INTRODUCTION

Cystic fibrosis (CF) is a genetic disorder caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, which encodes the CFTR protein, a chloride and bicarbonate channel localized in the apical plasma membrane of epithelial cells. CF results in chronic respiratory infections and bronchiectasis, being the most common life-shortening genetic disease in the White population, with prevalences varying in different ethnic backgrounds and countries. In Brazil, the prevalence of CF is estimated to be from 1:7,500 to 1:15,000 live births, depending on the region.

Brazilian national mortality data originate from death certificates that are provided by doctors or those prepared through reports from witnesses and are documented in civil registry offices. Demographic and medical data from death certificates are coded and processed by vital epidemiological surveillance services located in each of the federal states and the Federal District and sent to the Ministry of Health to be consolidated as data from the whole country. Primary mortality statistics is traditionally presented according to the underlying cause. However, in recent decades, there has been an increasing demand to considering all causes of death stated on death certificates, not only the underlying cause. Such data are called “multiple causes of death”, and they provide information on the whole range of lethal processes that culminate in death, thereby offering new elements and perspectives for their prevention.

The epidemiological knowledge on CF in Brazil has significantly been improving since the Brazilian CF Patient Registry started collecting data in 2011. This database currently comprises data from over 5,000 patients. However, the estimated prevalence of CF indicates that there might be a significant number of undiagnosed patients or disengaged patients from traditional CF health care centers. Therefore, the present study aimed to describe CF-related causes of death and mortality based on data from death certificates using the multiple-cause-of-death methodology.

METHODS

Annual mortality data were extracted from the Brazilian National Ministry of Health Mortality Database using the multiple-cause-of-death methodology. For the 1999-2017 period, we selected all deaths related to CF (ICD-10 category E84), listed as a cause of death on any line or in any part of the International Form of Medical Certificate of Cause of Death (the medical certification section of the death certificate). Complications of the underlying cause (part I of the medical certification section) and contributing causes (part II of the medical certification section) were jointly designated as associated (non-underlying) causes of death.
The causes of death were automatically processed using the software Seletor de Causa Básica (Underlying Cause Selector) provided by the Brazilian Ministry of Health, which involves the use of algorithms and decision tables that incorporate the WHO mortality standards and the etiological relationships among the causes of death. To reconstruct the morbid process leading to death, all causes of death listed in the medical certification section of the death certificate were considered, including those classified or considered as ill-defined or defined as modes of death by the WHO.

Using mortality rates, proportions, and historical trends, we studied the distributions of the following variables: sex, age at death (divided into 5-year age brackets), year of death, underlying cause of death, associated (non-underlying) cause(s) of death, total contribution of each cause of death, mean number of causes of death listed per death certificate, and geographical distribution of deaths. Medical and demographic variables were processed using dBASE III Plus, version 1.1 and dBASE IV (Ashton-Tate Corporation, Torrance, CA, USA); EpInfo, version 6.04d (dbDOS™ PRO 6 DOS-based emulation); and Excel. We used a freeware multiple-cause tabulator software in order to present the associated causes and calculate the mean number of causes per death certificate.

CF-related mortality rates (per 1,000,000 population) were calculated per year and for the entire period (2000-2017) based on the number of deaths reporting CF as an underlying or associated cause. In order to calculate the mean mortality rate, the overall number of deaths was divided by the sum of the respective annual population counts for the 18-year study period. Mid-year estimates of the Brazilian population were used (except for the year of 1999, which lacked an acceptable mid-year estimate of the annual population). We used the software Epidat, version 4.2 (Dirección Xeral de Innovación e Xestión da Saúde Pública, Xunta de Galicia, Spain) in order to standardize crude and mean mortality rates in accordance with the new WHO standard population. Crude and standardized rates were calculated by 5-year age brackets.

For the presentation of the associated causes listed on the death certificates on which CF was mentioned as one of the causes of death, we prepared special lists showing the causes that are usually associated with CF, as well as those mentioned more frequently. Duplication/multiplication of causes of death was avoided when present in abbreviated lists. The number of causes depends on the range of the class in the ICD-10 (constituted by subcategories, categories, blocks, and chapters); therefore, if two or more causes mentioned in the medical certification section were included in the same class, only one cause was computed.

