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Survival-Adjusted FEV1 and BMI Percentiles for Patients with Cystic Fibrosis before the Era of Triple CFTR Modulator Therapy in Germany

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Keywords

Cystic fibrosis · FEV1 · BMI · Percentile · Mortality attrition · Survival · Disease severity

Abstract

Background: Pulmonary disease is the major cause for morbidity and mortality in cystic fibrosis (CF). In CF, forced expiratory volume in 1 s (FEV1) referenced against a healthy population (FEV1%predicted) and body mass index (BMI) do not allow for the comparison of disease severity across age and gender. ***Objectives:*** We aimed to determine updated FEV1 and BMI percentiles for patients with CF and to study their dependence on mortality attrition. ***Methods:*** Age- and height-adjusted FEV1 and BMI percentiles for CF patients aged 6–50 years were calculated from 4,947 patients of the German CF Registry for the period 2016–2019 utilizing quantile regression and a Generalized Additive Model for Location, Scale and Shape (GAMLSS). Further, survival-adjusted percentiles were estimated. ***Results:*** In patients with CF, FEV1 increased throughout childhood until maximal median values at 16 years in females (2.46 L) and 18 years in males (3.27 L). During adulthood, FEV1 decreased substantially. At 17 years of age, the 25th BMI percentile of patients with CF (females 18.50 and males 18.15 kg/m^2) was below the 10th BMI percentile of the German reference cohort. From the age of 20 years, survival (96.3%) decreased tremendously. At 50 years of age (survival 15.0%), the 50th CF-

Registry working group of the German CF Registry, https://muko.info/register.

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specific FEV1 or BMI percentile among the survivors corresponded to the 92.5th percentile among the total CF birth cohort. ***Conclusions:*** Continuously updated disease-specific FEV1 and BMI percentiles with correction for survival may serve as age-independent measure of disease severity in CF (accessible via https://cfpercentiles.statup.solutions).

Introduction

Chronic progressive lung disease remains the most common cause for morbidity and mortality in patients with cystic fibrosis (CF) and forced expiratory volume in 1 s (FEV1) measured by spirometry is one of the best validated outcome parameters for CF disease progression [1–3]. Structural lung damage appears in early childhood of patients with CF, far before the occurrence of altered lung function or respiratory symptoms [4–6]. In adults with CF, FEV1 ranges from almost normal to substantial reduced lung function in end-stage lung disease with advanced bronchiectasis and respiratory failure [1, 7, 8]. Due to chronic airway destruction and recurrent acute exacerbations, pulmonary function keeps falling gradually over lifetime in CF patients, with the rate of deterioration mainly determined by the disease phenotype [1, 9]. In addition, malnutrition is known to be an important factor in poor lung growth and a predictor for later lung function in CF patients [10–12]. Low body mass index (BMI) is associated with reduced respiratory muscle strength, increased number of exacerbations, limited lung function, and higher mortality [1, 10–13].

Due to the remarkable advances in CF therapy after the approval of highly effective modulator treatments (HEMTs), maintaining near-to-normal lung function is becoming a reasonable therapeutic goal and in clinical practice FEV1 is usually referenced against a lung-healthy population (FEV1%predicted) [1, 14]. However, this approach does not distinguish mild from severe CF lung disease in different birth cohorts. A recent Australian registry study found that FEV1%predicted decreases in patients with CF depending on age, with the steepest decrease occurring between the ages of 6 and 30 years. Multivariate analysis identified the age at visit as one significant predictor of FEV1%predicted [10, 14]. These findings suggest that the natural history of CF, in addition to the age, height, and gender-related trends in FEV1 seen in healthy individuals, may contribute to the decline in FEV1%predicted in patients with CF. In the event of a similar FEV1%predicted, the younger patient would therefore suffer from a more severe lung disease than the older patient with CF. For the understanding of age-independent influences on CF lung disease, for example, genetic modifiers or environmental influences, CF-specific percentiles accounting for the age-dependent lung function loss could therefore provide a valuable tool [15–18].

