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ORIGINAL ARTICLE

Clinical factors associated with pulmonary and extrapulmonary complications in patients with cystic fibrosis. A single-center observational study

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Abstract

Introduction: Cystic fibrosis (CF) affects the exocrine epithelium, forming a thick mucus that obstructs the ducts of the different organswith the lungs and pancreas being the most affected. This study aimed to determine the association between clinical factors and complications, as well as the survival of CF patients treated at a pediatric reference center in Mexico.

Methods: This observational, longitudinal study was conducted at the National Institute of Pediatrics in Mexico from April 2012 to April 2022. Children with cystic fibrosis were entered into the study with a nonprobabilistic sample. The variables were demographic, pulmonary and extrapulmonary complications and mortality. The association was made with chi-square and survival with Kaplan-Meir.

Results: Seventy-one patients were analyzed,including 41 infants(62%) and 12 preschoolers (16.9%). There were 40 men (56.3%)Fifty-seven cases (80.3%) had an infectious exacerbation, 11 cases (15.5%) had allergic bronchopulmonary aspergillosis, 9 cases (12.7%) had pulmonary hypertension, 5 cases (7%)had pneumothorax, 12 cases (16.9%) had mechanical ventilation, 70 cases (985%) had pancreatic insufficiency,and 10 cases (14%) had hepatobiliary disease. There was an association ofextrapulmonary complications with the F508 phenotype. Overall survival was 150 months. In patients with invasive mechanical ventilation, survival was 55 months (P<0.001); in patients withoninvasive mechanical ventilation, it was 106 months (P<0.001)In patients with pneumothorax, it was 25 months (P<0.00); and in patients with allergic bronchopulmonary aspergillosis,it was 125 months (P<0.0).

Conclusion: The most significant extrapulmonary complication in CF patients is pancreatic insufficiency. The presence of pneumothorax markedly decreases survival.

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Introduction

Cystic fibrosis is the most prevalent chronic, monogenic, hereditary disease worldwide 1[]. It has a prevalence in Caucasians of 1 to 3,500 livebirths and affects both developed and underdeveloped countries, taking into account that the real prevalence in Latin American countries is poorly documented 2[]. This disease affects the exocrine epithelium, forming a thick mucus that obstructs the ducts of different organs,with the lungs and pancreas being the most affected [3]. This disease was first described in the 1930s as a recessive genetic disorder, and over the years, more than 2,000gene mutations affecting this disease have been discovered [4].

A diagnostic tool called sweat chlorine was developed, in which it was observed that patients with cystic fibrosis had a high amount of chlorine in the sample collected [5]. Other screenings and diagnostic methods are available, such as neonatal and genetic tests [1]. Due to early diagnosis and timely treatment, there has been an increase in survival in developed countries; however, mortality in children under 18 years of age continues to be high in Latin America. One of the causes identified is the low socioeconomic level, which makes it impossible for patients to regularlyvisithealth areas, lack of public health systems, and mainly associated comorbidities, whether pulmonary or extrapulmonary [1].

In an investigation carried out by Restrepo- Gualteros et al [6] on the pulmonary compilcations presented by this group of patients, itwas mentioned that the main complicationwas pulmonary exacerbation, and Pseudomonas aeruginosa was the causative agent that caused further destruction of the lung parenchyma, thus increasing the risks of early mortality and progressive decline in lung function. Other associ- ated complications that are less frequent include hemoptysis, pneumothorax, and allergic bronchopulmonary aspergillosis.

Extrapulmonary diseases are described in a study by Vargas Guzmán et al. [7], which states that pancreatic insufficiency is the most prevalent gastrointestinal condition, being observed in more than 80% of patients. Other complications described were meconium ileus, the first clinical maniefstation in cystic fibrosis of up to 20% in the neonatal stage; distal intestinal obstruction syndrome; constipation, gastroesophagea l reflux disease, liver, and biliary disease, among others.

As a systemic disease, cystic fibrosis presents various complications, which cause adverse effects and increased mortality risk. In a meta-analysis carried out by Restrepo-Gualteros et al. on pulmonary complica- tions presented in both adults and children, theyde- scribed the presence of hemoptysis in 16-20%, allergic bronchopulmonary aspergillosis in 6-25%, and pneumothoraxin 50% of these pulmonary complications.Of these pulmonary complications, the leading cause of death was respiratory failure in 72% [6, 8]. However, extrapulmonary complications also occupy an important place in morbidity and mortality, with severe liver disease being the secondleading cause of death at 6.7%. Likewise, Vargas et aldescribed other extrapulmonary complications, such as meconium ileus in 20%, distal intestinal obstruction syndrome in 10 to 47%, and gastroesophageal reflux disease in 15 to 55%[6, 8, 9].