We used ANOVA in order to compare the mean numbers of causes mentioned on the death certificates and the Kruskal-Wallis H test to compare the median age at death between groups. We used the Joinpoint Regression Program, version 4.7.0.0 (National Cancer Institute, Bethesda, MD, USA) to evaluate changes in age-standardized rate trends. Assuming a Poisson distribution, joinpoint analysis chooses the best fitting point (or points) at which the rate significantly increases or decreases. To provide uniformity and synthesis, we allowed one joinpoint. Values of p < 0.05 were considered significant.

RESULTS

For the 1999-2017 period, the overall CF-related number of deaths was 2,854 in Brazil: 1,387 (48.6%) in males and 1,467 (51.4%) in females (Table 1). A mean number of 150 deaths occurred per year, ranging from 68 in 1999 to 289 in 2017. CF was reported to be the underlying cause of death in 2,384 death certificates (83.5%) and an associated (non-underlying) cause of death in 470 (16.5%). A large variation among the distribution of deaths in the Brazilian states, the Federal District, and regions was noticed; for instance, between 1999 and 2017, although only 6 deaths occurred in the state of Roraima (northern region), 696 deaths were reported in the state of São Paulo (southeastern region) for the same period. The median age at death was also significantly different according to the Brazilian regions (Table 1 and Figure 1).

Mortality rates for the 2000-2017 period are presented in Table 2 and Figure 2. There was an insignificant higher standardized mean death rate among males (0.8619 deaths per million population) when compared with that among females (0.8345 per million population) and an upward trend in the death rate for both genders (Figure 2). Among males, the standardized mortality rate increased from 0.54 (0.00-0.89) to 1.37 (0.50-1.86) per million population, whereas, among females, it increased from 0.48 (0.00-0.86) to 1.38 (0.50-1.86) per million population from 2000 to 2017. A significant annual percent change was identified among males and females—6.84% (5.3-8.4%) and 7.50% (6.6-8.4%), respectively. Accordingly, a constant, significant upward trend in the annual percent change was found in all of the age brackets studied, except for males in the 0- to 4-year age bracket.

Regarding the age at death, approximately 20%, 25%, 50%, and 25% of the patients died at under 1, 4, 22, and 65 years of age, respectively. However, mean and median ages at death significantly increased during the study period. The medians in 1999 and in 2017 were 10.5 years and 50.5 years in males, and 6.5 years and 61.5 years in females, respectively (Figure 3).

The major associated causes of death in which CF was identified as the underlying cause of death (n = 2,384) are presented in Table 3, in accordance with the ICD-10 structure. Diseases of the respiratory system accounted for 77.0% of the associated causes, followed by infectious diseases (31.0%), and ill-defined causes (24.5%). The crude mean number of causes of death per death certificate was 3.41 ± 1.16 in those 2,384 death certificates in which CF was the underlying cause of death. Transplant-related mortality was reported in only 3.3% of the cases (Table 3).
DISCUSSION

The present study clearly demonstrates that CF-related mortality rates increased in Brazil from 1999 to 2017, and there was a significant increase in the age at death during the same period. These results are counterintuitive because the advances in CF diagnosis and treatment might result in an increase in the age at death, but not in the mortality rates. To our knowledge, this is the first study of CF-related mortality in Brazil using the multiple-cause-of-death methodology, and it suggests that the diagnosis of CF might be increasing in the country.

The finding that CF was identified as the underlying cause in most of the certificates (83.5%) stands for the severe fatality of this condition. A study of CF-related mortality in the United States between 1979 and 1991 evaluated 6,500 deaths and reported that CF was the underlying cause of death in 92.5% of the death certificates.\(^{(14)}\) A similar finding was described in Italy, where 480 CF-related deaths were identified from 2003 to 2011, CF reported to being the underlying cause in 87.5% of the death certificates.\(^{(15)}\) In the past, CF was associated with mortality in the early years of life, a scenario that is currently different due to intensive treatment.\(^{(1,2,16)}\) Despite major treatment advances, CF remains associated with reduced survival, especially in developing countries.\(^{(16)}\) Data from the Brazilian CF Patient Registry indicate that the median age of survival in the country is 43 years of life,\(^{(8)}\) whereas the median age at death is 15.7 years (interquartile range: 10.5-22.2); however, there might be some bias in these data because they are mostly related to patients under treatment in specialized CF centers.

