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CYSTIC FIBROSIS

# Nutritional Status in Childhood as a Prognostic Factor in Patients with Cystic Fibrosis

Moshe Ashkenazi[1,2] · N. Nathan[2] · I. Sarouk[1,2] · B. E. Bar Aluma[1,2] · A. Dagan[1,2] · Y. Bezalel[1,2] · S. Keler[1,2] · D. Vilozni[1,2] · O. Efrati[1,2]

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## Abstract

**Introduction** There is a strong association between cystic fibrosis and malnutrition, mainly because of the higher energy needs combined with lower intake. There is also a well-established correlation between good nutritional status and better lung function. To date, however, there are no studies examining nutritional status in childhood and adult lung function. To respond to this need, this innovative study explored the long-term correlations between nutritional status in childhood and lung function in adulthood for the same patient population.

**Methods** A retrospective patient file study was conducted to identify putative correlations between nutritional status in childhood and lung function in adulthood. The medical archives at Sheba Medical Center were examined for a period of 31 years between 1986 and 2017 for age, gender, mutations, pancreatic sufficiency or insufficiency (PI/PS), sputum cultures, cystic fibrosis related diabetes, body mass index (BMI) at the age of 10, and $FEV_1$ at 20 and 30 in patients who underwent or did not undergo lung transplantation.

**Results** The database was composed of the records of sixty-five patients, thirteen of whom underwent lung transplantation. The correlations ($R^2$) between BMI at age of 10 years and $FEV_1$ at the age of 20 and 30 years were 0.35 and 0.28, respectively, $p < 0.001$. A BMI of lower than −0.75 at the age of 10 emerged as a risk factor for lung transplantation (OR 3.42 $p = 0.023$) and had a negative predictive value of 90%. Kaplan–Meier survival curve showed significant lower lung transplantation rate in the group of BMI *z* score higher than −0.75 at the age of 10 years. Logistic regression found nutritional at the age of 10 years as a dominant risk factor for lung transplantation.

**Conclusions** This study reports a clear, significant and important correlation for the first time between nutritional status in childhood and lung function for the same patients at adulthood. Hence, nutritional status sets a clear trajectory and should be treated aggressively. The findings emphasize the importance of new-born screening and early implementation of nutritional guidelines for cystic fibrosis patients.

**Keywords** Cystic fibrosis · Nutrition · Body mass index · Lung function · Lung transplantation

## Background

Cystic fibrosis (CF) is the most prevalent genetic disorder in the Western world with a prevalence of 0.74 and 0.8 in 10,000 in the European Union and the USA, respectively [1]. The clinical hallmarks of CF are progressive lung disease and malnutrition, but other body systems are affected as well. There is a well-known, strong association between CF and malnutrition which derives partly from a combination of lower energy intake, greater essential fatty acid turnover and higher energy expenditure, which is mainly attributed to ongoing pulmonary infection and inflammation [2, 3]. Malabsorption also furthers malnutrition, primarily from

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✉ Moshe Ashkenazi
docashkenazi@gmail.com

1 Pediatric Pulmonology and National CF Center, Edmond and Lily Safra Children's Hospital, Sheba Medical Center, Tel-Hashomer, Ramat Gan, Israel

2 Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel

pancreatic insufficiency and loss of fat in the stool. Factors such as intestinal inflammation, bacterial overgrowth, low insulin levels, cystic fibrosis related diabetes (CFRD) and impaired bicarbonate secretion contribute as well to energy loss [4].