There are publications where it is mentioned that patients diagnosed at late ages and with a severe genotype of the disease have greater complications and a higher risk of mortality, hence the interest in carrying out this study to comparatively evaluate these clinical factors and the complications that they may present this group of pediatric patients, hoping that these data will somehow optimize time management and increase survival and quality of life in these patients.

The objective of this study was to determine the association between clinical factors and pulmonary and extrapulmonary complications in patients with cystic fibrosis treated at the National Institute of Pediatrics in the period from April 2012 to April 2022.

Materials and methods

Design of the investigation

This is an observational, longitudinal study, and the source was retrospective.

Scenery

The study was conducted at the Pneumology Service of the National Institute of Pediatrics in Mexico. DF. The study period was from April 1, 2012, to April 30, 2022.

Inclusion criteria

Children under 18 years of age diagnosed with cystic fibrosis entered the study. Cases with incomplete electronic records that did not allow analysis were eliminated from the study.

Study size

The population consisted of patients admitted to the institution who met the admission requirements. The sample calculation was nonprobabilistic, with a census type of all possible cases.

Variables

The variables were age at diagnosis, sex, genotype, colonization by an infectious agent, invasive mechanical ventilation, noninvasive mechanical ventilation, pulmonary arterial hypertension, infectious exacerbation, hemoptysis, pneumothorax, allergic bronchopulmonary aspergillosis, age at presentation of pulmonary complications, pancreatic failure, hepatobiliary diseases, distal intestinal occlusion syndrome, meconium ileus, gastroesophageal reflux, vasculitis, diabetes, age at presentation of extrapulmonary complications,and status at the last visit.

Data sources/measurement

The data were collected from the electronic file. The database was coded with serial numbers, thus protecting the confidentiality of the information and identity of the patients.

Statistical method

A descriptive analysis was carried out with summary and dispersion measures for the numerical variables; for the qualitative variables, proportions will be used, in addition to those presented in graphs and tables. The hypothesis tests used Ch-isquare for the qualitative variables and the T test for the quantitative variables with normal distribution;in case of not presenting a normal distribution, nonparametric statistics were used. The Kaplan- Meir test was used to assess overall survival and adjusted for the variables of interest. The statistical package SPSS v.25 (Armonk, NY: IBM Corp.) was used for the analysis.

Results

The study included 71 patients.

General characteristics

A total of 71 patients were studied, with a more significant predominance in the younger infant age, 62% (n=41), followed by 16.9% (n=12) in preschool age (Figure 1). There were 40 male patients and 31 women, resulting in a prevalence of 1.4:1.

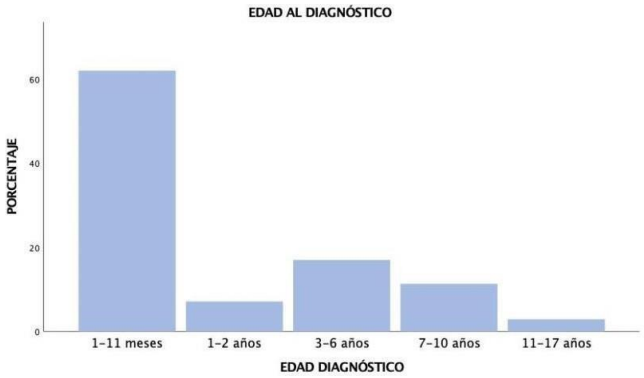


Figure 1. Age at diagnosis of cystic fibrosis.

Pulmonary complications

Table 1 shows the infectious pulmonary complications n=57 (80.3%) of the patients had an infectious exacerbation at some point; allergic bronchopulmonary aspergillosis occurred in 11 cases (15.5%,) and 56.4% (n=40) ofpatients were colonized by some infectious agent (Table 1).

Figures 2 and 3 show the ages of the presentation of infectious pulmonary complications, where it is observed that the primary age of the infectious exacerbation was in the stage of 1-11 months in 49.1% (n=28), subsequently in the age of 36 years in 24.6% (n=14). Regarding allergic bronchopulmonary aspergillosis, the most frequent age of presentation was school age and adolescence (7-17 years) in 36.4% (n=4).

