IVA) in 2019, we now have sweat chloride, demographic, and clinical outcome data for all four commercially available modulators in use in the United States. We present an update on change in sweat chloride after initiation of ivacaftor (IVA), lumacaftor/ivacaftor (LUM/IVA), and tezacaftor/ivacaftor (TEZ/IVA), including new participants at younger ages, and new data on the association between change in sweat chloride after initiation of ELE/TEZ/IVA.

Methods: Eligible subjects who have been prescribed any of the four commercially approved CFTR modulators for 90 days or longer were enrolled for a single visit to collect sweat to be analyzed for sweat chloride at their local laboratory. Diagnostic premodulator sweat chloride values were obtained from chart review. Clinical data obtained at this visit were augmented with data obtained from the Cystic Fibrosis Foundation Patient Registry (CFFPR). Subjects who switched to an alternative prescribed commercially approved CFTR modulator for 90 days or longer were eligible to re-enroll in the study.

Results: CHEC-SC began in 2018. As of February 2022, more than 3,500 subjects aged 0.88 to 77 years were enrolled from 51 U.S. sites in the CF Therapeutics Development Network; 36% of 526 IVA subjects were aged 0 to 11, 35% of 783 LUM/IVA subjects were aged 2 to 11 years, and 9.7% of 699 TEZ/IVA and 7.5% of 1,532 ELE/TEZ/IVA subjects were aged 6 to 11. The IVA group had the greatest percentage of Hispanic subjects (11%). Regarding *CFTR* genotype, 52% of the IVA group had gating mutations, and 100% of LUM/IVA, 90% of TEZ/IVA, and 57% of ELE/TEZ/IVA were homozygous for F508del. Median time from start of prescribed modulator to postmodulator sweat chloride collection was 2.48 years for IVA, 1.76 years for LUM/IVA, 0.57 years for TEZ/IVA, and 1.14 years for ELE/TEZ/IVA.

Pre- and postmodulator sweat chloride results are presented in Figure 1. Average sweat chloride changes tracked consistently with those reported in clinical trials, with the greatest change observed with ELE/TEZ/IVA (–59.9 ± 23.6 mmol/L). This change resulted in the greatest proportion of sweat chloride values falling below the diagnostic value for CF of 60 mmol/L: 79% after ELE/TEZ/IVA (pre 3.5%). The average sweat chloride change with IVA was –31.9 ± 30.5 mmol/L overall; –50.7 ± 25.8 mmol/L for those with gating mutations, and –20.3 ± 21.3 mmol/L for R117H. Average sweat chloride change was –20.8 ± 19.3 mmol/L for LUM/IVA and –10.5 ± 17.6 mmol/L for TEZ/IVA. Pre- and postmodulator sweat chloride less than 60 mmol/L were 19.9% and 64.4%, respectively, with IVA, 0.1% and 10.9% with LUM/IVA, and 3.9% and 6.8% with TEZ/IVA. Heterogeneity in sweat chloride changes across key population factors and among rare genotype groups, as well as changes in patients changing modulator regimens, are being evaluated. The first analysis covering all CFTR modulators evaluating the association between sweat chloride response and FEV_1 change across the large CHEC-SC population, accounting for genotype and age group, will be presented at the North American Cystic Fibrosis Conference.

Conclusions: CHEC-SC is the largest study characterizing changes in modulator-induced sweat chloride and clinical outcome changes and factors associated with these changes across the CF population.

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Factors associated with survival of Mexican patients with cystic fibrosis—a cohort study

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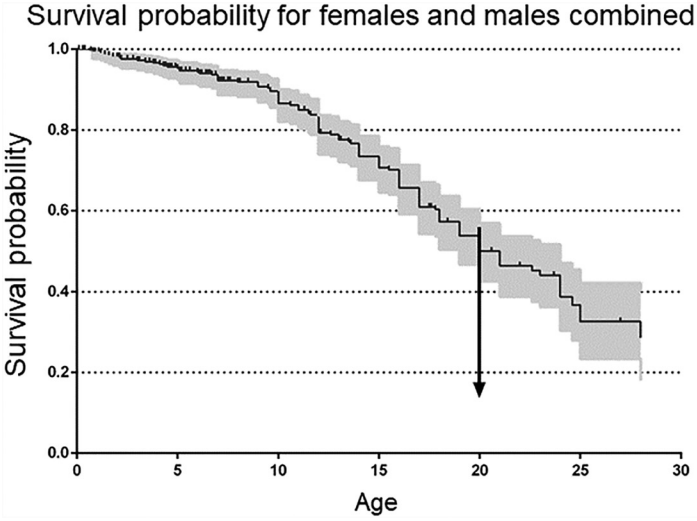
Background: Cystic fibrosis (CF) is one of the most common autosomal diseases in Mexico, with an estimated prevalence of 1 in 8,500. Many factors can affect survival, including nutritional status, colonization by *Pseudomonas aeruginosa,* and pulmonary function. Early identification of these factors allows therapy to be initiated to improve survival and quality of life.

