14,174 in 2006 to €21,920 in 2011 and €44,585 in 2017, which was an increase of 214% over 10 years (e-figure 2). In 2017, 72% of the mean cost per patient was due to medications, with 71% of those costs accounted for by CFTR modulators.

This project is one of the first linkages between a French registry and the SNDS. As both datasets included complementary data, the linkage allowed the broadening and improving of the information available on CF patients, constituting an exhaustive data source to expand the scope of scientific research on all facets of CF [12-14]. Data linkages are increasingly performed, notably in public health and epidemiology [15, 16]. The validity of our method is supported by data recorded in the CF Registry [11]. For instance, dispensing data showed that in 2017, modulator therapies were provided at least once to 18.3% of our study cohort versus 17.9% of those in the CF Registry.

While many studies conducted in other countries have used prescribing data from electronic health records or questionnaires [17-21], the claims data used in our study provided information on the actual dispensing of therapies by community pharmacies, which is a significant advantage, as these data are more reflective of real consumption than prescribing data. Moreover, using claims data that reflect real-world HCRU prevents selection and recall biases that may be present in studies employing surveys or questionnaires. Finally, as the method of assessing costs in this study was based on the actual use of healthcare resources, it was highly accurate: the SNDS includes exhaustive individual information on reimbursements.

Regardless of the age group, the most common drugs used were antibiotics, pain relievers, fat-soluble vitamins, pancreatic enzymes, bronchodilators, and RhDnase. With increasing age, oral corticosteroids were more frequently used. The decrease in RhDnase and oral/intravenous antibiotic consumption after 30 years could be due to a higher percentage of transplanted patients in this age group (Table 3). Regarding CFTR modulators, their mean individual costs decreased with age, as patients who had undergone lung transplantation were not eligible for these therapies [22], nor were some patients with genotypes associated with age.

The increase in the costs for CF care observed between 2006 and 2017 reflected practice changes following the 2006 recommendations of the French Health Authority (updated in 2017) [23] and the European standards of care [2, 3, 24]. This cost increase is explained by the rising number of available treatments, first inhaled antibiotics, which were

introduced in 2006, and, more recently, CFTR modulators, which have been available since 2014. The mean individual costs for the medications of interest increased from €5,707 per patient in 2006 (date of the introduction of inhaled tobramycin) to €9,195 in 2017. Specifically, with regard to the CFTR modulator therapies, the mean individual costs per patient increased from €286 in 2014 (date of the introduction of ivacaftor) to €22,829 in 2017 (introduction of lumacaftor/ivacaftor by the end of 2015), confirming recent results from Ireland [25]. In France, Horvais et al. (2006) estimated an annual cost of care of €16,189 per patient for the 2000-2001 period [12], with medications accounting for 69% of the total cost. Our results showed an average cost per patient of €14,174 in 2006, which was slightly lower than Horvais' annual cost. In another French cost analysis, Huot compared 2000 (€16,474) with 2003 (€22,725) [11]. In these two studies, costly intravenous antibiotic treatments at home accounted for 20% of the total cost, which could explain a portion of the discrepancy with our figures. From 2007 to 2009, a medico-economic evaluation was conducted by the NHS to assess the cost of care of all chronic diseases in France. Almost 5,600 patients had a chronic disease status for CF [26]. The average annual cost reimbursed by the NHS was €22,454 per patient [26], or more than 110 million euros for all CF patients [9]. Medications accounted for the greatest proportion of the costs (37%), followed by hospitalisations (34%), medical devices (11%) and physiotherapy (10%). Our results for 2007 were slightly lower, but this may be explained by the fact that the costs computed in our study were for the overall cohort of CF patients, whereas those presented by the French NHS were calculated for consumers only [9]. A more recent study was carried out in CF patients in France on the cost of illness in 2012, but the assessment of costs was based on a questionnaire, with a limited study sample size (N=240) [27]. According to that study, the total average annual cost of CF was €29,746 per patient in 2012. Our results are slightly lower; however, they used a different methodology, allowing them to include costs related to informal care that could not be captured by our approach. In addition, our assessment relied on robust data, as we used HCRU reimbursed by the NHS and recorded at the time of care to prevent recall or desirability biases.