Table 1.Frequency of infectious and noninfectious pulmonary complications in patients with cystic fibrosis.

Characteristic	Frequency no, (%)
Infectious lung complications	
infectious exacerbation	57,(80.3%)
Allergic bronchopulmonary aspergillosis	11,(15.5%)
Colonization by an infectious agent	40,(56.4%)
Noninfectious pulmonary complci ations	
Pulmonary arterial hypertension	9, (12.7%)
Pneumothorax	5, (7%)
Hemoptysis	2, (2.8%)
Invasive mechanical ventilation	10, (14.1%)
Noninvasive mechanical ventilation	2, (2.8%)
Extrapulmonary complications	
Pancreatic insufficiency	70, (98.5%)
Hepatobiliary disease	10, (14%)
Ddistal ileus obstruction Sd.	13, (18.3%)
Meconium ileus	12, (17%)
Gastric reflux disease	26, (36.6%)
Vasculitis	1 (1.4%)
Diabetes	3 (4.2%)

Table 1 shows the noninfectious pulmonary complications, of which the most frequent were invasive mechanical ventilation in 14.1% (n=10), followed by pulmonary arterial hypertension in 12.7% (n=9) and pneumothorax in 7% (n=5).

Figure 2 shows that infectious pulmonary complications such as pulmonary arterial hypertension obtained a higher percentage in the age of 7-10 years 44.4% (n=4), pneumothorax between 1-11 months and 11-17 years, with a percentage of 40% (n=2), respectively.

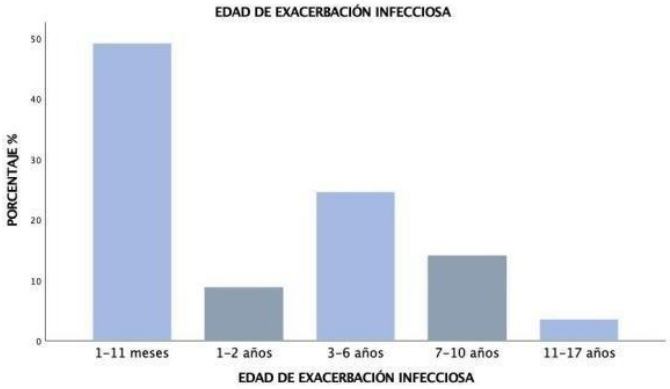


Figure 2. Age of infectious exacerbation

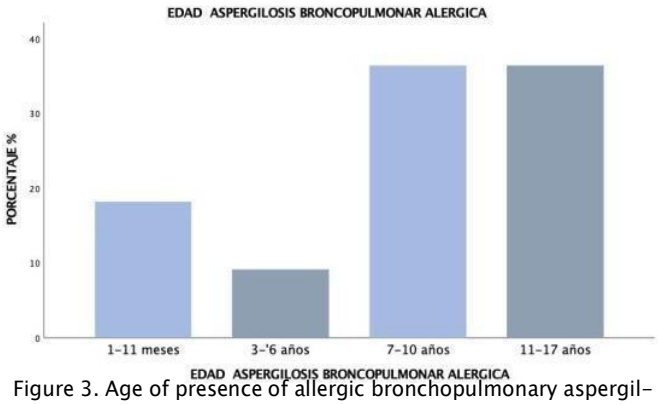


Figure 3. Age of presence of allergic bronchopulmonary aspergillosis.

Extrapulmonary complications

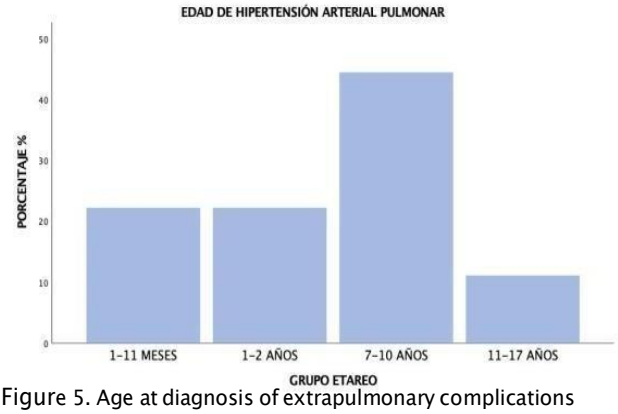
Table 1 shows the extrapulmonary complications, of which the most frequent was pancreatic insufficiency in 98.5% (n=70), followed by gastroesophageal reflux in 36.6% (n=26), and in third is the syndrome of obstruction of the distal ileum in 18% (n=12).

