Survival Probability of Adults With Cystic Fibrosis Depending on Their Biological Status

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Primary research

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Abstract

Background: Cystic fibrosis (CF) is one of the most common autosomal recessive disease, and the type of mutation is recognized as one of the most important factors determining the survival rate. Factors contributing to disease exacerbations, and survival rate are poor nutritional status, lung failure, and infection development by *Pseudomonas Aeruginosa*.

The study aimed to evaluate the effect of the severity of mutation, nutritional status, lung function, and *Pseudomonas aeruginosa* infection on survival rate in adult patients with Cystic Fibrosis.

Material and methods: A study of 124 (68 ♂ and 56 ♀) CF patients aged from 18 to 51 years were evaluated for: a) type of mutation in the CFTR gene, b) nutritional status (BMI), c) lung function (FEV1%), and d) *Pseudomonas aeruginosa* (PA) infection. For statistical calculations, Kaplan-Meier analysis of survival and Chi-squared test for multiple samples were used.

Results: Both the type of mutation (Chi^2=12.73, df= 3, p=0.005), lung function (Chi^2 = 15.20, df = 2, p = 0.0005), PA infection (Chi^2= 11.48, df= 3, p= 0.009), and BMI (Chi^2=31.08, df=4, p<0.000) significantly differentiated the probability of survival of CF patients. The shortest life expectancy was observed in patients with a severe type of mutation on both alleles, FEV1% between 40-70%, subjects in whom Pseudomonas culture was extensively drug-resistant or pandrug-resistant, and patients whose BMI was lower than 18.5 kg/m². The period from 30 to 40 years of age was of the most critical in CF adults' lifespan. Furthermore, most exacerbations occurred between 20 and 35 years of age.

Conclusions: All factors included in the study significantly influenced the survival rate of patients with cystic fibrosis. In the face of the growing population of CF patients, the research on factors affecting their life expectancy seems to take on greater importance.

Background

Cystic fibrosis (CF) is one of the most common autosomal recessive disease caused by 2102 mutations of the *CFTR* gene [1]. The type of mutation is recognized as one of the most important factors determining the survival rate. Severe mutations of at least one allele reduce the survival of CF patients and are associated with lung function decrease [2]. It is already known that the main factors contributing to disease exacerbations are lung failure and infection development [3]. One of the most important pathogens in CF adults, causing chronic infection and evolve into antibiotic resistance is Pseudomonas aeruginosa (PA). Previous studies showed that PA, mainly multidrug-resistance culture is associated with morbidity and mortality in CF patients [5]. The decline in lung function is also associated with poor nutritional status [6–9].

Nowadays, as reported by recent studies, the number of CF adults is growing steadily [10]. The majority of previous studies about CF survival concentrated on groups of younger patients. Therefore, there is an urgent necessity to take a view of biological status and survival in an emerging group of older, adult

patients. Moreover, such analysis will show how genetic and biological variables change life expectancy through the life years. A multicenter report on CF patients over forty conducted by Hodson et al. 2008 [11] and showed that significant numbers of patients are now surviving to 40 years or more, however, the answer to the question of why some CF patients live longer than others is still unclear. Hence, the study aimed to evaluate the effect of lung function, Pseudomonas aeruginosa infection, nutritional status, and the severity of mutation type on survival rate in CF adult patients.

Methods

Data about 124 adult CF patients were collected between 2010 and 2018 at the Department of Pulmonology, Allergology, and Respiratory Oncology Poznan University of Medical Science in Poland. All adult CF patients (N = 124) aged 18 to 51 years were included in the study, of which 21 died during the research. The group consisted of 68 women and 56 men. Only adult patients over 18 years with confirmed CF diagnosis and recognized mutation on at least one chromosome have been entered into a database. CF adults, who underwent a lung transplant or were pregnant, smoked, used systemic glucocorticosteroids or had pulmonary exacerbation during four weeks preceding the study were excluded.

Information about the type of mutation, nutritional status, lung function, and PA infection were collected. Data about the type of mutation of the *CFTR* gene were obtained from the archives of medical records of the Department of Pulmonology, Allergology, and Respiratory Oncology of the University of Medical Sciences in Poznan. To systematize a host of known mutations, all patients were divided into four groups based on severity, with consideration given to the widely accepted mutation classification in the *CFTR* gene [12–13] (Table 1): 1- patients with severe types of mutation (I, II, III mutation class) on both alleles (I-III/I-III), 2- heterozygous patients with a severe type of mutation on one allele and mild (I-III/IV-V) or unclassified mutation (other mutations, including those unknown) on another allele (I-III/u), 3- patients with mild types of mutation (IV and V mutation class) on both alleles (IV-V/IV-V), 4- unclassified mutations (u/u) (Table 2).

