Disparities in cystic fibrosis survival in Mexico: Impact of socioeconomical status

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Abstract

Background. Median survival age in cystic fibrosis (CF) has increased in developed countries. Scarce literature exists about survival in Latin American, especially in Mexico. The aim of our study was to assess the median age of CF patients' survival in Mexico over a 20-year period. Methods. We conducted a retrospective study, with all patients registered and followed in the CF Center in Monterrey, Mexico from 2000 to 2020. Median survival age was the primary outcome, assessed with the Kaplan-Meier analysis. Influence of clinical, biological, and demographic factors on survival were analyzed with the Cox regression model. Results. Two-hundred five patients were included. Median survival for the cohort was 21.37 years (95% CI $17.20 - 25.55$). In the multivariate Cox regression model, low socioeconomic status (hazard ratio [HR] 4.21, 95% CI $2.43 - 7.27$), chronic Pseudomonas aeruginosa (P. aeruginosa) infection at 6 years (HR 10.45, 95% CI $5.66 - 19.28$), and pancreatic insufficiency (HR 3.13, $1.38 - 7.13$) were independent risk factors for mortality. Conclusion. Median survival in Mexican patients with CF is lower than in high-income countries, and socioeconomic status plays a conspicuous role in the disparity. To increase patient survival for those residing in low-income countries, public health authorities must design policies that fully cover diagnosis and treatment strategies for the CF population.

INTRODUCTION

Cystic fibrosis (CF) is a hereditary disease, transmitted in an autosomal recessive manner; its prevalence varies by country, according to ethnic composition. In Mexico, its prevalence is estimated to be approximately 1: 8,500 to 1: 10,000 in live newborns.[1]

Survival of those with CF has improved markedly in developed countries, due to early diagnosis, multidisciplinary care, aggressive nutritional supplementation, novel inhaled treatments, eradication of *Pseudomonas aeruginosa* (*P. aeruginosa*), and lung transplantation. [2]

Despite advances, there is a great deal of variability in disease progression, severity, and survival in different countries and geographic settings.[3, 4] There are several factors related to survival, such as the cystic fibrosis transmembrane conductance regulator (CFTR) genotype,[5] initial presentation of the disease,[6] nutritional status,[7] sputum bacteriology,[8, 9] diabetes,[10-12] socioeconomic status (SES),[13] pulmonary exacerbations,[14] gender,[15] and follow-up in a specialized center.[15]

In England and Wales, children with CF from lower socioeconomic groups were nearly three times more likely to die at an early age than those of higher economic status.[13] In Latin America, particularly Mexico, limited information exists on the survival of CF patients, including factors that impact survival. To address this, the aim of our study is to assess the median age of CF patient survival in northeast Mexico over a 20-year period.

MATERIALS AND METHODS

We conducted a retrospective study, including all patients with CF who were registered and followed between April 2000 and April 2020 in the CF Center at University Hospital (Dr. José E. González in Monterrey Mexico). Demographic, clinical, and biological variables were documented, such as gender sex, age at diagnosis, SES, pancreatic status, CFTR genotypes, and diagnosis of chronic infection with *P. aeruginosa* at 6 years. Age at diagnosis was categorized as [?] 2 years, 3 – 18 years, > 18 years. SES was evaluated using the Asociacion Mexicana de Agencias de Inteligencia de Mercado y Opinion (AMAI) score, with patients divided in high (AB, C+, and C) and low socioeconomic levels (C,D, and E)[16]. A pancreatic-insufficient or pancreatic-sufficient classification was based on enzyme usage.[2] Genotype was classified as homozygous for F508Δ mutation, heterozygous for F508Δ mutation, and other or missing. Quarterly sputum or oropharyngeal swab bacteriology in the first 6 years were evaluated to detect chronic infection with *P. aeruginosa,* using Leeds Criteria.[17]

The Mexican health system is complex; it is comprised of two sectors: public and private. The public sector includes: (1) Social security institutions [Instituto Mexicano del Seguro Social (IMSS), Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado (ISSSTE), Petróleos Mexicanos (PEMEX), Ministry of Defense (SEDENA), Ministry of the Navy (SEMAR), and (2) programs that cover the population without social security [Ministry of Health (SSa), State Health Services (SESA), IMSS-Oportunidades (IMSS-O), Seguro Popular (SPS)]. The private sector is comprised of insurance companies and service providers, working in both private clinics and hospitals.[18] Access to tobramycin varies according to health coverage; currently, patients belonging to ISSSTE, PEMEX, SEDENA SEMAR, SPS, and the majority of patients from private health insurance companies have access to this drug.

This study was approved by the Institutional Research Ethics Committee.

Statistical analysis

SPSS v. 22 (IBM SPSS Statistics, IBM Corporation, Chicago, IL, USA) was used for data analysis. Descriptive analysis for continuous variables was performed. Categorical variables were displayed as absolute numbers and percentages. Median survival age was the primary outcome,[19] assessed by the Kaplan-Meier analysis; groups were compared with the log-rank test. Duration of survival was defined as the time between the date of birth and date of death, or the last follow-up. Median age at death was calculated for all individuals in the cohort. Influence of risk factors was assessed by a uni- and multivariate Cox regression model, with 95% confidence intervals (CI). A P value < 0.05 was considered significant.

