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Original Article

Health care resource utilization preceding death or lung transplantation in people with cystic fibrosis
HCRU before transplant or death in cystic fibrosis

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ABSTRACT

Background: We studied the health care resource utilization (HCRU) and associated costs in the year preceding LT in pwCF or death without LT, and we estimated the overall cost of LT.
Methods: We performed a linkage between 2006 and 2017 data from the French CF Registry (FCFR) and the French health claims database (Système National des Données de Santé; SNDS). The HCRU and associated costs were described the year before LT or before death without LT, and two years after LT.
Results: Among the 7,671 patients included in the FCFR, 6,187 patients (80.7 %) were successfully matched to patients in the SNDS (males (m): 51.9 %, mean±SD age at the end of follow-up: 24.6 ± 13.6). Overall, 166 patients died without LT (m: 47.6 %, age at death: 30.4 ± 14.5) and 767 patients with primary LT (m: 48.2 %, age at transplantation: 28.0 ± 9.1) were identified. HCRU was lower among patients who died without receiving LT, with marked differences in the cost of hospital stays. The mean total cost per patient was €66,759 ± 38,249 in the year before death, €149,374 ± 62,678 in the year preceding LT, €63,919 ± 35,399 in the first year following LT, and €42,813 ± 39,967 in the second year of follow-up.
Conclusion: Our results indicate that HCRU was two times lower in the year before death in non-transplant pwCF than in the year before LT, which may reflect inappropriate care of CF in patients who died without receiving LT. It also shows the cost associated with LT.

1. Introduction

Cystic fibrosis (CF) is an autosomal recessive disease caused by a mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene coding for a CFTR protein normally present at the apical pole of epithelial cells. To date, more than two thousand mutations in the gene have been identified. The pathophysiology of CF explains the multiple clinical manifestations of the disease, which mainly affect the respiratory tract, pancreatic ducts, sweat glands, and the gastrointestinal, biliary, and genital tracts [1–3]. Impaired lung function, which is the leading cause of morbidity and mortality, has benefited from advances in mucociliary clearance, inhaled and systemic antibiotic therapy and lung transplantation (LT) [4].

LT is the gold standard treatment improving survival and quality of life in people with cystic fibrosis (pwCF) suffering from severe and

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Abbreviations

LT	Lung transplantation
BMI	Body mass index
CMU-C	Free-access-to-care status
CF	Cystic fibrosis
CFTR	Cystic fibrosis transmembrane conductance regulator
ETI	Elexacaftor/tezacaftor/ivacaftor
FEV1	Forced expiratory volume in one second
FCFR	French cystic fibrosis registry
HCRU	Health care resource utilization
ICD-10	International Classification of Diseases - 10th revision
pwCF	People with cystic fibrosis
SNDS	Système National de Données de Santé

irreversible end-stage lung disease despite standard recommended treatments [5]. In 2021, patients living with LT represented 13 % of all patients included in the French Cystic Fibrosis Registry (FCFR), and 21 % of the adult (≥18 years) population [6]. A recently published analysis by Coriati et al. showed that French pwCF were now more likely to receive a lung transplant than to die [7]. The improved access to LT allowed by the implementation of the High Emergency Lung Transplantation (HELT) program, which gives priority to patients at highest risk for death unless they have rapid access to LT, in France since 2007 may explain the higher survival compared with other countries with similar healthcare systems [8]. Further progress is however still awaited, as a study analyzing causes of deaths in French pwCF after the implementation of the HELT program found that half of pwCF deaths occurred in patients who had not received a LT, while up to at least one-third could have been eligible for a lung transplant [9].

This study involved FCFR patients' data, selected between 2006 and 2016, linked with patients' data from the Système National des Données de Santé (SNDS) between 2006 and 2017. The aim was to measure health care resource utilization (HCRU) and associated costs in the year before death occurring in pwCF who had never received a LT, or in the year before LT, and in the first and second year of follow-up after LT in pwCF who had received a primary LT.

2. Methods

2.1. Study design and data sources

This retrospective observational study was performed using data from the FCFR and the SNDS. The FCFR was established in 1992 and follows pwCF from 47 CF centers. It is estimated that >95 % of the French CF population is captured within the registry, with a low rate of loss to follow-up (<3 %) [7]. The Registry collects annual data including anthropometric measurements, medical follow-up, prescribed treatments, respiratory and bacteriological data. The SNDS is the French nationwide claims database covering 99 % of the French population [10, 11].

