Respiratory Medicine 258 (2026) 108886

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: www.elsevier.com/locate/rmed

Original Research

Malnutrition in childhood interstitial lung diseases is associated with reduced lung function and greater disease severity: insights from the chILD-EU registry

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ARTICLE INFO

Keywords:
Children
Interstitial lung diseases
Lung function
Malnutrition

ABSTRACT

Background: Malnutrition is a recognized but insufficiently investigated concern in children with childhood interstitial lung diseases (chILD). The relationship between nutritional status and pulmonary function in this population remains poorly understood. This study aimed to evaluate the frequency and impact of malnutrition in chILD and to identify associated clinical factors.

Methods: We analyzed baseline and follow-up data from the chILD-EU registry, including anthropometric measurements, disease severity scores, pulmonary function tests, and treatment information. Malnutrition was defined as a weight-for-age (WFA) z-score < -2. Multivariable linear regression models were used to assess the association between malnutrition and lung function after adjustment for potential confounders. Longitudinal

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https://doi.org/10.1016/j.rmed.2026.108886
Received 27 November 2025; Received in revised form 5 May 2026; Accepted 8 May 2026
Available online 12 May 2026

mixed-effects models were applied to evaluate the relationship between time-varying nutritional status and lung function over time.

Results: A total of 3351 visits from 766 children were analyzed. At baseline, 38.9% of children were malnourished. Children with malnutrition had significantly lower lung function compared with those without malnutrition (both $p < 0.001$). In multivariable analyses adjusting for age, sex, prematurity, diagnostic category, and disease severity, malnutrition remained independently associated with reduced lung function ($zFEV_1$ $\beta = -0.83$, $p = 0.007$; zFVC $\beta = -1.35$, $p < 0.001$). In longitudinal mixed-effects models including baseline and follow-up visits, improvements in WFA z-scores were associated with improved lung function over time ($zFEV_1$ $\beta = 0.33$, $p < 0.001$; zFVC $\beta = 0.37$, $p < 0.001$).

Conclusion: Malnutrition is common among children with chILD and is independently associated with impaired lung function and greater disease severity. Improvements in nutritional status are associated with improved pulmonary outcomes during follow-up, highlighting the importance of routine nutritional monitoring and multidisciplinary care.

1. Introduction

Malnutrition is defined by the World Health Organization (WHO) as an imbalance between the availability of nutrients and energy intake and the body's requirement for development, maintenance, and cellular function [1]. In children, this imbalance commonly manifests as a weight-for-age (WFA) z-score below standard reference values. In the context of chronic disease, malnutrition can result from inadequate intake, increased energy expenditure, altered nutrient absorption, or impaired metabolic utilization [1]. Its consequences are significant and include immune dysregulation with increased susceptibility to infections, impaired physical and neurocognitive development, prolonged hospital stays, and elevated healthcare costs [2].

Childhood interstitial lung diseases (chILD) represent a rare and heterogeneous group of chronic respiratory disorders associated with considerable morbidity and an estimated mortality rate of approximately 15% [3,4]. Children with chILD frequently experience persistent respiratory symptoms such as dyspnea, chronic cough, and increased work of breathing, and often require long-term therapies including supplemental oxygen, corticosteroids, or other immunosuppressive treatments. These disease-related burdens, together with recurrent exacerbations and hospitalizations, can substantially impair health-related quality of life [3–5].

The relationship between nutritional status and pulmonary outcomes has been well established in other chronic pediatric respiratory diseases, particularly cystic fibrosis (CF), where poor nutritional status is associated with reduced lung function and worse clinical outcomes [5]. In contrast, data regarding nutritional status in children with interstitial lung disease remain limited [6,7]. Most existing evidence on nutrition and ILD originates from adult populations. Studies in adults with ILD have reported malnutrition prevalence ranging from approximately 9% to 55% and have demonstrated associations between poor nutritional status, reduced exercise capacity, impaired quality of life, and worse clinical outcomes [8–11]. For example, severe malnutrition in adults with restrictive lung disease has been associated with reduced exercise capacity independently of lung function [8], and compromised nutritional status may further impair daily functional capacity and overall well-being [9].

In addition to nutritional factors, comorbid conditions may also influence nutritional status in children with chILD. Gastroesophageal reflux disease (GERD), for example, appears to be highly prevalent in pediatric ILD populations, affecting up to half of patients, and may contribute both to pulmonary pathology and nutritional impairment [12,13].

Despite these observations, no large multicenter pediatric cohort study has systematically evaluated the prevalence and clinical impact of malnutrition in children with chILD. We therefore aimed to investigate the frequency of malnutrition and its association with pulmonary function and disease severity in a large international cohort of children enrolled in the chILD-EU registry. As a secondary objective, we explored clinical factors associated with impaired nutritional status in this population.

2. Methods

2.1. Study design and population

This observational cohort study was based on data from the chILD-EU Register, a web-based platform collecting data of rare pediatric lung disorders with a focus on chILD (www.childeu.net) [14]. The diagnosis of chILD was established according to clinical guidelines from the American Thoracic Society and the European management platform for pediatric ILD and confirmed by a multidisciplinary diagnostic review team, including radiologists, pathologists, and physicians with expertise in chILD [14–16]. Following inclusion in the registry, patients were evaluated every 6 months during the first year and then annually thereafter. Although registry follow-up was scheduled at 6 months during the first year, 6-month data was not included in the present analyses because data completeness at this time point was limited across participating centers. To ensure consistency and comparability, analyses were restricted to baseline, 1-year, and 2-year follow-up visits with chILD enrolled between 2014 and 2021. The minimum data set includes demographics, signs of diseases, clinical examination, laboratory and imaging results, and the peer-reviewed diagnostic classification. We followed the Declaration of Helsinki and STROBE reporting guidelines to ensure completeness and transparency.