Corey et al. [5] found a 9-year gap in the median survival rate of CF patients in Toronto and Boston (30 years and 21 years, respectively) which they attributed to the aggressive nutritional program with high fat and high caloric content administered to Canadian patients that resulted in a significantly higher body mass index (BMI). They concluded that nutritional guidance and intervention programs in US CF patients needed to be revised. However, a recent study [6] indicated US CF patients (below the age of 40) exhibited better lung function and higher BMIs than Canadian patients, which the authors attributed to improved nutritional interventions in US CF patients as well as other factors such as earlier implementation of new-born screening program in the USA. A few other studies have found strong associations between nutritional status at the age of 2 or 3 and lung function at the age of 6 among CF patients [7–9] and between nutritional status at the age of 6 and lung function at the age of 8 [10]. A worsening of nutritional status was clearly associated with decreases in lung function in these patients [10]. The current ESPEN-ESPGHAN-ECFS guidelines emphasize the importance of nutritional support and recommend the clinicians to consider the use of enteral tube when oral feeding failed to achieve acceptable rates of nutritional status and growth [11].

Yen et al. explored the relationships between nutritional status at younger ages and clinical outcomes at the age of 18 [12]. They indicated that CFRD, acute exacerbations, hospital admission days, and survival at age 18 were highly correlated with nutritional status at age 4. However, the findings are inconsistent as regards nutrition and lung function; specifically, a comparison of US and Australian CF cohorts revealed better nutritional outcomes among Australians, but no differences in lung function [13].

Given these conflicting results, the aim of the current study was to explore the relationship between nutritional status in late childhood (at the age of 10) with lung function in adulthood (at the ages of 20 and 30) to better understand whether nutritional status could be used as a prognostic factor for lung transplantation.

## Methods

A retrospective case study was conducted on data collected from the medical archives of the National CF Center at the Edmond and Lily Safra Children's Hospital, Sheba Medical Center, Israel, from 1986 to 2017. The study was approved by local ethics committee. No informed consent was needed. Inclusion criteria were patients with a pathological sweat test and genetically confirmed CF (2 disease-causing mutations) who were treated in at Sheba before the age of 10 for a minimum of10 years. Patients who were older than 10 when they were first associated with the center or were lost to follow-up before age of 20 were excluded. The parameters obtained were age, gender, mutations, pancreatic sufficiency or insufficiency (PI/PS), sputum cultures, cystic fibrosis related diabetes (CFRD), BMI at the age of 10 (value and $Z$ score according to the Centers for Disease Control and Prevention charts), $FEV_1$ at the ages of 20 and 30 (% predicted).

To evaluate the relationships between BMI and lung function, a linear regression was conducted between these parameters for the different age groups. An unpaired $t$ test was performed to compare the BMI of transplanted versus non-transplanted patients as well as the BMI for the CFRD and non-CFRD patients. Significance was set at $p<0.05$. A stepwise Cox regression was performed with lung transplantation (yes or no) and age of lung transplantation as dependent variables. The independent variables were gender, presence of severe mutation as class I mutation (most of the W1282X—the Ashkenazi Jewish mutation) or class II mutation (F508del or N1303K), CFRD, chronic carriers of Pseudomonas aeruginosa in the sputum and BMI $z$ score at the age of 10 years. Confidence interval was 95%. We divided the patients to two groups according to their BMI $z$ score at the age of 10 years, above and under $-0.75$ $z$ score; then, a Kaplan–Meier curve was created to compare the prognosis related to lung transplantation or survival.

## Results

We collected data from 65 patients (thirty males), with an average age of $29.98 \pm 7.09$ years. Of these, 50 patients (77%) had two severe mutations (nine patients were homozygous for F508del), 15 patients had one severe and one mild mutation. Forty-three patients (66%) were chronic carriers of Pseudomonas aeruginosa. Most of the patients were already pancreatic insufficient at the age of 10 (59/65, 90.7%). CFRD was recorded for thirty patients (46%) by the end of the research follow-up. None of the patients died before lung transplantation, no follow-up was done after the lung transplantation.

In the patient group, 13 (20%) underwent lung transplantation at an average age of $29.1 \pm 6.1$ years. Figures 1 and 2 depict the linear regression between the BMI $Z$ scores at the age of 10 and $FEV_1$%pred. at the ages of 20 and 30, respectively. Average BMI in percentiles ($\pm$SD) was 31.58 ($\pm$23.56) and 37.78 ($\pm$27.94) at the ages of 20 years and 30 years, respectively.

