ELSEVIER

Journal of Cystic Fibrosis 10 (2011) 313–317

Journal of Cystic Fibrosis

www.elsevier.com/locate/jcf

Original Article

Absence of a gender gap in survival. An analysis of the Italian registry for cystic fibrosis in the paediatric age

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On behalf of the Italian Registry for Cystic Fibrosis Collaborative Group [1]

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Received 30 December 2010; received in revised form 28 February 2011; accepted 8 March 2011
Available online 22 April 2011

Abstract

Background: The existence of gender-related differences since childhood in survival of cystic fibrosis (CF) patients has been recently challenged.
Methods: We evaluated the effect of gender on survival of 2293 CF patients born after 01/01/1988, followed up by 29 CF centres until 31/12/2004 and recorded in the Italian Registry for CF (IRCF).
Results: We observed similar annual mortality rates in females (3.59‰) and males (4.00‰), similar survival curves (log-rank test p=0.64) and similar hazards of death (hazard ratio adjusted for presence of symptoms at diagnosis, meconium ileus, F508del mutation and age at diagnosis: 1.29, 95%CI: 0.60; 2.76). However, excess mortality due to CF was higher for females (5.9) than males (5.1).
Conclusions: In our population CF females do not experience higher mortality than males but, due to the disease, they lose the expected survival advantage occurring in the general population at this age. We do not exclude, however, that differences in mortality will establish after adolescence.

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1569-1993/$ - see front matter
doi:10.1016/j.jcf.2011.03.007

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1. Introduction

The severity of cystic fibrosis (CF) is highly variable and may be influenced by numerous factors including mutations in the CFTR gene, genetic background, pancreatic status, age and symptoms at diagnosis, chronic pulmonary infections due to specific microorganisms, metabolic complications, and social conditions [1]. Gender has also been reported to influence outcome: females have been reported to die earlier than males, although no exhaustive explanation is available [2–4]. Recent data, from single centres, have challenged this view suggesting that gender difference in survival [5] or severity [6] of CF is no longer seen in current practice, at least in younger generations of patients.

We analyzed the Italian Registry for CF (IRCF), which collects data from all the Italian CF Centres prospectively since 1988 [7,8] to evaluate whether gender affects survival in the Italian CF paediatric population.

2. Patients and methods

We analysed data from the subset of 2293 CF patients born after 01/01/1988 followed up until 31/12/2004 by 29 Italian CF centres and recorded in the IRCF. We restricted the analysis to this cohort of patients to avoid selection bias triggered by long-survivors effect: since the deaths that occurred before 1988 were necessarily not recorded by the IRCF, survival probability would be overestimated, because the survivors contribute to the denominators of the mortality rates, while their dead contemporaries will be missing from the numerators.

In 1993, a law was put into effect in Italy, stating that at least one centre specialised in CF care should be set up in each of the 20 Italian regions. The law further gave the CF centres the exclusivity on giving payment exemptions for the treatments necessary for CF. This put the CF centres in the privileged position of seeing most likely at least once all CF patients: due to the high costs of CF care, it is highly unlikely that a person diagnosed with CF has never been in contact with one of the 29 paediatric CF centres operating in Italy.

The IRCF therefore based its data collection on the CF centres, considering each centre an exhaustive source of information within the region it operated, and aiming at covering the Italian territory by involving all the existing CF centres in the data collection.

All the existing CF centres contribute to the IRCF data collection since 1988, therefore the registry database can be reasonably considered an unbiased collection of data on CF patients living in Italy since 1988.

The CF centres were asked to report to the IRCF only patients meeting the CF diagnosis criteria defined by the IRCF clinicians. In the first years of IRCF activity, only patients with Chloride values above 60 mmol/L in the sweat test were included in the registry, then modified inclusion criteria were adopted [9]. When new cases of CF were yearly transmitted to the IRCF, adherence to inclusion criteria was checked and in case of lack of adherence the centres were asked to revise the data and provide evidence that the criteria were met.

When the IRCF was activated, it included 2007 prevalent CF cases. Since then, 3061 incident cases (patients newly diagnosed with CF, who were not necessarily born after 01/01/1988) have been registered up to 31/12/2004 (date of last update of the IRCF). Data collected include patients' demographics, mode of diagnosis, genotype, transplantation status, date and cause of death, anthropometric measures, pulmonary function measures and occurrence of complications. For the purpose of this study, we analysed only the following subset of data: gender, date of birth, status as of 31/12/2004 (alive, dead, lost to follow-up), date of death/loss to follow-up, mode of diagnosis, solid organ transplantation, and genotype.