2.2. Data assessment and variables

Data was collected during baseline and follow-up visits. Collected values included demographic characteristics, growth parameters including WFA z-scores (primary endpoint), height for age z-scores, body mass index (BMI) z-scores, pulmonary function tests data including percent predicted forced expiratory volume in the first second (FEV_1) and forced vital capacity (FVC), disease severity Fan scores, respiratory rate z-scores, and oxygen saturation [17–19]. Anthropometric measurements, including body weight and height/length, were recorded during routine clinical visits at participating centers and entered into the chILD-EU registry by local clinical teams. These measurements were obtained according to local pediatric clinical practice. However, the registry does not provide detailed center-level information on measurement standardization procedures, staff training, equipment type, repeated measurements, or calibration protocols. The chILD-EU registry includes automated data validation procedures. When implausible or inconsistent values are entered, automated queries are generated and the submitting centers are asked to verify the data.

The respiratory rate and oxygen saturation in room air were measured twice over 1 min, as the patient was awake at rest for 5 min. Respiratory rate z-scores were calculated using age-specific references [19]. Disease severity was assessed using the Fan severity classification for childhood interstitial lung disease. This system categorizes disease severity based on clinical status and respiratory support requirements,

ranging from asymptomatic disease to severe disease requiring intensive respiratory support. The Fan score is a five-point severity scale commonly used in pediatric interstitial lung disease research to describe clinical severity. Disease severity was categorized using an adapted disease Fan severity score as follows: (1) asymptomatic, (2) symptomatic with normal room air oxygen saturation under all conditions, (3) symptomatic with normal resting room air saturation but abnormal saturation (SaO_2<90%) with sleep or exercise, (4) symptomatic with abnormal resting room air saturation <90%, and (5) symptomatic with pulmonary hypertension [18–21].

Spirometry was performed in accordance with ATS/ERS standards [21]. FEV_1 and FVC measurements were expressed in liters and referred to a healthy population as a percentage of predicted values, with age- and sex-specific adjusted scores (z-scores) calculated using the Global Lung Function Initiative reference values [22].

2.3. Definition of malnutrition

Malnutrition was defined according to WHO Child Growth Standards as a WFA z-score < −2.0, indicating moderate to severe undernutrition. WFA z-scores were calculated based on age- and sex-specific WHO reference values [23].

2.4. Statistical analysis

The statistical evaluation of the data was performed using SPSS software V.22.0 for statistical analyses. For all data, we reported the median and interquartile range (IQR) for continuous data, while we calculated the means for discrete variables such as the Fan severity score. Pearson's chi-square test and Fisher's exact test were used to evaluate categorical variables. Differences between children with and without malnutrition were calculated using the Mann-Whitney *U* test for independent samples. The relationship between data that did not conform to normal distribution was evaluated using Spearman's correlation test. To evaluate the association between nutritional status and lung function at baseline, multivariable linear regression analyses were performed. Lung function parameters ($zFEV_1$ and zFVC) were included as dependent variables. Nutritional status indicators (WFA z-scores in the primary analysis) were entered as independent variables, and models were adjusted for age at visit, sex, gestational age, diagnostic category, and Fan severity score. Because patients contributed repeated measurements over time, longitudinal analyses were additionally performed using linear mixed-effects models. In these models, lung function parameters ($zFEV_1$ and zFVC) were treated as dependent variables, and anthropometric indicators were included as time-varying predictors. A random intercept for each patient was incorporated to account for within-subject correlation across visits. Repeated measurements across visits were modeled using a first-order autoregressive covariance structure. All models were adjusted for age at visit, sex, gestational age, category, and Fan severity score. Model parameters were estimated to use restricted maximum likelihood (REML). Sensitivity analyses were conducted using alternative anthropometric indicators, including BMI z-scores and height-for-age z-scores, to assess the robustness of the association between nutritional status and lung function. The same multivariable regression and longitudinal mixed-effects modeling approaches were applied using these alternative nutritional indicators. The level for statistical significance was set at 0.05.

3. Results

We analyzed the data of 3351 visits of 766 children from 22 countries followed in the chILD-EU Register.

3.1. Malnutrition at baseline

At baseline (n = 766), malnutrition—defined as a WFA z-score < −2—was present in 298 (38.9%) children, at a median age of 2.3 (IQR, 0.5 to 9.5) years. There were no significant differences in gender or age between children with and without malnutrition. Demographic and clinical characteristics are presented in Table 1.

Children with malnutrition had significantly lower anthropometric measures: the median height z-score was −2.2 (IQR, −3.5 to −1.2), the median BMI was −1.9 (IQR, −2.9 to −1.2), and the median WFA z-score was −2.9 (IQR, −4.0 to −2.4). Malnutrition was more prevalent in the following diagnostic chILD subgroups: A2 (growth abnormalities/deficient alveolarization), Ay (unclear RDS in late preterm neonates), and B3 (immunocompromised or post-transplant patients) ($p < 0.001$, $p < 0.001$, and $p < 0.03$, respectively) and less prevalent in A3 (infant conditions of undefined etiology). Children with a low Fan severity score (1 or 2) exhibited a lower prevalence of malnutrition ($p = 0.03$, $p = 0.01$, respectively). Co-morbidities such as immunodeficiency, heart disease, kidney disease, and thyroid dysfunction were more common among malnourished children (Table 1). Among 80 patients with malnutrition and available spirometry, the median $zFEV_1$ was −3.9 (IQR, −5.1 to −1.8), the median $predFEV_1$ was 50.3 (IQR, 33.1 to 72.6), the median zFVC was −3.5 (IQR, −5.7 to −1.9), and the median predFVC was 56.1 (IQR, 36.2 to 72.6). All lung function indices were significantly lower in malnourished children (Table 1a, Fig. 1).

