The significant impact of meconium ileus on clinical outcomes among Brazilian individuals with cystic fibrosis—a retrospective analysis of a patient registry

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Summary

Background Meconium ileus (MI) is one of the earliest manifestations of cystic fibrosis (CF), affecting 15–20% of individuals. The impact of MI on health outcomes has yet to be elucidated and may vary based on the amount of health care resources. The aim of this study was to investigate the clinical impact of MI on outcomes among Brazilian CF individuals using data from the Brazilian Cystic Fibrosis Patient Registry.

Methods This retrospective cohort study included data from individuals with CF from 53 reference centres in Brazil. Data from individuals with a history of MI during the neonatal period were compared to those of the non-MI individuals. Demographic data, genotype, lung function, nutritional data, microbiological data and survival data were compared between groups. The impact of MI on lung function and anthropometric outcomes was evaluated using mixed effects models after adjusting for age. Individual survival data were analyzed by Kaplan–Meier curves, log-rank tests and Cox proportional hazards models.

Findings Among the 5128 individuals included in the registry, 369 (7·2%) were diagnosed with MI at birth. The occurrence of MI was associated with an earlier diagnosis of CF but a lower mean Z score for weight (–0·32, 95% CI –0·46 to –0·18, $p < 0·0001$) and height (–0·28 95% CI –0·40 to –0·15, $p < 0·0001$). Lung function was significantly lower among those affected by MI (reduction of –4·3% 95% CI –8·0 to –0·5, $p = 0·028$) up to the age of 18 years. A greater prevalence of *Pseudomonas aeruginosa* colonization was observed in the MI group (79·1% (272/344) versus 64·5% (2818/4367); $p < 0·0001$). Survival was significantly worse in the MI group, and the results of the Cox regression model revealed that the impact of MI on mortality was significant after controlling for other risk factors (HR = 1·84, 95% CI 1·50–2·25, $p < 0·0001$).

Interpretation CF individuals affected by MI had more severe and earlier declines in lung function, slower rates of weight and height gain, and lower survival rates. These findings underscore the importance of early identification and tailored management strategies for this high-risk subgroup.

Funding None.

Keywords: Meconium ileus; Cystic fibrosis; Anthropometric variables; Nutritional status; Pulmonary function

Introduction

Cystic fibrosis (CF) is a genetic condition that results from dysfunction of the *cystic fibrosis transmembrane regulator* (*CFTR*) protein and is associated with reduced life expectancy.[1] One of the earliest manifestations of CF is meconium ileus (MI), which is defined as an

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Translation: For the Portuguese translations of the abstract see Supplementary Materials section.

Research in context

Evidence before this study

Meconium ileus is a well-recognized early manifestation of cystic fibrosis (CF), often serving as a sentinel sign of the disease. To assess the existing literature on its impact, we conducted a comprehensive search on PubMed using the terms "meconium ileus" AND "cystic fibrosis" AND "outcomes" for studies published between 1997 and 2024. Our search was restricted to observational or comparative studies, clinical trials, and meta-analyses. A total of 25 studies met our inclusion criteria, the majority of which were retrospective case–control cohorts or analyses based on patient registries. Previous research has established an association between meconium ileus and more severe *CFTR* genetic variants, suggesting a potential link to disease severity. However, the long-term clinical implications of meconium ileus remain uncertain. Notably, most available studies originate from high-resource settings, leaving a gap in knowledge regarding its incidence and impact in low-resource environments, where disparities in access to care may influence outcomes. Further research is needed to clarify the prognostic significance of meconium ileus and to determine whether it serves as an independent predictor of disease progression in individuals with cystic fibrosis.

Added value of this study

This study leverages a large, nationally representative dataset from the Brazilian Cystic Fibrosis Patient Registry, making it one of the most comprehensive analyses of individuals with cystic fibrosis (CF) and meconium ileus to date. By examining a substantial cohort, our findings provide robust evidence that meconium ileus is not merely an early manifestation of CF but also a significant determinant of long-term health outcomes. Our results demonstrate that individuals with CF who present with meconium ileus experience distinct disease trajectories, with measurable impacts on survival and other key clinical outcomes. Furthermore, this study addresses a critical knowledge gap by providing data from a middle-income country, where access to CF care and resources may differ from high-income settings.

