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Original article

Stunting is an independent predictor of mortality in patients with cystic fibrosis

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SUMMARY

Background & aims: Some studies have shown a direct relationship between nutritional status and survival in Cystic Fibrosis (CF) patients. Body wasting, defined as a percentage of the ideal body weight for age, has been shown to be an independent predictor of mortality in CF. With respect to height only two studies were performed and these studies suggested that stunting is an important determinant of survival but both did not adjust statistical analysis for confounding variables.
We aimed at determining the association between stunting and risk of mortality in CF patients.
Methods: 393 CF patients older than 6 years of age, 95 deceased, as cases, and 298 live, as controls, were enrolled in a nested case-control study. Stunting was defined by a height percentile < 5th. We performed a multivariate statistical analysis including height percentile and the following possible confounding variables: age, gender, Body Mass Index (BMI), Forced Expiratory Volume in 1 s (FEV_1), genotype, pancreatic status, CF-related diabetes, colonization with *Pseudomonas aeruginosa* and/or *Burkholderia cepacia*.
Results: In the adjusted analyses stunting (OR 2.22 [IC 95%1.10–4.46]), wasting (OR 5.27 [IC 95% 2.66–10.41]), and FEV_1 < 40% of predicted (OR 10.60 [IC 95% 5.43–20.67]) resulted the covariates that significantly predict the risk of mortality.
Conclusions: Our study shows, for the first time, that stunting is a significant and independent risk factor for mortality in CF patients, and warrants an intervention of nutritional rehabilitation. Considering that nutritional interventions in stunted patients should be prolonged, are invasive and expensive, and might affect self-esteem and body image, their efficacy should be fully assessed by Randomised Controlled Trials.

1. Introduction

Cystic Fibrosis (CF) is an autosomal recessive disorder, caused by mutations in a single gene on the long arm of chromosome 7 that encodes the CF transmembrane conductance regulator (CFTR).[1] Despite impressive advances in understanding the molecular basis and pathophysiology of this disorder, it remains the most common life-shortening genetic disorder in the white population. Today, the estimated median predicted survival age is 36.5 years.[2] Nutrition is a critical component of the management of CF, and nutritional status is directly associated with both pulmonary status and survival.[3] Because of poor clinical outcomes in cystic fibrosis are often associated with undernutrition, normal growth and development should be achieved in cystic fibrosis, and nutritional counseling is a paramount at all ages. Prevention and early detection of growth failure is the key to successful nutritional intervention. The advance in nutritional management is certainly one factor that has contributed to the improved survival in recent decades.[4] Corey et al. for the first time, highlighted the importance of achieving normal nutritional status in CF.[5] With respect to wasting, Sharma et al. demonstrated that it is a significant and independent predictor of survival in CF patients.[6] With respect to height, stunting is common in CF[7,8] but only two studies performed

Abbreviations: CF, Cystic Fibrosis; CFTR, CF transmembrane conductance regulator.

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did not demonstrate it as an independent predictor of mortality because they did not take into account the confounding variables.[5,9]

The aim of our study was to determine whether stunting is an independent mortality risk factor in a nested case–control study within a CF population cohort.

2. Subjects and methods

Sicily is the largest island in the Mediterranean, with more than 5 million inhabitants (95% Caucasian), and about 50,000 newborns per year. The Italian National Health System supports and accredits at least one CF center per region and some satellite centers in some large regions, such as Sicily. These centers offer specialized services to patients with CF, which are multidisciplinary and provide a team approach to care. Services include pulmonary medicine, nutrition, social work, respiratory therapy as well as other disciplines. Four hundred and seventy-one patients were followed up at the Regional Center in Palermo and at the Satellite Center in Messina, up to 31 December 2007. Inclusion criteria were availability of clinical and anthropometric data up to December 2007. Our retrospective nested case–control study comprises a cohort of 393 CF patients older than 6 years of age, 193 pediatric (younger than 18 years) and 200 adult patients. Ninety-five patients who died, 47 pediatric and 48 adult, represent the cases. Two hundred and ninety-eight alive patients, 146 younger and 152 older than 18 years, represent the controls.

