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Low-income status is an important risk factor in North East Mexican patients with cystic fibrosis

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ABSTRACT

Background. Factors such as environment, income status, as well as access to proper healthcare influence the survival and quality of life of people affected by chronic diseases including cystic fibrosis (CF). Survival factors in Mexican patients with CF have not been reported before, even when it has been estimated that this disease could not be negligible in the Mexican population. **Objective.** To compare the influence of the mutant allele ΔF508 and environmental factors on the survival of Mexican CF patients. **Material and methods.** We collected epidemiological data of 40 patients molecularly tested between 1987 and 2008 in the Clínica de Fibrosis Quística from the Hospital Universitario of the Universidad Autónoma de Nuevo León in Northeastern México. Kaplan-Meier plots and survival statistics were estimated and compared. **Results.** Survival analysis revealed statistical significance for low-income status ($p = 3.13 \times 10^{-6}$), cor pulmonale ($p = 0.00169$), severe pulmonary disease ($p = 0.00136$), and BMI ≤15 kg/m^2 ($p = 0.00678$). Statistical significance was not observed for the predominant allele ΔF508 considering two ($p = 0.992$), one ($p = 0.503$) or no ($p = 0.403$) mutant allele. **Conclusions.** Low income status was the most detrimental factor; followed by cor pulmonale, severe pulmonary disease and BMI ≤ 15 kg/m^2 for the survival in North East Mexican patients with CF. Carrying the ΔF508 allele did not influence survival.

Key words. Cystic fibrosis. Mexican population. Low Income Status. Survival. ΔF508.

El nivel de ingresos bajos es un factor de riesgo importante en pacientes con fibrosis quística del noreste de México

RESUMEN

Antecedentes. *Factores como el medio ambiente, el nivel de ingresos, así como el acceso a atención médica adecuada influyen en la supervivencia y calidad de vida de las personas afectadas por enfermedades crónicas como la fibrosis quística (FQ). No existen reportes de la supervivencia en pacientes mexicanos con FQ, incluso cuando se ha estimado que esta enfermedad puede no ser insignificante en la población mexicana.* ***Objetivo.*** *Comparar la influencia del alelo mutante ΔF508 y factores ambientales en la supervivencia de los pacientes mexicanos con FQ.* ***Material y métodos.*** *Se colectaron datos epidemiológicos de 40 pacientes analizadas molecularmente entre 1987 y 2008 en la Clínica de Fibrosis Quística del Hospital Universitario de la Universidad Autónoma de Nuevo León, en el noreste de México. Se realizaron gráficas de supervivencia Kaplan-Meier a partir de los datos colectados para este estudio.* ***Resultados.*** *Las gráficas Kaplan-Meier arrojaron significancia estadística para el nivel de ingresos bajo ($p = 3.13 \times 10^{-6}$), cor pulmonale ($p = 0.00169$), enfermedad pulmonar severa ($p = 0.00136$) e índice de masa corporal ≤ 15 ($p = 0.00678$). No se observó significancia estadística para el alelo predominante ΔF508 considerando dos ($p = 0.992$), uno ($p = 0.503$) o ningún alelo mutante ($p = 0.403$).* ***Conclusiones.*** *El nivel de ingresos bajo fue el factor más perjudicial para la supervivencia, seguido de cor pulmonale, enfermedad pulmonar grave e IMC ≤ 15 kg/m^2 en pacientes del noreste de México con FQ. Portar el alelo ΔF508 no influyó en la supervivencia.*

Palabras clave. *Fibrosis quística. Población mexicana. Estado de bajos ingresos. Sobrevivencia. ΔF508.*