Since the data from FCFR and SNDS do not contain direct identifiers, a linkage was performed to associate the records likely to belong to the same individual. A scoring system was assigned to a combination of variables available in both data sources, and a decision algorithm was applied. The linkage variables were gender, month and year of birth, date of spirometry tests, death status, month and year of death, month and year of transplantation, region of residence, and date of sweat tests. A number of points was allocated to pairs of SNDS and RFM identifiers. For example, if they had the greatest number of complete dates of spirometry in common, they had 1 point. We then proceeded with 4 successive rounds of linkage. In the first round, we identified pairs of identifiers with 7 points in common, which was the maximum, then at least 4 points, then less than 4 points if they had at least one sweat test date and one region in common. In each case, if the identifier in the RFM corresponded to a single identifier in the SNDS, or vice versa, the identifiers were considered to be linked. If not, the identifiers were set aside and we tried to separate them using comorbidities (i.e., presence or absence of (pneumothorax, pancreatic insufficiency, diabetes, cancer, acute pancreatitis, and aspergillosis) recorded in the two data sources. The final step was to check the consistency of death and transplant information for each pair of identifiers. The dataset resulting from this linkage has previously been used to assess HCRU and costs among French pwCF between 2006 and 2017 [12].

2.2. Study population

The 2006–2016 patient data from the FCFR were linked to data of patients with a chronic disease status or a hospital diagnosis for CF in the SNDS over the study period, from January 1, 2006, to December 31, 2017. Two subgroups of pwCF were identified: patients who died without LT, and patients who received a primary LT.

Patients who died without LT were selected if they had no medical procedure or diagnosis of hospitalization for LT and if they had a date of death recorded in the SNDS. Patients with a date of hospitalization for LT recorded in the FCFR before 2006 and patients with less than one year of follow-up before the date of death were excluded from the analyses.

Patients with a primary LT were selected if they had at least one medical act for LT in the SNDS. Patients with a previous medical act or diagnosis of hospitalization for another transplantation than LT, patients with a LT prior to 2006 record in the FCFR and patients with less than one year of follow-up before LT were excluded from the analyses.

Patients were studied in the year before LT or death. Patients with a primary LT were also analyzed in the first- and second-year following LT. The day of LT was included in the pre-transplantation period. As the present study focused on patients with LT who survived, those whose follow-up ended during the studied year, who were lost to follow-up, or who died before the end of the study period were excluded from post-operative analyses.

2.3. Statistics

Outcomes of interest were described either by sample size (N), mean and standard deviation (SD), or median, first and third quartiles for quantitative variables, or by sample size (N) and frequency for qualitative variables. Socioeconomic characteristics of patients with CF were identified from the SDNS. Clinical characteristics of patients were identified from the FCFR data. Characteristics of patients who died without having received a LT and patients with a LT were compared using Pearson $\chi 2$ test or Fisher's exact test for categorical variables, Student *t*-test or Mann-Whitney U test for continuous variables. As the SNDS database and the French Cystic Fibrosis Registry do not record causes of death, the main diagnosis (ICD-10 code) of the last known hospitalization in the two months preceding death was assumed to be the cause of death. If several hospitalizations have occurred during this period, the one for which the mode of discharge was death and/or the one with the most recent discharge date was selected. The diagnoses were classified into three categories: J96 "Respiratory failure", E84 "Cystic fibrosis", and "Other". We were unable to approximate the cause of death for non-hospitalized patients over this period HCRU related to CF was identified using data from the SNDS in the year preceding primary LT or in the year preceding death, and at one- and two-years' follow-up after LT. HCRU covered CFTR modulators, other cystic fibrosis treatments (e.g., inhaled RhDNase and antibiotics, oral and intravenous antibiotics, pancreatic enzymes, vitamins, antidiabetic treatments), visits to healthcare professionals, medical procedures and devices, hospitalizations, emergency room visits, transport, and sick leave compensation. It was characterized by the number of users and the units

dispensed. Associated costs were estimated from the National Health System perspective and were compared between patients who died without LT and patients with LT using Mann-Whitney U test.

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

2.4. Ethics

This observational study was conducted using anonymized data after approval by the French Institute for Health Data (approval n° 217, on 12/01/2016) and the French Data Protection Authority (approval n° DE-2018-001, on 03/12/2018). Written informed consent was not required for participation in this study, in accordance with national legislation and institutional requirements.

