

Original Article

Causes of death in French cystic fibrosis patients: The need for improvement in transplantation referral strategies!



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Abstract

Background: Little data exist on causes of death in cystic fibrosis (CF) patients in the era of lung transplantation.

Methods: Deaths in CF patients in France (2007–2010) were identified using the French CF Registry and causes of deaths were determined based on medical files by a mortality adjudication committee.

Results: Of 256 deaths, half occurred after lung transplantation and were related to early or late complications of transplantation, whereas half occurred in patients who did not receive lung transplantation and were primarily related to respiratory failure or massive hemoptysis. Among patients who did not receive lung transplantation, only 19% died while waiting on a lung transplantation list. Lack of listing for lung transplantation was primarily related to late, or to lack of transplantation referral, rather than to contraindication to transplantation.

Conclusions: These data suggest that improvement in transplantation referral strategies may result in transplantation-related survival benefits.

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Keywords: Respiratory failure; Hemoptysis; Cystic fibrosis exacerbation; Lung transplantation

Abbreviations: IQR, interquartile range (IQR); MAC, mortality adjudication committee

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1. Introduction

Cystic fibrosis (CF) is a genetic disease that involves the lungs, the pancreas, and the liver [1]. Respiratory manifestations are usually predominant with the progressive development of bronchiectasis, chronic airway infection with bacteria (e.g. *Pseudomonas aeruginosa* and/or *Burkholderia cepacia*) [1], and respiratory complications (e.g., exacerbations, hemoptysis and pneumothorax) [2]. Although significant improvements in survival have been achieved by multidisciplinary care at specialized CF centers [3,4], respiratory failure still occurs,

and in this situation, lung transplantation becomes an option with the potential to improve life expectancy [5].

Respiratory disease is considered the main cause of death in CF patients, accounting for up to 85% of deaths [6]. However, few studies have assessed causes of death in CF patients, and these studies relied on data obtained in death certificates [7], in mailed surveys from CF physicians [8], or from CF registries [9]. A limitation of these approaches relates to lack of precision for specific causes of death. Furthermore, older studies did not take into account lung transplantation, which was not widely available at that time [7], and post-transplantation deaths were not specifically identified in recent CF registry reports [10,11].

The 2011 French CF Registry report revealed that nearly 60 deaths per year occurred in France, and only half of these deaths occurred after lung transplantation [12]. The registry did not contain sufficient data to understand why half of the patients dying with CF did not receive lung transplantation, while lung transplantation is available in 11 transplantation centers distributed throughout France and is fully funded by a governmental healthcare organization. Therefore, medical files of CF patients whose deaths were recorded between 2007 and 2010 in the French CF Registry were obtained from CF centers and were studied by an independent mortality adjudication committee (MAC). The aims of this study were (1) to describe specific causes of death and (2) to determine reasons for not receiving lung transplantation. Some of these data were presented at recent international meetings [13,14].

2. Methods

2.1. Identification of deaths in CF patients

The French CF Registry was used to identify deaths. This registry, which collects data on CF patients followed in the network of accredited French CF centers, reflects approximately 88% of the total French CF population [12]. Deaths in CF patients were identified from 2007 to 2010. This timeframe was chosen because a high-emergency transplantation program, allowing for rapid transplantation in patients at imminent risk of death, was introduced in France in 2007 [15], and because 2010 was the last year data was available when this study was initiated.

2.2. Data collection and ethics

For each patient, the medical file was obtained from the CF center where death was declared. Physicians were requested to provide all medical documents in the last three years prior to death, which included clinic notes, hospitalization reports, letters between physicians, and pulmonary function tests. The study was approved by the Committee on Human Health Research (CCTIRS #12704).

2.3. Operation of the mortality adjudication committee

The MAC was composed of two pediatricians (AM, MA), five adult CF physicians (CM, CH, RK, DH, PRB), and two

lung transplantation specialists (VB, DG). Operation of the MAC was derived from the method described by McGarvey et al. [16,17]. Each medical file was analyzed by three independent experts to assign the cause of death and complete an endpoint adjudication form. During MAC meetings, the three opinions were reconciled during a discussion and a final summary form was completed. If the cause of death was not unanimous, the case was further reviewed and discussed with the aim of developing a consensus, which we were able to obtain in all cases. When a medical file did not contain sufficient information to determine cause of death, every effort was made to obtain additional information by contacting primary care or CF physicians, and allied healthcare professionals.

2.4. Adjudication of causes of death

The primary cause of death was attributed to the medical condition that prompted each patient to present for medical treatment. For example, a patient presenting to the hospital for massive hemoptysis, who died a week later with multiorgan failure following intubation, was classified to have died from massive hemoptysis. A case was adjudicated as “unknown” when available information did not provide an identifiable cause of death.

Causes of death after lung transplantation, and timing of death after lung transplantation were based on published reports by the Registry of the International Society for Heart and Lung Transplantation [18]. The primary causes of death after transplantation included bronchiolitis obliterans syndrome, graft failure, infection, malignancy, and technical causes. Technical causes referred to surgical complications (e.g., hemothorax, suture problems) in the perioperative period, and to immediate or delayed airway complications (e.g., fistula, anastomosis necrosis) [19].

Causes of death in individuals who did not receive lung transplantation included respiratory failure (pulmonary exacerbations), hemoptysis, pneumothorax, *cepacia* syndrome [20], meconium ileus, liver disease, malignancy, and suicide. Causes of death that were not related to CF were grouped as miscellaneous causes. For patients who died while waiting for lung transplantation, the date of listing for transplantation was obtained. For those who died while they were not listed for transplantation, the reasons for not being evaluated and/or listed for transplantation were determined. These reasons included individual choice to not pursue lung transplantation by the patient, denial for transplantation because of contraindications [21,22], currently undergoing transplantation evaluation, and no documentation that lung (re)transplantation was even considered by the medical team.

2.5. Statistics

All data are n (%) or median [interquartile range (IQR)], unless otherwise specified. Comparisons between women and men for age of death were performed using the Mann–Whitney test. Comparisons of specific causes of death were performed using Fisher’s exact test. Analyses were performed using Prism 5.0 (Graphpad Software Inc., San Diego, CA).

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