Table 1
Classification of the CFTR gene mutations (Lubamba et al. 2012; Boeck et al. 2014)

Class	Consequences	List of mutations attributed
I	CFTR is not synthesized because of stop codons or splicing defects	G542X, W1282X, R553X, 3950delT
II	CFTR is synthesized but in an immature and is mostly degraded by the ubiquitin–proteasomal pathway	F508del, N1303K
III	CFTR is synthesized and transported to the plasma membrane, but its activation and regulation by ATPor cAMP are disrupted	G551D, G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, G1349D
IV	CFTR is synthesized and expressed at the plasma membrane, but chloride conductance is reduced	R334W, G314E, R347P, D1152H
V	CFTR synthesis or processing is partly defective	3849 + 10 kb C→T, 3272-26 A→G, 2789 + 5G→A
Unclassified		All other mutations, including those unknown

Table 2
Number and percentage of adult CF people in the category of CFTR mutation, nutritional status, lung function, and *Pseudomonas aeruginosa* infection

Variable	**N**	**N %**
Genotype		
I-III/I-III	40	32.26
I-III/IV-V or I-III/u-u	31	25.00
IV-V/IV-V	24	19.35
u/u	29	23.39
FEV1%		
FEV1%>70	31	25.00
FEV1% 70 – 40	47	37.90
FEV1% < 40	46	37.10
Pseudomonas aeruginosa		
Non-PA	36	29.03
Non-MDR	37	29.84
MDR	24	19.36
XDR/PDR	27	21,77
Nutritional status		
BMI ≥ 25	5	4.03
BMI 18.5–24.9	74	59.68
BMI 17-18.49 (class II malnutrition)	24	19.35
BMI 16-16.99 (class I malnutrition)	9	7.26
BMI < 16 (emaciation)	12	9.68

Lung function was determined by a spirometry test using a diagnostic Jaeger MasterScreen system (Erich Jaeger GmbH; Würzburg, Germany). Data about predicted forced expiratory volume in 1 second (FEV1%) were collected from 124 patients. According to the Cystic Fibrosis Trust [14], all subjects were divided into three subgroups based on FEV1%: 1- patients within the norm (FEV1%>70), 2- with moderate pulmonary impairment (FEV1% 70 – 40), and 3- severe pulmonary impairment (FEV1% < 40) (Table 2).

The microbiological examination carried out by a microbiological laboratory was performed in all patients. Microbiological data allowed us to classify patients into the following groups (Table 2): 1- *Pseudomonas* culture-negative (non-PA,), and 2- *Pseudomonas* culture-positive (PA). Drug susceptibility was measured using the Eucast v.6.0 method. PA positive patients were divided into 2a – patients in whom all antibiotics used to treat infections caused by bacterial colonization were fully effective (non-multidrug resistant/non-MDR), 2b - subjects in whom *Pseudomonas* culture was insensitive (resistant or moderately sensitive) to at least one antibiotic from at least three groups of antibacterial drugs (multidrug-resistant, MDR) and 2c- patients in whom *Pseudomonas* culture was extensively drug-resistant (XDR) or pandrug-resistant (PDR). The above division was made by the definitions from the work of Magiorakos et al. [15].

Nutritional status was determined based on BMI (*Body Mass Index*) calculated by dividing body weight by height squared (kg/m2). To obtain this data anthropometric measurements were taken. The body height was measured without shoes and in underwear, with a GMP anthropometer, with a measurement accuracy of 1 mm. Bodyweight was measured using a medical scale with a measurement accuracy of 100 g. To exclude measurement errors, all measurements were performed by one experienced researcher. Based on the BMI, a group of CF adults was divided into five (Table 2): emaciation (BMI < 16), class II undernutrition (BMI = 16-16.99), class I undernutrition (BMI = 17-18.49), within the norm (BMI = 18.5–24.9), and overweight (BMI ≥ 25).

The study was performed with the approval of the local research ethics committee (resolution No. 51/17). All participants had provided their written informed consent of participation in this study.

The effect of nutritional status, lung function, PA infection, and the severity of mutation type on survival was determined with the Kaplan Meier method. Differences in the survival rate within the study groups were assessed with the Chi-squared test for multiple samples. A p-values < 0.05 defined statistically significant differences. Statistical elaboration was conducted with Statistica v12.0 commercial package (StatSoft; Tulsa, OK).

Results

Survival analysis using the Kaplan-Meier method has shown that the survival of CF patients remains at the level of 100% up to 20 years of age; afterward, it began to decline gradually (Fig. 1). The decline in the probability curve shows that almost 27% of patients will not exceed 30 years of life, and almost 48% of patients will not exceed 40 years of life.