3. Results

3.1. Patient characteristics

A flow chart is presented in supplementary material (Figure S1). There were 7671 patients included in the FCFR in 2006–2016. The linkage between the FCFR and the SNDS was possible for 6187 (80.7 %) patients (males (m): 51.9 %, mean age: 24.6 ± 13.6). The socioeconomic and clinical characteristics of the overall study population have been described elsewhere [12]. Among these 6187 patients, 166 patients died without having received a LT, and 767 patients were identified with primary LT. A total of 625 patients were analyzed at 1-year follow-up and 523 at 2-year follow-up after LT.

Table 1 shows the characteristics of the study population. There were no significant differences in terms of gender, age at death or at LT, and percentage of patients with free access to care between patients who died and those with LT. Median FEV1 was 39.6 % in patients who died without LT and 30.0 % in patients with LT ($p < .0001$). The median BMI was similar in both groups (18.3 and 18.5 $kg.m^{-2}$, respectively). Among patients who died without having received a lung transplantation, 22 patients (13.3 %) were on a transplant waiting list. The delay between registration on a waiting list for LT and death was 289.3 ± 464.1 days, whereas it was 213.7 ± 323.4 days from registration to transplantation in patients with a LT. The main diagnosis of hospitalization found in the two months prior to death was respiratory failure for $N = 50$ (32.1 %) of patients and CF for $N = 36$ (23.1 %) of them. A total of $N = 70$ (44.9 %) patients had other main diagnoses.

3.2. HCRU in the year preceding death or primary lung transplantation

Table 2 is a summary table of HCRU in the year before death among patients who died without LT, and in the year before LT among patients who received a primary LT. The detailed HCRU is presented in supplementary material (Table S2). Overall, there was a lower consumption of specific CF treatments in deceased patients compared to transplanted patients (443 vs. 785 units dispensed per consumers). Deceased patients were less likely to use oral or intravenous antibiotics, including azithromycin (62.0 % of consumers among patients who died vs. 76.5 % in patients with LT), intravenous (18.1% vs. 30.0 % of consumers) and oral (50.0% vs. 59.6 % of consumers) corticosteroids, and intravenous fluids (66.9% vs. 84.1 % of consumers). Furthermore, the number of intravenous fluids dispensed was also lower in patients who died without a LT (104 units) than in patients with a LT (195 units). On the other hand, they consumed more anxiolytics (4 vs. 2 units dispensed) than patients with LT. Of note, patients who died without having a LT had fewer private practice visits with medical doctors, physiotherapists and nurses than transplanted patients (227 vs. 292). Finally, deceased patients without LT had fewer medical devices (32 vs. 59 units dispensed), and fewer oxygen therapy (36.7% vs. 47.3 % of consumers), and enteral nutrition (21.1% vs. 33 % of consumers).

The mean costs and percentages of total mean cost per patient and per type of expenses are presented in Fig. 1 and supplementary material (Table S3). Hospital stays accounted for the largest expenditure with a mean cost of €36,707.2 ± 28,842.5 per patient in the year before death and €104,810.2 ± 51,773.6 ($p < .0001$) per patient in the year before LT, of which €77,350.1 ± €44,630.1 related to LT hospitalization. It was followed by CF treatments (except CFTR modulators) with a mean cost per patient of €14,816.6 ± 11,378.3 and €21,951.8 ± 15,737.5 respectively ($p < .0001$). The costs of consultations and visits, medical devices and transports were also higher in patients with LT (all $p < .0001$). Other costs were not significantly different between the groups of patients. Overall, the mean total cost per patient was €66,758.7 ± 38,248.6 in the year before death, while it was €149,373.6 ± 62,678.2 in the year before LT ($p < .0001$).

Table 1
Socioeconomic and clinical characteristics of patients with cystic fibrosis who received a primary lung transplantation ($N = 767$), and patients with cystic fibrosis who died without having received a lung transplantation ($N = 166$), SNDS, 2006–2017.