For better comparability of lung disease severity of CF patients of different age, CF-specific reference equations of FEV1 and BMI were proposed for North America and Europe [15–18]. As life expectancy of patients with CF is steadily increasing, age range in CF becomes broader and the proportion of adult patients is growing significantly [1, 19, 20]. The higher mortality of patients with severe CF lung disease results in a positive selection of mild disease phenotypes in older patients [18]. However, survival data of patient registries can be used to correct CF-specific FEV1 and BMI percentiles for mortality attrition [18]. Since age-adjusted lung function continuously increased over the past decades, recurring updates of CF-specific percentiles are essential [15–18]. In particular, the widespread usage of the triple cystic fibrosis transmembrane conductance regulator (CFTR) modulator therapy with ivacaftor/tezacaftor/elexacaftor since 2020 may lead to significant health benefits for the majority of patients with CF. To estimate these effects, health data from the pre-HEMT era are necessary. The aims of this study were, therefore, (1) to determine updated disease-specific FEV1 and BMI percentiles for a representative central European country as measure of disease severity in CF from a most recent time span before HEMT approval and (2) to correct those for mortality attrition. To achieve this goal, we analyzed FEV1 and BMI data of the German Cystic Fibrosis Registry from 2016 to 2019 [3].

Methods

Study Population

In this retrospective population-based registry study, we used data from patients with CF registered in the German Cystic Fibrosis Registry between 2016 and 2019, containing patients from 92 CF centers in Germany (Table 1). For the German Cystic Fibrosis Registry, a central ethical approval was obtained. Informed consent was acquired from every registry participant or their legal guardian. We included all patients with at least one recorded lung function in the first year of the study period. Patients that underwent lung transplantation were excluded from analysis after transplantation. FEV1%predicted was calculated from raw FEV1 utilizing the Global Lung Initiative (GLI) prediction equations [14].

Table 1. Study population per year

	2016	2017	2018	2019
CF centers (*n*)	92	90	90	87
Percentile estimation				
Patients (*n*)	4,947	4,624	4,499	4,337
Correction factor estimation				
Patients (*n*)	3,758	4,078	4,311	4,536
Visits (*n*)	13,334	14,323	15,209	15,845

Computational Analysis

The German Cystic Fibrosis Registry consists of two documentation levels: while level 1 records patient data only once yearly at the date with the best FEV1%predicted, level 2 additionally aggregates the clinical data of all visits in the calendar year. To maximize the number of study subjects, we used the annual data set of level 1 (Table 1). Since the resulting selection error might lead to an overestimation in FEV1 curves, we utilized the continuous data of level 2 for the calculation of a correction factor as reported previously [16]. In brief, the average difference between the best FEV1 value and an unselected FEV1 value was determined for each age and gender and then subtracted from individual FEV values of level 2. Locally estimated scatterplot smoothing regression was applied for smoothing. For this purpose, all data sets from level 2 available in the respective calendar year were used, independently of the cohort examined longitudinally for percentile estimation (Table 1). Disease-specific FEV1 and BMI percentiles were then estimated for patients from 6 to 50 years utilizing two established approaches, nonparametric quantile regression and a Generalized Additive Model for Location, Scale and Shape (GAMLSS) based on a Box-Cox-Cole-Green distribution method [15–17, 21–23]. According to previous studies [16], cubic b-splines with 6 nodes were applied to determine the nonlinear effect of age or height on FEV1 and BMI. The best fitting model was chosen by the Bayesian information criterion and contains a log link for both mu and sigma and cubic splines of degree 5. To avoid computational instabilities and artefacts at the limits of the studied age interval, FEV1 values outside this range were included into percentile estimation. The German CF Registry was founded 1995 and no complete birth cohorts are available for the period before. Therefore, survival was estimated by the approach suggested by Taylor et al. [18]: For patients born in 1995 or later, survival was calculated by dividing the number of CF patients alive on December 31th, 2017 (middle of observation interval) by the number of registered CF births in the respective birth cohort. For patients born before 1995, the number of documented births in the registry was compared with the theoretical number of CF births calculated from the total population (Federal Statistical Office of Germany) [24]. On average, one CF birth was recorded in the registry per 4,000 live births in Germany. Survival was then estimated for each CF birth cohort as the ratio of patients alive on December 31th, 2017, and the expected number of patients born in the corresponding birth cohort (1/4,000). Derived survival curves were smoothed by locally estimated scatterplot smoothing regression. As proposed by Taylor et al. [18], age-specific, survival-adjusted percentiles Xcorr were calculated from the uncorrected percentile X value, the cohort survival percentile S, and the cohort mortality percentile 1-S as follows:

Table 2. Clinical characteristics of patients with CF at beginning of the study period