In our study group, all patients who lived to the age of 40 are still alive (N = 7). At the time of writing this article, three subjects were 41 years old, and four were: 42, 43, 49, and 51 years old.

The probability of survival was different depending on the severity of mutation type (Chi^2=12.73, df = 3, p = 0.005). The average life expectancy of patients with I-III/I-III mutations was the lowest. The survival curve (Fig. 2) in this group decreases after the age of 20, and the probability of death before the age of 35

was almost 60%. In this group, there were no people over 40 years of age. Subjects with I-III/IV-V or I-III/u mutations lived longer than in group I-III/I-III. The survival curve in this group began to decline after 23 years, and the probability of death before reaching 32 was over 40%. It is seen that the curve stabilized after 32 years of age. Besides, it should be emphasized that there is one person in this group who has reached the age of 49. Among patients with I-IV/I-IV mutations, the decline in the survival curve was small, and the curve stabilized after 25 years of age. However, it can be seen that 40 years of age is a critical moment because only three patients still live who are over this age. In the group with u/u mutations, there are no dead people, their survival is stable. In this group, two people were over 40 and one was over 50 years old (Fig. 2).

The factor that significantly differentiated patients in terms of life expectancy was also lung function (Chi^2=15.20, df = 2, p = 0.0005). Those CF patients whose FEV1%>70% live the longest, there are no deceased people in this group, but there are people over 40 and 50 years old. The survival curve of CF adults with FEV1% between 40–70% was steeper. The chance that these patients would live to be 40 years old was almost 50%. Approximately 20% will die before the age of 34 and another 28% of patients before reaching 40 years of life. The lowest life expectancy applies to patients with FEV1%<40. The probability of survival in this group began to decrease after reaching the age of 20. The survival curve was very steep up to the critical point of 26 years of age. In this group, the probability of death before the age of 30 was almost 50%, and only about 35% of patients have a chance to live to be 40 years old (Fig. 3).

Kaplan Meier survival analysis showed also that PA significantly influenced the length of the patient's life (Chi^2=11.48, df = 3, p = 0.009). The longest average life expectancy is indicated among non-PA and non-MDR patients (Fig. 4). The survival curve was comparatively stable in both groups. The probability of exceeding 40 years of age in these patients was approximately 80%. The average life expectancy was lower in MDR patients. The probability of survival was decreasing after 22 years of life. The probability of exceeding 30 years of age was less than 60%. The survival of XDR and PDR patients was the most detrimental. The probability of survival was decreasing steadily from 20 to 40 years of age. Further, nutritional status assessed by BMI (Fig. 5) significantly influenced the length of patients' life (Chi^2=31.08, df = 4, p < 0.000). There were no deceased people among overweight patients, their survival curve was stable. The survival curve of the properly nourished patients (BMI 18.5-24.99 kg/m^2) was characterized by a slight decline of up to 30 years of age. The highest decrease occurred between 30 and 40 years of age. In a group of CF adults within the norm, life span exceeds 50 years. In turn, in all groups of undernourished subjects, the survival curve dropped significantly after reaching the age of 20 years. The life expectancy of the respondents in these groups did not exceed 34 years of age. The survival curves of all three subgroups were steep. All patients with BMI < 16.00 died before 30 years. The probability of survival among emaciated adults was significantly lower than those from I and II class of undernutrition.

Discussion

The probability of survival among CF adults is a result of both genetic and environmental factors shaping the course of the disease. In our CF group survival curve started to decrease after twenty and turned to be stable after forty years of age. Most of the deaths occurred in the period between 30–40 years of age. The fundamental factor contributing to average life expectancy was the type of mutation. Since the early nineties of twentieth-century mutation causing CF has been grouped in five classes based on molecular mechanisms of CFTR chloride channel dysfunction [16], which reflects the disease phenotype. Our research indicated the difference in life expectancy between groups of CF patients distinguished based on the severity of the mutation. Patients with a mild mutation on one allele or both alleles lived longer than subjects from the group with severe types of mutation on both alleles. Similar results have been shown by McKone et al. [17], who found that the mortality rate is lower among patients with IV and V mutation class comparing to II class (F508del homozygotes). Currently, there are proceeding molecular studies concerning cell and gene therapy, posing a milestone in CF treatment. New strategies of therapy allow the transfer of the wild-type CFTR gene to airway cells [18]. Apart from genetic treatment, an important role is played by the early determination of the CFTR gene mutation type and the rapid implementation of modern methods of treating patients. Neonatal screening allows for early diagnosis and therefore contributes to better growth and pulmonary outcomes [19]. A patient who already undergoes proper medical care at the first stage of the disease, using knowledge about the effects of a given mutation, has a chance for a much longer life compared to statistics carried out in previous decades. Our study showed, however, that independently of other factors, a strong influence of the genetic factor on the rate of disease progression is still observed. The most critical period in CF adults with a severe type of mutation is between 20 to 30 years of life. Similarly, for I-III/IV-V patients' crucial stage of the disease occurs between 25 to 31 years of life. Accordingly, to this result, the most influential impact of CFTR mutation is observed from 20 to about 31 years on the lives of CF people.