	Patients who died without having received a lung transplantation ($N = 166$)	Patients with a lung transplantation ($N = 767$)	*p values*
Sex			
Men	79 (47.6 %)	370 (48.2 %)	0.88
Women	87 (52.4 %)	397 (51.8 %)	
Age at death or LT			
Mean (std)	30.4 (14.5)	28.0 (9.1)	0.44
Median (Q1-Q3)	27.0 (21.0–37.0)	26.0 (22.0–33.0)	
Min–Max	2.0–83.0	7.0–60.0	
Free-access-to-care status	18 (10.8 %)	64 (8.3 %)	0.30
Genetic mutations			
F508del/F508del	65 (39.2 %)	392 (51.1 %)	**0.011**
F508del/Other	72 (43.4 %)	279 (36.4 %)	
Other mutations	22 (13.3 %)	84 (11.0 %)	
Missing data	7 (4.2 %)	12 (1.6 %)	
History of *Pseudomonas* infection			
No	0 (0 %)	1 (0.1 %)	**0.0007**
Yes	143 (86.1 %)	724 (94.4 %)	
Missing data	23 (13.9 %)	42 (5.5 %)	
FEV1 (in% predicted)			
Mean (std)	39.6 (17.5)	30.0 (10.3)	**<0.0001**
Median (Q1-Q3)	36.8 (27.0–47.1)	28.0 (23.0–35.0)	
Min–Max	14.0–110.0	10.0–92.0	
Missing data	19 (11.4 %)	58 (7.6 %)	
BMI			
Mean (standard deviation)	18.3 (2.7)	18.5 (2.4)	0.46
Median (Q1-Q3)	18.3 (16.4–19.8)	18.3 (16.9–20.0)	
Min–Max	11.7–26.1	13.3–30.5	
Missing data	11 (6.6 %)	8 (1.0 %)	

Values are for the sample size and frequency, unless noted otherwise. *P values* are for differences between patients who died without having received a LT and patients with a LT on the basis of Pearson $\chi 2$ test, Mann-Whitney U test, Student *t*-test or Fisher's exact test as appropriate.
*FEV1 was the last available data before death or in the year N-1 before LT.

3.3. Overall cost of lung transplantation

Fig. 2 represents the mean total costs and the percentages of the

Table 2
Health Care Resource Utilization in the year before death in patients without lung transplantation who died ($N = 166$), or in the year before lung transplantation in patients with a primary lung transplantation ($N = 767$), SNDS, 2006–2017.

	Patients who died without a lung transplantation ($N = 166$)			Patients with a lung transplantation ($N = 767$)		
	Number of consumers (%)	Mean number of dispensed units * (SD)	Median number of dispensed units * (Q1–Q3)	Number of consumers (%)	Mean number of dispensed units * (SD)	Median number of dispensed units * (Q1–Q3)
CFTR modulator therapies (ivacaftor or lumacaftor/ivacaftor)	3 (1.8 %)	3.3 (2.5)	3.0 (1.0–6.0)	18 (2.3 %)	4.6 (4.1)	3.0 (1.0–8.0)
Other CF treatments	161 (97.0 %)	550.0 (520.0)	443.0 (195.0–761.0)	755 (98.4 %)	920.8 (692.7)	785.0 (406.0–1 268.0)
Other medicines	160 (96.4 %)	55.5 (56.9)	39.0 (17.0–70.5)	750 (97.8 %)	54.6 (52.4)	40.0 (22.0–67.0)
Medical procedure in community-based practice	54 (32.5 %)	2.4 (1.7)	2.0 (1.0–4.0)	251 (32.7 %)	2.0 (1.5)	1.0 (1.0–2.0)
Medical procedure during hospitalization in the public sector	147 (88.6 %)	43.0 (48.8)	26.0 (11.0–53.0)	701 (91.4 %)	33.1 (48.9)	19.0 (11.0–32.0)
Dental procedures outside hospital	12 (7.2 %)	3.6 (3.5)	1.5 (1.0–5.5)	63 (8.2 %)	3.0 (2.1)	2.0 (2.0–4.0)
Biological tests outside hospital	116 (69.9 %)	30.1 (44.2)	15.0 (4.0–35.5)	541 (70.5 %)	24.8 (33.5)	15.0 (6.0–33.0)
Hospitalizations	160 (96.4 %)	9.2 (6.7)	8.0 (4.5–12.5)	765 (99.7 %)	10.5 (5.4)	10.0 (7.0–14.0)
Private practice consultations	157 (94.6 %)	300.2 (349.3)	227.0 (89.0–369.0)	737 (96.1 %)	399.8 (646.0)	292.0 (146.0–498.0)
Public hospital practitioners (all specialties)	119 (71.7 %)	4.5 (3.7)	4.0 (2.0–6.0)	547 (71.3 %)	5.7 (4.6)	5.0 (2.0–8.0)
Emergency room visits not followed by hospitalization	36 (21.7 %)	1.7 (0.9)	1.0 (1.0–2.0)	127 (16.6 %)	1.5 (1.0)	1.0 (1.0–2.0)
Medical devices	151 (91.0 %)	113.4 (184.2)	32.0 (16.0–85.0)	732 (95.4 %)	168.2 (235.5)	59.0 (25.0–217.0)
Transports	147 (88.6 %)	11.5 (11.8)	8.0 (4.0–16.0)	695 (90.6 %)	15.0 (12.8)	13.0 (6.0–20.0)
Daily benefits in case of sick leave (in nb of days)	32 (19.3 %)	173.6 (128.4)	141.5 (51.0–307.5)	182 (23.7 %)	192.9 (123.8)	180.5 (81.0–322.0)

