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Effect of lung transplantation on the survival of patients with cystic fibrosis: IMaCh contribution to registry data

Trapianto di polmone e sopravvivenza in fibrosi cistica: il contributo di IMaCh all'analisi di dati di registro

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Abstract Using the Interpolated Markov Chain (IMaCh) software, we analyse transitions from different degrees of pulmonary function and mortality with and without transplantation, and compute life expectancy for cystic fibrosis patients, starting from different level of their respiratory health. We use data from the French Cystic Fibrosis Registry. The period of the study is 2008–2013 (7112 patients). Individuals enter the analysis in different years and their health status is regularly monitored. Health refers to the *volume* of air that can forcibly be blown out in first 1 second, after full inspiration (FEV_1). Globally, we found higher mortality for those who have been transplanted but also lower probability of transition towards critical respiratory functions.

Abstract Lo studio analizza i dati del registro francese della fibrosi cistica utilizzando il software IMaCh - Interpolated Markov Chain. Vengono stimate le transizioni di salute e mortalità in presenza/assenza di trapianto di polmone e calcolata la speranza di vita a partire da diversi livelli di funzionalità polmonare. Quest'ultima è misurata attraverso il volume di aria espirata nel corso del primo secondo di una espirazione massima forzata (FEV_1). Lo studio è svolto su 7112 pazienti presenti nel Registro tra il 2008 e il 2013. I pazienti che hanno subito un trapianto di polmone mostrano una mortalità più alta, ma anche una minore probabilità di transizione verso livelli critici di funzionalità polmonare.

Key words: Interpolated Markov Chain (IMaCh), Registry data, Cystic fibrosis

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1 Background

Cystic fibrosis (CF) is a multiorgan genetic disease that affects primarily the lungs and often leads to progressive respiratory insufficiency and premature death. CF is the most common hereditary disease among children in Europe (12,3 per 100.000). Median age of survival with CF has increased in several countries, and nowadays a steadily growing number of patients are adults.

Actually, among CF patients, morbidity and mortality is mostly caused by bronchiectasis, small airways obstruction, and progressive respiratory impairment (Nkam (2017)).

In the last decades, remarkable improvements in quality of life and clinical outcomes in patients with cystic fibrosis have been achieved thanks to innovative therapies. Although, for those patients who failed to respond to standard therapy lung transplantation remains the only treatment option with the potential to ameliorate symptoms, preserve quality of life, and extend life (Thabut et al. (2013)). In particular, bilateral lung transplantation has been shown to be an important therapeutic option for end-stage CF pulmonary disease (Hirche (2014)).

Several statistical models have been developed to identify prognostic factors in CF patients. One of the most significant predictors for survival is the Forced Expiratory Volume in 1 second (FEV1). Patients with low FEV1 may be referred for lung transplantation with the aim of improving their life expectancy and their quality of life (Nkam (2017)). Although, predicting life and health expectancy with or without transplantation is still a major issue.

In France, a national cystic fibrosis Registry (Registre français de la mucoviscidose) was created in 1992, and managed by the Institut National d'Etudes Démographiques (INED) since 1998. In October 2001 the Ministry of Health introduced systematic neonatal screening for cystic fibrosis on a national scale, and universal screening of newborn babies was introduced in 2003.

A number of studies have been carried out on this kind of data using classical statistical model (Nkam (2017)). Using the latest version of Interpolated Markov Chain (IMaCh) approach we analyse transitions from different degrees of pulmonary function and mortality and we compute life expectancy at different ages with and without transplantation.

2 Data: the French Cystic Fibrosis Register

Data are collected via questionnaires sent once a year to the healthcare centres cooperating with the Registry, in mainland France and Réunion Island. Individuals enter the Registry in different years and patient health status is regularly monitored. For each annual survey, each participating center reports on the patients seen at least once in the year. In particular, patients may visit their health center either a few times each year, or only once, or not every year according to their state of health. Globally,

the number of patients treated in the healthcare centres cooperating with the Registry increased from 2,168 in 1994 to 6,408 in 2013. Actually the Registry contains longitudinal data on more than 8,000 patients, which represents approximately 90% of all CF patients in France (Bellis et al. (2015)).