CF evolves differently being influenced by various factors, e.g. biological factors, socio-economic status, health care, or lifestyle [20–22]. Priority in CF treatment is proper lung function and prevention of undernutrition. These factors are the basis for maintaining a stable patient. The results of this and previous studies [22] confirm the impact of lung function and nutritional status on the survival of CF adults. Severe and moderate pulmonary impairment has a major impact on average life expectancy. Critical moments concern exclusively adults with FEV1%<70%. Our results are consistent with other authors [23–24]. The significant impact of lung function as a predictor of mortality has been emphasized by many researchers [25–26]. Henry et al. [27] after performing stepwise regression, showed that lung function described by FEV1% has the main effect on patient's survival. According to Belkin et al. [28], FEV1%<30% increases the risk of death among both CF adult and pediatric patients. Similarly, our analysis showed that FEV1%<40% is critical for patients' mortality, unable them to live into 40 years. Furthermore, in a group of patients with severe pulmonary impairment, the majority of subjects die before 30 years old. Effective pulmonary disease therapy can, therefore, form the basis for preventing exacerbations and contribute to better survival of CF patients. Our probability of survival analysis highlights the problem of serious pulmonary exacerbations occurring between 20 and 40 years old. After exceeding 40 years of life the survival curve is mostly stable. A study of Simmonds [23] comparing CF

adult patients aged ≥ 40 with those, who died before 30 years of age showed also, that patients without respiratory disease and with higher BMI were more likely to live into 40 years of age.

Of crucial importance for the course of lung disease are pathogen infections. Among CF adults, PA is the most frequently occurring pathogen, concerning approximately 80% of the population [29]. Our studies showed that the presence of PA decreases average life expectancy. Previous studies conducted among children confirm the adverse effect of PA on survival, lung function, and weight percentiles [30]. The negative impact of this pathogen remains in adulthood, with a tendency to exacerbate. Courtney et al. [26] showed that PA infection significantly affects CF adults' mortality. Their studies revealed that the majority of patients who died (98%) had a chronic infection of this pathogen. We showed that the most critical point in survival is when PA become fully or partly resistant to antibiotic treatment. Lechtzin et al. [29] obtained similar results, confirming that multiple-antibiotic-resistant PA is associated with FEV1% reduction and pulmonary disease.

Moreover, exacerbations in lung function may severely affect nutritional status in CF people. Our study showed very explicit differences in the probability of survival with nutritional status. A significant number of patients died before turning 30 in a group of patients with a BMI < 18.5. Undernourished CF adults lived no longer than 34 years old. Undernutrition in CF is severely affected by pancreas insufficiency, fat malabsorption, micronutrient deficiencies, and increased energy expenditure [31]. Furthermore, energy losses in the course of lung disease exceed dietary intake. In turn, poor nutritional status may be a subsequent considerable factor in the CF adult lifespan. This is confirmed by previous studies [21–25]. Research by Yen et al. [9] showed that higher body weight in childhood is associated with fewer pulmonary exacerbations and better survival through the age of 18 years. In turn, according to Courtney et al. [26], BMI is not a reliable predictor of mortality but has a significant impact on pulmonary disease. However, studies conducted by Sharma et al. [32] showed that body wasting has a significant impact on the probability of survival in CF adult patients regardless of lung function.

Conclusions

In summary, we can assume that genetic factors pose a major impact on the average life expectancy in CF adults. However, if patients can step into adulthood despite severe CFTR mutation, the influence of other factors increases. The shortest average life expectancy is indicated in people exhibiting moderate and severe lung impairment, antibiotic resistance, PA infection, and consequently poor nutrition. Severe mutation type, FEV < 40%, BMI < 18.5, and XDR or PDR PA infection precluded CF adults from exceeding 40 years of age. These factors are the most alarming in the course of illness, contributing to disease exacerbations. In comparison, among patients with lung function within the norm and BMI above 25, no one has died. CF adults above 40 remained in groups of an unknown or mild type of mutation, with normal or moderate lung function, with no PA infection, or with strains susceptible to antibiotic treatment. Our study allowed us to determine that period from 30 to 40 years of age is of the most critical in CF adults' life span. Furthermore, most exacerbations occur between 20 and 35 years of age. However, the distinguished period is wide and unspecified and there are still not enough studies among adult CF

people. That is why more research should be done to precise the impact of different factors on survival in an emerging group of adult CF people.