In multivariable linear regression models adjusting for age at visit, sex, diagnostic category, gestational age, and Fan severity score, malnutrition remained independently associated with lower lung function at baseline. Specifically, children with malnutrition had significantly lower $zFEV_1$ values ($\beta = -1.28$, 95% CI −1.89 to −0.68; $p < 0.001$) and zFVC values ($\beta = -1.80$, 95% CI −2.50 to −1.10; $p < 0.001$). Higher Fan severity scores were also independently associated with lower lung function ($zFEV_1$: $\beta = -0.52$, 95% CI −0.75 to −0.29; $p < 0.001$; zFVC: $\beta = -0.60$, 95% CI −0.87 to −0.33; $p < 0.001$). In contrast, age at visit, sex, gestational age, and diagnostic subgroup were not significantly associated with lung function in the adjusted models. Results are summarized in Table 3.

3.2. Changes in malnutrition over time

At the first-year follow-up visit with available data, malnutrition persisted in 122 of the 500 children (24.4%). Among the 122 children with malnutrition, the median z-height was −1.6 (IQR, −2.5 to −0.5) and the median zBMI was −1.6 (IQR, −2.3 to −1.1). The median zWFA was −2.7 (IQR, −3.4 to −2.2) and was lower in children with malnutrition (Table 2). Higher Fan severity scores were also higher in children with malnutrition than without. Among 48 malnourished children with spirometry. The median $zFEV_1$ of 48 patients was −3.2 (IQR, −5.1 to −1.8), the median $predFEV_1$ was 57.2 (IQR, 35.8 to 74.0), the median zFVC was −3.1 (IQR, −4.8 to −1.2), and the median predFVC was 60.9 (IQR, 44.0 to 72.6). All lung function results were lower in children with malnutrition (Table 2).

At the second-year follow-up, malnutrition was present in 108 of 391 children (27.6%). Malnourished children continued to have significantly lower scores across anthropometric, respiratory rate, and lung function parameters compared to those without malnutrition (Table 2).

Longitudinal mixed-effects models including repeated measurements across visits were performed to evaluate the association between nutritional status and lung function over time. In these models, WFA z-scores were included as a time-varying predictor and analyses were adjusted for age at visit, sex, gestational age, diagnostic category, and Fan severity score. Higher WFA z-scores were significantly associated with better lung function over time. Specifically, WFA z-scores were positively associated with $zFEV_1$ ($\beta = 0.33$, 95% CI 0.14 to 0.52; $p = 0.001$) and zFVC ($\beta = 0.48$, 95% CI 0.25 to 0.70; $p < 0.001$). Higher Fan severity scores were independently associated with lower lung function ($zFEV_1$: $\beta = -0.55$, 95% CI −0.78 to −0.32; $p < 0.001$; zFVC: $\beta = -0.64$, 95% CI −0.91 to −0.37; $p < 0.001$). Diagnostic category was also associated with lung function variability across patients ($zFEV_1$

Table 1
Baseline characteristics of children with and without malnutrition in the chILD-EU registry.

Table 1a. Demographic and clinical characteristics of children with and without malnutrition at baseline

	Children with malnutrition	Children without malnutrition	
	n (%) or median, IQR	n (%) or median, IQR	p
All[1]			
Gender	298 (38.9)	468 (61.1)	
Female	149 (50.0)	207 (44.2)	0.25[a]
Male	149 (50.0)	261 (55.8)	0.28[a]
Age at visit (years)	2.3 (0.5 to 9.5)	3.5 (0.6 to 10.0)	0.14[b]
Gestational age			
Term	199 (68.4)	375 (85.4)	**< 0.001**[a]
Preterm	92 (31.6)	64 (14.6)	**0.01**[a]
Growth parameters			
Height z-score of children	−2.2 (−3.5 to −1.2)	−0.4 (−1.3 to 0.3)	**< 0.001**[b]
BMI z-score of children	−1.9 (−2.9 to −1.2)	−0.1 (−0.8 to 0.8)	**< 0.001**[b]
WFA z-score of children	−2.9 (−4.0 to −2.4)	−0.5 (−1.2 to 0.3)	**< 0.001**[b]
Respiratory rate (z-score)	2.7 (0.7 to 5.2)	2.2 (0.4 to 4.1)	**0.02**[b]
O_2 saturation (%)	96.0 (93.0 to 98.0)	97.0 (94.0 to 98.0)	**0.009**[b]
Pulmonary function test results (n = 246)			
FEV_1 (z-score)	−3.9 (−5.1 to −1.8)	−1.8 (−3.3 to −0.2)	**< 0.001**[b]
FEV_1 (% pred)	50.3 (33.1 to 72.6)	73.2 (56.0 to 90.0)	**< 0.001**[b]
FVC (z-score)	−3.5 (−5.7 to −1.9)	−1.3 (−3.0 to 0.3)	**< 0.001**[b]
FVC (% pred)	56.1 (36.2 to 72.6)	81.5 (61.5 to 95.1)	**< 0.001**[b]
Fan 5 point severity scale [1]			
Asymptomatic (1)	22 (7.5)	57 (12.6)	**0.03**[a]
Symptomatic and normal room air oxygen saturation under all conditions (2)	69 (23.4)	151 (33.4)	**0.01**[a]
Symptomatic and normal resting room air saturation, but abnormal saturation with sleep or exercise (3)	51 (17.3)	85 (18.8)	0.64[a]
Symptomatic and abnormal resting room air saturation (4)	71 (24.1)	90 (19.9)	0.22[a]
Symptomatic with pulmonary hypertension (5)	82 (27.8)	70 (15.5)	**< 0.001**[a]
Specific general medical history[1]			
Gastroesophageal reflux	29 (9.9)	34 (7.5)	0.26[a]
Autoimmune disease	14 (4.8)	20 (4.3)	0.77[a]
Immunodeficiency	20 (6.8)	14 (3.0)	**0.01**[a]
Heart disease	85 (28.9)	92 (20.0)	**0.01**[a]
Intestine disease	29 (9.9)	31 (6.7)	0.13[a]
Kidney disease	28 (9.6)	19 (4.1)	**0.003**[a]
Liver disease	16 (5.5)	20 (4.3)	0.49[a]
Lymphatic system disease	9 (3.1)	6 (1.3)	0.08[a]
Musculoskeletal system disease	44 (15.0)	50 (10.8)	0.11[a]
Nervous system disease	45 (15.4)	56 (12.1)	0.23[a]
Skin disease	32 (11.0)	34 (7.4)	0.10[a]
Thyroid gland disease	21 (7.2)	16 (3.5)	**0.02**[a]
Treatments[1]			
Steroids, systemic	101 (35.2)	158 (34.6)	0.88[a]
Azathioprine	11 (3.8)	21 (4.6)	0.61[a]
Macrolide, long term	79 (27.3)	95 (20.8)	0.07[a]
Hydroxychloroquine	53 (18.3)	71 (15.5)	0.35[a]
Immunglobulins (iv/sc)	12 (4.1)	8 (1.8)	0.06[a]
NO inhaled	21 (7.3)	16 (3.5)	**0.02**[a]
Ventilation methods[1]			
Oxygen supplementation	153 (52.6)	187 (40.9)	**0.02**[a]
Non invasive ventilation	34 (11.7)	43 (9.5)	0.36[a]
Ventilation (invasive, except neonatal ventilation)	35 (12.1)	35 (7.7)	0.05[a]
ECMO/other support	4 (1.4)	3 (0.7)	0.31[c]
Surgery of the intestine (PEG, Fundoplicatio)[a]	49 (16.7)	46 (10.1)	**0.01**[a]