The present study identified a worrying upward continuous trend in adjusted mortality rates related to CF regardless of sex and age brackets from 2000 to 2017. Contrasting results of CF-related mortality

| Variable                  | Deaths, n | Median age, years | IQR       |
|---------------------------|-----------|-------------------|-----------|
| CF death qualification    |           |                   |           |
| Underlying cause          | 2,384     | 23.5              | 7.5-65.5  |
| Non-underlying cause      | 470       | 15.5              | 0.3-69.5  |
| Gender                    |           |                   |           |
| Male                      | 1,387     | 22.5              | 2.5-64.5  |
| Female                    | 1,467     | 24.5              | 5.5-69.5  |
| Brazilian regions         |           |                   |           |
| North                     | 202       | 38.5              | 2.5-69.5  |
| Northeast                 | 562       | 19.5              | 2.5-58.5  |
| Southeast                 | 1,360     | 29.5              | 8.5-70.5  |
| South                     | 542       | 19.5              | 2.5-58.5  |
| Central-west              | 188       | 10.0              | 0.5-54.5  |
| Years                     |           |                   |           |
| 1999                      | 68        | 7.50              | 0.5-24.5  |
| 2000                      | 88        | 8.50              | 0.5-29.5  |
| 2001                      | 82        | 13.5              | 1.5-61.5  |
| 2002                      | 86        | 7.50              | 0.5-18.5  |
| 2003                      | 73        | 7.50              | 0.5-40.5  |
| 2004                      | 92        | 13.5              | 2.0-26.5  |
| 2005                      | 123       | 11.5              | 0.7-47.5  |
| 2006                      | 124       | 19.5              | 4.0-55.0  |
| 2007                      | 117       | 19.5              | 0.6-58.5  |
| 2008                      | 109       | 18.5              | 0.8-65.5  |
| 2009                      | 168       | 20.0              | 1.5-67.0  |
| 2010                      | 156       | 35.0              | 8.5-70.5  |
| 2011                      | 172       | 24.5              | 1.5-72.5  |
| 2012                      | 173       | 22.5              | 0.8-62.5  |
| 2013                      | 201       | 32.5              | 7.5-67.5  |
| 2014                      | 224       | 31.5              | 12.5-71.5 |
| 2015                      | 251       | 40.5              | 13.5-69.5 |
| 2016                      | 258       | 43.0              | 13.5-72.5 |
| 2017                      | 289       | 56.5              | 18.5-74.5 |

Source: Brazilian National Ministry of Health. Unified Health System Information Technology Department. IQR: interquartile range; and CF: cystic fibrosis.
Cystic fibrosis-related mortality trends in Brazil for the 1999-2017 period: a multiple-cause-of-death study

Trends have been reported in other countries, such as Spain and Italy, as well as in the European Union. In Spain, for the 1981-2016 period, there was an overall slight decrease in the age-adjusted mortality rate. In 27 countries of the European Union, a continuous downward trend in CF-related mortality rates was observed from 1996 to 2010, although there were differences by country and sex. In Italy, for the 1970-2011 period, CF-related mortality rates decreased in newborns and in children, whereas they increased in adolescents and young adults until 1990, but then decreased; however, in patients older than 19 years of age, they started to increase in 1990.

The increasing mortality trend shown in the present study is unlikely to be caused by a worsening of medical treatment of CF patients over time. It is probably due to a greater number of deaths being attributed to CF in more recent years. In addition, it might be related to improvements in the clinical diagnosis of CF and to the adoption of CF newborn screening (CF-NBS). Although there are data indicating that CF-NBS could decrease CF-related neonatal mortality, it could also increase death reporting due to a well-established CF diagnosis. The implementation of CF-NBS started in 2000-2001 in some Brazilian states (Santa Catarina, Paraná, and Minas Gerais), but it was only started in São Paulo, the most populous Brazilian state, in 2010. Data from the Brazilian Ministry of Health describe an increase in the number of newly diagnosed cases of CF—from 132 in 2014 to 167 in 2018—and an increase of nearly 50% in the number of CF cases in regular follow-up during the same period. Theoretically, all Brazilian states have been performing CF-NBS since 2013, but there is evidence that there are inequalities among the regions/states.