Implications of all the available evidence

These findings underscore the importance of early identification and tailored management strategies for this high-risk subgroup, informing both clinical decision-making and public health policies aimed at improving long-term prognosis in CF populations worldwide.

obstruction at the level of the terminal ileum that occurs during the perinatal period and is caused by the impaction of abnormally thick meconium.[2]

The prevalence rate of MI ranges from 15 to 20% among individuals diagnosed with CF; furthermore, MI is associated with the presence of *CFTR* variants that compromise the expression and/or function of the CFTR protein more severely.[2,3] Therefore, a diagnosis of MI has been considered to be a risk factor for worse outcomes in people with CF.[4] However, previous studies from Israel and Europe have indicated that CF individuals with or without a previous diagnosis of MI reported similar outcomes in terms of lung function, nutritional status, and survival rate.[5,6] However, more recently, a study from Australia reported that CF individuals with MI had worse outcomes in terms of lung function, nutrition, and the prevalence of chronic infection by *Pseudomonas aeruginosa*.[7] The differences between previous studies regarding the clinical outcomes associated with MI among CF individuals may be due to different degrees of access to clinical approaches, surgical approaches, or nutritional interventions across different countries,[8] but no previous study has explained these differences. Furthermore, there is a lack of information about the effects of MI on people with CF in different socioeconomic settings, such as low- and middle-income countries (LMICs).

The estimated prevalence of CF in Brazil is approximately 1:7500–15,000 live births, depending on the geographic region.[9] CF care in Brazil has improved in the last decade, with earlier diagnosis, increased proportion of adult individuals and decreased proportion of mucoid *P. aeruginosa* infections over time.[10] There are currently more than 50 CF centers, but these are mainly located in the Southeast and South regions. Newborn screening for CF (CF-NBS) started in 2000–2001 in three Brazilian states (Santa Catarina, Paraná and Minas Gerais), but only in 2010 did it start in São Paulo, the most populous Brazilian state. The activity is coordinated by the Ministry of Health, and uses the IRT/IRT methodology, in laboratories located in each state. Theoretically, CF-NBS is available in the whole country since 2013, but less efficiently in the North and Northeast regions.[11] Access to CF treatment is also not uniform in Brazil, with an apparent relation with other health and social indexes.[12]

The Brazilian CF Patient Registry has been collecting clinical, functional and microbiological data prospectively since 2009, thus enabling research on the impact of MI on people with CF in Brazil.

The aim of this study was to investigate the clinical impact of MI on outcomes among Brazilian CF individuals using data from the Brazilian Cystic Fibrosis Patient Registry, by comparing the clinical characteristics, anthropometric data, lung function and survival rates of Brazilian CF individuals with and without MI. We hypothesized that the occurrence of MI is associated with worse clinical outcomes among CF individuals in Brazil.

Methods

Study design

This retrospective cohort study included Brazilian individuals with CF whose data were collected from the Brazilian Cystic Fibrosis Patient Registry (REBRAFC), comprising the years 2009–2018, and extracted in March of 2020. Data were entered into the registry database by health care professionals through a specific online platform. Usual inclusion criteria for the CF Patient Registry is a clinical diagnosis of CF (established by either clinical symptoms or by positive result in newborn screening), plus a positive sweat chloride test or the identification of two CFTR variants established as CF-causing. The summarized data are freely accessible and available at the website www.gbefc.org.br. The data collected in the registry include demographic characteristics, diagnostic characteristics, and annualized outcomes such as anthropometric measurements, microbiological and pulmonary function results, and treatment data.[10]

The data were anonymized before analysis. The demographic data examined herein included sex, current age (using the most recent date of either spirometry or anthropometric measurement), age at diagnosis, race (defined by the assistant doctor and expressed here as 'white' or 'nonwhite'), and region of birth. Genotyping results were categorized on the basis of F508del variant identification; furthermore, genotyping results were classified as 'positive', 'inconclusive' or 'negative' using the CFTR2 database as a reference to define the identified variants as 'CF-causing' or 'non–CF–causing'. Cases defined as 'positive' have two 'CF-causing' variants or two copies of a 'CF-causing' variant. Inconclusive cases have at least one 'CF-causing' variant. Negative cases have no variant identified, or only 'Non CF-causing' variants were described. The clinical data analysed herein included anthropometric data up to the age of 18 years, including Z scores for weight, height and body mass index (BMI) based on CDC standards.[13] Pulmonary function test results express the best value for each given year and were calculated as a percentage of the predicted forced expiratory volume in the first second (FEV1), which was obtained using the GLI reference equation.[14] The microbiological data examined here included the proportion of individuals with isolated mucoid or nonmucoid strains of *P. aeruginosa* in that given year.

Ethics approval

The registry was approved by the involved Institutional Ethics Committees and is registered in Plataforma Brasil under number 36387920·6·0000·0068. Consent for data inclusion in the database was obtained either directly from adult individuals or by parents and/or legal guardians of underage individuals. Individuals aged 6 years or older also had to consent to have their data included in the platform.