Table 1b. Comparison of children with and without malnutrition at baseline visit in chILD-EU Register according to countries and chILD categories

	Children with malnutrition	Children without malnutrition	
	n (%)	n (%)	p
Country[1]			
Germany	165 (39.0)	258 (61.0)	0.96[a]
Poland	12 (29.2)	29 (70.8)	0.20[a]
Italy	8 (29.6)	19 (70.6)	0.32[a]
Switzerland	11 (52.3)	10 (47.7)	0.21[a]
Turkey	36 (56.2)	28 (43.8)	0.004[a]
UK	34 (34.6)	64 (65.4)	0.39[a]
Others	32 (34.7)	60 (65.3)	0.41[a]
Category of chILD[1]			
A1-Diffuse developmental disorders	11 (36.6)	19 (63.4)	0.79[a]
A2-Growth abnormalities deficient alveolarization	34 (61.8)	21 (38.2)	**< 0.001**[a]
A3-Infant conditions of undefined etiology	36 (24.0)	114 (76.0)	**< 0.001**[a]
A4-related to alveolar surfactant region	78 (46.1)	91 (53.9)	0.05[a]
Ax-unclear RDS in the mature neonate	3 (23.0)	10 (77.0)	0.23[c]

(*continued on next page*)

Table 1 (*continued*)

Table 1b. Comparison of children with and without malnutrition at baseline visit in chILD-EU Register according to countries and chILD categories

	Children with malnutrition	Children without malnutrition	
	n (%)	n (%)	p
Ay-unclear RDS in the almost (30-36 wks) mature neonate	11 (84.7)	2 (15.3)	**< 0.001**[c]
B1-related to systemic disease processes	29 (33.3)	58 (66.7)	0.29[a]
B2-in the presumed immune intact host, related to exposures (infectious/non-infectious)	36 (36.0)	64 (64.0)	0.55[a]
B3-in the immunocompromised host or transplanted	25 (54.3)	21 (45.7)	**0.03**[a]
B4-related to lung vessels structural processes	18 (27.6)	47 (72.4)	0.06[a]
B5-related to reactive lymphoid lesions	2 (25.0)	6 (75.0)	0.42[c]
By-unclear NON-neonate	12 (50.0)	12 (50.0)	0.25[a]
Bz	3 (50.0)	3 (50.0)	0.55[c]

BMI: body mass index, WFA: weight-for-age, FEV_1: forced expiratory volume in 1 s, FVC: forced vital capacity, IQR: interquartile range, ChILD-EU: European Management Platform for Childhood Interstitial Lung Disease, iv: intravenous, sc: subcutaneous, NO: Nitric oxide, ECMO: Extracorporeal membrane oxygenation, PEG: Percutaneous endoscopic gastrostomy, Fan score: five-point severity scale for childhood interstitial lung disease.
Data are presented as n (%) for categorical variables and median (interquartile range [IQR]) for continuous variables unless otherwise specified.
ChILD-EU: European Management Platform for Childhood Interstitial Lung Disease, RDS: Respiratory distress syndrome.
[1]Comparison were made between a variable and the cumulated other variable within this group.
[a] Pearson's Chi-square test.
[b] Mann-Whitney *U* test.
[c] Fisher's exact test.

Table 2
Clinical and nutritional parameters of children with and without malnutrition during follow-up in the chILD-EU registry.