INTRODUCTION

Cystic fibrosis (CF) is an autosomal recessive disease caused by mutations in the CF transmembrane conductance regulator (CFTR) gene, affecting Caucasian population with an estimated incidence of one in 3,000 live births. CF has been diagnosed in all racial and ethnic groups. In Hispanics, incidence has been reported to be 1/4,000-1/10,000,[1] and it has been estimated that around one in 8,500 children born with CF every year in México.[2] The Mexican Association of Cystic Fibrosis (AMFQ, http://www.fibrosisquistica.org. mx) had registered only 1,200 CF cases in 25 years; this means that about 15% of them are diagnosed, six thousand of Mexican CF children do not have access to specialized treatment or medical care, and one in 60 Mexicans is carrier of one of the CF mutated alleles (personal communication). A new born screening from Mexico City reported 2 out of 7,193 live births, which suggests that this disease could not be negligible in Mexican population.[3] Around 1,900 mutations/variants have been reported for the CFTR gene with ΔF508 being the most prevalent (50-60%, http://www.genet.sickkids.on.ca/app). In Mexican population, a previous study in 40 unrelated patients reported a frequency of 45% for ΔF508, and five more mutations (G542X, 3849 + 10 kb C → T, N1303K, S549N, and 621 + 1 G → T) were detected.[4] A recent report in 230 CF Mexican patients resulted in the characterization of 77.7% of the CF alleles with a total of 46 different mutations detected.[5]

The CFTR mutation profile is dependent on the patient's genetic background.[6-7] Allelic heterogeneity in Mexican CF patients is attributed to their complex ethnic composition,[8] complicating the full coverage of the molecular diagnosis. Misdiagnosis and failure of monitoring and treating of CF, along with environmental factors, play an essential role in the survival and quality of life of CF patients. Such latter factors include income status as well as cultural, community, and healthcare-related influences and long-term medical monitoring.[9]

In this study, we analyzed the genetic CFTR profile, epidemiologic and environmental factors that could influence the survival in a group of 40 Mexican CF patients from Northeastern México.

MATERIAL AND METHODS

Forty patients with long term medical monitoring from the Clínica de Fibrosis Quística (Centro de Prevención y Rehabilitación de Enfermedades Pulmonares Crónicas (CEPREP), Hospital Universitario Dr. Jose E. Gonzalez, Universidad Autónoma de Nuevo León, Monterrey, México) recruited between 1987 and 2008 were included. This study was adhered to the ethical principles of The Declaration of Helsinki,[10] and was approved by the institution's Research and Ethics Committee (Registry number BI09-003).

In most cases, CFTR molecular diagnosis was previously established. For those patients without a previous molecular diagnosis, DNA was obtained from peripheral venous blood and CFTR molecular screening was done by PCR and reverse dot blot hybridization with the INNO-LiPA CFTR36 Kit (Innogenetics, Gent, Belgium). This kit is based on the simultaneous detection and identification of 36 CF-related mutations and their wild-type sequences in human whole blood, dried blood spots, and buccal brush samples. In addition, probes for the identification of the Tn polymorphism within intron 8 are included (www.innogenetics.com).

Parameters included in the data analyses were: age at diagnosis and age at death, pancreatic insufficiency (PI), mild, moderate and severe pulmonary disease (according to forced expiratory volume in 1 second or FEV1 for adults and children, and clinical data for small children), liver disease, positive cultures for *Pseudomonas aeruginosa* and *Burkholderia cepacia,* type 1 diabetes mellitus (DM), *meconial ileus* (MI), *cor pulmonale*, body mass index (BMI), and income status according to the 10 x 6 Rule of AMAI (Mexican association of market research and public opinion agencies; www.amai.org) for towns with more than 50,000 habitants. The 10 x 6 AMAI rule is an index that ranks households in six levels, considering nine characteristics or possessions of the household and the education level of the person who contributes with the most of the income. It includes technology and entertainment, basic and practice home infrastructure, health infrastructure and human capital. Points were assigned at the selected variables considering the coefficient of each regression values on family income. Families were classified as high-income (A, B, C + and C), average income (D +), and low income (D and E).[11]

Statistical analyses

Kaplan-Meier plots, survival analysis, and Fisher exact tests were estimated using the R software (http://cran.r-project.org). The Log-Rank test was

used to estimate significances in the difference between survival curves.