Statistical analysis

Our study included all patients registered from 2009 to 2018; therefore, a sample size calculation was not performed. The obtained data were exported to spreadsheets in Microsoft Excel version 2010 (Microsoft, Washington, United States) and analyzed using the statistical software R version 4.3.0 and the *Statistical Package for the Social Sciences* (SPSS) version 19.0 (IBM, Armonk, USA).

Categorical data are described as absolute and relative frequencies. Continuous data are presented as means and standard deviations (SD) or medians and interquartile ranges (IQRs) depending on the distribution of each variable. Pearson's chi-square test, or the chi-square test with Yates' continuity for 2 × 2 contingency tables, were used for categorical variables. Student's t-test or the Wilcoxon Rank Sum test were used for continuous data, as appropriate.

The individuals were continuously monitored by the responsible physician at each research center, where they underwent anthropometry and spirometry. The data were recorded annually; therefore, each individual had multiple observations, one per year. The best result of spirometry of the given year is registered, with anthropometry of the same date. For patients without spirometry, the most recent anthropometry was included (the last observed in the given year). To accommodate the dependence structure of the data, the association of MI diagnosis with anthropometric measures (expressed as Z scores for weight, Z scores for height and BMI percentiles) was examined by using a mixed effects model with the patient identifier as the random effect and z-scores (or percentile) as the dependent variable. These models included MI, age group (up to 5 years, >5 to 10, >10 to 15, >15 to 20, >20 years) and the interaction MI*age group. Since the interaction effect was not significant, we chose to present only the estimates related to the effect of the MI group (mean difference, corresponding 95% confidence intervals, and p-values).

Mixed effects models were also used to examine the spirometry outcomes, specifically forced expiratory volume in 1 s (FEV1% pred). Since the lungs in young children are still developing and the spirometry test requires some ability, the accuracy and reliability of lung function data may be compromised. Therefore, only children over the age of 5 were included in this analysis. Due to the interaction between MI group and age, the estimates for the MI group were presented by age categories. In addition to stratification by age groups in 5-years intervals, we also provide a division according to pediatric age (up to 18 years and over 18 years).

The association between MI and mortality was investigated using a survival analysis approach. As patients were diagnosed at different ages, the data were analyzed in a counting process format, with the age of diagnosis as the initial time and the age of death or last

follow-up as the final time. In this way, the number of patients at risk can increase over time, as patients were not considered at risk until cystic fibrosis (CF) was diagnosed. Moreover, patients who died from other causes, such as accidents or unknown reasons, were censored. The prognosis of both groups was illustrated using Kaplan–Meier curves. Although we produced KM estimates based on all available patients, we chose to display data up to 18-years, as few individuals with MI were followed into adulthood. The effect of MI on survival was analysed through Cox proportional hazard models. In the first step, we fitted univariate models for MI and potential confounders selected based on previous knowledge (genotype category, region of origin, and colonization by mucoid *P. aeruginosa*, this latter as a time dependent covariate). Secondly, we fitted a fully adjusted model that included all variables considered in the initial step. We tested the proportional hazards assumption using the Schoenfeld residuals proportionality test[15] and examined Schoenfeld residual plots. No violations of the assumption were found. Results from the Cox model were presented as hazard ratios (HR) with 95% confidence intervals. The significance level was set at 0·05.

Role of funding source
There was no funding for this study.

Results

This study included a total of 5128 individuals with CF who had data available up to the year of 2018. These data came from 53 different CF centres across Brazil.

Among the 5128 participants, 369 (7·2%) had a diagnosis of MI at birth. Most of the individuals with MI (n = 292/369, 79·1%) underwent surgical treatment. The demographic characteristics and age at diagnosis are summarized in Table 1. The MI group exhibited a significantly lower median current age (8·4 IQR 4·4–15·1 versus 12·9 IQR 6·3–19·3 years, p < 0·0001). As expected, the median age at diagnosis was significantly lower in the MI group (2·3 months IQR 1·0–3·6) than in the non-MI group (13·3 months IQR 2·3–92·2) (p < 0·0001). A total of 438 individuals (8·5%) were diagnosed in the adulthood, and all of them were in the non-MI group. The proportion of White individuals was higher in the MI group (83·5% 308/369) than in the non-MI group (67·5% 3213/4,759, p < 0·0001). In terms of geographical origin, a smaller percentage of individuals with MI were observed in the North (3·2% 7/219) and Northeast Regions (3·5% 30/869), when compared to

