PREDICTORS OF MORTALITY IN CHILDREN WITH CYSTIC FIBROSIS

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Abstract

Background: There is a lack of studies on outcomes in cystic fibrosis (CF) in children from developing countries like India. Identifying risk factors for mortality may help identify the high-risk group and plan policy management of such patients. Objective: To determine the factors associated with outcomes among Indian children with CF. Design: Retrospective analysis of data collected from January 2010 to Dec 2020. Setting: Tertiary care hospital in Northern India. Participants: Children diagnosed with CF during the study period. Methods: We extracted data related to demography, clinical features, laboratory data and outcome from children's medical records with CF. Bivariate and multivariate analysis was performed to identify variables associated with mortality. Results: We enrolled 178 children, and there were 32 (18.0%) deaths. Significant factors associated with mortality included history of neonatal complications; hazard ratio (HR): 8.5 (95% CI, 3.0 - 23.9, $p < 0.001$), low Z-scores for body mass index (BMI) at the time of diagnosis; HR: 7.1 (95% CI 2.3 - 22.0, $p < 0.001$), FEV1/FVC at the time of diagnosis; HR: 5.1 (95% CI, 1.65 - 15.4, p-value < 0.004), and FEV1 25-75; HR: 3.6 (95% CI, 1.1- 11.8, p-value $= 0.03$). Conclusions: Factors associated with increased risk of mortality included presence of neonatal complications, low BMI and lower pulmonary function test results. Low BMI and low PFT indices are modifiable and possibly can be improved by early diagnosis. A new-born screening test may help in early diagnosis and identification of the neonatal problem of CF.

Predictors of mortality in children with cystic fibrosis

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Introduction

Cystic fibrosis (CF) is an autosomal recessive monogenic disorder with a prevalence of around 3000 per 10,000 in the western world (1). CF, the commonest inherited life-limiting illness, was initially considered to be affecting the Caucasians only. With increasing awareness, many cases are being recognized in India; however, its exact prevalence is unknown. This condition is not recognised at many peripheral centres due to a lack of awareness and inaccessibility to diagnostic facilities. The children with CF in India are usually diagnosed late. Indian patients differ from their counterparts from the developed world in being frequently malnourished, having clinical evidence of fat-soluble vitamin deficiencies and more chances of being colonized with Pseudomonas (2,3). The mutation profile is also different, with a lower prevalence of ΔF508 (4). Management of CF in India is complex due to inadequately trained manpower, lack of financial support, limited availability and high cost of pharmacologic agents. The determinants of early death in Indian children with CF from limited small studies may include severe malnutrition, colonization with Pseudomonas at the time of diagnosis, more than four episodes of lower respiratory infection per year and age of onset of symptoms before two months of age (5,6).

Data are scarce regarding determinants of mortality in children with cystic fibrosis from developing countries like India. Identifying risk factors for mortality may help identify the high-risk group and plan management of such patients, specifically in a limited resource setting. We determined the factors associated with outcomes among Indian children with cystic fibrosis.

Methods

This was a retrospective study in which we collected the data of children diagnosed with cystic fibrosis from January 2010 to December 2020 at All India Institute of Medical Sciences, New Delhi. An institutional ethics committee approved this study. We included all patients with cystic fibrosis age less than 18 years under follow-up care of Pediatric chest clinic. We diagnosed CF by clinical phenotype and two sweat chloride values of >60 mEq/L or identifying two diseases causing mutations. Patients with incomplete data, precisely the diagnostic test results and whose outcome was not known, were excluded.

Data on demographic variables, clinical features, family history, type of mutations, compliance to therapy, age of airway colonisation with bacteria, lung function parameters, number of hospitalisations and duration of hospitalisation were extracted on a pre-designed proforma. Shwachman and Kulezycky (SK) severity scores were used to calculate and grade the severity of illness (7).