RESULTS

The epidemiological data of the 40 Mexican CF patients are summarized in table 1. Epidemiological and molecular data were classified according to the survival (n = 24) and non-survival (n = 16) status. Most of the CF patients arrived from the state of Nuevo León and neighboring states (Northeastern México).

When compared between live and deceased, *cor pulmonale* (p = 0.0006, OR = 16.4, CI = 3.33-81.21), severe pulmonary disease (p= 0.0024, OR = 8.36, CI = 1.97-35.46), low income status (P = 0.0078, OR = 17.88, CI = 1.91-166.78) and coinfection [*P. aeruginosa and B-cepacia* (p = 0.02, OR = 4.8, CI = 1.21-19.7] resulted with statistical significance. There were not statistically significant differences for the rest of the epidemiologic and genetic data.

Genotype frequencies for the CFTR gene are described in table 2. A complete genotype characterization was achieved in 55 % of the CF patients; in 37.5% of the CF patients, only one mutation was identified, and in 7.5% of the CF patients, both mutations remained undetected. As shown in table 1, the most prevalent genotypes were ΔF508/other (40%) and ΔF508/ΔF508 (30%). The overall frequency of the ΔF508 allele among CF patients was 50%.

Eight other mutations were detected: G542X (6.25%), S549N (6.25%), and 2789 + 5G → A (5.0%), along with 3849 + 10 kb, G85E, R1162X, I148T and R334W (1.25% each). Twenty-one of the total CFTR alleles (26.3%) remained undetected.

Survival analysis are shown in figures 1 and 2 for significant non-genetic data and ΔF508 status respectively.

Table 1. Epidemiological data of the 40 CF Mexican patients.

Variable	Survived (n =24)	Deceased (n = 16)
Birth place		
Nuevo León	17	14
Tamaulipas	3	0
Coahuila	2	2
Oaxaca	1	0
Querétaro	1	0
Age at diagnosis (range)	4.0 ± 3.3 (5mo-12 yrs)	6.8 ± 9.2 (0 mo-34 yrs)
Survival current age	16.1 ± 5.8 (6-31 yrs)	NA
Age at death	NA	13.4 ± 11.0 (6-38 yrs)
Pancreatic insufficiency	20	16
Middle pulmonary disease	9	1
Moderate pulmonary disease	10	4
Severe pulmonary disease	5	11
Liver disease	4	3
P. aeruginosa	16	16
P. aeruginosa + B. cepacia	5	9
Diabetes	1	0
Meconial ileus	0	1
Cor pulmonale	5	13
BMI	15.8 ± 2.2	14.6 ± 2.4
High income status	11	5
Medium income status	12	4
Low income status	1	7
Access to medical services	19	12
ΔF508/ΔF508	6	6
ΔF508/Other	8	8
Other/Other	10	2

BMI: body mass index kg/m^2. NA: not applicable.

Non genetic data showed statistical significance for low-income status ($p = 3.13 \times 10^{-6}$), *cor pulmonale* ($p = 0.00189$), severe pulmonary disease ($p = 0.00136$), and BMI ≤ 15 kg/m^2 ($p = 0.00678$). We observed that low-income was the highest risk factor having a hazard ratio greater than 10. In addition, we observed that BMI ≤ 15, *cor pulmonale*, and pulmonary disease were correlated to low-income status (Fisher exact test $p = 0.046$, $p = 0.014$, and $p = 0.042$ respectively). From the 8 low-income patients, 7 had low BMI, 6 had severe pulmonary disease, and 7 had *cor pulmonale*. There were not statistically significant differences for diabetes ($p = 0.16$), *meconial ileus* ($p = 0.405$), tobramycine ($p = 0.055$), corticosteroid treatment ($p = 0.331$), pancreatic insufficiency ($p = 0.149$), hepatic disease ($p = 0.442$), *P. aeruginosa* ($p = 0.174$), *B. cepacia* infection ($p = 0.165$) and gender ($p = 0.205$). *B. cepacia* infection was always present as secondary infection to *P. aeruginosa*.