List Of Abbreviations

CF – Cystic fibrosis

CFTR - Cystic Fibrosis Transmembrane Conductance Regulator

PA - *Pseudomonas aeruginosa*

FEV1% - predicted forced expiratory volume in one second (percentage of predicted value)

non-PA – *Pseudomonas aeruginosa* culture-negative

non-MDR - non-multidrug resistant

MDR - multidrug-resistant

XDR - extensively drug-resistant

PDR - pandrug-resistant

BMI - Body Mass Index

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Figures

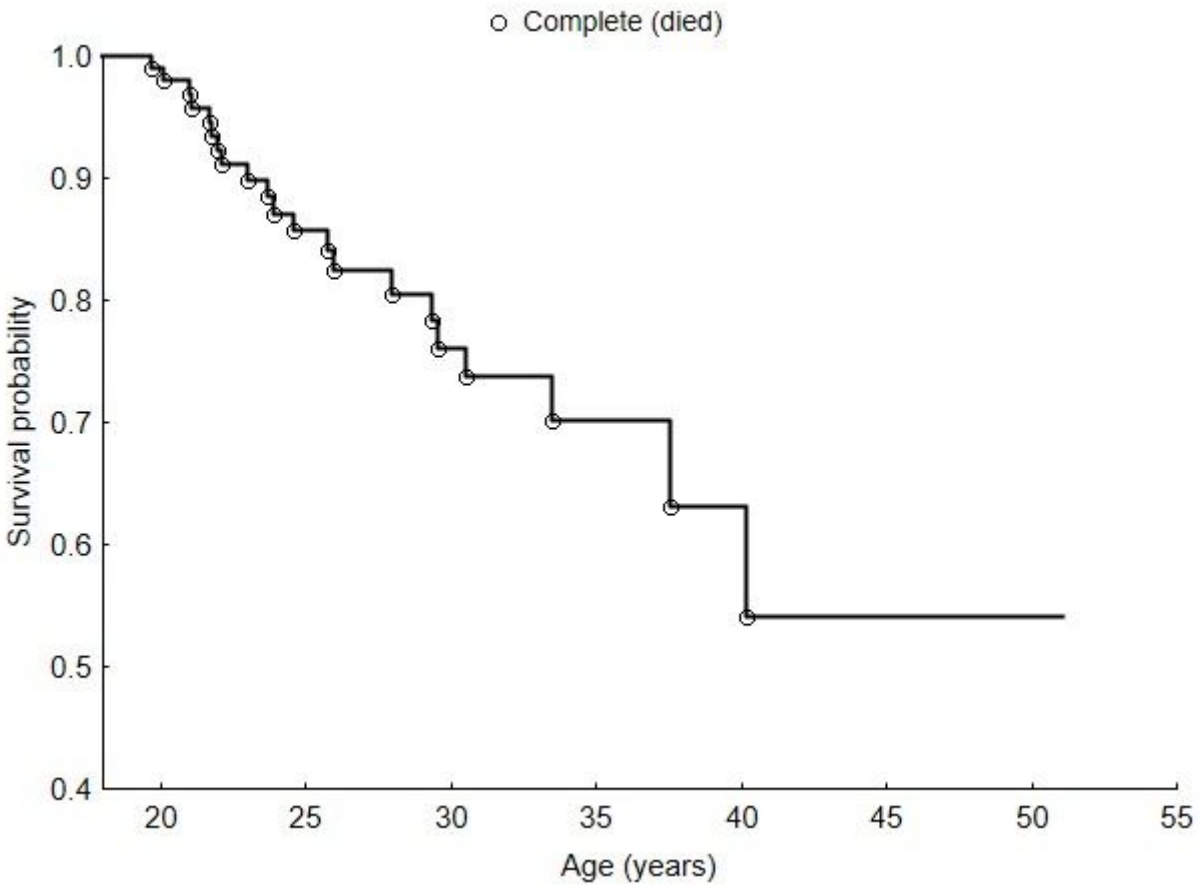

Figure 1

Kaplan-Meier plot for the age of patients with cystic fibrosis

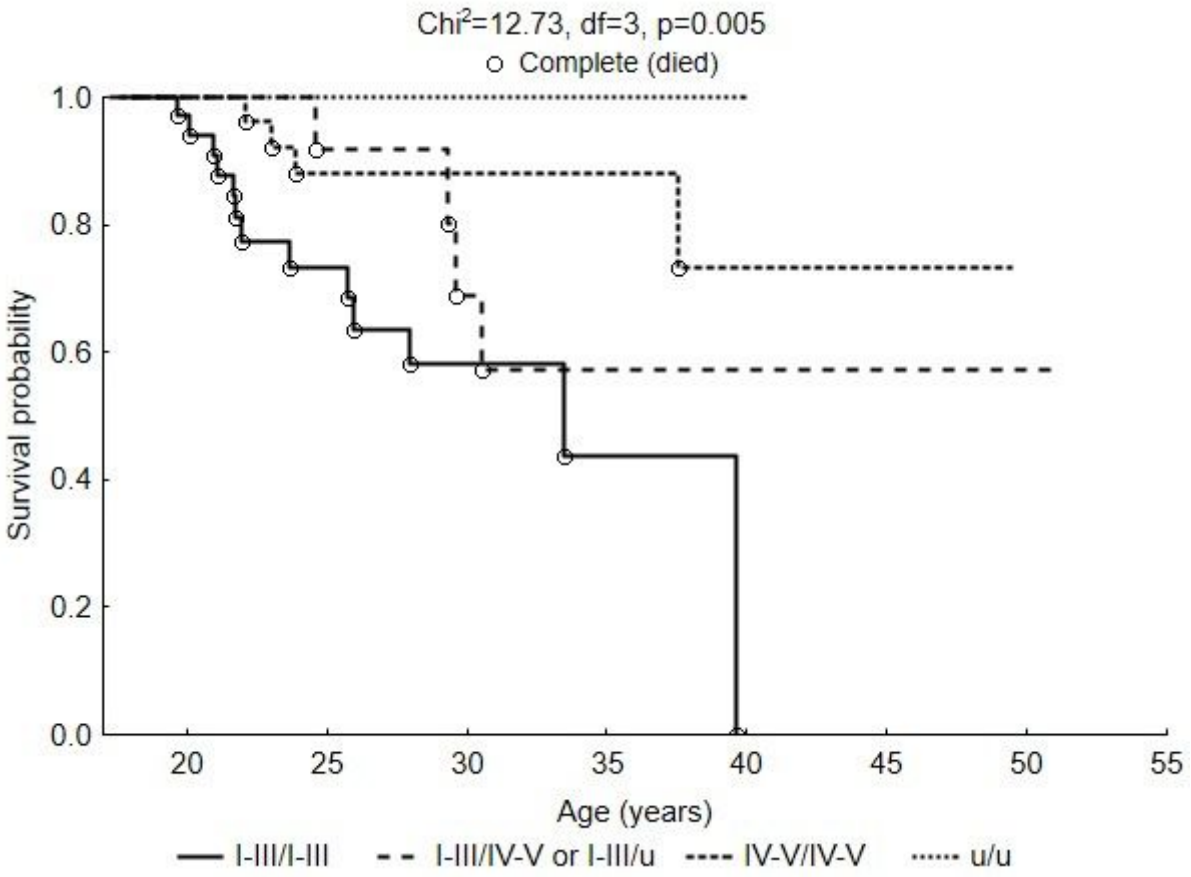

Figure 2

Probability functions depicting the age of patients with cystic fibrosis in categories of mutation