Statistical analysis : We entered data in a Microsoft excel sheet and exported it to Stata for analysis. Stata 15.0 [Stata Corp., College Station, TX] statistical software was used for data analysis. Comparison of all variables was carried out between those who died and survived. Continuous variables were compared using a t-test or Mann-Whitney test as appropriate. We reported categorical data as frequency (%) and compared using chi-square or fisher-exact test. Kaplan Meier analysis followed by the log-rank test was used to analyse the bivariable association of various potential factors with time to death as an outcome. Subsequently, stepwise Cox regression analysis with potential risk factors and time to death as the outcome

was performed with inclusion and exclusion criteria as p (0.05) and p (0.1), respectively. In this study, a p-value of <0.05 was considered statistically significant.

Results

We enrolled 178 children (114, 64.0% boys) with cystic fibrosis in the study. There was a total of 32 deaths (18.0 %). Out of these, 12 deaths happened in boys (37.5%) and 20 in girls (62.5%). Detailed demographic, clinical details and laboratory findings of the study population are mentioned in table 1. The proportion of female was more in the died group. Kaplan Meier survival analysis (Figure 1) was suggestive of girls' shorter life span than boys. Age of onset of symptoms, registration and diagnosis was significantly high in the died group. The number of hospitalizations before diagnosis and between diagnosis and death or last follow-up were more in the dead group. Z-score for weight and BMI and SK score were not different between the groups at diagnosis, but all were low in the died group at the last follow up visit or death (Table 1). Among laboratory parameters, total leukocyte count and age at first colonization were more in the died group. History of consanguinity was present in 18 (10.1%) children; 13 in survived group and 5 in the died group. Twenty (11.2%) children had a family history of CF, and 47 (26.4%) children had a history of sibling death.

Airway was colonised in a total of 116 (65.73%) children, of which 24 (21.36%) children had died during the study. The most common aetiological agent for first colonisation was Pseudomonas in 91 (78.5%) children, followed by staphylococcus in 22 (18.9%) and Burkholderia species in 3 (2.5%) children. The most common aetiological agent at last colonisation was Pseudomonas in 64 (55.5%) children, followed by staphylococcus in 4 (3.4%) children. Around 48 (41.4%) children had no colonisation at the end of the study period.

We tested for two common mutations, and these were identified in 37 children (20.8%). The most common mutation was heterozygous delta F 508 (53.8%), followed by 3849+10 kb (25.64%) and homozygous delta F 508 in 7.7% of children.

CF-related complications are mentioned in table 2. The mean ± SD age of developing ABPA was 12.1±3.9 years. The average value of total IgE was 2369.23 IU/L, and the average value of aspergillus specific IgE was 36.78 IU/L. A total of 41 children (29 survived, 12 died) had elevated total IgE. The mean ± SD age of developing distal intestinal obstruction syndrome (DIOS) was 12.7±9.5 years. Mean ±SD age of developing haemoptysis was 15.2±1.8 years. More proportion of CF children who died had ABPA and DIOS (Table 2).

Predictors of mortality

To assess the predictors of mortality, we performed bivariate, and multivariate COX regression analysis of independent variables and results are mentioned in Table 3. On Bivariate analysis, factors associated with increased mortality were neonatal complications, BMI for age z score at the time of diagnosis, FEV1/FVC, FEF25-75, recurrent pneumonia, total IgE level (IU/ml), HCO3 level at the time of admission (mEq/l), SK severity score at the time of admission, and age at the time of diagnosis.

On multivariable Cox regression analysis, significant factors associated with mortality included the presence of neonatal complications, low z-scores for BMI at the time of diagnosis, low FEV1/FVC and low FEF25-75 at the time of diagnosis (Table 3).

Discussion

This study found that neonatal complications, low FEV1/FVC, low FEF25-75 and low body mass index were associated with increased mortality in Indian children with cystic fibrosis. European cystic fibrosis society patient registry database of 2007 suggested that low BMI, chronic pancreatic insufficiency, chronic colonisation with Pseudomonas and development of cystic fibrosis-related diabetes mellitus increases the risk of having poor lung function as demonstrated by poor FEV1 value (8). However, our study patients did not have a statistically significant incidence of CFRD, chronic colonisation with Pseudomonas or chronic pancreatic insufficiency. Moreover, as per the natural history of the disease, the complications like CFRD

usually develop in the second decade of life. In our study population, most children had died just after the first decade of life at an average age of 13.5 years (95% CI- 8.3 -17.0).