Figure 3 shows that extrapulmonary complications such as pancreatic insufficiency, gastroesophageal reflux disease, and distal ileus obstruction syndrome occurred more frequently from the infant stage in 94.4% (n=67) and 51.9% of patients, respectively (n=14) and 53.8% (n=9), respectively. Hepatobiliary disease was mainly observed inpatients aged 3-6 years and 7-10 years, both in 30% (n=3).

Association analysis

Table 2 shows the association between genotypes and infectious pulmonary complications, in which statistical significance was found between the relationship of souls with patients with other lesscommon genotypes with pulmonary complications in general, with a *P value* = 0.05, in addition to the association trend to the statistical significance that there is no relationship between patients who do not have a defined genotype and allergic bronchopulmonary aspergillosis *P*(=0.064). The rest of the variables had no statistical significance in the relationship between genotypes and other infectious pulmonary complications.

Figure 4. Age at diagnosis of noninfectious pulmonary complications in patients with cystic fibrosis.



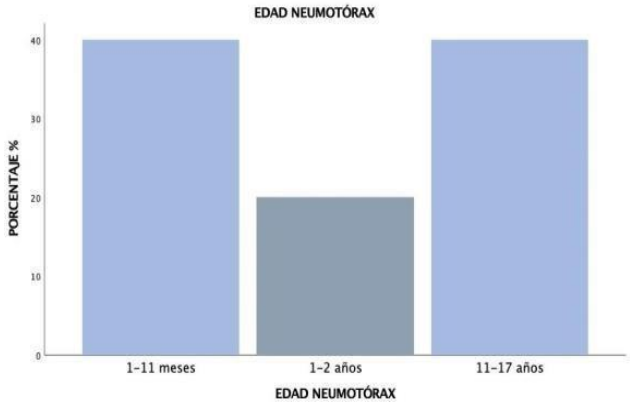
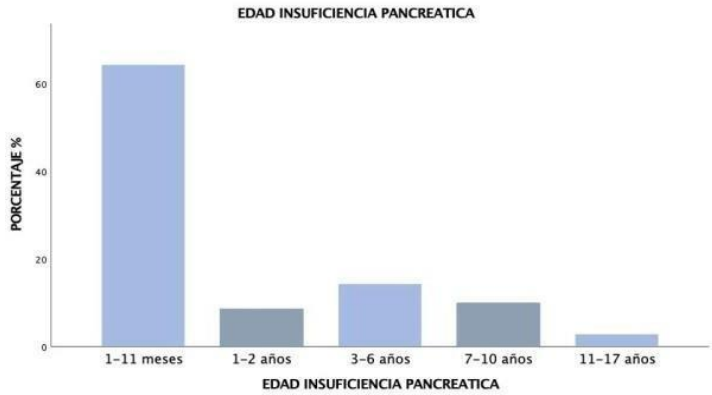
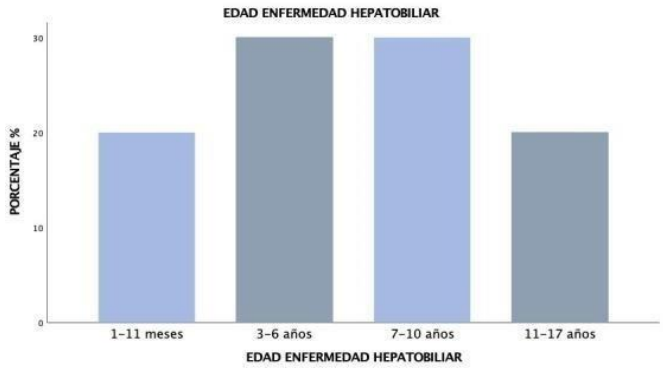


Figure 5. Age at diagnosis of extrapulmonary complications





A statistically significant association was obtained between the F508 genotype and pulmonary complications ofnoninfectiousorigin,with a *P value* of <0.001. Regarding the variables age and sex, there was no statistical significance with pulmonary complications, both infectious andnoninfectious.

There was no association between the age of presentation and the presence of vasculitis. The presence of diabetes had a significant association with ages 1 to 6 years versus children 7 to 17 years*P*(< 0.001).