	MI group n = 369	Non-MI group n = 4759	p value
Sex—n(%)			0·15
Male	178 (48·2%)	2486 (52·2%)	
Female	191 (51·8%)	2273 (47·8%)	
Current age (years)[a]			
Median (IQR)	8·38 (4·5–15·1)	12·88 (6·3–19·3)	<0·0001
Age at diagnosis (months)			
Median (IQR)	2·28 (0·96–3·6)	13·32 (2·28–92·16)	<0·0001
Race—n(%)			<0·0001
White	308 (83·5%)	3213 (67·5%)	
Nonwhite	61 (16·5%)	1546 (32·5%)	
Brown	47 (12·7%)	1232 (25·9%)	
Black	12 (3·3%)	300 (6·3%)	
Asian	2 (0·5%)	10 (0·2%)	
Indigenous	0 (0·0%)	4 (0·1%)	
Region of origin[b]**–n(%)**			<0·0001
North	7 (1·9%)	212 (4·5%)	
Northeast	30 (8·1%)	839 (17·6%)	
Midwest	24 (6·5%)	286 (6·0%)	
Southeast	183 (49·6%)	2251 (47·3%)	
South	112 (30·4%)	990 (20·8%)	
Sweat chloride test (mmol/L)	n = 279	n = 4068	
Mean (sd)	95·3 (27·3)	90·4 (26·2)	0·0020
Patients with follow-up	n = 344	n = 4367	
Pancreatic insufficiency[c]—n (%)	340 (98·8%)	3552 (81·3%)	<0·0001
Intestinal obstruction syndrome[c]—n (%)	47 (13·7%)	75 (1·7%)	<0·0001
Liver disease[c]—n (%)	105 (30·5%)	755 (17·3%)	<0·0001

SD: standard deviation; IQR: interquartile range. [a]Age at the last spirometry or anthropometric assessment. [b]194 individuals did not have information on the region of origin. [c]Observed in only 4711 cases with follow-up (344 from MI group and 4367 from non-MI group).

Table 1: **Demographic characteristics and clinical variables of the included individuals (n = 5128).**

7·7% (24/310), 7·5% (183/2434), and 10·2% (112/1102) of the individuals from the Midwest, Southeast, and South Regions. Only 10·0% (37/369) of patients in the MI group were from the North and Northeast regions, whereas this percentage was significantly higher at 22·1% (1051/4759) in the non-MI group (Table 1).

Within the overall cohort, 4076 individuals (79·4%) had a history of genetic testing. Among the subset of 324 individuals with a documented history of MI who underwent genetic testing, 70·4% (228/324) exhibited at least one copy of the F508del variant, while the frequency among individuals in the non-MI group was 49·8% 1868/3752 (Table 2). The proportion of individuals with negative genotyping results was significantly lower in the MI group (4% 13/324) than in the non-MI group (12·5% 470/3,752, p < 0·0001).

Out of a total of 5128 patients, 4711 were followed over time. The median follow-up time was 4 years (IQR 3–6), ranging from 1 to 9 years. Each year, anthropometric measurements and pulmonary function tests were registered, resulting in 19,981 observations from 4711 patients.

The history of MI was associated with decreased weight and height measurements. According to the mixed effects model, individuals diagnosed with MI displayed a mean reduction of 0·32 points (CI 95% 0·18–0·46) in the Z score for weight (p < 0·0001) and 0·28 points (CI 95% 0·15–0·40) in the Z score for height (p < 0·0001) after controlling for age groups (up to 5 years, >5 to 10, >10 to 15, >15 to 20, >20 years). However, there was no significant difference detected in the BMI data (Table 3).

Due to the interaction between meconium ileus (MI) and age (p = 0·0038), lung function outcomes were investigated after stratifying individuals into age groups. Two types of stratification were considered, as shown in Table 3. In the stratified analysis by 5-year intervals, a significant difference was found only among children aged 6–10 years, with a reduction of 4·7% (95% CI 0·3–9·1, p = 0·034). The interaction becomes clearer when considering the pediatric age group (up to 18 years versus over 18 years). In the younger group (≤18 years), the presence of MI was significantly associated with a lower percentage of individuals predicted to have forced expiratory volume in 1 s (FEV1% pred), exhibiting an average reduction of 4·7% (CI 95% 3·4–16·6) (p = 0·028). Conversely, no significant association was observed within the older subset (p value = 0·87).

Regarding the prevalence of *P. aeruginosa* colonization of the respiratory tract, a higher incidence was observed among individuals with documented MI history, including individuals with mucoid strains (p value = 0·031) and those with nonmucoid strains (p value < 0·0001) (Table 4). When specifically examining *P. aeruginosa* identification among individuals younger than 5 years, no significant difference was found in the overall *P. aeruginosa* detection rate. However, an increased prevalence of mucoid *P. aeruginosa* was observed in those with a history of MI (p value = 0·034).