Earlier studies done in adults reported that low FEV1 was associated with increased mortality (8). It has been demonstrated by Kerem et al. that patients with an FEV1 value $< 30\%$ predicted to have a 40- 50% chance of dying with two years in a cohort followed up for 12 years (9). FEV1 was the strongest predictor of mortality in a study conducted by Huang et al., although the authors mentioned that other lung function test indices were not strong predictors of mortality (10). There was a trend of low FEV1 in the died group in our study (Table 1), but it was not a predictor of mortality in COX regression analysis. A possible explanation may be early death (average age at death 13.5 years) in our cohort before they had very low FEV1. FEV1 is effort dependent and FEV 25-75 is relatively less dependent on patient's effort. However, low FEF25-75 and the low ratio of FEV1/FVC is a relatively novel finding of the present study.

The case fatality rate in our study was 18.0%. A study done by Courteny et al. indicated an average case fatality rate of 24.6 in adults (11). Lower BMI and lower PFT results are in general associated with higher mortality reported from various studies from different parts of the world (12-14), as seen in our study.

The average age at death was 13.5 years in our study, which is much lower than the average life expectancy of CF patients in western countries (15). This is possibly due to the early diagnosis and availability of CF specific drugs in western countries. CF in developed countries is no longer a paediatric disease than developing countries where it still qualifies to be a disease of children. Most children had died in the first half of the second decade of their lives. This shortened life span in developing countries like India is attributed to delay in diagnosis and lack of proper medical facilities even after diagnosing disease. Because of the lack of national guidelines and support, most children are treated symptomatically without giving them advanced care in CF specific drugs. Since the cost of CF specific drug therapy is exorbitantly high, most parents cannot bear the cost of treatment and hence prefer symptomatic medical/surgical management as necessary. Average age at which symptoms appeared first and at which diagnosis of CF was confirmed was 6 months (95 %- 1.5,24) and 60 months (95%- 17,120) in the group that had died during the period of the study. Even in our study, the time lag between the onset of symptoms to diagnosis of CF was around two to four years. This delay is attributed to lack of suspicion at primary/secondary care centres due to lack of awareness, non-availability of diagnostic tests, and further delay in referral to higher centres equipped with CF specific care. Most children had poor nutrition status at the diagnosis itself. Family history of CF was found in very few children in our study, and it did not contribute to increased mortality.

We had more representation of male children in our study cohort; however, the death rate at the end of the study period was higher in female children (Figure 1). This corresponds to the earlier studies conducted by Kerem et al. (9) and Rosenfeld et al. (16) in the adult population. Although the exact cause as to why female children have higher mortality is not known to us, it may be related to better nutritional status and better medical care given to male children in India. However, further research is required to know the exact cause of higher mortality in female children because even in developed countries where no preferential treatment is given to male children, mortality is reported higher in female children (9,16).

Homozygous Delta F 508 is the commonest mutation in western countries and is associated with higher mortality. A mutation study revealed that heterozygous delta F508 is the most common mutation in this study cohort. An earlier study done by Connor et al. found that heterozygous delta F508 mutation was associated with a reduced risk of mortality compared to homozygous delta F508 mutation (17). Another study done by Johansoen et al. (18) suggested that homozygous delta F508 has a higher risk of mortality than other mutations. If we compare the studies of Connor et al. and Johansoen et al., it is evident that the presence of heterozygous delta F508 mutation was associated with lower mortality. However, there was no association between the type of mutation and the risk of mortality in our study. This is possible because we could not do a complete mutation study of the entire study cohort due to the lack of facilities and heterogeneous mutation profile in our population.

BMI was a significant predictor of mortality in our study. This is again corresponding to an earlier study by

Kerem et al. (9), Bell SC et al. (19) and Fired et al. (20). However, Courteny et al. conducted a study on predicting mortality in adult CF patients and found no correlation of increased mortality with BMI (11).