Age, years	
Median (IQR)	21 (13–31)
Range	3–78
Sex, *n*(%)	
Males	2585 (52.3)
Females	2362 (47.7)
BMI, kg/m^2	
Median (IQR)	19.5 (16.9–22.0)
Range	11.5–46.2
FEV1% predicted GLI	
Median (IQR)	79.0 (55.0–96.0)
Range	11–146
CFTR genotype, *n* (%)	
F508del/F508del	2323 (47.0)
F508del/other	1938 (39.2)
Other/other	640 (12.9)
Unknown	46 (0.9)
Ethnicity, *n* (%)	
Caucasian	4634 (93.7)
Turkish	161 (3.3)
Asian	18 (0.4)
African	11 (0.2)
Mixed	27 (0.5)
Other	45 (0.9)
Unknown	51 (1.0)
Pancreatic status, *n* (%)	
Insufficient	4508 (91.1)
Sufficient	363 (7.3)
Unknown	76 (1.5)
Last CFTR modulator therapy, *n* (%)	
Yes	1631 (33.0)
Ivacaftor/tezacaftor	700 (14.1)
Ivacaftor/lumacaftor	525 (10.6)
Ivacaftor mono therapy	375 (7.6)
Other	31 (0.6)
No	3316 (67.0)

BMI, body mass index, FEV_1% predicted GLI, forced expiratory volume in 1 second % predicted after Global Lung Initiative, CFTR: cystic fibrosis transmembrane conductance regulator, IQR: interquartile range 25–75th percentile.

$$Xcorr = X \times S + (1 - S)$$

All statistical procedures were conducted with R 4.1.0 (R Core Team. R: a language and environment for statistical computing. R Foundation for Statistical Computing. *Vienna Austria* 2).

Results

Patient Characteristics

4,947 patients with CF were included into the study (18,407 visits). Post-transplant measurements of 151

patients (3.1%) were excluded from the year of lung transplantation and 181 patients (3.7%) died during the conduct of study. Baseline patient characteristics are summarized in Table 2. The cohort covered a wide age range from 3 to 78 years and a broad spectrum of pulmonary function with FEV1%predicted from 11 to 146%. Females and males were represented in roughly equal proportions, with a slight surplus of males, especially in older ages (online suppl. Fig. 1; for all online suppl. material, see www.karger.com/doi/10.1159/000529524). The majority of study subjects were pancreatic insufficient and F508del homo- or heterozygous (Table 2). Most patients could be assigned to Caucasian or Turkish population (white background, $n = 4795$, 96.9%), which is why no separate analysis was carried out for the various ethnic groups (Table 2).

CF-Specific FEV1 Percentiles

Disease-specific percentiles were similar in quantile regression and GAMLSS method. In the following text, data of the GAMLSS model are used as suggested previously [14, 23]. CF-specific FEV1 percentiles according to age are displayed in Figure 1a (male), b (female). At an age of 6 years, the median FEV1 was 1.03 L in girls and 1.10 L in boys. FEV1 of girls and boys increased continuously throughout childhood, started to diverge between sexes from the age of 12 years (median FEV1 in females 2.03 L and in males 2.15 L) and reached maximal median values at 16 years for females (2.46 L) and at 18 years for males (3.27 L). At an age of 21 years, FEV1 had the widest spread in both sexes with a difference between the 3rd and the 97th percentile of 4.34 L in males and 3.06 L in females. During adulthood, FEV1 decreased substantially to median values of 1.38 L in females and 1.95 L in males at 50 years of age. Of note, in patients below the 50th percentile the decrease of FEV1 started earlier in life (Fig. 1a, b). Height-adjusted FEV1 percentiles are shown in Fig. 1c, d. Up to a height of 130 cm in females and 145 cm in males, FEV1 increased almost linearly. Above these values, the slopes of the curves diverged from each other: In higher percentiles, the linear increase continued, whereas in lower percentiles hardly any association of FEV1 and body height was observed. As expected, females had lower FEV1 values than males for the same age or height. These differences were particularly evident in high percentile ranges (Fig. 1a, b).