Overall survival was 150 months, approximately 42%. Survival wassignificantlylower in patients with invasive mechanical ventilation(*P* < 0.001) at 55 months; in patients with noninvasive mechanical ventilation, it was 106 months (*P* <0.001) and in patients with pneumothorax, it was 25 months(*P* <0.001). Survival with allergic bronchopulmonary aspergillosis was 125 months, *P* < 0.01. There were no other differences in survival with other variables (Figure 6).

Table 2. Association between genotypes and other pulmonary complications with cystic fibrosis.

Genotype	Extrapulmonary complication		*P*
	Yes	No	
F508	5 (7.1%)	13 (18.6%)	0.002
G542	1 (1.4%)	5 (7.1%)	
N1303K	2 (2.9%)	1 (1.4%)	
Others	2 (2.9%)	10 (14.3%)	
no gene	1 (1.4%)	30 (42.9%)	
Genotype 4			
BUT			0.056
PC	9	52	
no genotype			
	Yes	No	0.064
Aspergillosis	2	9	
F508 genotype			
	Yes	No	<0.001
NICP	10	8	

PC: Pulmonary complication. NICP: noninfectious pulmonary complication.

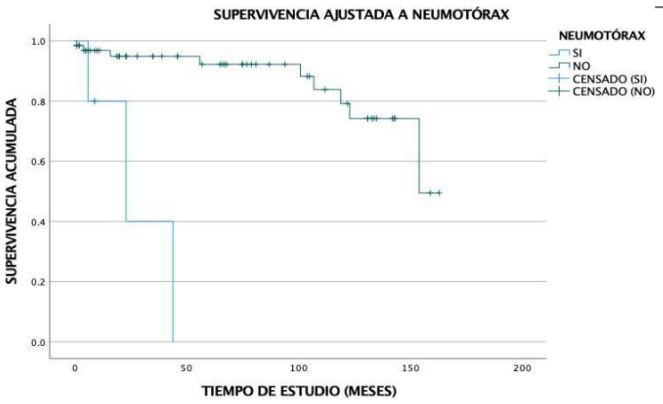


Figure 2. Adjusted survival for pneumothorax.

Discussion

Cystic fibrosis is the most common autosomal recessive disease worldwide. Due to this condition, more than 2,500 mutations of the CFTR gene of chromosome 7 have been discovered. Despite being a chronic and fatal disease, more remarkable survival has been seen in developed countries than in underdevelo ped ones, either due to the facilities of a health system where timely treatment and prevention of both pulmonary and extrapulmonary complications are provided [1]. However, in underdeveloped countries, the late age at diagnosis of the disease and the incidence of both pulmonary and extrapulmonary complications at early ages mean that the mortality of patients with cystic fibrosis is at pediatric ages [6,7]. For this reason, the main objective of this research was to determine the association between clinical factors and pulmonary and extrapulmonary complications in patients with this condition. In this study, it was observed that the age at diagnosis, which presents a bimodal pattern, is predominant in younger infants at 62%, followed by school age at 16.9%. Compared with a systematic review by Shi et al. [10], in China, with a population of 113 patients, the median age at diagnosis was 8.7 years. At the same time, in the United States, a multisystem study by Coverstone et al. [11] reported that the predominant diagnostic age is under six months in more than 70% of cases. We found a male predominance in a ratio (male: female) of 1.4:1, in contrast to what was reported by Shi et al. [10] since its frequency is predominantly in females in a 1.6:1 ratio.

Regarding infectious pulmonary complications, we found that infectious exacerbation was the leading cause of complicationsin 80.3% of patients,followed by allergic bronchopulmonary aspergillosis in 15.5%. Of this same group of patients, 55.4% were found to be colonized mainly with Staphylococcus aureus, followed by Pseudomonas aeruginosa. In a cohort study conducted by Lubovich et al. [12], where 117 pediatric patients and infectious exacerbations were studied, it was determined that 50 patients had presented infectious exacerbation for an average of 40.6% of the cases; of these, the colonization predominated by Staphylococcus aureus (RR: 2.32*P* =0.002) and Pseudomonas aeruginosa (RR: 1.89;*P* = 0.01).

In noninfectious pulmonary complications, the most frequent was invasive mechanical ventilation at 14.4%. Contrary to Lubovich et al.[2], since the predominance of ventilation was noninvasive, 18% of patients presented an infectious exacerbation requiring a device to improve pulmonary ventilation.