* Values are the mean or median number of units dispensed (i.e., prescribed, dispensed and reimbursed) per consumer in the year prior to death in patients with cystic fibrosis without lung transplantation who died, or in the year prior to lung transplant in patients cystic fibrosis with lung transplantation.

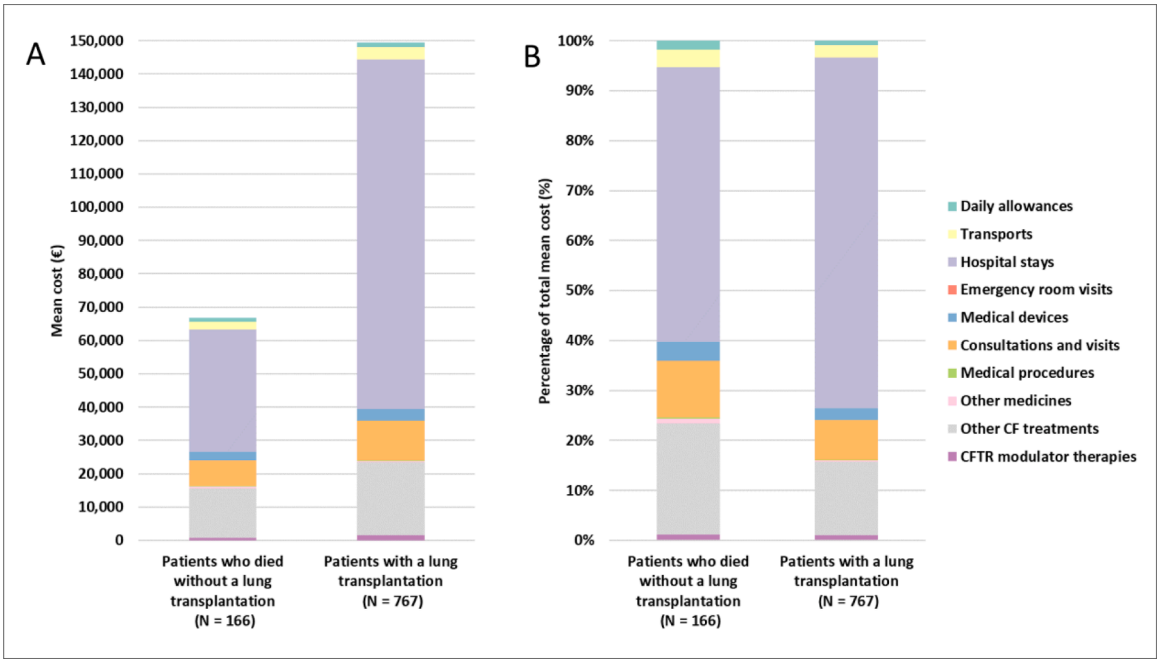

Fig. 1. Mean costs in Euros (panel A) and percentages of total mean cost (panel B) per patient with cystic fibrosis and per type of expenses in the year before death in patients who died without lung transplantation ($N = 166$), or in the year before lung transplantation in patients who received a primary lung transplantation ($N = 767$), SNDS, 2006–2017. Cystic fibrosis treatments refer to drugs of interest for the management of cystic fibrosis other than CFTR modulators. Other medicines refer to drugs other than CFTR modulators and drugs of interest in the management of cystic fibrosis.