The finding that the median and the mean age at death increased significantly for the 1999-2017 period was anticipated, because of advances in CF

Figure 1. Medians and interquartile ranges of age at death related to cystic fibrosis according to the regions in Brazil, 1999-2007.
treatment; however, this is a paradoxical finding in the context of the upward trend in CF-related mortality rates, which cannot be attributed to the introduction of CFTR modulator therapies, because such medications are yet to be available for the majority of patients with CF in Brazil. Although the expansion of CF-NBS have significantly contributed to earlier CF diagnosis in Brazil, our findings regarding the age at death are unlikely to be related to CF-NBS due to its recent implementation in most Brazilian states. Conversely, there is a clear contribution of CF-NBS to the number of newly diagnosed cases of CF.

The disturbing finding that 25% of the deaths were reported in the 0- to 4-year age bracket, conversely, might be related to earlier diagnosis by CF-NBS. One finding in the present study might alternatively indicate a distinct scenario for the increase in the number of CF-related death reports in older age brackets (> 25 years of age): the age at death was high in the northern region, but the number of CF patients was small, probably due to the lack of consistent access to reliable CF diagnostic testing, leading to misreporting or misdiagnosis of the disease in some of the cases here reported.

The use of the multiple-cause-of-death methodology allowed the recovery of data of all associated causes of death, reported as comorbid conditions in the death certificates in which CF was the underlying cause. As expected, most of such associated conditions were respiratory diseases (77%), followed by infectious diseases (31%). Previous studies in the USA and in Italy selected only a subset of associated causes, chosen according to their prevalence and clinical relevance regarding CF. Some differences could be noticed between our results and theirs: the contribution of pneumonia (39.7%) in Brazil was greater than that verified in the USA (18.3%) and in Italy (19.8%).

Table 2. Standardized mortality rates related to cystic fibrosis and joinpoint analysis according to sex and age brackets. Brazil, 2000-2017.

| Sex     | SMR per million population | APC (95% CI) |
|---------|-----------------------------|--------------|
|         | 2000 | 2017 | Mean |                          |
| Male    |      |      |      |                          |
| Age bracket, years |      |      |      |                          |
| 0-4     | 1.92 | 2.31 | 2.47 | 1.30 (-0.9 to 3.6)       |
| 5-24    | 0.40 | 0.87 | 0.55 | 6.23* (3.6-8.9)          |
| 25-64   | 0.10 | 0.80 | 0.39 | 9.42* (6.2-12.7)         |
| 65 and +| 2.16 | 5.93 | 3.35 | 9.20* (6.2-12.3)         |
| Overall | 0.54 | 1.37 | 0.86 | 6.84* (5.3-8.4)          |

| Female  |      |      |      |                          |
| Age bracket, years |      |      |      |                          |
| 0-4     | 2.12 | 2.14 | 2.33 | 3.91* (1.3-6.6)          |
| 5-24    | 0.41 | 1.02 | 0.62 | 5.87* (3.4-8.4)          |
| 25-64   | 0.17 | 0.63 | 0.36 | 8.56* (6.0-11.2)         |
| 65 and +| 0.73 | 6.52 | 2.90 | 10.94* (7.4-14.6)        |
| Overall | 0.48 | 1.38 | 0.83 | 7.50* (6.6-8.4)          |

Source: Brazilian National Ministry of Health, Unified Health System Information Technology Department. SMR: standardized mortality rate; and APC: annual percent change. *APC is significantly different from zero at alpha = 0.05.

Figure 2. Age-standardized death rates related to cystic fibrosis according to sex. Brazil, 2000-2017.
Table 3. Associated (non-underlying) causes in death certificates (N = 2,384) in which cystic fibrosis was identified as the underlying cause. Brazil, 1999-2017.