There was a positive correlation between BMI at the age of 10 and $FEV_1$ at the age of 20 and 30 (Figs. 1, 2). The $R^2$

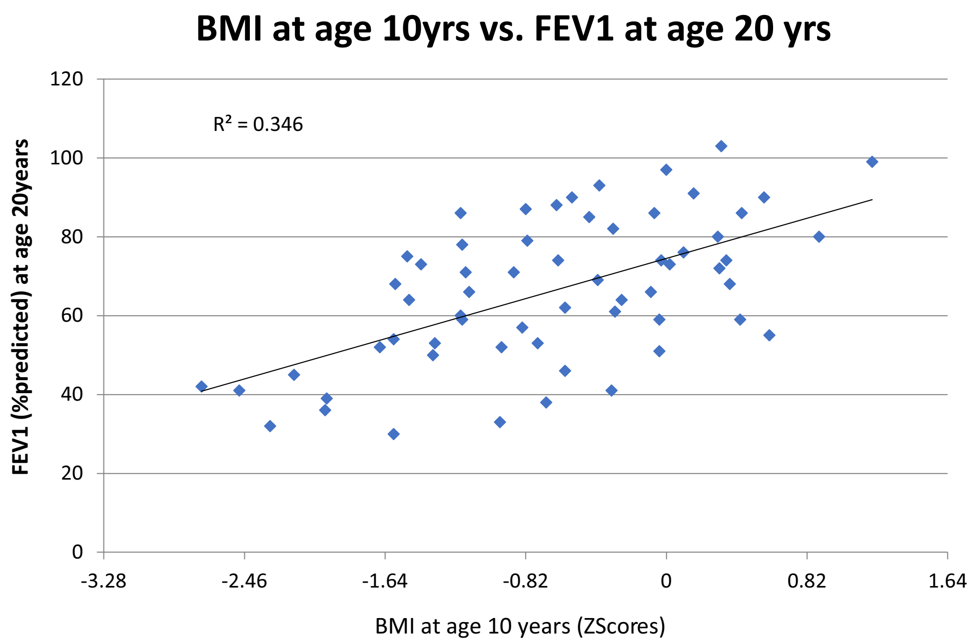


**Fig. 1** Correlation between BMI at age 10 and $FEV_1$%pred. at age 20; $R^2 = 0.346$

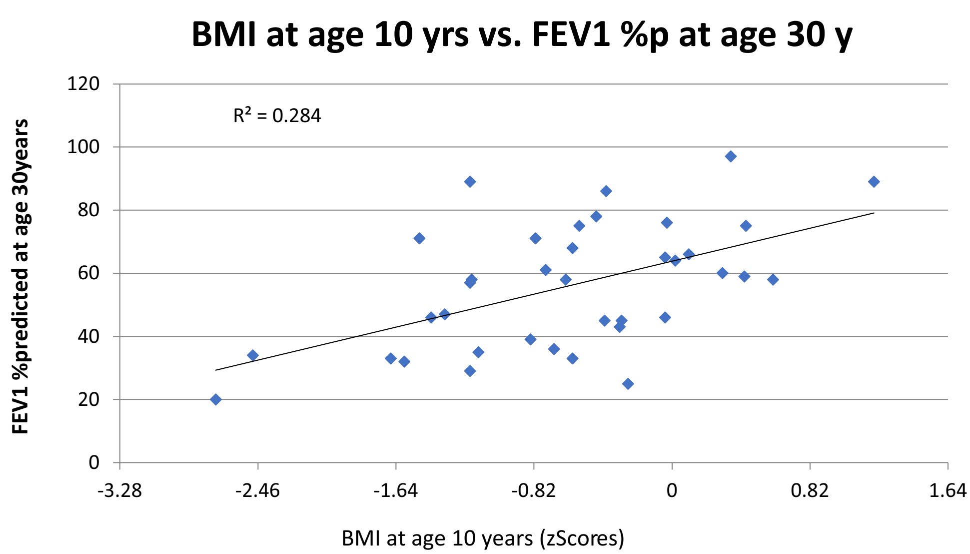


**Fig. 2** Correlation between BMI at age 10 and $FEV_1$%pred. at age 30 years; $R^2 = 0.284$

values were 0.346 and 0.284, respectively, and both curves were statistically significant ($p < 0.001$). An additional linear regression test was performed to compare the patient groups as a function of mutations (severe–severe and severe–mild) and showed that the $R^2$ values were similar.