RESULTS

A total of 210 individuals with CF were followed in the CF Center from 2000 to 2020; five patients were excluded due to missing data and 205 patients were included in the study cohort. Ninety-nine patients were female (48.3%). Mutation analysis was available for 156 patients (76.1%). Patient characteristics are described in Table 1. Median age at diagnosis was 1 year (1 month – 34 years). Median survival age for the cohort was 21.37 years (95% CI 17.20 – 25.55). Median survival age for high SES was 29.46 years (95% CI 24.09 – 34.83) vs 15.12 years (95% CI 11.78 – 18.45) for low SES (p < 0.001). Patients with a diagnosis of chronic infection of *P. aeruginosa* at 6 years had a median survival of 12.41 years (95% CI 10.11 – 14.73) compared to 35.25 years (95% CI 26.61 – 43.70) for patients with no evidence of chronic infection at 6 years (p=0.030). Differences in median survival age are presented in Table 2. Survival curves by SES and by *P. aeruginosa* chronic infection status are displayed in Figure 1. Differences in survival were statistically significant (p<0.001, p<0.001).

Median age at death for the cohort was 12.46 years (1 month – 43.65 years). Median age at death in the first 5-year period (2000 – 2005) was 9.55 years (1 month – 30.61 years), while for the last 5-year period (2016 – 2020), it was 15.49 years (5 months – 39.27 years) (p=0.012). Median age at death according to gender, SES, presence of chronic *P. aeruginosa* infection at 6 years, pancreatic status, and genotype are shown in Table 3.

Uni- and multivariable Cox regression analyses for mortality are shown in Table 4. Variables that reached

significance in the multivariate model were chronic *P. aeruginosa* infection at 6 years, low SES, and pancreatic insufficiency.

DISCUSSION

Disparities in CF survival are the result of a deeply complex interaction between many factors, with SES playing a conspicuous role. Worldwide, median survival in patients with CF varies from country to country; it is estimated between 40 – 50 years, with a lower median survival and worse prognosis in female patients.[2, 15, 20] With current treatment strategies, most patients will be able to reach adulthood; however, it remains a life-shortening disease. In addition, new therapies with CFTR modulators and inhaled antibiotics are not widely available in low-middle income countries, such as Mexico, issues that decidedly limit survival in CF patients.

Among factors that influence survival, socioeconomic status plays a major role in CF as in many other chronic diseases.[13, 21, 22] The low SES is related to food insecurity, air pollution, reduced access to prompt diagnosis, and specialized treatments due to their high cost and a lack of healthcare coverage.[23] Patients with low SES and CF have higher mortality,[24] worse lung function,[25] lower body mass index, more pulmonary exacerbations,[26] and higher risk of *P. aeruginosa* infection.[27]

In addition, chronic infection with *P. aeruginosa* is a factor closely linked to the SES in Mexico, as many low-income children do not have access to inhaled antibiotics. The only inhaled antibiotic available (tobramycin) costs around $2000 dollars per month and is not supplied by social security institutions that provide care for more than half the patients. As previously reported by our group, Mexican CF patients tend to have their first infection with *P. aeruginosa* early in life, [28] while a significant percentage (37%) present chronic infection with this bacterium at 6 years of age.

In the present study, patients with low SES were four times more likely to have shortened survival, compared to their high SES counterparts; median survival for the low SES group was half that observed in the high-income group. Chronic infection with *P. aeruginosa* and pancreatic insufficiency, along with low SES, were independent predictors of mortality.

Regarding CFTR genotypes and their connection to median survival, no significant difference was observed in the study population. Yet, patients with pancreatic insufficiency, a marker for severe mutations, had significantly lower survival rates than those with sufficiency.

In relation to the CFTR genotype, the risk of meconium ileus (MI) varies between 12.5% to 24.9%, as reported by the United States Patient Registry.[29] In our cohort, the frequency of MI was 7.8%. A similar frequency (7.3%) was reported by another group in Mexico.[30] This low prevalence rate may be attributed to high heterogeneity in CFTR mutations found in the Mexican population.[31]

In our study, CF-related diabetes was present in 7.3% of patients, while in the literature the incidence varies according to age, from 2.5% in children and reaching 40 – 50% in adults.[10, 12] This relatively low frequency may be due to the cohort being comprised of a young population, as the number of patients who reached adulthood remained low.

As previously mentioned, gender is an additional factor that impacts survival. The cause of this gender gap in CF remains unclear, but some studies suggest that it may be related to reduced activity levels, poor nutritional status, and the effect of estrogens in female patients.[32-34] In this cohort, male patients had greater survival, but this difference was statistically insignificant.

In our population, median survival was 21.4 years, with these values below the median reported in high-income countries; for example, Canada has a median survival of 49.7 years.[2] These data must be interpreted, while looking at several limitations: the study was conducted in a single center in North Mexico, its retrospective nature, and mutation analysis was not available to all patients. Despite these limitations, our study provides valuable information as its design, based on longitudinal follow-up by the same specialized team,

minimized results bias as a consequence of heterogeneity in therapeutic interventions. Moreover, there is scarce information on survival in patients residing in Latin America, especially in Mexico.

In conclusion, socioeconomic status plays a decisive role in CF patient survival, together with *P. aeruginosa* chronic infection, independent risk factors which are closely linked. To increase patient survival in low-income countries, public health authorities must design policies that fully cover diagnosis and treatment strategies in the CF population.

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