CF-Specific BMI Percentiles

Further, development of nutritional status in CF was investigated. CF-specific BMI percentiles adjusted for age corresponded to characteristic BMI growth curves (Fig. 2a, b) [16, 25]. Compared to the general population [25], nutritional deficiency of CF patients occurred early in childhood and increased with age. At an age of 6 years, median BMI of girls (15.03 kg/m^2) and boys with CF (15.18 kg/m^2) was only slightly below the German reference values (50th BMI percentile of general population, girls 15.49 kg/m^2 and boys 15.53 kg/m^2) [25]. In both sexes, BMI increased during childhood and adolescence but less steep than in the reference cohort [25]. At an age of 17 years, the 25th BMI percentile of patients with CF (females 18.50 kg/m^2 and males 18.15 kg/m^2) was already lower than the 10th BMI percentile of the German reference cohort (females 18.63 kg/m^2 and males 18.44 kg/m^2) [25], indicating that more than 25% of these adolescents with CF were underweight. During adulthood, BMI percentile curves flattened with median BMI of 20.3–21.2 kg/m^2 for females and 20.2–22.8 kg/m^2 for males.

Effect of Mortality Attrition on CF-Specific Percentiles

During childhood and adolescence, mortality of the analyzed CF cohort was minimal with survival rates above 95%. However, from the age of 20 years survival decreased noticeably. Figure 3 illustrates the substantial effect of survival adjustment on disease-specific percentile values in adulthood. After correction for mortality attrition, a patient with a disease-specific FEV1 or BMI percentile of 50% would lay on the 50.35th percentile at the age of 6 years and on the 51.55th percentile at the age of 19 years. From the age of 20 years, the survival-adjusted percentile of that patient would increase rapidly to a value of 92.50% at the age of 50 years, indicating that approximately 92.50% of the CF patients in the original birth cohort would have an FEV1 or BMI lower than this individual patient. In the lower percentile ranges, this effect was even more obvious. Patients on the third percentile of their surviving peers were already above the 75th percentile at the age of 45 years when compared to their total birth cohort (Fig. 3).

Online Calculator

The proposed percentiles are accessible to the public via an online calculator (https://cfpercentiles.statup.solutions). Based on the input variables gender, age (years), height (cm), FEV1 (L), and weight (kg), the following output parameters can be estimated for an individual patient (Table 3; online suppl. Fig. 2):

- First, the parameter survival provides the percentage of patients who survived until the age of the patient.
- The FEV1 and BMI percentile values represent the percentage of alive CF patients with the same age,