We used standardised mortality ratios (SMRs) to evaluate excess mortality due to CF in both sexes using the Italian population as a reference, as from the annual reports of the National Institute of Statistics [10].

We performed survival analysis using the Kaplan–Meier method and Cox regression models to evaluate the effect of gender on survival, taking into account well known risk factors and potential confounders such as mode of diagnosis, year of diagnosis, age at diagnosis and genotype. We included in the final model the factors that were reported as confounders from the literature or that we considered confounders from our data due to the change from crude to adjusted hazard ratio of death.

We used Log-rank tests, likelihood-ratio, Wald, and chi-square statistics to check statistical significance of the results obtained. We set the level of significance at $p < 0.05$.

Analyses were performed with SAS (version 9.1.3, SAS Institute Inc, Cary, NC) and PS Power and Sample Size Calculations (version 3.0.34).

3. Results

3.1. Main characteristics of patients

Table 1 summarizes the main characteristics of the 2293 CF paediatric patients (1141 F, 1152 M) included in the IRCF born after 1988 and followed-up until December 2004. The incidence of disease certification in the IRCF throughout the years 1988–

Table 1
Main characteristics of the 2293 CF patients born after 01/01/1988 included in the Italian Registry for Cystic Fibrosis.

	Females	Males
Number of patients in the Registry		
n	1141	1152
Mean annual incidence of disease certification (per 10,000)	2.55	2.42
Age (years) on 31.12.2004		
Min	0.11	0.08
Max	16.99	17.00
Mean	8.59	8.53
s.d.	4.80	4.73
Median	8.68	8.63
At time of diagnosis (%)		
Positive at neonatal screening	53.03	50.78
Presence of symptoms	68.60	71.17
Presence of meconium ileus	17.29	15.62
Age (years) at diagnosis		
Min	at birth	at birth
Max	16.01	15.76
Mean	1.09	1.03
s.d.	2.31	2.13
Median	0.20	0.23
Genotype		
Number of patients genotyped	1049	1041
Genotype UN/UN (%)	4.58	6.15
Sweat test		
n with Chloride values <60 mmol/L (%)	74(6.5)	67 (5.8)
F508del mutation (%)		
Homozygotes	23.83	25.65
Compound heterozygotes	47.28	43.13
Neither allele F508del	28.88	31.22
Pancreatic status		
Pancreatic insufficiency (%) at last follow-up visit	77.0	73.76
Number of transplants		
Lung	8	3
Liver	1	2
Status		
Alive	1062	1070
Lost to follow-up	41	40
Dead for CF	35	39
Dead other cause	3	3
Age (years) at death (CF-related)		
Min	0.05	0.02
Max	14.77	15.76
Mean	6.80	5.65
s.d.	5.27	5.41
Median	9.24	5.41

2004 is similar for males and females: 2.55 per 10,000 person-years in females and 2.42 per 10,000 person-years in males (95% CI for rates difference: −0.007; 0.332 per 10,000). The pooled incidence estimate, 2.48 per 10,000 person years (95% CI: 2.38; 2.59), is comparable to 2.36 (95% CI: 2.25; 2.47) per 10,000 person years, incidence estimated with the registry data over a shorter time period [8]. There were no gender-related differences in the age at diagnosis, frequency of positive neonatal screening, presence of symptoms at diagnosis and occurrence of meconium ileus. We observed similar proportions of patients showing sweat test values <60 mmol/L for males (5.8%) and females (6.5%).

Fourteen patients (9 females and 5 males) underwent pulmonary or liver transplantation. Although there were more females in the lung transplanted group, the numbers are too small to allow statistical comparisons.

The distribution of mutations in the CFTR gene was similar in males and females: F508del accounts for 47.5% of mutations in females and 47.2% in males, whereas unknown mutations account for 17.1% of alleles in females and 18.8% in males. Fig. 1 shows the distribution by gender of the 12 most frequent mutations after F508del.