At first year				At second year		
	Children with malnutrition (n = 122)	Children without malnutrition (n = 378)		Children with malnutrition (n = 108)	Children without malnutrition (n = 283)	
	n (%) (median, IQR)	n (%) (median, IQR)	p	n (%) (median, IQR)	n (%) (median, IQR)	p
Growth parameters of children						
Height z-score	−1.6 (−2.5 to −0.5)	−0.6 (−1.3 to 0.2)	**< 0.001**[b]	−1.4 (−2.2 to −0.2)	−0.5 (-1.4 to 0.2)	**< 0.001**[b]
BMI z-score	−1.6 (−2.3 to −1.1)	0.1 (−0.5 to 0.9)	**< 0.001**[b]	−1.7 (−2.5 to −1.3)	0.1 (-0.4 to 0.7)	**< 0.001**[b]
WFA z-score	−2.7 (−3.4 to −2.2)	−0.5 (−1.2 to −0.2)	**< 0.001**[b]	−2.7 (−3.6 to −2.3)	−0.8 (-1.4 to −0.1)	**< 0.001**[b]
Absolute changes in zWFA	0.5 (1.0 to 2.0)	0.3 (0.9 to 1.9)	**< 0.001**[b]	0.17 (0.2 to 1.5)	0.1 (0.1 to 1.4)	**< 0.001**[b]
Respiratory rate z-score	1.8 (0.4 to 4.1)	0.6 (−0.3 to 2.4)	**0.001**[b]	1.2 (0.0 to 3.3)	0.3 (−0.7 to 1.9)	**0.03**[b]
O_2 saturation (%)	97.0 (95.0 to 99.0)	98.0 (96.0 to 98.0)	0.09[b]	96.0 (95.0 to 98.0)	97.0 (96.0 to 98.0)	**< 0.001**[b]
Pulmonary function test results (n = 194)						
FEV_1 z-score	−3.2 (−5.1 to −1.8)	−2.0 (−3.0 to −0.1)	**0.01**[b]	−3.0 (−4.7 to −1.3)	−2.0 (−3.2 to −0.2)	**0.001**[b]
FEV_1 %pred.	57.2 (35.8 to 74.0)	72.4 (59.2 to 87.0)	**< 0.001**[b]	56.2 (39.9 to 72.6)	72.9 (58.5 to 91.1)	**< 0.001**[b]
FVC z-score	−3.1 (−4.8 to −1.2)	−1.5 (−2.8 to −0.2)	**< 0.001**[b]	−3.0 (−4.7 to −1.0)	−1.6 (−2.9 to −0.1)	**0.001**[b]
FVC % pred.	60.9 (44.0 to 72.6)	78.5 (65.7 to 91.0)	**< 0.001**[b]	62.4 (45.3 to 77.1)	77.3 (63.1 to 90.8)	**< 0.001**[b]
Fan 5 point severity scale[A]						
Asymptomatic (1)	27 (24.1)	128 (36.4)	0.05[a]	22 (22.7)	115 (44.2)	**0.003**[a]
Symptomatic and normal room air oxygen saturation under all conditions (2)	34 (30.4)	112 (31.8)	0.81[a]	34 (35.1)	78 (30.0)	0.44[a]
Symptomatic and normal resting room air saturation, but abnormal saturation with sleep or exercise (3)	22 (19.6)	69 (19.6)	1.00[a]	17 (17.5)	32 (12.3)	0.23[a]
Symptomatic and abnormal resting room air saturation (4)	19 (17.0)	23 (6.5)	**0.001**[a]	11 (11.3)	19 (7.3)	0.25[a]
Symptomatic with pulmonary hypertension (5)	10 (8.9)	20 (5.7)	0.23[a]	13 (13.4)	16 (6.2)	**0.03**[a]

ChILD-EU: European Management Platform for Childhood Interstitial Lung Disease, IQR: interquartile range, BMI: Body mass index, WFA: Weight-for-age, O_2: Oxygen, FEV_1: forced expiratory volume in the first second, FVC: forced vital capacity, pred.: predicted.
[c] Fisher's exact test.
Data are presented as n (%) or median (IQR). P values represent comparisons between children with and without malnutrition at each follow-up time point.
[a] Pearson's Chi-square test.
[b] Mann-Whitney *U* test.

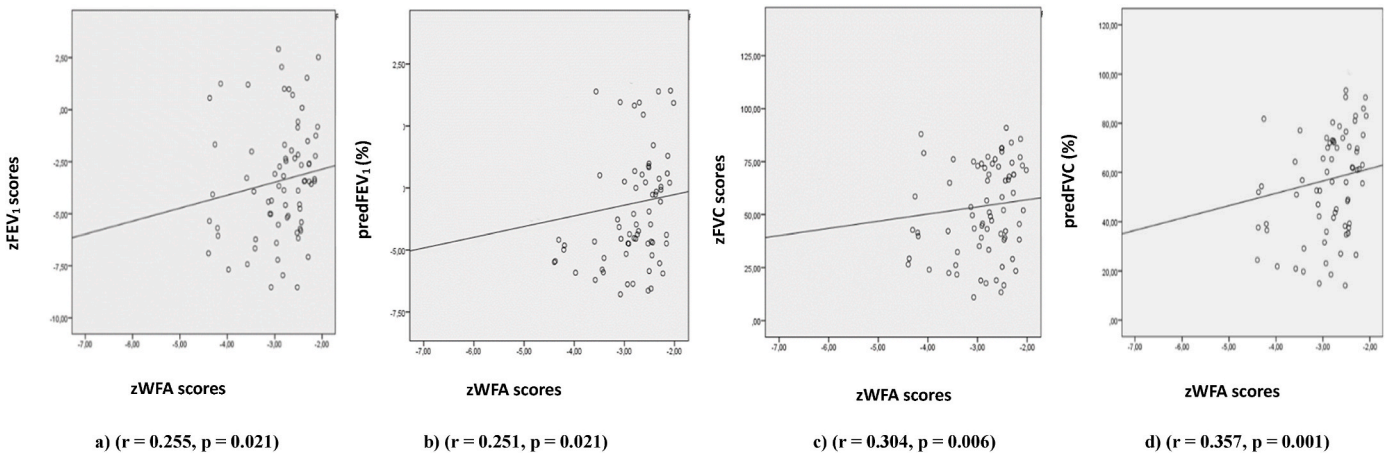
p = 0.002; zFVC p = 0.009). In contrast, age at visit, sex, and gestational age were not significantly associated with lung function in the adjusted models.

Sensitivity analyses were performed using alternative anthropometric indicators, including BMI z-scores and height-for-age z-scores, to evaluate the robustness of the observed associations between nutritional status and lung function.