An unpaired *t* test was performed to compare BMI at age 10 of the future lung transplanted patients vs. the non-transplanted patients. The mean BMI *Z* score for the first group was $-1.03 \pm 0.68$, and $-0.37 \pm 0.83$ for the second group with a p value of 0.0107 (Fig. 3). An unpaired t-test comparing BMI at the age of 10 between patients who would eventually develop CFRD and those who did not yielded a mean BMI *Z* score of $-0.49 \pm 0.76$ and $-0.26 \pm 0.86$, respectively (NS).

Of the future lung transplanted group, 9 patients (69%) had a BMI *Z* score of less than $-0.75$, whereas in the non-transplanted group, 16 patients (31%) had a BMI *Z* score of less than $-0.75$. Thus, the calculated sensitivity and specificity were 69% for both, whereas the negative predictive value (NPV) and positive predictive value (PPV) were 90% and 36%, respectively. The stepwise Cox regression (Fig. 4a) showed significant result for low BMI *z* score as a risk factor for future lung transplant with borderline results for presence of Pseudomonas aeruginosa in the sputum and the severe class II mutations represented by F508del (significance of 0.023, Hazard 0.438 with CI 95% for Hazard 0.215–0.890) showed an Area Under the Curve (AUC) of 0.796 (Fig. 4). Calculated from the ROC curve, a BMI value below a $-0.75$

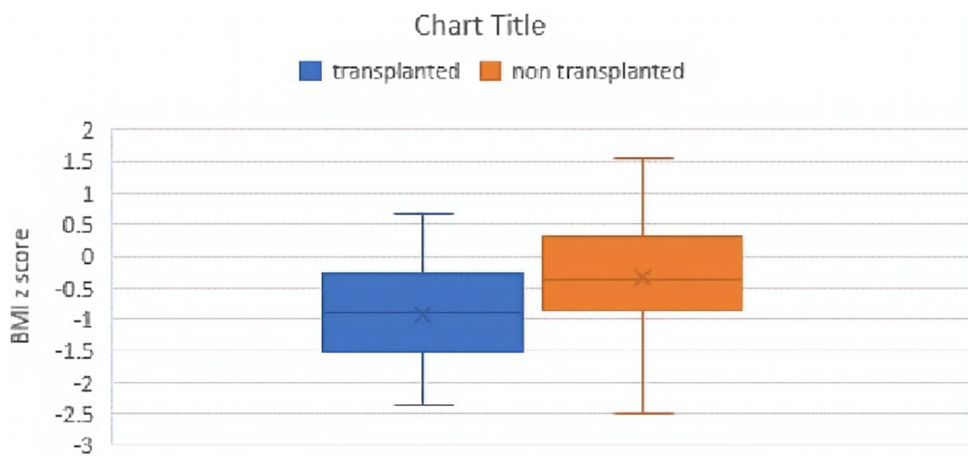


**Fig. 3** BMI *Z* scores at age 10 years for future transplanted patients versus non-transplanted patients at the same age (can be read from text or from chart)

**Variables not in the Equation**[a]

| | Score | df | Sig. |
|---|---|---|---|
| MALE | 1.543 | 1 | 0.214 |
| F508del | 3.277 | 1 | 0.070 |
| w1282x | 0.064 | 1 | 0.801 |
| CFRD | 0.414 | 1 | 0.520 |
| p.aeruginosa | 3.206 | 1 | 0.073 |
| BMI10z_score | 5.379 | 1 | 0.020 |

a. Residual Chi Square = 11.301 with 6 df Sig. = .080

**Fig. 4** Stepwise Cox regression analysis shows significant result for BMI *z* score at the age of 10 years as a risk factor for lung transplant, whereas class II mutations (represented by F508del) and chronic carriers of Pseudomonas aeruginosa had borderline results

*Z* score at the age of 10 had a relative risk ratio for future lung transplantation within 30 years of 3.42 (CI 1.1799 to 9.9128, $p = 0.023$).