Among other analysis, the Forced Expiratory Volume in 1 second, after full inspiration (FEV_1) is measured in patients aged 6 years old or over. In case of multiple measures during the same year, only the best value of FEV_1 is recorded. This measure is considered good when it is greater than 80% of the predicted value. On the contrary, we consider that patients having a FEV_1 lower than 40% of the predicted value may be referred for lung transplantation, with the aim of improving their life expectancy and their quality of life.

The data examined in this article concern the deaths of patients included in the Registry database from 2008 to 2013. The database provides up to 6 measures for each individual, one for each year. A total of 7,112 patients were registered between 2008 and 2013. As 1,308 patients do not have any measure of the FEV_1 (they are mostly children under the age of 6), only 5,804 patients have been considered for the analysis. During the period, the median age of patients increased, the transplantation rate increased as well and the death rate decreased (see table 1). In 2013 a total of 668 lung transplanted patients was still alive.

Table 1: *Characteristic of the Register Population*

	2008	***2009***	***2010***	***2011***	***2012***	***2013***
Patients (N)	5,419	5,700	5,685	6,077	6,277	6,408
Median age of patients (years)	17.2	18.2	18.7	19.2	19.7	20.3
Max age of patients (years)	75	77	80	87	88	87
Adults >=18 (%)	44.8	46.2	47.9	48.7	49.8	51.0
Mean FEV_1	71.0	71.0	71.8	75.9	77.0	77.7
std FEV_1	26.9	26.7	26.3	25.8	25.5	25.1
Death (N)	56	64	56	67	51	45
Mortality rate (x1000)	10.3	11.2	9.9	11.0	8.1	7.0
Median age at death (years)	29.7	25.2	29.1	26.5	32.3	34.6
Transplantations (N)	61	70	72	96	94	94
Transplantations (x1000)	11.3	12.3	12.7	15.8	15.0	15.0
Age at transplantation (year)	26.2	26.1	27.6	27.3	29.4	27.6

3 Methods

We estimated the age-specific flows of entry into and exit from critical respiratory functions, and the matrix of the transition probabilities between good (coded 1) and

severe (coded 2) FEV_1 and death (coded 3), using version 0.99 (r19) of the software IMaCh (Interpolation of Marcov Chains)[1].

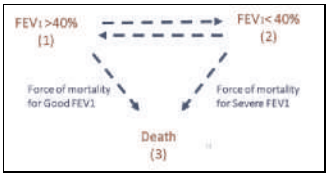

Figure 1: *States and possible transitions among states*

The probability for an individual aged x, observed in the health state i to find him/herself in state j after one year is indicated by p_{ij}^{x} and the transition probabilities are estimated based on a series of 3 × 3 matrices:

$$p_{ij}^{x} = \begin{pmatrix} p_{11}^{x} & p_{12}^{x} & p_{13}^{x} \\ p_{21}^{x} & p_{22}^{x} & p_{23}^{x} \\ 0 & 0 & 1 \end{pmatrix}$$

The first and the second rows represent transitions for individuals who begin the interval respectively in good and severe FEV_1. The third row represents the absorbing state of death. The probabilities of transition are then parameterized using the following multinomial logit model:

$$\ln \frac{p_{ij}^{x}}{p_{ii}^{x}} = \alpha_{ij} + \beta_{ij} x + \gamma_{ij} z$$

Where z is a time varying covariate which could influence the transition from one state to another or to death. This covariate corresponds to the answer to the question: "Was the patient already transplanted (1) at the time of each FEV_1 measure or not (0)?".

A complicating factor was that, if patients have had the opportunity to be transplanted in year t, the $FEV_1(t)$ might be measured before or after transplantation, but this information was not recorded. Moreover, some patients might have no measure at all during the year of transplantation.

[1] IMaCh is a publicly available computer program introduced by Lièvre, Brouard and Heatcote (2003) and mostly used for the estimation of Health Expectancy from longitudinal surveys. It allows to estimate transition probabilities by the method of maximum likelihood, using a discrete time embedded Markov chain approach. Transitions are supposed to occur at any time and death is always an additional competing risk. See Brouard (2019) for theory and applications. Several applications can also be found in literature, see for example Molla and Madans (2008) and Giudici et al. (2013).