In multivariable regression models adjusted for age at visit, sex, gestational age, diagnostic subgroup, and Fan severity score, BMI z-scores were positively associated with lung function parameters. Specifically, higher BMI z-scores were associated with higher $zFEV_1$ values (β = 0.44, 95% CI 0.25 to 0.63; p < 0.001) and higher zFVC values (β = 0.58, 95% CI 0.35 to 0.81; p < 0.001).

In contrast, height-for-age z-scores were not independently associated with lung function ($zFEV_1$: β = 0.05, 95% CI −0.14 to 0.24; p = 0.610; zFVC: β = 0.14, 95% CI −0.08 to 0.36; p = 0.21).

Longitudinal mixed-effects models further supported these findings. Time-varying BMI z-scores were significantly associated with lung function over time ($zFEV_1$: β = 0.33, 95% CI 0.14 to 0.52; p = 0.001), whereas height-for-age z-scores did not show a significant association



a) (r = 0.255, p = 0.021) b) (r = 0.251, p = 0.021) c) (r = 0.304, p = 0.006) d) (r = 0.357, p = 0.001)

Fig. 1. Correlations of lung function and nutritional status in children with malnutrition at baseline according to Spearman's correlation tests.

Table 3
Multivariable linear regression models evaluating factors associated with lung function at baseline.

Predictor	$zFEV_1$ β (95% CI)	p value	zFVC β (95% CI)	p value
Malnutrition	−1.28 (−1.89 to −0.68)	**< 0.001**	−1.80 (−2.50 to −1.10)	**< 0.001**
Fan severity score	−0.52 (−0.75 to −0.29)	**< 0.001**	−0.60 (−0.87 to −0.33)	**< 0.001**
Diagnostic category	0.06 (−0.05 to 0.17)	0.27	0.06 (−0.06 to 0.19)	0.34
Age at visit	−0.05 (−0.11 to 0.01)	0.12	−0.007 (−0.08 to 0.06)	0.85
Female sex	0.43 (−0.13 to 1.00)	0.13	0.44 (−0.21 to 1.10)	0.18
Gestational age	0.19 (−0.68 to 1.07)	0.66	0.22 (−0.78 to 1.23)	0.66

FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; CI: confidence interval.
Baseline multivariable models were adjusted for:

- Age at visit
- Sex
- Prematurity
- Diagnostic category
- Fan severity score

Mixed-effects models included:

- Random intercept for patient ID
- Fixed effects for visit time
- Adjustment for age, sex, prematurity, diagnostic category, and Fan severity score.

(p = 0.703). Overall, these analyses confirmed the robustness of the association between weight-related nutritional indicators and lung function.

At baseline (n = 766), malnutrition—defined as a WFA z-score < −2—was observed in 298 children (38.9%). During follow-up, the proportion of children classified as malnourished decreased. At the first-year visit with available data (n = 500), malnutrition was present in 122 children (24.4%). At the second-year follow-up (n = 391), 108 children (27.6%) remained malnourished. These longitudinal observations suggest that nutritional status may improve in a subset of children with chILD during follow-up; however, persistent malnutrition remains common, underscoring the importance of continuous nutritional monitoring and support in this population.

3.3. Correlation between nutritional status and lung functions

In children with malnutrition, absolute changes of zWFA from baseline to 1-year and from 1-year to 2-year follow-up correlated positively with changes in lung function: Change in, $zFEV_1$ from baseline to year 1: r = 0.45, p = 0.001; change in $zFEV_1$ from year 1 to year 2: r = 0.46, p = 0.010 (Fig. 2).

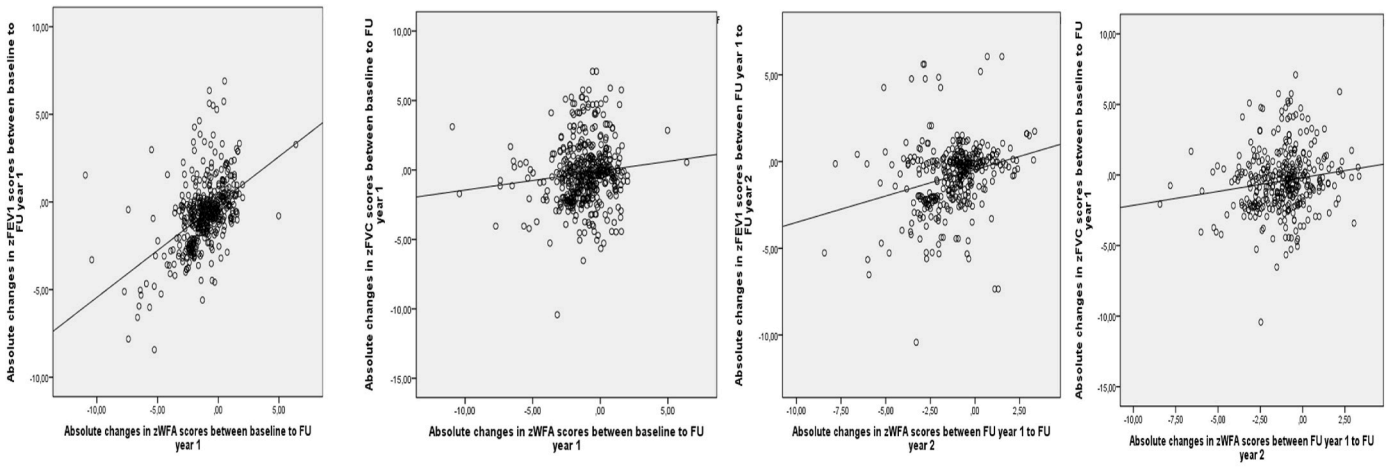
4. Discussion

To our knowledge, this is the first large-scale study to investigate the prevalence of malnutrition in chILD and its clinical associations. We found that malnutrition was highly prevalent at baseline (38.9%) and remained common at follow-up, affecting 27.6% of children at the second-year visit. During follow-up, the proportion of children classified as malnourished decreased, suggesting that nutritional status may improve in a subset of children over time. Importantly, malnutrition was significantly associated with disease severity and poorer lung function.