Presence or absence greaterthom the ΔF508 allele was not significant for two positive alleles ($p = 0.992$), one positive allele ($p = 0.503$) or non-mutant allele ($p = 0.403$). Contrary, non-genetic information such as low-income, data was highly significant.

Table 2. Genotype frequencies from the 40 Mexican CF patients.

Genotype	n (%)
ΔF508/ΔF508	12 (30.0)
ΔF508/X	10 (25.0)
X/X	3 (7.5)
ΔF508/G542X	2 (5.0)
S549N/S549N	2 (5.0)
G542X/X	2 (5.0)
ΔF508/3849 + 10Kb	1 (2.5)
ΔF508/S549N	1 (2.5)
ΔF508/2789 + 5G → A	1 (2.5)
ΔF508/G85E	1 (2.5)
2789 + 5G → A/2789 + 5G → A	1 (2.5)
G542X/R1162X	1 (2.5)
2789 + 5G → A/X	1 (2.5)
I148T/X	1 (2.5)
R334W/X	1 (2.5)
Total	40 (100)

X: unknown mutation.

DISCUSSION

Low income status is an important predictor of survival disease outcome in many chronic polygenic

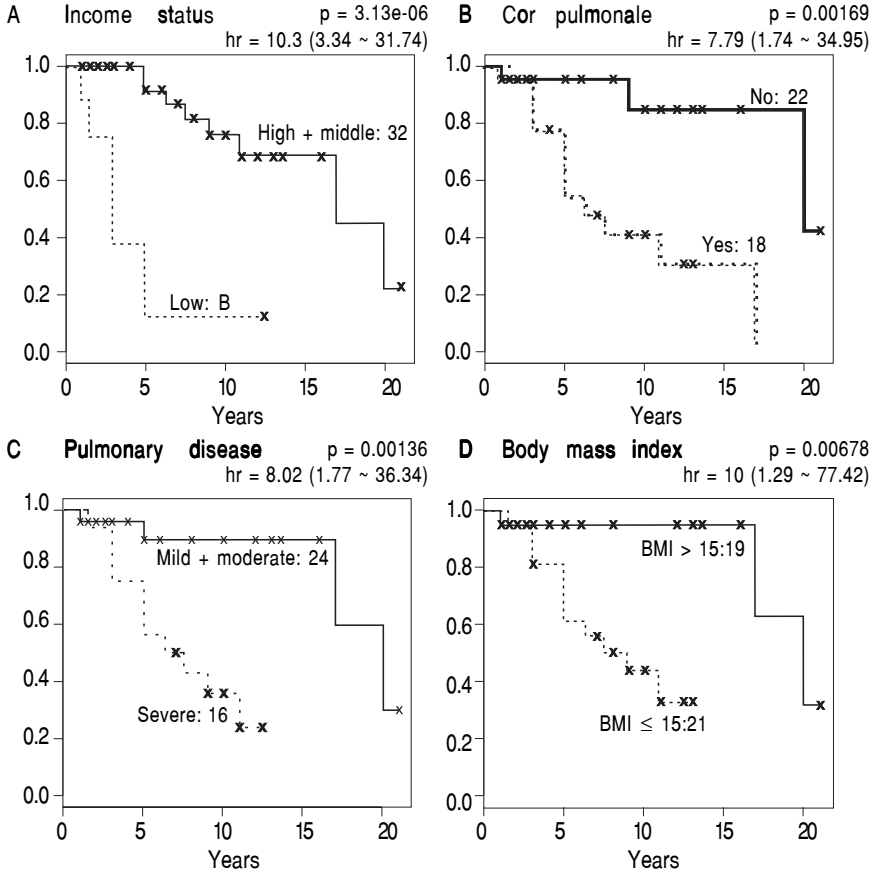

Figure 1. *Kaplan-Meier survival curves for significant factors [low income status (A),* cor pulmonale *(B), severe pulmonary disease (C), and BMI < 15 kg/m^2 (D)] are shown. X denotes censored information. p-values represent statistical difference of survival. hr: stands for hazard ratio, which include confidence intervals in parentheses.*