According to the survival analysis, individuals with a documented history of MI exhibited a significantly worse survival outcome (p value = 0·0001), with a noticeable decline in the survival curve within the initial two-year period (Fig. 1 and Supplementary Figure S1b).

The Cox regression model revealed compelling evidence of the enduring and significant influence of MI on survival, even after adjusting for covariates that have been recognized to contribute to prognostic decline, including regional origin, genotype category, and mucoid *P. aeruginosa* colonization (HR = 1·84, 95% CI 1·50–2·25, p < 0·0001) (Table 5 and Supplementary Table S6).

Genotype category	MI group n = 324 n (%)	Non-MI group n = 3752 n (%)
Positive	266 (82·1%)	2422 (64·6%)
F/F	120 (37·0%)	854 (22·8%)
F/non F	108 (33·3%)	1014 (27·0%)
Non F/non F	38 (11·7%)	554 (14·8%)
Inconclusive	45 (13·9%)	860 (22·9%)
Negative	13 (4·0%)	470 (12·5%)

F/F: homozygous F508del; F/non-F: heterozygous F508del.

Table 2: **Genotyping results according to meconium ileus status (n = 4076).**

	MI group mean (sd)	Non-MI group mean (sd)	Mean difference (95% CI)	p value
Anthropometric data				
Weight (Z Score)	−1·25 (0·08)	−0·93 (0·04)	−0·32 (−0·46 to −0·18)	<0·0001
Height (Z Score)	−0·99 (0·07)	−0·72 (0·04)	−0·28 (−0·40 to −0·15)	<0·0001
BMI (Percentile)	36·61 (2·42)	39·95 (1·66)	−3·33 (−7·07 to +0·40)	0·080
Lung function by age group				
FEV1% pred (6–10 years of age)	83·3 (2·1)	88·0 (0·7)	−4·7 (−9·1 to −0·3)	0·034
FEV1% pred (>10–15 years of age)	75·3 (2·4)	77·8 (0·7)	−2·5 (−7·5 to 2·5)	0·33
FEV1% pred (>15–20 years of age)	65·4 (3·1)	68·9 (0·8)	−3·4 (−9·8 to 2·9)	0·28
FEV1% pred (>20 years of age)	58·8 (4·3)	59·0 (0·8)	−0·2 (−8·8 to 8·5)	0·97
Lung function by pediatric age group				
FEV1% pred (≤18 years of age)	76·2 (1·8)	80·5 (0·6)	−4·3% (−8·0 to −0·5)	0·028
FEV1% pred (>18 years of age)	59·8 (3·5)	60·4 (0·7)	−0·7% (−32·2 to 30·7)	0·87

CI: Confidence interval, BMI: Body mass index, FEV1%pred: Percent of predicted forced expiratory volume in 1 s.

Table 3: **Mixed model estimates for the effect of MI on anthropometric and lung function parameters.**

All ages[a]	MI group n = 344 n (%)	Non-MI group n = 4367 n (%)	p value
P. aeruginosa	272 (79·1%)	2818 (64·5%)	<0·0001
Mucoid *P. aeruginosa*	137 (39·8%)	1482 (33·9%)	0·031
Ages up to 5 years old[a]	**n = 184 n (%)**	**n = 1495 n (%)**	**p value**
P. aeruginosa	117 (63·6%)	853 (57·1%)	0·11
Mucoid *P. aeruginosa*	33 (17·9%)	181 (12·1%)	0·034

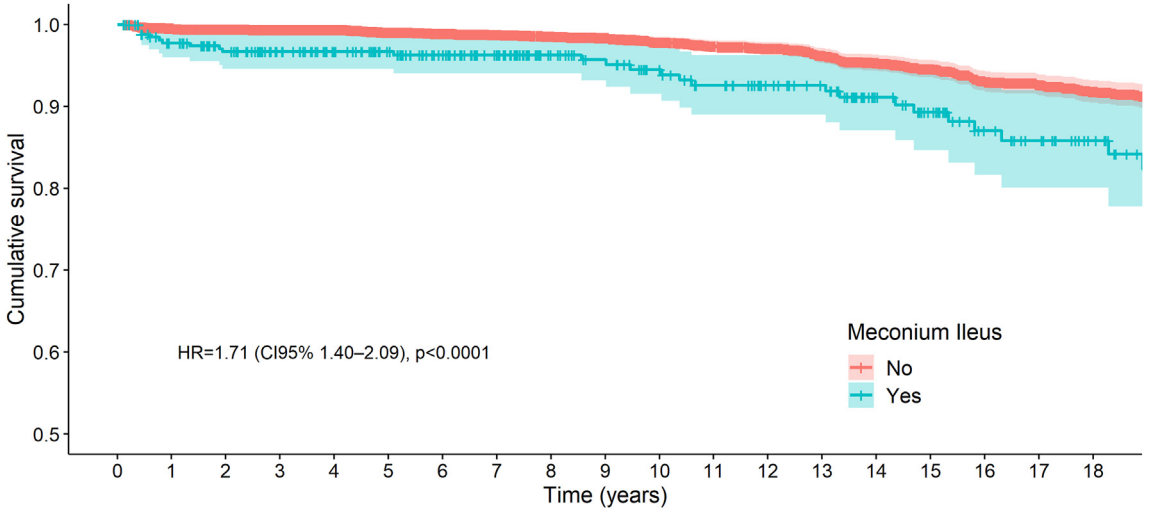
[a]*P. aeruginosa* colonization data is captured annually, therefore these data refer to the whole period of follow up (for all ages) or the follow-up period up to 5 years of age.