Undernutrition remains a major global health problem and is estimated to contribute to approximately 45% of deaths among children under five years of age, particularly in low- and middle-income countries [23,24]. While wasting affects an estimated 6.8% of children globally [25], the prevalence of malnutrition in our chILD cohort far exceeded population estimates, underscoring the vulnerability of this patient group. In adults, studies have demonstrated a correlation between low BMI and weight loss and higher mortality rates. In adult patients with ILD, malnutrition has been linked to reduced exercise capacity, decline in lung function, and increased mortality [26,27]. Malnutrition was seen in 66.67% of infants with bronchopulmonary dysplasia (BPD), markedly higher than 36.88% in the group without BPD. Malnutrition was an independent risk factor for the duration of invasive respiratory support during hospitalization [28]. Bouvart et al. [29] determined that the prevalence of malnutrition among children with CF is 46%. Further research revealed that children with CF who had lower height-for-age, WFA, and BMI z-scores also had lower FEV_1 z-scores [30]. Similar concerns apply to children with chILD, in whom chronic respiratory disease may increase energy requirements and reduce appetite and nutrient absorption. Therefore, it is important to closely monitor and provide appropriate dietary guidance to mitigate weight loss over the course of treatment.

The relationship between nutritional status and pulmonary outcomes has been well described in CF. In children with CF, improved nutritional status and growth parameters, including weight and stature, have been associated with better lung function and a slower decline in pulmonary function over time. Consequently, nutritional optimization has become a central component of CF management strategies (5, 29, 30). Although the pathophysiological mechanisms underlying chILD differ from those of CF, our findings suggest that nutritional status may similarly influence respiratory outcomes in this population, emphasizing the importance of early nutritional assessment and targeted nutritional support in children with chILD.

We found that malnutrition was more frequent in specific diagnostic



a) (r = 0.502, p < 0.001) **b) (r = 0.134, p = 0.004)** **c) (r = 0.295, p < 0.001)** **d) (r = 0.212, p < 0.001)**

Fig. 2. Correlations of absolute changes in zWFA scores in children with malnutrition according to Spearman's correlation tests FEV1: forced expiratory volume in the first second, FVC: forced vital capacity, pred.: predicted, WFA z-score: Weight-for-age z-score, FU: Follow-up.

subgroups like A2 (growth abnormalities with deficient alveolarization), Ay (unclear RDS in late preterm neonates), and B3 (immunocompromised or transplanted). In contrast, children in the A3 group (which is typically with milder, self-limiting conditions like Neuroendocrine cell hyperplasia of infancy (NEHI)) had lower rates of malnutrition. These findings support the concept that underlying disease severity and complexity contribute substantially to nutritional risk [31,32].

Children with ILD often exhibit numerous extrapulmonary comorbidities, including immunodeficiency, heart disease, autoimmune disease, musculoskeletal system diseases, and nervous system diseases [33]. Children with malnutrition showed a higher frequency of immunodeficiency, cardiac and renal disorders, and thyroid dysfunction at the baseline visit. At the second-year visit, additional associations with liver diseases and lymphatic and musculoskeletal diseases were noted. Heart disease was the most common comorbidity of all. These findings align with current guidelines recommending echocardiography in all children with ILD to identify concomitant heart disease and pulmonary hypertension and exclude heart diseases that may present with symptoms similar to or exacerbate ILD [34].

Gastroesophageal reflux (GERD) has been implicated in both malnutrition and ILD progression, but in our cohort, its recorded prevalence was relatively low (8.2%) compared to other studies [12,13]. This may indicate underdiagnosis, especially if symptoms are subtle or obscured by respiratory signs, or if GERD is not systematically screened during follow-up [12,35]. Percutaneous Endoscopic Gastrostomy (PEG) and fundoplication were more common in children with malnutrition, indicating that gastrointestinal complications were more severe or persistent in this group. However, antireflux surgery should be reserved for rare cases and performed when other treatments are insufficient. In particular, children with malnutrition and swallowing dysfunction should be evaluated for PEG in the early phase.

In line with previous adult studies, we found that low BMI and zWFA were associated with poorer lung function and higher respiratory rate [11,36,37]. Improvements in WFA over time were positively correlated with spirometry results and oxygen saturation, while higher respiratory rates were associated with poorer nutritional status. These findings further support the potential importance of nutritional status as a modifiable factor in chILD management and prognosis, and early detection of malnutrition in children with ILD and implementation of suitable dietary interventions are crucial.

Importantly, the association between malnutrition and impaired lung function remained significant after adjustment for potential confounding factors. In multivariable linear regression models adjusting for age at visit, sex, diagnostic subgroup, gestational age, and Fan severity score, malnutrition was independently associated with lower $zFEV_1$ and zFVC values at baseline. These findings suggest that the relationship between nutritional status and pulmonary function is not merely explained by differences in disease severity or demographic characteristics. In contrast, age, sex, gestational age, and diagnostic subgroup were not independently associated with lung function in the adjusted models, highlighting the particularly strong relationship between nutritional status and pulmonary impairment in children with chILD.

Longitudinal analyses confirmed the relationship between nutritional status and pulmonary function. In mixed-effects models accounting for repeated measurements, higher WFA z-scores were significantly associated with better lung function over time. This finding suggests that improvements in nutritional status may be accompanied by improvements in pulmonary function in children with chILD. Consistent with our baseline analyses, higher Fan severity scores were associated with poorer lung function, supporting the validity of the clinical severity classification used in the registry. Together, these findings emphasize the potential importance of nutritional status as a modifiable factor influencing respiratory outcomes in this population.