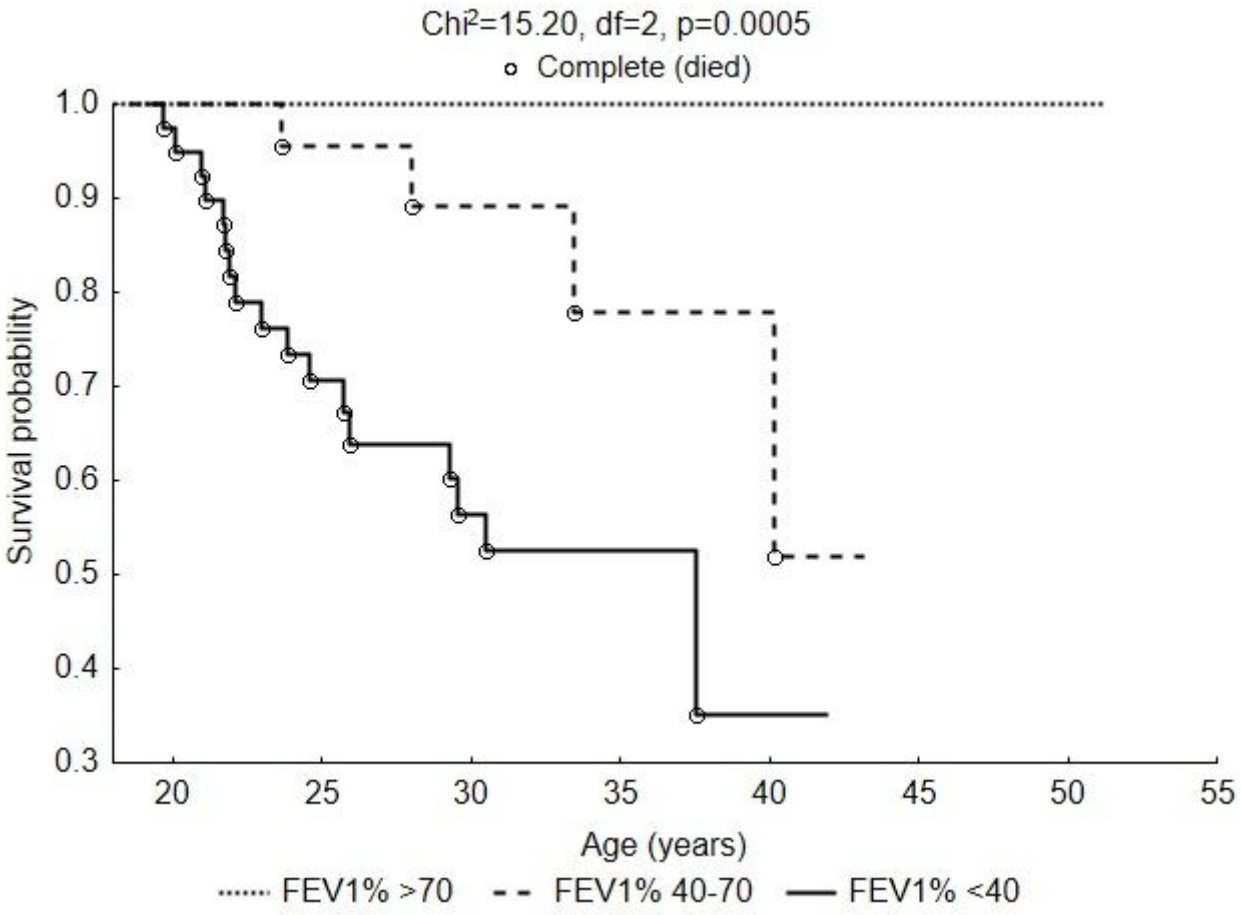

Figure 3

Probability functions depicting the age of patients with cystic fibrosis in categories of lung function (FEV1%)