To overcome this problem, we set up a decision rule based on the expected increase in the ventilation capacity just after the surgery.

4 Results

Figure 2 shows the transition probabilities from different initial state of respiratory function for non-lung transplanted (z = 0) and lung transplanted (z = 1) patients.

As expected, the probability of dying is always higher among those with severe FEV_1 (p_{23} vs p_{13}) and for transplanted patients (z=1 vs z=0), and the probability of recovering (p_{21}) is decreasing with age.

The transplantation modifies mainly the transition rate towards severe FEV_1 (p_{12}) which is lower for those who have been transplanted.

On the basis of transition probabilities estimates, IMaCh computes life expectancy for patients in state 1 and 2 by age, given that they were in that state initially. Globally, total life expectancy at birth for the analysed population is 54 years and, at any age, patients may expect to live 11 years in critical respiratory health. Life expectancy for lung transplanted patients is almost totally free from severe respiratory distress. At the age of 27 (median age of transplantation) they may expect to live 21 years (Figure 3).

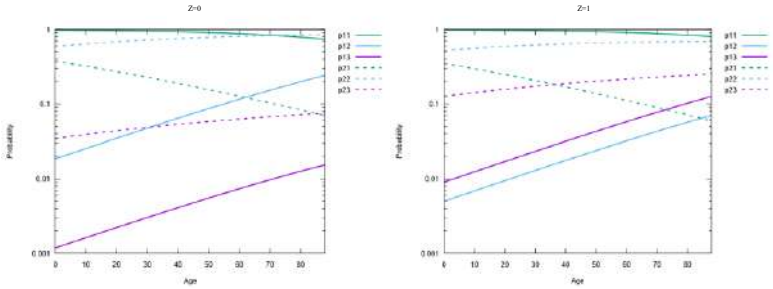

Figure 2: *Conditional probabilities to be observed in state j being in state i, 12 months before (z = 0) and after (z = 1) lung transplantation*

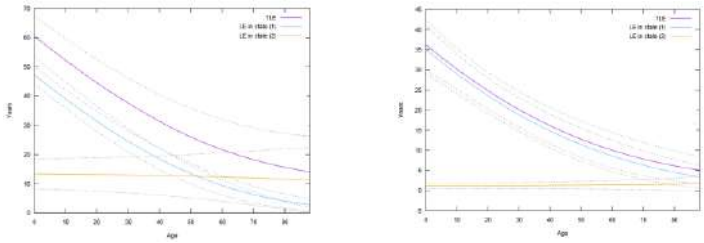

Figure 3: *Life expectancies according to the state of health for non-transplanted (on the left) and transplanted (on the right) patients*

5 Conclusions

The aim of our analysis was to compute life and health expectancy for CF patients with and without lung transplantation, starting from Registry data and using the latest version of IMaCh software.
For a given year, registry data do not necessarily provide the exact date at which respiratory health is measured and neither the date of the surgery in case of transplantation. To overcome this lack of information we set up a decision rule based on the expected increase in the ventilation capacity just after the surgery, and create a time dependent covariate which indicates, for each year, if the patient was already transplanted at the time of the respiratory measure or not.
Globally, we found higher mortality for those who have been transplanted but also lower probability of transition towards critical respiratory functions.
Our approach allows a more complex life expectancy analysis than classical approach on median age at death and contribute to exploit CF registry data. Nonetheless, the study is not without limitation. Indeed, CF prognostic factor are very complex. In particular, female gender is recognized in several studies as having a negative impact on survival. Moreover, in addition to compromised respiratory function, mortality in CF may be also related to liver complications or compromised nutritional status (Buzzetti et al. (2008)). Finally, we did not distinguish single lung and double or heart-lung transplantation.
To conclude, the French Registry of Cystic Fibrosis provides an excellent basis for measuring and monitoring mortality and survival of CF patient in France and our study suggests a useful approach to the registry data analysis.

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