Table 4: **Colonization status of *Pseudomonas aeruginosa* according to the occurrence of meconium ileus (n = 4711).**

Discussion

While MI is an early and severe manifestation of CF, its impact on health outcomes have been a matter of debate in the literature.[6,7,16] This study aimed to investigate the clinical impact of MI among Brazilian CF individuals, using the data collected by the Brazilian Cystic Fibrosis Patient Registry. Brazilian CF individuals with MI exhibited early and pronounced decreases in pulmonary function, weight, height, and survival rates compared to individuals without MI. These outcomes underscore the short-, medium-, and long-term implications of meconium ileus for individuals with CF in Brazil. To our knowledge, no previous large-sample study has examined MI among CF individuals from diverse socioeconomic backgrounds, in a country with continental dimensions such as Brazil. Furthermore, the registry contains follow-up data spanning several years, thus enabling the analysis of long-term outcomes.

A previous long-term follow-up study from Israel have reported that MI was not a risk factor for altered nutritional status, pulmonary function or survival, and while we assume a significantly different genetic background of the populations of these countries, we believe that the impacts of MI are influenced by factors such as the time and circumstances of diagnosis.[6] However, MI is indeed associated with CFTR-specific variants that determine pancreatic insufficiency and severe disease. F508del, G542X, W1282X, and R553X are the most frequent variants associated with MI.[3,17,18] The homozygous F508del genotype, the most common among CF individuals worldwide, is strongly correlated with the presence of MI.[3,17,18] Within our sample, we also observed a higher proportion of individuals with MI harbouring at least one F508del variant (70·4%), while the frequency was 49·8% among those without meconium ileus. Gorter et al. compared the clinical presentation and diagnostic characteristics of meconium ileus between newborns with and without CF and found that all newborns in the complex meconium ileus group were homozygous for the F508del variant.[17] In newborns with simple meconium ileus, other mutations were detected. A higher incidence of MI has been reported in newborns carrying F508del or G542X, while G551D and R117H were associated with a decreased incidence.[17] Some modifier genes located on chromosomes 4q35·1, 8p23·1, 11q25 and 19q13 have also been



	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Number at risk – MI: No	693	1945	2075	2102	2082	2053	2008	1949	1870	1806	1733	1669	1605	1502	1381	1235	1121	955	805
Number at risk – MI: Yes	125	279	260	243	230	213	195	170	162	151	144	133	128	104	93	74	68	58	46
Censored – MI: No	143	168	144	172	172	151	164	175	192	139	144	138	122	157	161	159	140	186	163
Censored – MI: Yes	14	16	23	19	16	19	18	26	8	9	7	12	7	22	9	17	6	10	10

Fig. 1: Kaplan–Meier curve demonstrating the survival of CF individuals up to 18 years of age according to the meconium ileus status.

Model	Effect of MI HR (95% CI)	p value
Unadjusted	1·71 (1·40–2·09)	<0·0001
Adjusted by		
Genotype category[a]	2·01 (1·65–2·46)	<0·0001
+region of origin[b]	1·97 (1·62–2·41)	<0·0001
+colonization by mucoid *P. aeruginosa*[c]	1·84 (1·50–2·25)	<0·0001

CI: Confidence interval; HR: hazard ratio. [a]Variable including categories negative, inconclusive, positive, not performed. [b]Variable including categories Southeast, North, Northeast, Midwest, South. [c]Binary variable (yes, no) time dependent.