mean total cost per patient and per type of expenses, in the year before LT, and in the first- and second-year of follow-up after LT. Across all periods, the most important expenses were related to hospital stays. However, they were lower than before LT and accounted for €28,735.3 ± 31,435.7 in the first year after LT, and €19,353.1 ± 34,935.0 in the second year. The costs associated with consultations and visits and with medical devices were also lower in the postoperative period than before LT. While the cost of CF treatments other than CFTR modulators was similar in the year before and in the first year of follow-up after LT (€21,951.8 ± 15,737.5 and €22,078.7 ± 11,746.8, respectively), it

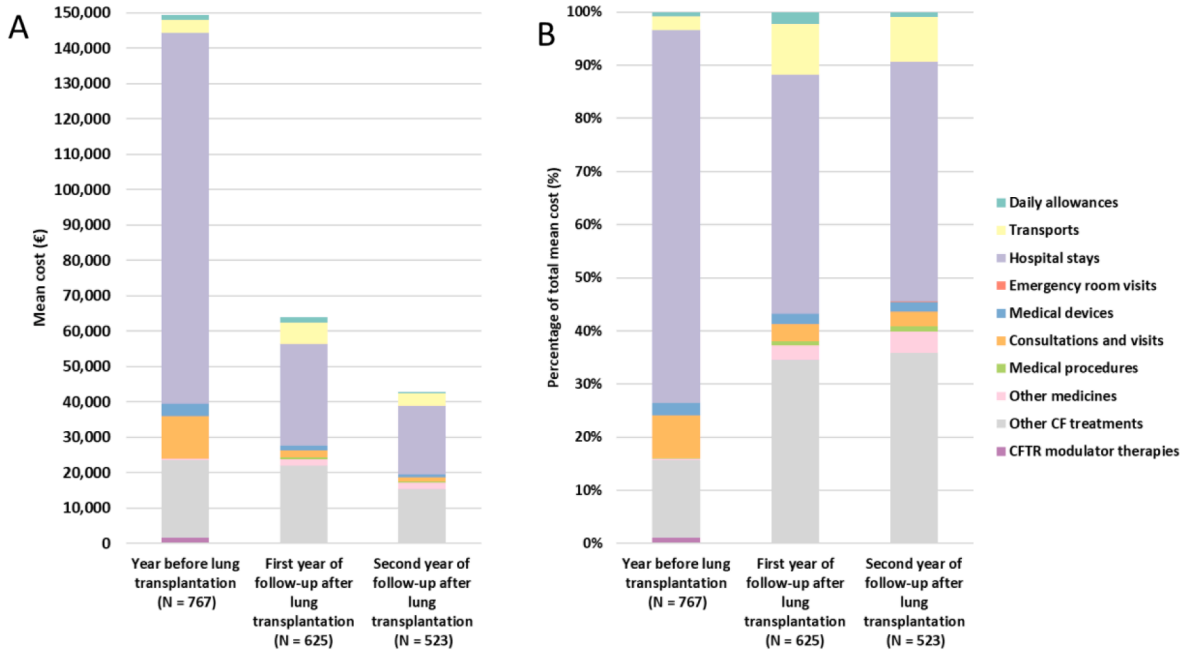

Fig. 2. Mean costs in Euros (panel A) and percentages of total mean cost (panel B) per patient and per type of expenses, in the year before lung transplantation, in the first and second year of follow-up after lung transplantation among patients with cystic fibrosis who received a lung transplantation. Cystic fibrosis treatments refer to drugs of interest for the management of cystic fibrosis other than CFTR modulators. Other medicines refer to drugs other than CFTR modulators and drugs of interest in the management of cystic fibrosis.

decreased to €15,336.2 ± 8063.2 in the second year. Decreased costs were also noted for daily benefits in case of sick leave (€1308.1 ± 3270.4 before LT, €1444.5 ± 3545.2 in the first year of follow-up and €424.0 ± 1749.0 in the second year). On the other hand, the use of other medicines (other than CF treatments) increased from €388 before LT up to €1744 in the first- and second-year follow-up. The cost associated with medical procedures, which was €151.4 ± 210.9 in the year before LT, increased to €489.6 ± 417.9 in the first year of follow-up and remained at €406.2 ± 381.6 in the second year. Overall, while the mean cost was €149,373.6 ± 62,678.2 in the year before lung transplantation, it was €63,918.7 ± 35,399.0 in the first year of follow-up, and €42,813.1 ± 39,966.8 in the second year.