During the observation period, 81 patients (3.6%, 41 females) were lost to follow-up. We therefore checked that there was not any informative censoring by verifying that the characteristics of the patients lost to follow-up were similar to the characteristics of the patients not lost to follow-up. We did not find any differences in genotype, age at diagnosis and symptoms at diagnosis. We further analysed for how long the patients lost to follow-up remained in the study, and the time to loss to follow-up was similar between sexes (mean for males: 13.2 years, for females: 13.1).

3.2. Survival analysis

In the period 1988–2004 the IRCF reports 80 deaths in the paediatric age (<18 years), and an annual mortality rate of 3.59‰ (95% CI 2.56; 5.02) for females and 4.00‰ (95% CI: 2.92; 5.51) for males. Age on 31st December 2004 was similar in males and females and, although age at death was slightly higher in females, this difference was not statistically significant (median age: 9.24 years females, 5.41 males, p=0.39).

Fig. 2 shows the Kaplan–Meier survival curves, separately by gender. The graph does not suggest any different pattern of survival, as further confirmed by the log-rank test (p=0.64): survival probability at 5 years from birth is 0.987 for females and 0.983 for males, at 10 years from birth is 0.980 for females and 0.971 for males.

After correcting for presence of symptoms at diagnosis, presence of meconium ileus, F508del mutation and age at diagnosis, females show a hazard of death 29% higher than males, though the finding is not statistically significant (hazard ratio: 1.29, 95%CI: 0.60; 2.76). We choose to adjust for these factors because they are known risk factors and potential

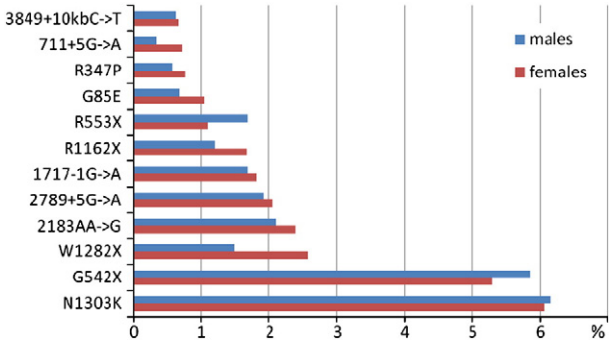

Fig. 1. CFTR mutations, by gender, of the 2293 CF patients born after 01/01/1988 included in the Italian Registry for Cystic Fibrosis. Only the 12 most common mutations, excluding F508del (47.5% in females, 47.2% in males), are shown.

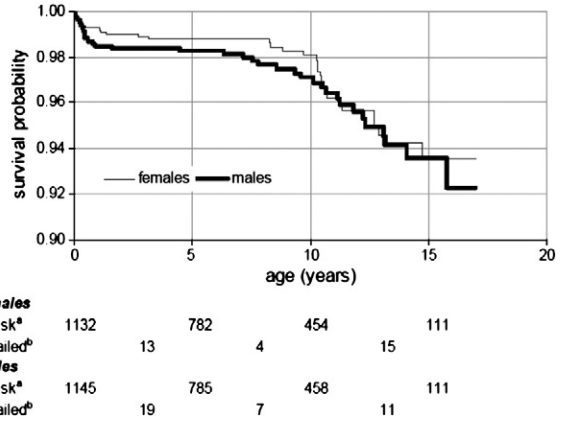

Fig. 2. Kaplan–Meier survival estimates (males vs females) of CF patients born after 01/01/1988 included in the Italian Registry for Cystic Fibrosis. Log-rank test 0.22, p=0.64. [a]At the beginning of the period, [b]during the period.

confounders: the crude hazard ratio estimate is 1.12 (95% CI: 0.70; 1.77).

However, male CF patients are 5.090 (95% CI: 5.0896; 5.0913) times more likely to die than Italian males without CF whereas female CF patients are 5.872 (95% CI: 5.8710; 5.8721) times more likely to die than their non CF counterparts. Therefore, females showed an excess mortality due to CF 15% higher than males.

4. Discussion

This is, to the best of our knowledge, the first longitudinal study run on a national basis, analysing survival of all newly diagnosed CF patients followed since birth throughout the paediatric age. Unlike previous studies, we did not find higher nor earlier mortality in females with respect to males.

Although 81 patients were lost to follow-up, we do not think that our findings are biased, since the proportion of patients lost to follow-up and the time to loss at follow-up were similar in males and females. Moreover, the baseline characteristics of this group of patients were similar to the patients not lost to follow-up; therefore we can reasonably assume that the patients not lost to follow up are representative of the entire population under study and that the survival patterns of the two groups are not different.

