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Review

Cystic fibrosis patient registries: A valuable source for clinical research☆

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Abstract

Cystic Fibrosis (CF) patient registries are valuable data sources for researchers studying the natural history, treatment paradigms, and long-term health outcomes of individuals with CF. In this review, we discuss the role of CF patient registries in facilitating comparative effectiveness research, particularly evaluating therapies and variation in health care delivery. We also discuss the limitations of registry-based research, particularly indication bias, as well as statistical methods that can be used to address these issues.

Keywords: Cystic fibrosis; Patient registry

Contents

1. Introduction

Broadly defined, a patient registry serves as an organized data collection tool incorporating clinical, sociodemographic, and other relevant health information obtained from multiple data sources across a health care system or systems [1]. Data included in registries should be collected using a standardized

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approach, and should be accessible to clinicians and researchers trying to understand and improve the health of a population. Applying a research lens, registry data is generally obtained through an observational study design, similar to classic cohort study designs in epidemiology. For decades, CF patient registries have been seen as a model for the development and use of patient registries of rare disease populations. Comprehensive registries for CF now exist throughout the United States, Canada, Europe, and Australia. The US Cystic Fibrosis (CF) Foundation Patient Registry (CFFPR), as an example, has become an important tool for health care providers, policy makers, and researchers for over five decades [2,3].

CF registries provide an avenue for the conduct of comparative effectiveness research (CER) and may also enable pragmatic, real-world clinical trials. In an accompanying review, Jackson and Goss discuss the origin of national CF registries, highlight the power of registries, explore issues related to international linkages of registries, and analyze how to sustain these registries into the future [4]. In this review, we highlight the promise and power of CF registries for such clinical research. In particular, we discuss the role of registries in conducting comparative effectiveness research of treatment approaches in CF and strengthening prospective observational studies. We also identify the challenges and limitations of registry-based research approaches, including statistical methods to address them.

2. Registry data as a valuable source for comparative effectiveness research

2.1. Comparative effectiveness research: A framework

Clinical research is traditionally designed using prospective designs developed with a single or limited set of questions and hypotheses in mind. In epidemiology, cohort studies are established to evaluate the impact of exposures on later health outcomes within a population. For rare outcomes, retrospective case-control studies are also used. When evaluating treatments or interventions, randomized controlled trials are considered the "gold standard". It is apparent that for many research questions, particularly in small populations, such classic study designs are impractical, expensive, and for some subgroups may be impossible to execute. Comparative effectiveness research (CER), defined as the conduct of research comparing the benefits and harms of different interventions, management strategies, or treatments on health outcomes in "real world" settings, can help overcome some of these limitations [5,6]. Whereas clinical trials serve the purpose of establishing efficacy of treatments or interventions, the overarching purpose of CER is to provide an evidence-base for patients, clinicians, and policymakers about which interventions may be most effective under specific circumstances or with specific populations. CER often evaluates a broader group of health-related outcomes than clinical trials, often incorporates patient-reported outcomes and focuses on priority areas of interest to patient communities. In addition, since patients who enroll in clinical trials may differ from non-research participants [7], registry-based CER studies provide a methodology to evaluate outcomes across a larger set of patients. Registry-based CER research also enables the comparison of interventions and treatments in a "real-world" setting, and allows for evaluation of heterogeneity of effects across different subgroups; in CF populations, CER can include the study of patient populations that otherwise would not be eligible for clinical trials due to common trial exclusion criteria such as severely decreased lung function and presence of certain airway infections or co-morbidities for example.

2.2. Comparative effectiveness research to evaluate variation in healthcare delivery

Variation in treatment approaches between CF clinics has been identified for decades. CER addressing this variation in clinical care practices using registry data allows for evaluation of the impact of such variation on health outcomes. One of the earliest examples this research approach was a landmark study comparing outcomes in patient registries of those with CF receiving care in Toronto compared to Boston in the 1970's [8]. During that era, patients in Toronto received differing nutritional recommendations emphasizing dietary fat intake, and they were found to have improved growth and survival despite similar lung function outcomes. In the modern-era, this study would be clearly considered CER. This study laid the groundwork for changes in nutritional CF care, and subsequent registry-based research has identified continued associations between better nutritional parameters and improvements in other health outcomes in several US and European registry analyses [9–11].

Variation in routine monitoring, frequency of hospitalizations, and use of chronic therapies has also been observed in CF registry-based studies. Although the Epidemiologic Study of CF (ESCF) was a North American based registry created primarily to evaluate long-term outcomes with dornase alfa therapy [12], data from ESCF also identified wide-ranging differences in practice patterns for routine monitoring visits and use of antibiotics and other chronic therapies [13,14]. Importantly, a 2003 analysis of ESCF showed significant differences in center-level outcomes based on these observed variations in care practices; namely centers that had increased numbers of monitoring visits and increased use of IV antibiotics had higher average lung function among their patients [15]. In a more recent UK CF registry study, a similar association was identified [16]. Waters and colleagues, using the Toronto CF Database, showed that subjects with pulmonary exacerbations treated with >14 days of antibiotics had a greater increase in lung function compared to those treated for ≤14 days, suggesting that peak lung function is not achieved in all patients within 14 days [17]. One important threat to interpreting possible center-level variation in care using registry data is a common lack of risk adjustment for the characteristics of the populations cared for at different centers. A recent UK registry based analysis showed that differences in median FEV1 across centers was minimal when adjustments for patient population characteristics were taken into account, concluding that apparent differences in outcomes were unlikely due to differing care practices [18]. Overall, CER approaches to critically evaluate specific components of "real world" CF care models and identify whether any particular

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