The Kaplan–Meier curve (Fig. 5) shows significantly (Mantle-Cox 0.024) lower survival or lung transplant rate for the group with BMI *z* score at the age of 10 years lower than − 0.75 *z* score.

## Discussion

We found a statistically significant positive correlation between BMI at the age of 10 and $FEV_1$ at the age of 20 and 30, indicating that the higher the BMI, the higher the lung function 10 or 20 years later. To the best of our knowledge, this is the first study to explore the long-term correlations between nutritional status at the age of 10 with lung function and severity of lung disease in adulthood over a period of 20-year follow-up for the same patient cohort.

The findings indicated $R^2$ values of 0.28–0.35 (Figs. 1, 2) which may be considered high, given the other multiple factors that determine lung function in CF patients such as colonization with pathogenic bacteria, mutations, CFRD, age of diagnosis, and cystic fibrosis liver disease. The multivariate analysis (Fig. 4) positioned BMI as a dominant parameter determining risk of future lung transplantation. Clearly, the results demonstrate that nutritional status is probably one of the most influential. Nevertheless, we assume that the lower value for $R^2$ at the age of 30 is biased toward lower values because the more severe patients with lower BMI and reduced lung function were transplanted already before the age of 30 and were not included in the 30-year patient group. Efrati et al. [14] found an improvement in nutritional status and BMI with concomitant improvement in pulmonary disease after PEG installation, which may suggest that BMI is not only a marker of disease severity but rather a parameter that is interrelated with pulmonary disease in CF.

Here, the BMI *Z* scores differed significantly at the age of 10 between the group of future transplanted CF patients and the non-transplanted group. Specifically, a BMI *Z* score below − 0.75 at the age of 10 predicted more rapid lung deterioration and thus should be seen as a risk factor for lung transplantation in the upcoming 30 years with a calculated relative risk of 3.42, a finding that is strengthened by the Kaplan–Meier survival curve that shows significant difference between the two groups. Although the relationship between nutritional status and clinical outcomes is known and has been described [13], and although low BMI is known to be a risk factor for severe pulmonary disease, this is the first study to indicate that low BMI in childhood can