Methods: All patients who attended the CF clinic were registered and underwent an anthropometric evaluation and pulmonary function evaluation with forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FCV); values greater than 80% were considered to be optimal lung function. A social evaluation was also performed. Pancreatic exocrine insufficiency was defined as a requirement for regular pancreatic enzyme supplementation. Undernutrition was considered a body mass index more than 2.0 standard deviations below the mean or weight for height more than 2.0 standard deviations below the mean. Government coverage of treatment was defined as the full supply of pancreatic enzymes, dornase alfa, nebulized tobramycin, salbutamol, vitamins, and oral antibiotics needed. Positive *P. aeruginosa* was determined from a sputum sample or cough swab before 7 years old. Survival from date of first assessment to the last visit was calculated using the Kaplan Meier method. Pearson correlation coefficients were calculated to test relationships between predictor variables.

Results: We included 341 patients from 1990 to 2018. Estimated median age of survival was 20 (95% CI, 17.3–23.0), and 55% of patients were diagnosed before the age of 2, with no significant effect on survival. Ninety-



Factors affecting survirval	OR (95% IC)	Valor p.
Diagnosis ≤ 2 years	0.9 (0.58-1.4)	0.65
Pancreatic insufficiency	0.08 (0.01-0.58)	0.001
FEV1 ≥ 80%	0.51 (0.03-0.09)	0.001
FVC ≥ 80%	0.05 (0.03 - 0.11)	0.001
Positive *P. aeruginosa* ≤ 7 years	5.19 (2.97-9.05)	0.001
Undernutrition	15.8 (8.4-29.7)	0.001
Treatment government cover	0.048 (0.02-0.1)	0.001

Figure 1 (abstract 44): Estimated median age of survival in Mexican patients with cystic fibrosis and related factors

one percent of the patients had pancreatic exocrine insufficiency, with $p < 0.01$ as a predictor variable for survival. Forty-four percent of patients had suboptimal values for FEV_1, and 26% patients had suboptimal values for FVC. Major effect on survival within 7 years were detected in patients with positive *P. aeuroginosa* and those with undernutrition. Sixty-one percent did not have government coverage of treatment, which had a clear effect on survival (Figure 1).

Conclusions: To our knowledge, this is the first report of survival in people with CF in Latin America. Median survival was 43.6 years in 2017 and 46.2 years in 2019 in the United States and 47 years in the United Kingdom in 2019, a difference of more than 2 decades from survival reported in our study. The predictor variables affecting survival are consistent those previously reported in the literature but not with diagnosis before 2 years old. There are two possible reasons for this: CF diagnosis based on newborn screening started in 2015, so it might be that the effect on survival was not yet evident, and patients with early diagnosis did not have full treatment coverage. Many interventions have been performed since the beginning of the cohort. We want to highlight the treatment coverage for the government from 2015 and the intervention of the nutrition team from 2006. The nutrition team was integrated full time into the CF clinic—counting fat grams, dynamically managing pancreatic enzymes, increasing energy density, providing recipes for a homemade elemental diet, and managing food portions, so we expect to see a greater effect on survival in the coming years. Treatment with CFTR modulators is not available in Mexico, so the survival results of this study are strongly associated with the multidisciplinary approach and continuous education of patients and parents, which has made an important difference in the quality of life of patients.

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Impact of early growth trajectories and cystic fibrosis transmembrane conductance regulator modulator therapy on puberty in cystic fibrosis

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Background: The advent of cystic fibrosis (CF) transmembrane conductance regulator (CFTR) modulators has led to a rapidly changing landscape in CF outcomes. It remains unclear to what degree puberty is affected in children with CF in this new era. Historically, children with CF experienced a 2- to 4-year delay in pubertal onset, possibly as a manifestation of poor nutrition or CFTR dysfunction [1,2]. CFTR modulators have the potential to affect pubertal timing by improving nutritional status and normalizing CFTR function in the hypothalamic-pituitary-gonadal axis [3]. Pubertal progression in CF has not been explored in the era of CFTR modulators, and the impact of early growth on puberty in CF is unknown.