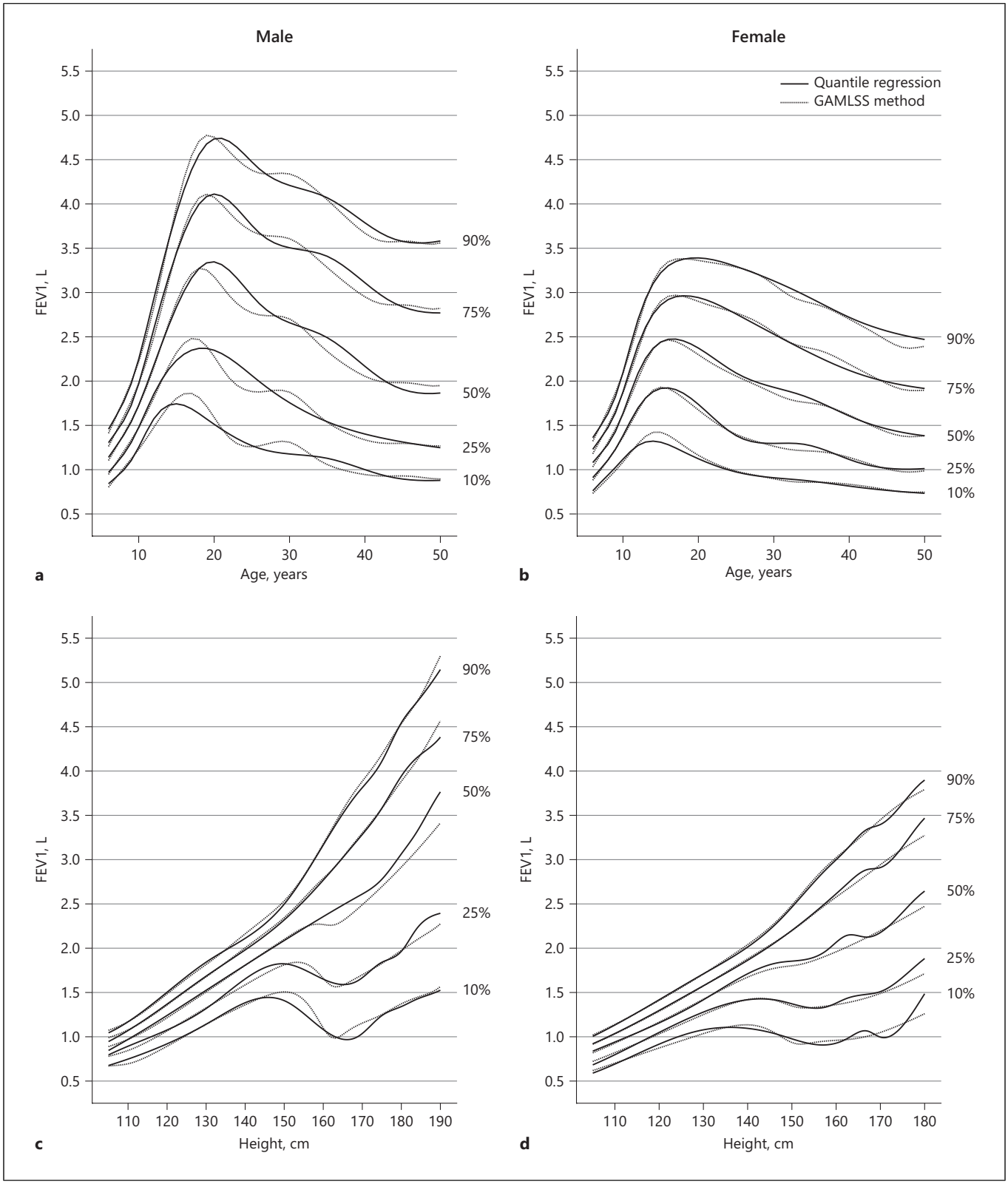

Fig. 1. Disease-specific percentiles of forced expiratory volume in 1 s (FEV1) according to age (**a**, **b**) and body height (**c**, **d**) by age in years for males and female patients with CF. Solid lines correspond to quantile regression, dotted lines to a Generalized Additive Model for Location, Scale and Shape (GAMLSS).

