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ORIGINAL ARTICLE

Application of competing risks analysis improved prognostic assessment of patients with decompensated chronic heart failure and reduced left ventricular ejection fraction

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Abstract

Objective: The Kaplan−Meier method may overestimate absolute mortality risk (AMR) in the presence of competing risks. Urgent heart transplantation (UHT) and ventricular assist device implantation (VADi) are important competing events in heart failure. We sought to quantify the extent of bias of the Kaplan−Meier method in estimating AMR in the presence of competing events and to analyze the effect of covariates on the hazard for death and competing events in the clinical model of decompensated chronic heart failure with reduced ejection fraction (DCHFrEF).

Study Design and Setting: We studied 683 patients. We used the cumulative incidence function (CIF) to estimate the AMR at 1 year. CIF estimate was compared with the Kaplan−Meier estimate. The Fine−Gray subdistribution hazard analysis was used to assess the effect of covariates on the hazard for death and UHT/VADi.

Results: The Kaplan−Meier estimate of the AMR was 0.272, whereas the CIF estimate was 0.246. The difference was more pronounced in the patient subgroup with advanced DCHF (0.424 vs. 0.338). The Fine−Gray subdistribution hazard analysis revealed that established risk markers have qualitatively different effects on the incidence of death or UHT/VADi.

Conclusion: Competing risks analysis allows more accurately estimating AMR and better understanding the association between covariates and major outcomes in DCHFrEF.

Keywords: Absolute mortality risk; Competing risks; Cumulative incidence function; Hazard of subdistribution; Decompensated heart failure; Prognosis

1. Introduction

Heart Failure (HF) is a growing global health problem [1]. It is estimated that HF afflicts 61 million people worldwide and more than six million either in the United States or Western Europe [1−3]. Despite advances in medical treatment, prognosis of HF remains grim [4,5]. Among ambulatory HF patients, 1-year mortality can range from 7% to 14%, depending on the studies published [6−8]. The prognostic outlook for advanced HF is definitely worse, with approximately four in 10 patients dying or undergoing urgent heart transplantation (UHT) or ventricular assist device implantation (VADi) within 1 year in the current therapeutic era [9]. An additional 8% undergo non-UHT [9]. Acute HF portends a definitely poor prognosis, with nearly 30% of the patients dying within 1 year [5].

Accurate estimation of absolute mortality risk (AMR) is an integral part of the complex process of clinical decision-making in HF, especially when advanced treatments are being considered. Accordingly, many prognostic studies have been performed to identify prognostic variables and quantify AMR, most commonly using the naïve Kaplan−Meier method with HT and VADi treated as censored observations. Heart transplantation and VADi, however, represent important competing risks [10−13]. According to Gooley et al., a competing risk is defined "as an event whose occurrence either precludes the occurrence of another event under examination or fundamentally alters the probability of occurrence of this other event" [14]. Thus, treating HT and VADi as censored observations

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What is new?

Key findings

- Failure to account for heart transplantation and VADi resulted in a 10% overestimation of 1-year mortality in hospitalized patients with decompensated HF with reduced ejection fraction. The extent of overestimation was particularly pronounced (25%) in the subgroup with advanced HF.
- The Fine−Gray competing risks analysis revealed that established risk markers have a qualitatively different effect on the incidence of death or UHT/VADi.

What this adds to what was known?

- Heart transplantation and VADi represent important competing risks in HF as they fundamentally alter the probability of occurrence of death. Little is known about the influence of these competing risks on estimate of mortality in patients with HF. This study highlights the influence of competing risks on estimate of mortality and the differential effect of established risk markers on the incidence of major events in decompensated HF with reduced ejection fraction. Our data may have implications for planning future prognostic studies.

What is the implication and what should change now?

- In most prognostic study of HF, competing risks are ignored. Our findings indicate that competing risks should be accounted for when assessing prognosis, particularly in patients with advanced HF who are more susceptible to undergo advanced treatments.

may violate the assumption of noninformative censoring and result in overestimation of the probability of the occurrence of death [15−18].

To circumvent the pitfalls of competing risks, the composite outcome of time to the first of death, UHT, and VADi is frequently used as an outcome measure alternative to mortality. This analytical approach, however, does not allow singling out the true incidence of each individual outcome and disentangling the effect of covariates on the hazard of the different types of events [15,19,20]. This limitation may be clinically relevant as, unlike mortality, time to UHT or VADi greatly depends on a clinical decision, although other factors such as patient preferences, chance (as the availability of a donor for UHT), or even too-late referral may be influential [21].

Competing risks of HT/VADi are most often ignored in prognostic studies of HF (Supplemental Table 1). The aim of this study was twofold: (1) to quantify the extent of bias of the naïve Kaplan−Meier estimate in estimating the incidence of death in the presence of competing events and (2) to analyze the effect of covariates on the hazard for death and competing events using a competing risks regression analysis. We used decompensated chronic HF (DCHF) with reduced ejection fraction as a clinical model to deal with these issues.

2. Methods

The study population consisted of 683 patients admitted for DCHF with reduced ejection fraction. We identified patients discharged with a primary diagnosis of HF (International Classification Code, Ninth Revision, code 428) using a computer-generated list obtained from our administrative database. Once these patients were identified, those fulfilling the inclusion and exclusion criteria were selected by reviewing medical records and hospital discharge letters in our electronic hospital information systems. Inclusion criteria were current hospitalization for DCHF, history of HF of at least 1 year, chronic treatment with standard therapies, and left ventricular ejection fraction (LVEF) of <0.40. Exclusion criteria were de novo acute HF; LVEF $\geq$ 0.40; acute HF listed as a secondary discharge diagnosis, developed after admission for another admitting diagnosis, or due to acute myocarditis or hypertrophic or restrictive cardiomyopathy, acute coronary syndromes, or angina pectoris; recent (<3 months) cardiac surgical or percutaneous procedures; planned coronary revascularization; congenital heart disease; and stenotic valvular disease. To limit the probability of noncardiovascular death, patients with history of or active cancer or other pre-existing noncardiovascular diseases with limited life expectancy also were excluded. Baseline covariates were collected from our electronic hospital information systems. Three mutually exclusive outcomes at 1 year were examined: death, UHT (United Network of Organ Sharing [UNOS] status 1)/VADi, and elective HT (UNOS status 2). One-year incidences of death, HT, and VADi are from admission date. Most patients were followed up at our outpatient HF clinics. Outcome status was ascertained by linking with the regional health information system, by interviewing patients, their relatives, and/or their treating physician, or by direct knowledge. The study was approved by the institutional review board. Patients' data were deidentified.

2.1. Statistical analysis

Data are reported as mean and standard deviation or median with 25th and 75th percentiles for continuous variables or percentage for categorical variables. We used Student's *t* test to compare mean or the Mann−Whitney test to