4. Discussion

Our study investigated HCRU and its associated costs in the year before death without LT or before primary LT in pwCF, and the overall cost of LT. HCRU was considerably lower in the year before death than before LT. This was particularly pronounced for CF treatments, hospital stays, and medical devices. This was reflected in the costs associated with HCRU, which were less than half in the year before death, compared with the year before LT.

As expected, both studied groups had a clinical phenotype of advanced lung disease [13] and low BMI. In the FCFR, there was one annual record of FEV1, which was the best of the year. Accordingly, we used the measurement from the year prior to the event of interest to minimize missing data in deceased patients and to have only pre-transplant measurements in LT patients. It is reasonable to assume that these results could have been even lower just before death or transplantation. Interestingly, it is noteworthy that we found no significant difference between the two groups of patients in terms of free-access-to-care status, which is associated with low socio-economic status. These findings contrast with those of Quon et al., who found that Medicaid patients were more likely not to be accepted for LT than non-Medicaid patients, regardless of demographic factors, disease severity, contraindications to lung transplantation and before or after use of the lung allocation score [14]. Another US study showed that socio-economic barriers were associated with a lower probability of being placed on the waiting list, regardless of the severity of CF [15]. A major difference is that the score used in the USA is not applied in France. Further work could be necessary to determine whether low economic status may be a risk factor for late referral for transplantation in France.

Our study shows that HCRU and costs were lower in patients who died without transplant compared to those who underwent LT, especially for CF treatments (except CTFRm), consultations and visits, medical devices and transports. Only 13.3 % of patients who died without LT were on waiting list for transplantation. Unfortunately, patients who were contraindicated for LT could not be identified either in the SNDS database or in the FCFR. Bronchial colonization with resistant microorganisms such as mycobacterium *Abscessus* or *Burkholderia cepacia* is an important risk factors to consider [16]. Beyond this, absolute contraindications are very rare in CF, given the young age of patients. In this context, our results suggest a potential lack of referral to transplantation center (as shown in a previous study [9]) and inappropriate care in patients who died without receiving LT. The national HELT program implemented in France since 2007, led to a significant decrease in the proportion of deaths without transplant in those with advanced lung disease [7]. Since then, it has been shown that the causes of death of French pwCF without LT were primarily related to late, or to lack of transplantation referral, rather than to contraindication to transplantation [17]. As suggested by previous publications, it is therefore important for CF centers to used standardized steps to lung transplant referral, for example routine screening for markers of disease severity, in order to avoid insufficient care and lack of referral [18,19].

The mean cost associated with HCRU was €149,374 in the year before primary LT (or €72,025 if the cost of LT hospitalization is excluded. There was a clear reduction in mean overall costs in the first- and second-year following transplantation (€63,919 and €42,813, respectively). These costs were calculated over 12-month periods before and after LT, and not by calendar year. However, it should be noted that, as indicated, costs in the pre-transplant period were much higher than

the average annual costs reported in the overall pwCF cohort, while in the post-transplant period they tended to approach the average annual cost measured in 2017, estimated at €44,585 [12]. It should be noted that the cost of CF was estimated at 0.19 % of the 166.97 billion euros reimbursed by the French health insurance system in 2019, which mainly concerned hospitalizations for other reasons (22 %), cardiovascular diseases and treatments (14 %), psychiatric diseases and treatments (14 %) and cancers (12 %) [20]. In the present study, detailing the distribution of the costs of the different items shows that hospital stays accounted for the largest expenses in the year prior to LT. Interestingly, in the postoperative period, the main expenses remained hospital stays, followed by the usual treatments recommended for CF [13]. In the overall cohort of patients, 72 % of the mean cost was for drugs, including 51 % for CFTR modulators which were newly available in 2017 [12]. In France, the access to highly effective modulator therapy (elexacaftor/tezacaftor/ivacaftor, ETI) for pwCF with advanced lung disease in early 2020 has resulted in a significant decrease in the number of LT, even among severe patients initially referred for transplantation [6,17,21]. The number of LT has dropped 10 times from about 80 to 8/year [22], resulting in an estimated avoided costs of higher than 18 million Euros. Before the availability of ETI, Durieu et al. attributed the rise in the mean annual cost associated with HCRU of pwCF between 2006 and 2017 to the arrival of CFTR modulators (at that time, ivacaftor and lumacaftor-ivacaftor) [12]. However, a study pointed out the important price of ETI, which is currently in the range of 200,000 Euros/patient/year [23]. Therefore, our data indicated that the costs of avoided LT may not completely offset the costs of modulator therapies. Nevertheless, we suggest that the clinical benefit observed for patients clearly outweighs the additional cost.