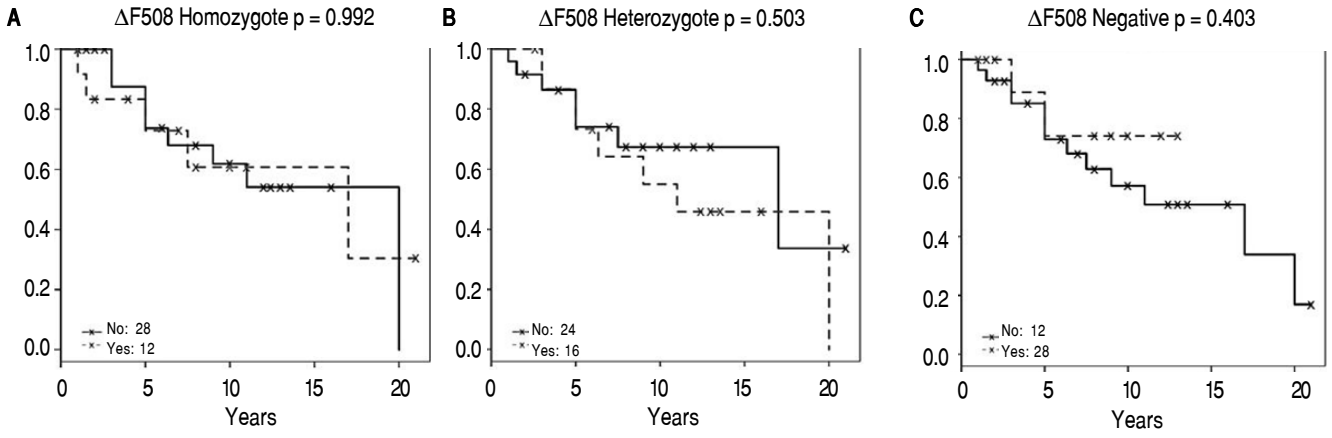

Figure 2. *ΔF508 influence on survival. The Kaplan-Meier plots for two (homozygote), one (heterozygote) or no (negative) ΔF508 mutant alleles are shown. p-values represent statistical difference of survival.*

diseases. In this study, it was the most important factor for survival in Mexican CF patients. In Northeastern México, medical care for CF patients is offered at the Clínica de Fibrosis Quística of the CEPREP (http://www.ceprep.edu.mx). Since 1987, about 200 patients have been diagnosed as CF based on clinical and molecular analyses. Once the diagnosis of CF is established, the lower adherence to medical treatment causes that only a small group of patients continue with long-term medical monitoring.

Adherence is the extent to which a person's behavior including taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a healthcare provider.[12] Most of our CF patients have access to medical services such as those provided by the Instituto Mexicano del Seguro Social (IMSS); alternatively, they could be subrogated to CEPREP for medical care and tests such as lung capacity testing, microbiological analyses, treatment, and rehabilitation. It has been reported that patients having therapies and disease management, survival of Mexican CF patients has reached 211 months.[13] However, the lower adherence to medical treatment in the poorest families has been attributed to lower education levels and less understanding of this disease, with these being decisive factors for poor prognosis.