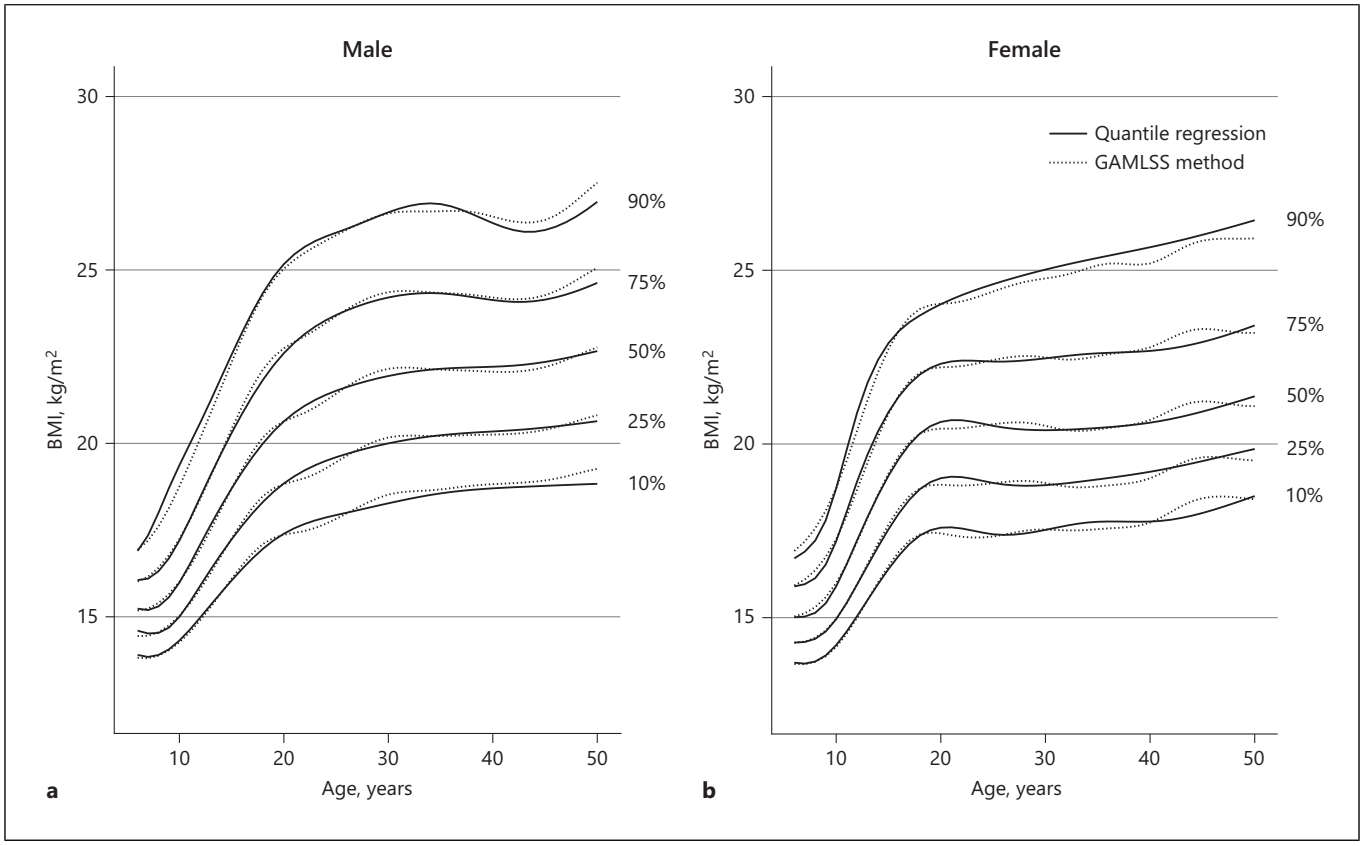

Fig. 2. Disease-specific body mass index (BMI) percentiles according to age by age in years – for male (**a**) and female (**b**) patients with cystic fibrosis (CF). Solid lines correspond to quantile regression, dotted lines to a Generalized Additive Model for Location, Scale and Shape (GAMLSS).

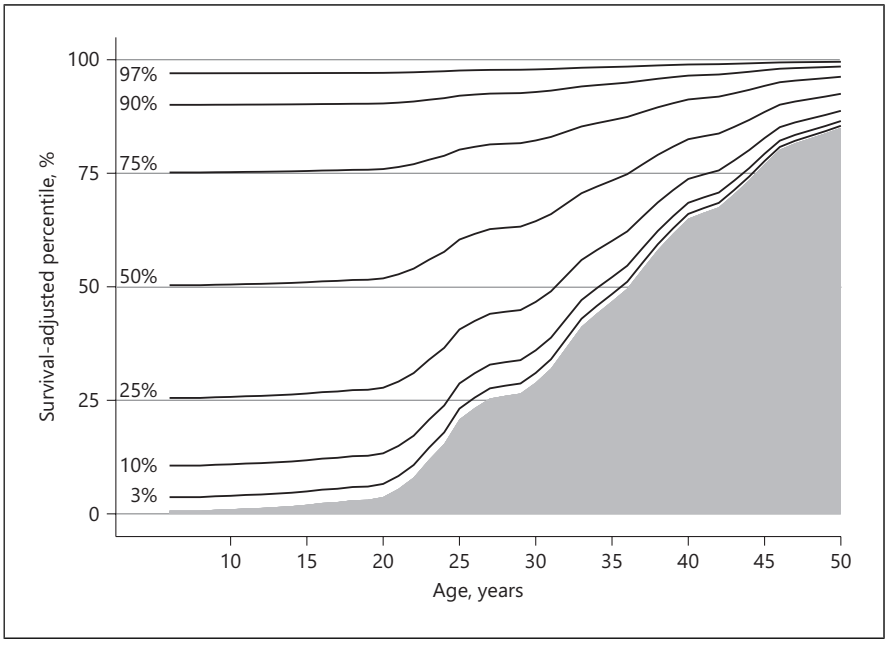

Fig. 3. Effect of correction for mortality attrition on the 3rd to 97th percentile of the surviving patients with cystic fibrosis (CF). The proportion of deceased patients is highlighted in gray. Note that at 50 years of age the 3rd–97th CF-specific percentiles among the survivors corresponded to the 85.45th to 99.55th percentile among the total CF birth cohort.

Table 3. Output parameters of the online calculator

Output parameters	Estimated percentage
Survival (%)	• Of CF patients who survived until the individuum's age based on survival analysis
FEV1 percentile (%)	• Of surviving CF patients with the same gender, age, and height that had a lower FEV1 than the individuum
FEV1 percentile survival corrected (%)	• Of the total CF birth cohort (including patients already died at the individuum's age) with the same gender and height that had a lower FEV1 than the individuum
BMI percentile (%)	• Of surviving CF patients with the same gender, age, and height that had a lower BMI than the individuum
BMI percentile survival corrected (%)	• Of the total CF birth cohort (including passed patients already died at that age) with the same gender and height that had a lower BMI than the individuum

height, and gender, which have a lower FEV1 than the respective patient.