There was no significant association of any lab parameter with the mortality on bivariate analysis. Although airway colonisation was seen in almost 2/3rd of our study population, it did not contribute to overall mortality. The most common bacteriological agent for colonisation was Pseudomonas, followed by staphylococcus and Burkholderia. Age of colonisation and the organism of colonisation had no bearing on overall mortality in our study. This contrasts to earlier studies where early colonisation and colonisation with species like Burkholderia were found to significantly contribute to mortality in patients with CF (20-24). A possible explanation for not finding an association between airway colonization and increased mortality in our study may be, that other factors like poor nutrition and not been able to afford the treatment contributed more to early mortality.

CF-related complications like ABPA, CF-related liver disease and Pulmonary artery hypertension was found in very few children, and it did not contribute to mortality.

The strengths of our study are that it was conducted over a large cohort that was followed over ten years and is likely to represent the disease-specific traits in the Indian population. This is one of the first few studies with a relatively large number of patients where we have tried to analyse the predictors of mortality in Indian children with CF.

There are few limitations also of our study. Few data were missing due to the retrospective nature of the study. We had no access to newer CF specific drugs like lumacaftor, Ivacaftor and Tezacaftor due to lack of funds, which might have some survival benefits. Finally, we could not do a complete genetic analysis of all the patients.

Conclusions

Our study reflects that patients who died had complications in the neonatal period. These patients also had lower BMI and lowered pulmonary function test results. The two variables, low BMI and low PFT indices are modifiable and can be improved by early diagnosis and early CF specific treatment. For early detection and prevention of neonatal complications, a robust neonatal screening programme should be developed and implemented so that new born babies can be delivered at specific centres equipped to handle the neonatal complications with the help of multidisciplinary team and suitable arrangements can be made for early/antenatal referrals.

WHAT THIS STUDY ADDS?

Out of the three significant predictors of mortality in this study, neonatal complications were not statistically associated with significant mortality in the previous studies. Hence this study highlights the importance of new-born screening for CF and the importance of early diagnosis and management.

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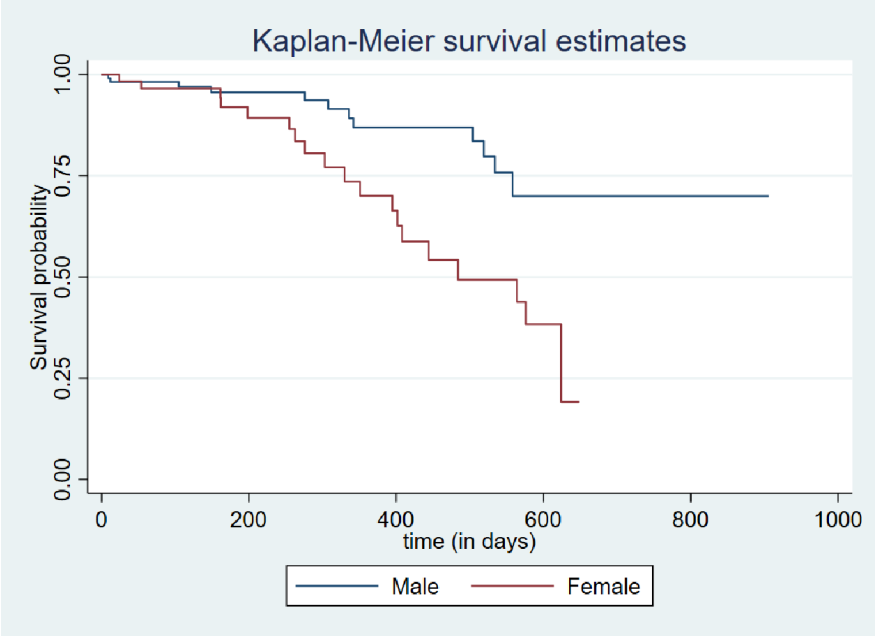

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