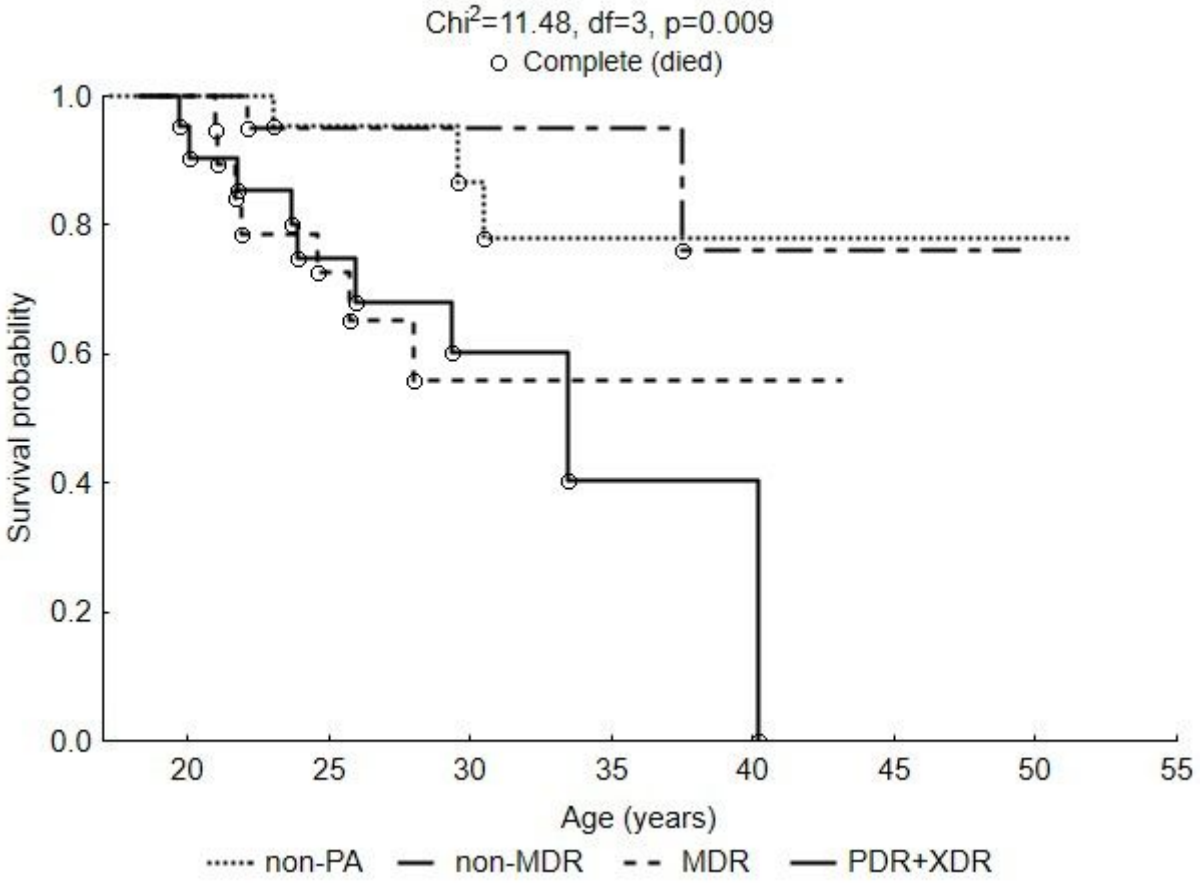

Figure 4

Probability functions depicting the age of patients in categories of Pseudomonas aeruginosa infection and antibiotic resistance (PA 4 categories)

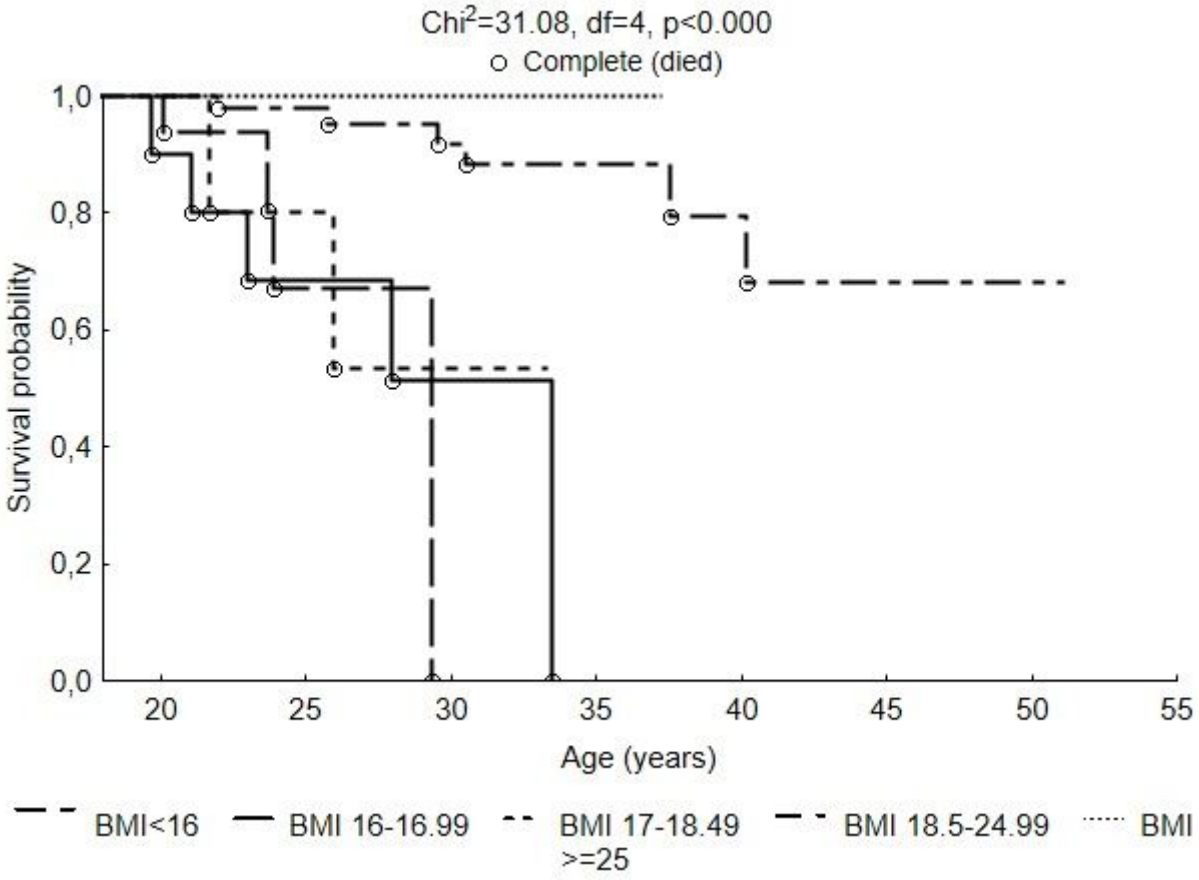

Figure 5

Probability functions depicting the age of patients with cystic fibrosis in categories of nutritional status (BMI)