Methods: Using national data from the U.S. Cystic Fibrosis Foundation Patient Registry (CFFPR), this study aims to analyze associations between early growth trajectories and puberty using peak height velocity (PHV) as a proxy measure. PHV (adolescent growth spurt) is the maximum rate of height increase for an individual. Age at PHV (APHV) is frequently used to approximate the timing of puberty. PHV and APHV will be derived using a shape-invariant mixed model to approximate growth. Individuals aged 18 to 21 between 2010 and 2019 with confirmed CF according to sweat test or genotype analysis were included. We will classify early growth trajectories (aged 0–6) based on weight for length (WFL) or body mass index (BMI) into mutually exclusive categories representing growth patterns that clinicians may seek to encourage (WFL-BMI always >50th percentile, increasing, or stable) or avoid (WFL-BMI decreasing). We will analyze the impact of early growth on APHV (primary endpoint), as well as actual PHV and final adult height (secondary endpoints). We will perform unadjusted analyses using t-tests or analysis of variance. We will perform adjusted analyses using multivariable linear regression, including various potential confounders and effect modifiers. We will conduct stratified analyses based on sex and modulator use. We will also split analyses according to birth cohort to determine whether pubertal patterns have changed over time. Lastly, we will compare PHV, APHV, and adult height with published North American longitudinal standards to compare pubertal outcomes of individuals with CF with those of the general population.

Results: We secured CFFPR data in late March 2022. Analyses are underway and are expected to be complete in 2 months. The dataset captures 12,615 people with CF: 52.5% male, 91.9% white, 5.2% Black, 0.7% Asian, and 2.2% of another race. Median age at CF diagnosis was 0.5 years. Sixty-three percent are treated with CFTR modulator therapy, although mean age at which therapy was prescribed is 21.7 years (after completion of puberty). Approximately 14% (894 male, 830 female) were started on CFTR modulator therapy before age 18. Mean adult height is at the 36th percentile.

Conclusions: Conclusions are pending analytic results.

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Lipid trends on highly effective modulators in cystic fibrosis

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Background: There are few reports of cardiovascular disease (CVD) in people with cystic fibrosis (PwCF), but with advances such as highly effective modulator therapy (HEMT), PwCF are living longer, with increasing exposure to CF-related diabetes (CFRD), and are increasingly overweight or obese. All these factors increase the risk of CVD. Prior studies of serum lipids in PwCF before the advent of HEMT typically demonstrated low total cholesterol (TC), low-density lipoprotein (LDL), and high-density lipoprotein (HDL). It is not known whether HEMT may change serum lipid profiles in PwCF, perhaps because of altered absorption or metabolism.

Methods: We addressed this knowledge gap using the Carolina Data Warehouse to identify PwCF aged 18 and older at the University of North Carolina (UNC) Cystic Fibrosis Center with available lipid panel data within 5 years before starting ivacaftor or elexacaftor/tezacaftor/ivacaftor and at any timepoint thereafter. Retrospective chart review was performed after obtaining institutional review board approval. Exclusion criteria included solid organ transplantation or type 1 diabetes. The primary endpoint was change in TC; secondary endpoints included changes in HDL, TC/HDL ratio, change in BMI, and a new diagnosis of hypertension. Unadjusted mean changes in TC were assessed using paired t-tests. Available samples were not consistently collected in the fasting state.

Results: We identified 42 patients meeting study criteria; 27 (64%) were female, 24 (57%) had CFRD, 12 (29%) had CF liver disease, and 36 (86%) were pancreatic insufficient. Mean age at HEMT initiation was 40 (range 16–73). On average, there was a 3-year interval between the pre- and post-HEMT lipid panel and 17 months between HEMT initiation and the post-HEMT lipid panel. We noted significant increases in TC, LDL, and TC/HDL ratio after HEMT (Table 1). There was no significant change in HDL. BMI rose significantly. At baseline, nine patients had diagnoses of hypertension; three additional patients were diagnosed after starting HEMT.