To our knowledge, this is the first study analyzing the HCRU and the costs associated with advanced lung disease, death and lung transplantation using linked data between CF patient registry and claims data. These analyses are crucial for assessing the overall impact of ETI on care pathways. A previous study has demonstrated the comparability of our study population with French pwCF from the FCFR [12].

Some limitations should however be pointed out. Indeed, the data used in this study cover the period from 2006 to 2017, which is not the most recent period. However, they are still relevant, since LT management remains unchanged despite decreased numbers of transplants observed since the availability of ETI with LT now mainly performed on patients who have no access to ETI. Datasets used in this study do not provide any direct information on causes of death, although it would have been of interest to know whether deaths were related to CF or not. However, we used a proxy for this information, based on the principal diagnoses of the hospitalizations closest to death. We hypothesize that accidental deaths may result in lower HCRU and associated costs than those related to CF. There was also no information on proposals or refusals for inclusion on a lung transplant waiting list while these data would have been of great interest for a better understanding of HCRU and associated costs in the year preceding death among pwCF who died. Of importance, it was not possible to isolate the cost of the LT procedure. Consequently, we used the total cost attributed to the hospital stay during which the LT was performed to estimate its cost. The indicated cost includes LT procedure as well as the immediate after-effects of the operation, such as a stay in intensive care, and all other costs associated with the patient's stay until discharge. As death is also known to be a costly event, it was decided to allocate the cost of transplantation in the pre-transplant period. Finally, we selected patients who were alive the full period (years $N + 1$ and $N + 2$) studied after LT. Individuals who died during the studied year were therefore not studied and we might have miss the HCRU related to the death. In this context, our cost estimate may be slightly underestimated, because it is based on a surviving population. Further studies are needed to explore costs associated with death in pwCF who have undergone a LT.

5. 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 is the first study to examine HCRU prior to death or primary LT in pwCF. The study also collected key data on the total cost of lung transplantation in pwCF. The results showed that HCRU was two times lower in the year before death in non-transplant pwCF than in the year before LT, which may reflect inappropriate care for some pwCF with advance lung disease who died without receiving LT. These data could be of interest to improve the care of patients not eligible for ETI.

Summary of conflict-of-interest statements

M. Belhassen, M. Bérard, and E. Guyot are full-time employees of PELyon. P.R. Burgel declares grants or contracts from GSK and Vertex to his institution; personal consulting fees from AstraZeneca, Chiesi, GSK, Insmed, Vertex, Viatris and Zambon; and support for attending meetings and/or travel from AstraZeneca and Chiesi. I. Durieu declares funding from the Association Vaincre La Mucoviscidose to her institution for the present manuscript and support for attending meetings and/or travel from Mylan. E Van Ganse declares personal consulting fees from PELyon in and outside the scope of this work and support for attending meetings and/or travel from AstraZeneca. M. Viprey declares grants or contracts from EPI-PHARE (ANSM/CNAM) to her institution. C. Dehillotte, L. Lemonnier and Q. Reynaud have nothing to disclose.

Guarantor: EG is the guarantor of the content of the manuscript, including the data and analysis.

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Role of the sponsor

The association Vaincre La Mucoviscidose provided data from the French CF Registry and participated in the interpretation of data and writing of the report.

Other contributions

N/A.

Credit author statement

M.bel., I.D., E.G. and Q.R. contributed substantially to the study design and interpretation of the results and were responsible for producing the initial draft of the paper. M.ber. carried out the statistical analysis. P.R.B., C.D., L.L., E.V.G., and M.V. contributed to the data interpretation and provided written comments, and feedback during manuscript development. All authors contributed to the review and editing and approved to the submitted version of the manuscript.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Isabelle Durieu reports financial support was provided by Vaincre la Mucoviscidose. Isabelle Durieu reports travel reimbursement was provided by Mylan. Eric Van Ganse reports financial support was provided by PELyon. Eric Van Ganse reports a relationship with PELyon that includes: consulting or advisory. Eric Van Ganse reports a relationship with AstraZeneca that includes: travel reimbursement. Marie Viprey reports a relationship with EPI-PHARE that includes: funding grants. Pierre-Régis Burgel reports a relationship with GSK that includes:

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jcf.2024.03.001.

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