- The FEV1 and BMI percentile values corrected for survival relate to the birth cohort of that patient and give the percentage of both living and passed clinical peers with lower FEV1 or BMI. Dead patients are assigned with an FEV1 or BMI values of 0. As a result, the FEV1 and BMI percentiles relative to the total birth cohort are higher than those relative to the living CF population.

Discussion

In this study, we calculated contemporary CF-specific reference equations of FEV1 and BMI for a representative central European country from the most recent era before the widespread usage of triple CFTR modulator therapy utilizing a large multicenter cohort. These disease-specific percentiles can be applied for the comparison of individual CF patients with their peers and thus for the classification of disease severity in CF across age-groups. Further, we determined survival of the underlying CF cohort and studied the effect of mortality attrition on disease-specific percentiles. Our data show that mortality has minor effects on disease-specific percentiles in childhood but remarkable influences in adulthood.

In clinical practice, FEV1%predicted of normal is essential to assess the clinical relevance of the lung function loss in individual patients with CF. The here proposed CF-specific BMI and FEV1 percentiles could additionally provide a tool to distinguish between mild and severe disease phenotypes within the CF cohort. This percentile-based comparison to the clinical peers could further help the physician to identify whether the loss of lung function of an individual patient is greater than expected or whether the patient gets better than prognosticated under a novel therapy regimen. Additionally, the proposed percentiles might be valuable parameters in the field of CF research. Clinical courses vary significantly among CF patients and FEV1 deteriorates still faster in CF over lifetime than in the general population. As a consequence, the use of FEV1%predicted as a single parameter does not allow for classification of disease severity in mixed cohorts of young and older CF patients. This applies in particular to studies correlating genetic modifiers or biomarkers with disease severity across ages, as, for example, a FEV1%predicted of 70% in a 40-year-old adult with CF indicates a rather mild disease, whereas the same value in a 10-year-old child would nowadays show a significant reduction of lung function. CF-specific BMI and FEV1 percentiles could add as age-independent parameters for CF lung disease in the context of clinical investigations. For this reason, CF-specific reference percentiles of high-income countries have been determined repeatedly in the past few years [15–18]. These studies demonstrated an increase of lung function in more recent time periods as well as regional differences among Canada, the USA, and Europe [16, 17]. In accordance, percentiles of the present study were slightly higher than the previous European data published in 2012 [16]. This might be due to improved treatment regimen, the high standard of care in CF centers in Europe, and, in particular, the evolving effect of therapies targeting the underlying defect in the CFTR protein [9, 26]. In the present study, already 33% of the CF patients were treated with CFTR modulators including ivacaftor, ivacaftor/lumacaftor, ivacaftor/tezacaftor, or a respective study medication, which corresponds to the total cohort recorded in the German CF Registry [19]. With the introduction of the first triple combination ivacaftor/tezacaftor/elexacaftor for patients either F508del homozygous or F508del heterozygous with a minimal function mutation in August 2020, and for patients with at least

one copy of F508del in April 2021, far-reaching health improvements for the majority of CF patients are expected [1, 26, 27]. The fraction of CF patients with close to normal lung function will likely increase. Currently, however, it is not foreseeable whether and when the lung function of CF patients will be comparable with lung-healthy people. Further, the increasing spread of newborn screening will likely contribute to an earlier onset of therapies and an improved health status in future CF generations [9, 28, 29]. In Germany, nationwide newborn screening was introduced in September 2016 [28]. However, as part of clinical investigations, newborns were screened for CF prior to this date, which may already have an impact on the current study [29]. For these reasons, regular updates and local sub-analyses of disease-specific percentiles would be beneficial for comprehensive CF patient care and comparisons of CF centers. Since calculated for the period before the approval of Tricafta®/Kaftrio® [27, 30, 31], the current CF-specific percentiles from 2016 to 2019 might serve as baseline for future studies on the effect of the wide-spread application of triple modulator combinations.

In a recent investigation, short-term decline of lung function in CF could not anticipate the subsequent rate of lung function decline over a longer period of time [32]. This puts further emphasis on the need for repeated FEV1 measurements in CF disease phenotyping [15–18, 33]. An alternative approach for CF severity classification, which is based on longitudinal data, is the estimation of FEV1% predicted at 20 years of age [33]. Interestingly, this almost corresponds to the maximal median FEV1 and the highest variability of lung function at young adulthood in the current as well as in previous studies on CF percentiles [15–18]. In line with this, CF modeling studies detected the highest correlation between FEV1%predicted and the age of death in adolescents between 15 and 20 years of age [34]. This supports the hypothesis that disease-specific FEV1 percentiles of young patients with CF might be predictive for future disease progression.