The 75% increase in the cost of hospital stays between 2006 and 2017 observed in our study reflects the increasing number of adult patients with pulmonary exacerbations and severe lung damage; the increasing number with emerging comorbid conditions, such as diabetes; and the increased number undergoing transplantation. Indeed, in 2007, adults represented 43% of the CF population in the French CF Registry, while in 2017, they represented 56% [11]. The number of transplantations also increased by 45% between 2006 and 2017 [11]. Our study identified higher

total costs in adults than in children, with adults having higher drug and hospitalisation costs, which was in agreement with the Chevreul study [27] and a recent US study conducted on the CF Medicaid population [28]. Outside France, several studies have estimated the cost of CF care [17-19, 21, 25, 28-30]. According to an observational cohort study using German claims data, pharmaceutical treatment and hospital care accounted for approximately 73.3% and 15.0% of the direct costs associated with CF, respectively, in 2016 [29]. This distribution of costs was similar to ours. The total annual average costs per CF patient differed across countries: €48,603 in the UK, €24,152 in Bulgaria in 2012, and €19,581 in Poland in 2013 [17, 20, 21]. In the United States, Grosse et al. studied healthcare expenditures for privately insured US patients with CF. In their study, average spending adjusted for inflation nearly doubled from roughly \$67 000 per patient in 2010 and 2011 to approximately \$131 000 per patient in 2016 [30]. However, any comparison of these studies is complex because of the multiplicity of the healthcare systems involved, the differences among the sources of data, and the perspective chosen [26].

Some limitations of our study must be acknowledged, the most important of which is the underrepresentation of children younger than 7 years (Figure 1). Indeed, as the linkage used the dates of spirometry and as spirometry is seldom performed before the age of 6, many younger patients could not be linked.

For similar reasons, the linkage led to an underrepresentation of deceased patients, as it was based on the death status, which is adequately identified only for patients affiliated with general health insurance.

Several cost of illness studies have been conducted over the past decades across a range of diseases, but few have addressed rare conditions, particularly CF. Our study provides updated figures on the cost of care in a great majority of the CF patients in France. This study was able to assess the cost impact of recent changes in disease management and therapies (i.e., CFTR modulators), unlike studies conducted before 2010. The French CF Registry added clinical data to the claims recorded in the SNDS to provide an exhaustive profile of CF patients. Beyond this initial global assessment, this linked dataset will allow an analytical study of different profiles of disease severity and in the future an evaluation of the impact of the use of modulators on the overall consumption of care.

Conclusion

This study was based on the linkage of clinical data from 80.7% of the patients recorded in the French Cystic Fibrosis Registry to the SNDS claims data. This was the first study of its kind to be conducted in France, where the HCRU of the overwhelming majority of the population is recorded and available for research purposes. The study

collected valid data on CF management and related costs. These findings showed that the mean annual cost per patient with CF more than doubled between 2006 and 2017, mostly due to a large increase in the cost of medications. This may be explained by the higher number of available treatments, especially driven by the introduction of ivacaftor in 2012 and ivacaftor/lumacaftor in 2016. The combination of an increase in the number of CF patients – particularly adult patients – and an increase in the annual cost per patient led to a substantial increase in the total cost of CF disease care for the health systems.

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Conflict of interest statements:

F. Dalon, M. Bérard and M. Belhassen are full-time employees of PELyon.

D. Walther was full-time employee of PELyon at the time of the study.

E. Van Ganse is the scientific advisor and shareholder of PELyon.

I. Durieu, Q. Reynaud, M. Viprey, L. Lemonnier and C. Dehillotte have nothing to disclose.

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