Table 5: **Effect of Meconium Ileus (MI) on survival–results of the univariate and multivariate Cox regression models.**

shown to contribute to the development of MI in newborns with CF.[17] An interesting finding of the current study was the proportion of negative results in genetic testing, which showed to be significantly lower among individuals with meconium ileus (4%) than among those without meconium ileus (12·5%). Since the Registry do not capture data on the methods used to genotype the cases, some of the negative cases may be related to previously used and limited genotyping strategies such as direct detection of the F508del variant, instead of the currently adopted extensive CFTR sequencing by NGS.[19]

After controlling for age, we observed an association between the presence of MI and reduced weight and height. In 2019, Tan et al. performed a retrospective study and found that CF individuals aged 2–20 years with meconium ileus had significantly lower BMI Z scores over time (estimated –0·25 SE [0·1], p = 0·02) than those without MI.[7] However, there were no significant differences in Z scores for height (estimate 0·040 SE [0·1], p = 0·7) or weight (estimate –0·17 SE [0·1], p = 0·2) in this age group or in the 0–2 years age group (p = 0·8 and p = 0·3 for height and weight, respectively). Efrati et al. also examined the mean Z scores for BMI at ages 1, 5, 10, and 20 years, as well as their averages at ages 5, 10, and 20 years; they found no significant differences in the average Z scores for BMI at any of the time points. Generalized linear models with repeated measures demonstrated changes in mean BMI values and Z scores for BMI scores over time (p < 0·0001), but there were no statistically significant differences between the study groups (p = 0·277), nor was there an interaction between changes over time and case or control status.[6] These differences may be related to inherent aspects of CF care in our country, including inaccessibility to early treatment with pancreatic enzymes replacement and nutritional supplements. While we do see improvements in the nutrition of the Brazilian CF population over time,[20] we still are far behind developed countries regarding nutritional endpoints, with a pronounced gap noticed in late infancy/adolescence.[10]

In our study, we found that MI was significantly associated with a lower predicted forced expiratory volume in 1 s (FEV1% predicted) in individuals under 18 years of age, with a mean reduction of 4·3% (95% CI –8·0 to –0·5, p = 0·028). Worse lung function in CF individuals with a history of MI has been reported in previous studies conducted in different countries[5,21–23] and has been linked to impacts on nutritional outcomes and body composition.[23,24] Most of these studies, however, were based on single-centre populations and included small sample sizes. A recent case–control study from Australia included data from the Australian CF Registry and showed similar results, i.e., worse lung function trajectories among those with MI, with a 7% mean reduction in FEV1 over time among individuals aged between 5 and 23 years.[7] We decided to stratify our analysis of the impacts of MI on lung function in two groups (those younger than 18 years of age and those older than 18 years of age) because the number of older individuals with MI was lower. The effects of MI on lung function were not significant for this age group –0·7% (95% CI –32·2 to 30·7, p = 0·87). One possible explanation for this finding is the lower survival rate observed in the MI group, which impacts the number of individuals with severe lung disease transitioning into adulthood.

The progression of lung disease in CF individuals is known to be influenced by colonization by *P. aeruginosa*, especially chronic or mucoid *P. aeruginosa*. In this study, individuals with a documented history of meconium ileus showed a greater incidence of respiratory tract colonization by *P. aeruginosa*, both with mucoid strains (p = 0·031) and with nonmucoid strains (p < 0·0001). The study with the most similar design used data from the Australian CF Registry and did not find a greater proportion of *P. aeruginosa* colonization among individuals with MI, but the mean age at first isolation was almost 8 years of age,[7] which is much older than that observed in CF cohorts.[25–28] A recent study from the London CF Cohort including individuals diagnosed by newborn screening reported a significant impact of early *P. aeruginosa* isolation on lung function parameters (lung clearance index), mainly when this first identification occurred before 6 months of age.[28] Although we did not identify a greater proportion of *P. aeruginosa*-positive individuals in the subgroup younger than 5 years of age with MI, the MI group had a greater proportion of individuals with mucoid *P. aeruginosa* strains in this age group, and these strains may lead to worsening lung function over time.

An important consideration in this study is understanding the immediate impact of meconium ileus complications on survival data, especially in early life. A previous publication from Brazil reported similar findings, while included only few MI cases from a single CF centre in Minas Gerais, and was published more than 20 years ago.[21] We certainly would expect a fairly

different scenario now, such as the one described in the United Kingdom in 2010, where they reported absolutely no impact on survival over time, and even a trend for better results of growth and lung function trajectories among the MI group.[29] These individuals are known to experience early complications associated with intestinal obstruction and often require surgical interventions early in life, and while this aspect was not associated to a worse prognosis in the UK,[29] our findings indicate that the reality of healthcare of CF in LMICs (such as Brazil) may be substantially different. This becomes evident when we look at the survival curve of affected individuals in this study, which shows a significant decline within the first year of life.