Exposure to polluted air both inside and outside the home, the habit of smoking and viral infections among others, can influence the progression of lung damage acting as modifiers of disease evolution, which we observed in survival differences for *cor pulmonale* and pulmonary disease. Further research in CF is needed to confirm this. A recent study conducted in Mexico in pandemic and post pandemic positive H1N1 patients, found that health-care-seeking behavior, poverty level, and the distribution of information affect the occurrence and severity of pneumonia due to H1N1 virus from a socioeconomic point of view. These socioeconomic factors may explain the different patterns of morbidity and mortality for H1N1 influenza observed among different countries and regions.[14]

Patients having no access to health care insurance may experience larger delays in diagnosis, which may have a high impact in outcome even early death. In the United States, Medicaid is associated with a significantly poor outcome, considering that sicker patients with low income status are more likely to receive Medicaid.[15] When low *vs.* high income status was compared in the records of the United States Cystic Fibrosis Foundation Patient Registry of 2003, a 44% increased risk of death was present in the lowest income category.[16] The Epidemiologic Study of Cystic Fibrosis (ESCF), which is a large, multicenter, longitudinal, prospective observational study of the clinical course of patients with CF in the United States and Canada, reported from data collected between 1994 and 2005 that CF health outcomes are correlated with the income status. Nevertheless, these disparities are not explained by differential use of health services, prescription of chronic therapy[17] or differential treatment of pulmonary exacerbations.[18] A recent report from the United States using data obtained from the ESCF of 4,751 patients enrolled between 2003 and 2005, and classified as non-Hispanic whites, African-Americans, and Hispanics, showed that low socioeconomic and minority status (ethnicity) may affect impor-

tant clinical and patient-reported outcomes across their life span.[19] This is in concordance to our results where low income as an estimated risk factor of 10 compared to higher incomes.

In our study, severe pulmonary disease ($p = 0.00136$) and a BMI ≤ 15 kg/m^2 ($p = 0.00678$) were important factors in survival for CF patients. This is in agreement with a study in Brazil conducted in 85 CF patients in which a BMI below the 10th percentile and an albumin level below 4.1 mg/dL were predictors of low FEV1, and consequently increased association with chronic methicillin resistant *Staphylococcus aureus* pulmonary colonization infection.[20] Overall, these results suggest that low-income status in CF northeast Mexican patients is influencing the health care and the diet.

ΔF508 mutant allele generally has been considered with a more severe clinical phenotype in Caucasian populations than heterozygotes and patients with no F508 allele.[21] However, in this study it was not significant for survival. CFTR mutations have been classified according their effects in one of these groups: the absence of synthesis (class I); defective protein maturation and premature degradation (class II); disordered regulation, such as diminished ATP binding and hydrolysis (class III); defective chloride conductance or channel gating (class IV); a reduced number of CFTR transcripts due to a promoter or splicing abnormality (class V); and accelerated turnover from the cell surface (class VI).[22] The common mutation ΔF508 is categorized as a class II defect. Patients with CFTR genotypes associated with severely reduced CFTR production (class I to III) had a very similar severe phenotype with higher mortality rates than patients with a CFTR genotype associated with some residual CFTR function (class IV to V).[22-23]

On the other hand, it has been proven that the mutation profile is dependent on the ethnicity of the group.[24] It is necessary to design a kit that is in accord with the profile of the Mexican population. CFTR molecular diagnosis in this study was done according to costs and availability of diagnostic kits. Consequently, 26.3% of the CFTR alleles remain undetected. However, seventy percent of the CF patients in our study were carriers of the mutation ΔF508, thus we suggest as a first screening tool, PCR specific for this mutation followed by polyacrylamide or capillary gel electrophoresis.

CONCLUSIONS

In summary, we found that in our CF patients group, low-income status was the most important risk factor, followed by *cor pulmonale*, severe pulmonary disease and a BMI ≤ 15 kg/m^2. We observed correlation of low-income status with *cor pulmonale,* pulmonary disease and BMI ≤ 15. The presence or absence of the DF508 allele does not influence survival. Notwithstanding we suggest its molecular screening as the first diagnostic approach step considering its prevalence in our studied group and the accessibility of its testing.

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