Sensitivity analyses using alternative anthropometric indicators further supported our primary findings. BMI z-scores demonstrated a significant association with lung function parameters, whereas height-for-age z-scores were not independently associated with pulmonary function. These findings suggest that weight-based indicators may be more sensitive in capturing clinically relevant changes in nutritional status in children with chronic respiratory disease. Similar observations have been reported in other chronic pediatric lung diseases, where body weight and BMI are more closely related to pulmonary outcomes than linear growth parameters. Together, these findings reinforce the potential importance of nutritional status as a modifiable factor influencing respiratory outcomes in children with chILD.

The most prevalent pharmacologic therapies for children with ILD are anti-inflammatory and immunosuppressive treatments such as corticosteroids, hydroxychloroquine, and azithromycin—which all may impact appetite, nausea, abdominal pain, gastrointestinal tolerance, and metabolism [7,38–40]. Although corticosteroids were the most commonly used therapy, no significant differences were observed between groups. Hydroxychloroquine use was numerically higher but not statistically significant, whereas inhaled nitric oxide was more frequently used in malnourished children, likely reflecting greater disease severity. Importantly, potential nutritional side effects of medication should be closely monitored.

4.1. Strengths and limitations

The strengths of this study include its large, multinational cohort from the standardized chILD-EU Register, with peer-reviewed diagnoses and comprehensive clinical data, such as growth, lung function, and disease severity measures. The longitudinal design with follow-up over two years allowed us to assess both prevalence and progression of malnutrition in relation to clinical outcomes, marking the first large-scale study to address this topic in children with ILD.

Limitations include its observational nature, which precludes causal inference, and reliance on registry data with variable completeness and follow-up duration. The absence of 6-month follow-up data may have limited our ability to capture short-term nutritional changes during early follow-up, particularly in younger children. Because anthropometric data were collected across multiple centers as part of routine clinical care, detailed information on measurement standardization, equipment type, and calibration procedures was not available in the registry, which may have introduced some degree of inter-center variability. In addition, data on dietary intake, resting energy expenditure, and body composition were not available in the registry dataset. These parameters may elucidate the mechanisms contributing to malnutrition in children with chronic respiratory diseases and warrant assessment in forthcoming prospective studies. The lack of mortality and loss to follow-up data may have introduced attrition bias, limiting interpretation of longitudinal changes in nutritional status. Lung function measurements were available primarily in older children able to perform reliable spirometry. Consequently, pulmonary function analyses may reflect a subset of patients within the cohort. To mitigate this limitation, statistical models were adjusted for age, and longitudinal mixed-effects analyses were performed to account for repeated measurements. Fraction of inspired oxygen (FiO_2) values were not available across centers, particularly in patients receiving variable oxygen delivery methods. Therefore, SpO_2/FiO_2 ratios could not be reliably calculated. Potential underreporting of gastrointestinal comorbidities such as GERD may also have affected findings, leading to an incomplete understanding of the overall health status of the patients in the study.

5. Conclusion

In our study, malnutrition is highly prevalent among children, particularly in those with more severe diseases and impaired lung function. It is associated with a greater burden of comorbidities and a more adverse clinical trajectory. These results underscore the necessity for regular nutritional evaluations and prompt, multidisciplinary interventions in malnourished children. Systematic nutritional management—including dietary counting, monitoring, and even, when necessary, supportive interventions such as enteral feeding—may help mitigate disease progression and improve outcomes. Further studies are needed to evaluate the long-term impact of targeted nutritional strategies in this vulnerable population.

CRediT authorship contribution statement

Tugba Ramasli Gursoy: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing. **Nagehan Emiralioglu:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing. **Matthias Griese:** Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing. **Elias Seidl:** Data curation, Project administration, Supervision, Visualization, Writing – review & editing. **Julia Rodler:** Conceptualization, Data curation, Methodology, Supervision, Writing – review & editing. **Nicolaus Schwerk:** Conceptualization, Investigation, Methodology, Software, Supervision, Writing – review & editing. **Julia Carlens:** Conceptualization, Formal analysis, Investigation, Supervision, Writing – review & editing. **Martin Wetzke:** Conceptualization, Data curation, Methodology, Supervision, Writing – review & editing. **Nadia Nathan:** Conceptualization, Data curation, Methodology, Supervision, Writing – review & editing. **Steve Cunningham:** Conceptualization, Investigation, Methodology, Supervision, Writing – review & editing. **Joanna Lange:** Conceptualization, Methodology, Software, Visualization, Writing – review & editing. **Katarzyna Krenke:** Conceptualization, Project administration, Validation, Visualization, Writing – review & editing. **Florian Stehling:** Conceptualization, Investigation, Software, Visualization, Writing – review & editing. **Susanne Hämmerling:** Conceptualization, Software, Supervision, Validation, Writing – review & editing. **Marijke Proesmans:** Conceptualization, Investigation, Validation, Visualization, Writing – review & editing. **Nicola Ullmann:** Conceptualization, Project administration, Software, Supervision, Writing – review & editing. **Frederik Buchvald:** Conceptualization, Software, Supervision, Visualization, Writing – review & editing. **Antonio Moreno Galdo:** Conceptualization, Investigation, Methodology, Visualization, Writing – review & editing. **Ayse Tana Aslan:** Conceptualization, Investigation, Methodology, Visualization, Writing – review & editing. **Nazan Cobanoglu:** Conceptualization, Data curation, Methodology, Visualization, Writing – review & editing. **Nural Kiper:** Conceptualization, Methodology, Supervision, Visualization, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

This work was supported by the COST Action CA16125 European Network for Translational Research in Children's and Adult Interstitial Lung Disease and by the Clinical Research Collaboration for chILD of the European Respiratory Society.

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