Regarding extrapulmonary complications in the study group, pancreatic insufficiency was hte primary manifestation (98.5%) compared to what Vargas Guzmán et al. presented in an observational study, in which only 15.4% of thepatients had exocrine pancreatic sufficiency. Regarding the ages of presentation of these complications, both pulmonary and extrapulmonary, insufficient literature describes these specific characteristics.

Regarding other pulmonary complications and genotypes, Lubovich et al. [12] associated the F508 genotype with Burkholderia cepacea infections (RR: 3.69; *P* = 0.002). In this investigation, Burkholderia cepacea infection occurred relatively frequently,and infection with other types of less frequent genotypes was also observed (*P* =0.02). No data associated with specific genotypes for these complications were foundfor patients who have presented with pneumothorax or empyema.

This study compared the presence of infectious pulmonary complications with various genotypes. We found that there was a relationship between less frequent genotypes (*P* =0.05) and noninfectious pulmonary complications, in addition to a significant relationship with the F508 genotype *P*(<0.001). In contrast to the study by Lubovich et al. 1[2], where these infectious exacerbations were seen to be primarily related to the F508 genotype, this study was most prevalent. For extrapulmonary complications, only a statistically significant relationship was found between age and

the presence of diabetes (P <0.001). In a multicenter, longitudinal study conducted between Austria and Germany [13], the median age of diabetes in cystic fibrosis patients was 15.9 years (31.8%) of the 1,178 patients studied.

In the evaluation of survival, it was observed that in pulmonary complications, patients who required invasive mechanical ventilation had higher mortality at approximately 75 months of up to 50%P(< 0.001); likewise, with the presence of pneumothorax P(<0.001) and the presence of allergic bronchopulmonary aspergillosis (P =0.034), mortality decreased signiif-cantly. Chamnan et al. [14], in a retrospective cohort study where the presence of diabetes was evaluated in patients with cystic fibrosis,found that the annual mortality of these patients was 2.2 (CI 95%, 2.-02.5) per 100 people who had both comorbidities. Regarding pneumothorax and vasculitis. There are no more descriptive studies with mortality findings in these patients. In extrapulmonary complications, the presence of higher short-term mortality was with those cases with vasculitis (P =0.03), in whom we showed a 0% survival before one year; no comparative studies were found about this type ofmanifestation in this context of evaluation for mortality.

Conclusions

The predominant age of diagnosis was in the younger infant stage and mainly in males:females with a ratio of 1.4:1. Of the infectious pulmonary complications, infectious exacerbation predominated in 80.3%, and this was seen to be significantly related to the infrequent genotypes, in contrast to the hypothesis made in which, according to the literature review, this is found chiefly related to genotypes F508 and G542. The infectious colonization that predominated was with Staphylococcus aureus, followed by Pseudomonas aeruginosa, and was mainly and significantly related to the less frequent genotypes. In noninfectious pulmonary complications, the most frequentwas the use of invasive mechanical ventilation, without evidence of a significant relationship with any specific genotype or with age or sex. Regarding clinical factors such as age, we found a significant relationship between diabetes and vasculitis in adolescent patients. There was no significant relationship between sex and pulmonary and extrapulmonary complications in this group of patients. Survival showed an overall mortality of 50% at 150 months. Patients with complications such as allergic bronchopulmonary aspergillosis, invasive ventilation, pneumothorax, and vasculitis presented significantly higher mortality than the rest of the previously mentioned complications. This is consistent with the literature where patients with vasculitis tend to have higher short-term mortality.

Abbreviations

Not declared.

Supplementary information

No supplementary materials are declared.

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Author contributions

Florisel Almonte Mora: Conceptualization, Data conservation, Acquisition of funds, Research, Resources, Software, Writing- original draft.
Francisco Javier Cuevas Schacht: Conceptualization, Data conservation, Supervision, Acquisition of funds, Research, Resources, Writin review and edition.
Oscar Alberto Pérez González: Conceptualization, Data conservation, Supervision, Acquisition of funds, Research, Resources.
All authors read and approved the final version of the manuscript.

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The authors financed the expense incurred in the production of this research The surveys did not constitute an additional cost to the patient or relatives.

Availability of data and materials

The data sets generated and analyzed during the current study are not publicly available due toparticipant confidentiality but are available through the corresponding author upon reasonable scholarly request.

Statements

Ethics committee approval and consent to participate

It was not required for an observational study.

Publication Consent

This doesnot apply to studies that do not publishMRI/CT/Rx images or physical examination photographs.

Conflicts of interest

The authors declare they have no conflicts of interes.t

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