Although we cannot exclude that the patients lost to follow-up died, it would be unreasonable to think that death would have occurred differently in the two genders to such extent as to bias our results (for example, assuming that all females died and none of the males did or vice versa).

SMRs revealed that, should the Italian CF population follow the same mortality patterns as the general population, we would expect females to have better survival than males. Therefore, we can speculate that CF has an effect on females that prevents them from experiencing a better survival.

In older cohorts of patients, higher mortality in females was reported already in childhood. In the Canadian registry [2], for years 1970–1989, the cumulative percent survival at 10 years of age was 89.1% for males and 85.0% for females. The CF Foundation Patient Registry data confirmed the existence of a gender gap in survival [3]: between 1988 and 1992, females had higher risk of death than males since 1 year of age and remained significantly higher until age 20. This analysis was repeated years later [4] and, although improvement occurred both in females and in males, the gender gap still persisted in the age group 2 to 20 years: females had a risk of death 1.76 to 1.27 higher than males in the age from 2–5 years to the age of 16–20 years. No gender-related differences were seen beyond this age.

In our study population survival at ten years of age was higher than that reported in these studies and similar for females (97.1%) and males (98.0%). There is some indication therefore that the differential effects of CF on patient's survival have decreased for more recent birth cohorts, as suggested by an analysis performed in UK for years 1947–2003 [11].

One reason for this reduction could be a "period effect". In our study population a large proportion of patients was diagnosed by neonatal screening or was diagnosed early (median age at diagnosis is 2.6 months); we speculate that early diagnosis, and therefore early treatment, might prevent the intrinsic gender gap in the severity of CF to manifest: modern treatments are more effective in prolonging life and eventually compensate the disadvantage in females. Moreover, screening programs allow recognising at birth patients with very mild mutations or totally asymptomatic which were usually diagnosed in the adult age.

Genetic background might also play a role in the different effect of gender on CF survival across countries. The major mutation F508del usually associated to a severe phenotype is less common in Italy, respecting a decreasing incidence from northern to southern regions of the northern hemisphere [12,13]. The proportion of pancreas sufficient patients, a genetically determined manifestation generally associated to a milder pulmonary disease, is slightly higher in Italians than in other populations. A generally "milder" disease could account for fewer differences in survival between males and females in our population.

Other factors have been reported to determine a gender difference in disease progression or severity in CF, such as decreased pulmonary function, diabetes, and early Pseudomonas aeruginosa colonization [14–17]. All these factors might play a role in the loss of a female advantage in survival probability observed in the general population.

Our findings of a lack of gender difference in survival are not isolated. A survival study performed by the CF Centre of Verona collecting all patients of north-eastern Italy did not find any gender difference in survival probability in the long-term follow-up of a population-based neonatal screening program implemented since the 1970s [5]. An analysis performed in a single CF Centre in London [6] compared cross-sectional and longitudinal studies of CF patients examining a number of outcome measures including mortality, height, weight, and lung function. There were no significant differences between genders and no clear trends could be recognized. The authors suggested that modern aggressive treatment regimens could have removed any adverse female gender bias from lung function and

concluded that there is no intrinsic reason why girls at least up to the age of 16 years should not have equally good lung function and nutrition as their male counterpart. Consistent with these findings, some years earlier Lai et al. [18] analyzed the data of the Wisconsin neonatal screening program. They did not find any significant gender differences in respiratory symptoms or chest radiographic severity scores between males and females during their first 10 years of life, although a disproportionately high number of males were referred for diagnostic sweat testing.

5. Conclusions

We conclude that in our population CF females do not experience higher mortality than males. However, due to the disease, females lose the expected survival advantage over males occurring in the general population at this age. We do not exclude, however, that differences in mortality will establish after adolescence and, since speculations have arisen that female sex hormones can impair function of alternative chloride channels [19,20], it would be interesting to analyze survival patterns after puberty.

6. Conflict of interest statement

None of the authors has any financial or personal relationships with other people or organisations that could influence the submitted work.

Acknowledgements

We would like to thank all the people who contributed with their work to the activity of the IRCF. We are also very grateful to the reviewers who helped us in considerably improving the original version of this paper.

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