| Associated causes of death (ICD-10 chapters and rubrics)                                      | n   | %    |
|------------------------------------------------------------------------------------------------|-----|------|
| Certain infectious and parasitic diseases (A00-B99)                                          | 788 | 31.1 |
| Intestinal infectious diseases (A00-A09)                                                    | 22  | 0.9  |
| Tuberculosis (A15-A19)                                                                       | 14  | 0.6  |
| Septicemias (A40-A41)                                                                       | 749 | 31.4 |
| Neoplasms (C00-D48)                                                                         | 23  | 1.0  |
| Diseases of the blood and blood-forming organs and certain disorders involving (D50-D89)    | 63  | 2.6  |
| Anemias (D50-D64)                                                                            | 26  | 1.1  |
| Other diseases of the blood and blood-forming organs (D65-D89)                             | 39  | 1.6  |
| Endocrine, nutritional, and metabolic diseases (E00-E90)                                     | 359 | 15.1 |
| Diabetes mellitus (E10-E14)                                                                  | 107 | 4.5  |
| Malnutrition (E40-E46)                                                                      | 168 | 7.0  |
| Mental and behavioral disorders (F01-F99)                                                    | 24  | 1.0  |
| Diseases of the nervous system (G00-G99)                                                    | 34  | 1.4  |
| Diseases of the circulatory system (I00-I99)                                                | 362 | 15.2 |
| Hypertensive diseases (I10-I13)                                                              | 74  | 3.1  |
| Ischemic heart disease (I20-I25)                                                             | 30  | 1.3  |
| Pulmonary heart disease and diseases of pulmonary circulation (I26-I28)                     | 93  | 3.9  |
| Cardiomyopathy (I42)                                                                        | 9   | 0.4  |
| Cardiac arrest (I46)                                                                        | 44  | 1.9  |
| Cardiac arrhythmias (I47-I49)                                                                | 26  | 1.1  |
| Heart failure (I50)                                                                         | 83  | 3.5  |
| Complications and ill-defined descriptions of heart disease (I51)                           | 9   | 0.4  |
| Diseases of the respiratory system (J00-J99)                                                | 1,836 | 77.0 |
| Pneumonia (J12-J18)                                                                         | 947 | 39.7 |
| Bronchitis (J40-J42)                                                                         | 3   | 0.1  |
| Emphysema (J43)                                                                               | 20  | 0.8  |
| Other chronic obstructive pulmonary disease (J44)                                            | 122 | 5.1  |
| Asthma (J45-J46)                                                                             | 7   | 0.3  |
| Bronchiectasis (J47)                                                                        | 59  | 2.5  |
| Other respiratory diseases principally affecting the interstitium (J80-J84)                  | 70  | 2.9  |
| Respiratory failure, not elsewhere classified (NEC) (J96)                                    | 1,093 | 45.9 |
| Other respiratory disorders (J98)                                                             | 179 | 7.5  |
| Diseases of the digestive system (K00-K93)                                                   | 129 | 5.4  |
| Paralytic ileus and intestinal obstruction without hernia (K56)                              | 23  | 1.0  |
| Diseases of liver (K70-K77)                                                                  | 49  | 2.1  |
| Other disease of pancreas (K86)                                                               | 21  | 0.9  |
| Diseases of the skin and subcutaneous tissue (L00-L99)                                       | 3   | 0.1  |
| Diseases of the musculoskeletal system and connective tissue (M00-M99)                       | 20  | 0.8  |
| Diseases of the genitourinary system (N00-N99)                                              | 150 | 6.3  |
| Renal failure (N17-N19)                                                                       | 133 | 5.6  |
| Pregnancy, childbirth, and the puerperium (O00-O99)                                          | 2   | 0.1  |
| Certain conditions originating in the perinatal period (P00-P96)                             | 84  | 3.5  |
| Disorders related to short gestation and low birth weight NEC (P07)                          | 28  | 1.2  |
| Respiratory and cardiovascular disorders of perinatal period (P20-P29)                      | 30  | 1.3  |
| Bacterial sepsis of newborn (P36)                                                             | 33  | 1.4  |
| Other intestinal obstruction of newborn (P76)                                                 | 11  | 0.5  |
| Congenital malformations, deformations, and chromosomal abnormalities (Q00-Q99)              | 32  | 1.3  |
| Symptoms, signs, and abnormal clinical and laboratory findings, NEC (R00-R99)               | 585 | 24.5 |
| Hemorrhage from respiratory passages (R04)                                                   | 33  | 1.4  |
| Other symptoms and signs involving the circulatory and respiratory systems (R09)             | 215 | 9.0  |
| Shock, not elsewhere classified (R57)                                                        | 88  | 3.7  |
| Cachexia (R64)                                                                                | 15  | 0.6  |
| Failure of multiple organs (R688)                                                             | 214 | 9.0  |
| Injury, poisoning, and certain other consequences of external causes (S00-T98)               | 50  | 2.1  |
| Foreign body in respiratory tract (T17)                                                       | 16  | 0.7  |
| Complications of procedures NEC (T81)                                                         | 20  | 0.8  |
| External causes of morbidity and mortality (V01-Y98)                                         | 92  | 3.9  |
| Surgical operation with transplant of whole organ and other (Y83-Y84)                        | 79  | 3.3  |
| Factors influencing health status and contact with health services (Z00-Z99)                 | 2   | 0.1  |