According to International guidelines, short stature (stunting) was defined by a height percentile <5th. Body wasting was defined by a body mass index (BMI) <10th percentile in pediatric patients, and <18.5 kg/m^2 in adult patients.[10–12] We classified patients taking the lowest height and weight values in our database. Weight and height in the study groups were measured by nurses and dieticians by using precision balances and stadiometers, and CDC growth reference curves were used to obtain centiles from the raw measurements. Patients were classified according to FEV_1 (forced expiratory volume in 1 s, expressed as percent of predicted values for height and gender) as having mild (>60%), moderate (40%–60%) or severe (<40%) pulmonary disease.[13] We considered the best FEV_1 value during the last year of observation, both in alive and in deceased patients. Genotype was classified in severe (presence of two mutations of class I, II, III), mild (presence of at least one CFTR mutation of class IV or V), and unknown (two unknown or not available mutations).[14,15] Regarding to microbiology we considered colonizations with *Pseudomonas aeruginosa* (at least 3 consecutive positive cultures over a period of at least 6 months) and/or with *Burkholderia cepacia* (at least one positive culture). For all the included patients, prognostic variables recorded every 12 ± 2 months during follow-up in a database were collected. Since no individual patient identification was involved and no study-driven clinical intervention was performed, a simplified Institutional Review Board approval was obtained and no patient consent was considered necessary.

3. Statistics

Statistical analyses were performed with Minitab statistical package. We assessed factors significantly correlated with the probability of mortality using a stepwise logistic regression analysis with mortality at endpoint as dependent variable. We did not use univariable screening as criterion for inclusion of covariates in the stepwise logistic regression because it has been demonstrated that it actually reduces the ability to detect significant covariates and then it was suggested avoiding this step entirely.[16] We included in the logistic regression analysis all covariates available in our data set that could be related to survival in CF patients according to literature data[17,18]: age, gender, BMI, FEV_1, genotype, pancreatic status, CF-related diabetes, infection with *P. aeruginosa* and/or *B. cepacia*. In the logistic regression analysis, the maximum likelihood estimate model was used to select the covariates that independently predicted mortality. Hosmer–Lemeshow goodness-of-fit test[19] was used to validate the statistical model. The predictive accuracy of the model was evaluated by calculation of the area under the receiver operating characteristic (ROC) curve. Data were presented as Odds ratios (ORs) with 95% Confidence Intervals (CIs). A P value < 0.05 was considered as significant.

4. Results

Demographic data and nutritional status of the patients included in the study are shown in Table 1. The prevalence of stunting considering all patients included in the study is 24.4%. It is similar in males and females (24.5% and 24.3%, respectively). The prevalence of stunting results significantly higher in pediatric alive patients than in adult ($p = 0.02$), while this difference is not statistically significant in the deceased group. The prevalence of wasting is 35.3%; it is not significantly higher in females than in males (38.3% and 32.3%, respectively). The prevalence of wasting between pediatric and adult patients is not significantly different neither in alive nor in deceased patients.

In the multivariate analysis, stunting, body wasting, and FEV_1 resulted the covariates that significantly predict the risk of mortality (Table 2). In particular, stunted patients have a twofold risk of mortality, wasted patients have a fivefold risk of mortality. Forced expiratory volume in 1 s <40% predicts mortality with a risk

Table 1
Demographic data of the enrolled patients.

	Alive	Deceased
N° subjects	298	95
Age		
Pediatric (%)	49	49.5
Adult (%)	51	51.5
Gender (%)		
Males	52.3	44.2
Nutritional status		
Stunting[a,j](%)	15.8	51.6
Wasting[b,k](%)	21.4	78.9
Height for age SD[c] score and ranges	−0.81 ± 1.08	−1.83 ± 1.18
BMI SD score and ranges	−0.33 ± 5.20	−2.37 ± 0.94
FEV_1 < 40% (%)	15.1	77.5
Genotype (%)		
Severe[d]	51.7	50.5
Mild[e]	11.7	4.2
Unknown[f]	36.6	45.3
Pancreatic insufficiency (%)	81.9	93.7
CF-related diabetes (%)	13.4	23.1
Microbiology (%)		
Pseudomonas a.[g]	34.2	23.1
B. cepacia[h]	10.0	17.9
Pseudomonas a. plus *B. cepacia*[i]	12.4	14.7

[a] Height percentile <5th.
[b] BMI percentile <10th.
[c] SD = Standard deviation.
[d] Presence of two mutations of class I, II, III.
[e] Presence of at least one CFTR mutation of class IV or V.
[f] Two unknown or not available mutations.
[g] Infection with *Pseudomonas aeruginosa*.
[h] Infection with *Burkholderia cepacia*.
[i] Infection with both *Pseudomonas aeruginosa* and *Burkholderia cepacia*.
[j] Stunting prevalence higher in pediatric alive patients than in adult ($p = 0.02$); not significant different in the deceased groups.
[k] Wasting prevalence not significant different: in pediatric versus adult patients; in alive versus deceased patients.