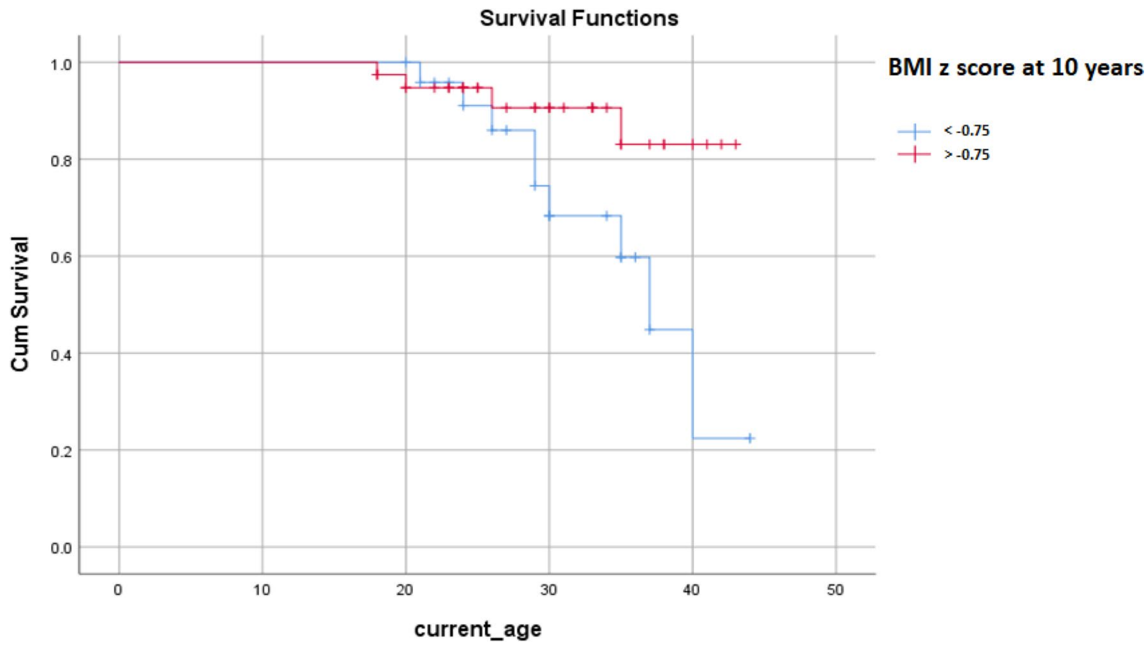


**Fig. 5** Kaplan–Meier curve for lung transplantation and survival shows significant higher rate for the patients with BMI lower than $-0.75$ *z* score at the age of 10 years

be used as a marker and a predicting factor for lung transplantation at older ages. Our study marks the importance of nutritional status among other poor prognostic factors in CF. In addition, we demonstrated that a BMI *z* score of less than $-0.75$ at the age of 10 is associated with higher lung transplantation rate. This finding should encourage physicians in CF centers to identify malnourished and anorectic patients and engage in aggressive nutritional support, e.g., PEG installation.

Nutritional status is critical not only as a risk factor for lung transplantation but also as a parameter that improves patients' survival after transplantation [15]. Data have indicated that poor nutritional status, low BMI and lean body mass depletion are important risk factors for morbidity and mortality especially in patients with end stage lung disease. Although we did not evaluate the role of noninvasive positive pressure ventilation devices, previous work by our group showed that the use of bilevel positive pressure ventilation (BiPAP) increased patients' BMI through by relieving the effort associated with breathing [15]. These findings complete our overall descriptive conclusion that BMI plays a role in early disease, in end stage lung disease and post-transplant.

Unfortunately, there is no CF newborn screening in Israel. The only available testing is a genetic screening panel of 14 mutations that is performed prior to conception. The panel has a sensitivity of 50–95%, depending on the population (Ashkenazi Jews, non-Ashkenazi Jews and Israeli Arabs). Hence, the implementation of new-born screening for CF in Israel should enable physicians to intervene earlier in terms of nutritional support as well, and as reported in the USA [6], improve the future clinical outcomes of CF patients in Israel.

There are number of limitations to this study which deserve attention. The primary one being that it was performed on a concise group of patients with a long-term follow-up period in which results were clear cut, thus emphasizing the importance of the findings. In addition, there are confounds that could have biased the results. For instance, given that low BMI is associated with poorer lung function, which is attributed to the fact that pancreatic insufficiency is associated with severe CF mutations and results in severer pulmonary disease.

Thus overall, low BMI at the age of 10 predicts lower lung function in adulthood and could be seen as a risk factor for lung transplantation within 30 years and probably the most influential among all parameters that were checked. The BMI *Z* score emerges as a good screening tool and severity marker of the disease and is a very early red flag for future lung transplantation. Nutritional status is a mandatory parameter for the follow-up and early treatment of CF patients. Aggressive intervention appears to be a mandatory consideration for the future health of CF children with a low BMI. Now, when the association between childhood's nutritional status and lung function in adulthood is shown, a prospective study exploring nutritional intervention should be conducted.

## Compliance with Ethical Standards

**Conflict of interest** The authors declare no conflict of interest.

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