Since CF is a rare disease, clinical observational studies in CF usually cannot focus on a specific age cohort, resulting in a wide spectrum of ages and disease severity. This applies to investigations on a broad spectrum of scientific questions, for instance on the underlying pathophysiology, the microbial colonization and infection, the diagnostic value of biomarkers, and, in particular, on genetic association studies [17, 18]. Also in CF clinical trials on therapeutic interventions or diagnostic procedures, inclusion or exclusion criteria are normally based on the FEV1%predicted referenced against a healthy population [27, 35, 36]. However, the current demographic developments and the widening of the age range in CF [19, 20] should be considered for severity classification. With the advent of the novel CFTR modulator therapies since 2012 [36], the identification of comparable CF cohorts is even more important in clinical trials and CF research [1, 15]. In line with previous studies [15, 16, 18, 33], the current results confirm that a fixed interval of FEV1%predicted referenced against healthy nonsmokers alone is most likely not sufficient for the classification of lung disease in CF as FEV1 has disease-specific dynamics in CF that substantially depend on age and height. CF-specific FEV1 and BMI percentiles without adjustment for survival allow for the classification of an individual within the group of surviving CF patients but not within the patient's entire birth cohort. According to North American findings, our data suggest that disease-specific percentiles should be corrected for mortality attrition to ensure comparability of different birth cohorts [16, 18]. This effect was most evident in low percentile ranges. Hence, we propose the application of CF-specific FEV1 and BMI percentiles with survival adjustment for disease phenotyping, especially as age-independent measure for diseases severity in CF observational studies and as a supplement to established eligibility criteria within the framework of CF clinical trials.

Our study has several limitations. First, the estimated percentiles represent only a single central European country. Former data of the European CF Society Registry indicate that there were no major variation among national FEV1 distributions in the period from 2004 to 2010 [16]. However, to examine the current transferability of FEV1 percentiles in Europe, further international studies are required. Second, the present study covers a time period before the approval of the first triple CFTR modulator combination [27] and CF percentiles are constantly developing. Regular recording of clinical data in patient registries and recurrent longitudinal analyses will be required to update CF percentiles continuously. For this reason, the German CF Registry constantly collects high-quality clinical data of CF patients as a basis for future research on CF percentiles. Third, since the German CF Registry did not follow all German CF patients from birth, survival of birth cohorts before 1995 had to be estimated from governmental data [24] and the estimated frequency of CF births as proposed previously for Canada [18]. The German CF Registry, though, is the key source for the health status of patients with CF in Germany, based on strict quality standards, and offered the best possible data basis for the current investigation [19]. Fourth, to keep assumptions on a

minimal level, survival and correction for mortality attrition were not adapted for gender. This should be included in upcoming large studies on survival in CF.

Conclusion

In summary, we estimated CF-specific FEV1 and BMI percentiles and correction for mortality attrition for a representative central European country from 2016 to 2019. CF-specific percentiles may serve as interpatient reference of disease severity across age-groups in clinical observational studies, patient care, and as additional eligibility criteria in CF clinical trials. Further, the current percentiles may serve as reference for the expected health impact of the widespread use of triple CFTR modulator therapy.

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Statement of Ethics

In this registry study, we used data from patients registered in the German Cystic Fibrosis Registry. For the German Cystic Fibrosis Registry, a central ethical approval was gained by the Ethics Committee of the Justus-Liebig Universität Gießen FB Medizin (AZ24/19). Written informed consent was acquired from every registry participant or their legal guardian.

Conflict of Interest Statement

SD was supported by the German Cystic Fibrosis Association, who made the payment for statistical analysis to STAT-UP Statistical Consulting & Data Science GmbH (MD and FK). None of the authors have any further direct conflicts of interest to declare in relation to this study.

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Author Contribution

S.D., L.N., M.M., and O.S. conceived the study. S.D., P.S., S.W., S.G., M.S., F.H., L.N., M.M., and O.S. designed the study with M.D. and F.K. performing the statistical analysis. S.D. wrote the first draft of the paper. All authors contributed to the subsequent rewriting and interpretation of the data.

Data Availability Statement

The percentiles are openly available via an online calculator on https://cfpercentiles.statup.solutions. All further data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding authors.

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