Regional disparities in access to diagnosis may also have influenced the results presented, as indicated by a considerably greater incidence of meconium ileus in the southern and southeastern regions of Brazil. It remains unclear whether these data truly reflect a higher incidence in these regions or simply indicate greater diagnostic accuracy due to traditionally better availability of medical-hospital resources. The differences in the prevalence of F508del variants among Brazilian regions do not account for the observed disparities.[19] Additionally, the proportion of CF diagnoses through newborn screening is significantly lower in the North and Northeast regions.[11,19] Therefore, we can conjecture that many individuals with CF manifesting MI in these regions may die without receiving a definitive CF diagnosis. Regarding access to care after CF diagnosis, this may also be different according to the Brazilian regions; while we do have a comprehensive national protocol for CF diagnosis and treatment, some regions do not have a consistent access to some of the medications, such as pancreatic enzymes or some inhaled antibiotics. This is in part due to the structure of the Brazilian Public Health System, where states and municipalities are also responsible to deliver part of the care, and this may not be fulfilled properly in some regions of the country. On the other hand, Brazil has recently incorporated some CFTR modulators (ivacaftor and elexacaftor/tezacaftor/ivacaftor) in the national protocol of CF care,[30] and therefore most eligible patients (6 years of age and older) are obtaining access to these transforming therapies.

An important limitation of this study is its retrospective nature, combined with the heterogeneity of the professionals and medical centres involved in data collection, without an individual review by the authors or supervisors of the Registry. The amount of missing data also imposes limitations on some results, especially those related to follow-up. We also did not analyse hospitalization rates, which have been shown to be higher in the MI group,[7] or pulmonary structural abnormalities (bronchiectasis), which have also been shown to be more frequent among CF individuals with MI.[31] These limitations do not undermine the added value of this study, but emphasise the need for continuous improvement of the REBRAFC, which are currently experiencing significant adjustments in its web platform.

In conclusion, by using the large dataset derived from the Brazilian Cystic Fibrosis Patient Registry, this study is one of the largest case series to analyse individuals with cystic fibrosis and meconium ileus. The results revealed that meconium ileus has a significant impact on many health outcomes for Brazilian individuals with CF, including survival. Given the complexity of CF treatment, including its costs and inaccessibility, identifying prognostic factors for this disease can help direct resource allocation to ensure targeted care. This approach is also valid for improving the early diagnosis rate of MI. In an era of increasing use of CFTR modulators among CF individuals across the globe, we hope that earlier treatment, such as the treatment of foetuses with MI,[32] may become the standard of care and reduce the burden of this severe complication of CF among affected individuals and their families.

Contributors

Luiz Vicente Ribeiro F. da Silva-Filho: conceptualized the study, supervised data collection and analysis, had access to raw data, verified the data, had final responsibility for the decision to submit for publication, interpreted the results, reviewed and submitted the manuscript.

Gianluca Belchior: had access to raw data, analysed the data, interpreted the results, drafted the manuscript.

Angela Tavares Paes: had access to raw data, analysed the data, interpreted the results, and drafted the manuscript.

Nicole Costa Soriano Freire: analysed the data, interpreted the results, and drafted the manuscript.

Cintia Steinhaus: interpreted the results, drafted the manuscript.

Matias Epifanio: interpreted the results and drafted the manuscript.

The Brazilian CF Registry Contributors Team: collected and analysed the data.

Data sharing statement

Will individual participant data be available (including data dictionaries)?	Yes
What data in particular will be shared?	Individual participant data that underlie the results reported in this article, after de-identification (text, tables, figures, and appendices)
What other documents will be available?	Statistical analysis plan, analytic code, informed consent form
When will data be available (start and end dates)?	Beginning 3 months and ending 36 months following article publication
With whom?	Investigators whose proposed use of the data has been approved by an independent review committee ("learned intermediary") identified for this purpose
For what types of analyses?	For individual participant data meta-analysis
By what mechanism will data be made available?	Proposals should be directed to luiz.vicente@hc.fm.usp.br to gain access, data requestors will need to sign a data access agreement

Declaration of interests
Luiz Vicente Silva-Filho has received research grants from Vertex Pharmaceuticals, TimPel and Fundación Infant; consulting fees from Vertex Pharmaceuticals and Omron, honoraria for lectures from AstraZeneca, Sanofi, Vertex Pharmaceuticals and Omron, and participate in advisory boards of Vertex Pharmaceuticals; Matias Epifanio has received consulting fees from Danone, and honoraria for lectures from Danone, Vertex Pharmaceuticals Cellera and EMS.

Appendix A. Supplementary data
Supplementary data related to this article can be found at https://doi.org/10.1016/j.lana.2025.101099.

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