Source: Brazilian National Ministry of Health, Unified Health System Information Technology Department. ICD-10: International Statistical Classification of Diseases and Related Health Problems, Tenth Revision. *Duplication/multiplication of causes removed from ICD-10 chapters.
the same occurred in regard to the proportions of septicemia (31.4%) and malnutrition/cachexia (7.6%) in Brazil when compared with those in Italy (16.9% and 2.5%, respectively).\cite{15,16} However, diabetes and renal failure were significant higher in Italy (16.5% and 12.9% respectively)\cite{15} than they were in our study (4.5% and 5.6%, respectively).

Epidemiological knowledge of CF in Brazil has changed in the last decade due to the Brazilian CF Patient Registry. Comprising more than 5,000 CF patients from over 50 CF referral centers in 22 Brazilian states, the Registry displays, among other data, annual CF-related mortality: from 2009 to 2017, only 297 deaths were entered into the Registry, whereas we compiled 1,897 CF-related deaths for the same period. This difference can be explained by the difficulties of access of CF patients to specialized CF centers (where patients are entered into the Registry) and by inaccurate completion of the causes of death in death certificates. Both situations are likely to occur, because the estimated prevalence of CF indicates a much greater number of patients in Brazil.\cite{3} Elbert et al.\cite{21} compared CF-related mortality data obtained from the American CFF Registry and the Multiple Cause of Death File (based on death certificates for US residents) for the 2012-2014 period. A very good overlap was found between the two systems in the 1- to 60-year age bracket (87% of the records). For those older than 75 years of age, there were fewer than 5 CF-related deaths in the CFF Registry, whereas there were 42 in the Multiple Cause Of Death File. A similar picture was observed in those under 12 months of age.\cite{21} We believe that some of the inconsistencies in our data could have the same explanation as that proposed by Elbert et al.\cite{21}: among younger patients, difficulties to access to specialized CF centers or very premature death; among older patients, inaccuracies of death cause entries in death certificates.

The advantages and limitations of mortality studies using methodologies based on registries or death certificates have been discussed by Quintana-Gallego et al.,\cite{18} who underscored that a coverage of nearly 100% of the population might be reached by means of death certificates. Population mortality statistics suffer from quantity and quality problems. For 2017, the Brazilian National Ministry of Health estimated a coverage of 96.3% in the whole country, ranging from 92.7% in the northern region to 100.0% in the southern region.\cite{22} Regarding quality, a recent surveillance study on statistics using the multiple-cause-of-death methodology in Brazil revealed that the crude mean number of causes per death certificate increased from 2.81 to 3.02 (an increase of 7.5%) for the 2003-2015 period; the proportion of death certificates with only one cause of death decreased from 20.32% to 13.75%; and the proportion of death certificates with ill-defined causes of death as the underlying cause decreased from 12.95% to 5.59% (a decrease of 56.22%).\cite{23} However, there are specific problems linked with CF. Although automatic processing of mortality data is used in Brazil, the inclusion of the causes of death is still a task performed by trained nosologists, who might make a mistake and introduce a wrong ICD-10 code. One of these risks happens with pulmonary fibrosis (ICD-10 four-character subcategory J84.1), which could be confounded with CF, or vice versa.\cite{10} This is more likely to occur with older patients, because CF is usually expected to reduce life expectancy. In addition, because CF is a relatively rare cause of death, decision tables for automatic processing might not include the ICD-related mortality rules and dispositions involving all conditions and their natural history. Finally, it is of utmost importance that physicians correctly state all causes of death in the death certificates.

In conclusion, the present study depicted a significant and continuous increase in CF-related death rates in
Cystic fibrosis-related mortality trends in Brazil for the 1999-2017 period: a multiple-cause-of-death study

Brazil in the last years, with a concurrent increase in the median age at death. We believe that these findings result from an increase in CF diagnosis in the country, and we hope that this upward trend in CF-related mortality rates will subside in the next few years, indicating that patients are receiving better health care.

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