Prediction of outcomes in patients with heart failure

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1 General introduction

Heart failure (HF) is a progressive disease for which comprehensive, long-term disease management is needed [1]. It is one of the major causes of morbidity and mortality in the developed countries, with a prevalence of 2-3% [2] and death rates of 20-40% within 1-year and up to 70% in 5 years of diagnosis [3]. It is a complex condition that can be caused by different reasons and it is often co-existing with other comorbidities. One common cause of HF is coronary artery disease, but many other factors including hypertension, obesity, diabetes, arrhythmias, heart valve disease can lead to HF [2, 4, 5, 6]. Managing HF is difficult because besides medical treatment it requires significant lifestyle changes such as exercise, restricted fluid and salt intake and medication adherence. Despite the improvements in disease management, HF patients need to learn how to live with the medication and daily limitations in mobility and nutrition. Therefore, HF is often associated with poor quality of life and multiple hospital admissions.

About 23 million adults worldwide have been diagnosed with HF [2], while one person in five is expected to develop HF at some point in their life, in economically developed countries [7]. 1–3% of all hospital admissions in Europe and the USA are related to HF, while HF is the most common cause of hospitalization in patients over 65 years [3]. In developed countries HF related costs are reflecting approximately 1–2% of all health-care expenditures [8]. Approximately 227,000 people with heart failure are living in the Netherlands [9] and 900,000 people in the UK. In the UK, HF patients are consuming up to 2% of total NHS expenditure [10]. High healthcare cost expenditures have been also reported for the US population [11], where over $30 billion is spent for HF patients annually [2, 12].

One way to reduce cost and disease burden is by keeping patients out of hospital. Approximately 25% of the HF patients are re-admitted within 30 days of discharge from the hospital [3]. These re-admissions may be partially caused by worsening HF or other cardiovascular reasons. However, other factors may contribute, such as comorbidity, frailty, poor cognition or social support or poor discharge services at hospital. Recurrent admissions represent a substantial impairment in a patient's quality of life and are associated with high costs and increased mortality [13].

Not all re-admissions are preventable, since they might be related to unavoidable progression of the disease [14, 15]. However, identifying and preventing re-admissions that can be avoided is a great benefit to both patients and the health care system. A

portion of re-admissions can be prevented by predicting if they will occur and tailoring disease management interventions accordingly.

TABLE 1.1: Heart failure statistics

Prevalence worldwide	23 million
Prevalence in USA	6.5 million [12]
Prevalence in UK	900,000
Prevalence in the Netherlands	227,000
HF hospital admissions	1–3% of total admissions in Europe and USA
30day re-admission rate	25%
1-year death rate	20-40%
5-year death rate	up to 70%

PREDICTION MODELS IN HF

Outcomes, validation and generalizability

Many studies have been conducted aiming to predict adverse events in HF patients in order to identify risk factors of these events and optimize the care provided to the patients and their quality of life. In a systematic review, Rahimi et al. (2014) reported 64 risk prediction models for HF patients: 43 for death, 10 for re-admission and 11 predicting both (composite outcome) [16]. The discriminatory ability of the models was significantly higher for prediction of death compared to the models predicting re-admission or the composite outcome. Conclusion of this study was that there are clinically useful and well-validated death prediction models available but re-admission or composite outcome models are mainly performing poorly. Other earlier systematic reviews also reported poor discriminative ability for re-admission and concluded that predicting re-admission is challenging [17, 18].

Overall, the similarities of the reported studies suggest potential generalizability and wider clinical use of a model, however models have been hardly tested in a different setting [16]. Validation of the models in an external population and calibration (agreement between prediction and observed outcomes) have been overlooked [19].

Methodology

In the development of these models, regression techniques were most often used. Attempts to improve the discriminative power of re-admission models by using more advanced machine learning techniques did not show any improvement implying that the poor performance is not related to methodological issues but possibly can be explained by other significant predictors that are still unknown to us [20]. Another advantage of regression models compared to machine learning techniques is that they are easily interpretable by the clinical audience and that they allow for validation and can be updated by simple adjustments to local settings [21].

Predictors

Rahimi et al. (2014) reported a list of the most often considered predictors. Variables

often appearing in the models predicting death were age, renal function, blood pressure, sodium level, ejection fraction, sex, NT-proBNP, New York Heart Association class, diabetes, weight/body mass index (BMI) and exercise capacity [16]. In models predicting re-admission age, sex, renal function, cardiovascular disease, and heart rate were the most common variables while renal function, NT-proBNP, history of HF, age and blood pressure were the most common variables in the composite outcome models [16]. Increasing age and renal dysfunction were the predictors overlapping in all three cases [Table 1.2]. Most of the identified predictors were related to demographic, HF or other clinical conditions, while other risk factors that may affect the outcomes, such as frailty [22], depression [23], poor cognition [24] or social factors [23] were overlooked.

TABLE 1.2: Common predictors of outcomes in HF patients [16]

Outcome	**Predictors**
Mortality	Age, sex, renal function, blood pressure, sodium level, ejection fraction, NT-proBNP, New York Heart Association class, diabetes, weight/body mass index (BMI), exercise capacity
Re-admission	Age, sex, renal function, cardiovascular disease, heart rate
Re-admission or morality	Age, renal function, NT-proBNP, history of HF, blood pressure

METHODOLOGY

We designed the OPERA-HF study, in the UK, to explore a wide range of variables that were not taken into account in previous research. In particular, we explored non-disease specific or non-clinical variables that could act as predictors for re-admission or mortality in patients with HF following an admission for HF. We aimed to identify variables that could improve the discrimination for re-admission or mortality prediction. In order to validate our findings and their generalizability beyond the development cohort we utilized the SAPHIRE study, a patient cohort from the US [Table 1.3].

TABLE 1.3: Study characteristics; patients eligible for our analysis: heart failure, survived discharge with available follow-up data

	OPERA-HF (N = 1094)	**SAPHIRE-HF/COPD (N = 513)**
Study design	Observational cohort	Observational cohort
Geographical location	Hull, UK	St. Louis, Missouri, US
Time window	Oct. 2012 − Nov. 2016	Oct. 2014 − Jan. 2017
30 day unplanned re-admission, n (%)	213 (19%)	72 (14%)
30-day mortality, n (%)	60 (5%)	27 (5%)
Age (years), median [IQR]	77 [68 − 83]	73 [62 − 82]
Women, n (%)	433 (40%)	265 (52%)
Length of stay (days), median [IQR]	10.1 [6.0 − 17.0]	4.8 [3.1 − 7.7]

OPERA-HF

The OPERA-HF is a prospective observational study enrolling patients hospitalized for HF in the Hull & East Yorkshire Hospitals NHS Trust, UK. The aim of the study is to create a holistic view of the patients, their general condition and co-morbidities, and to identify predictors of mortality and re-admission to hospital. The study started in October 2014 and we take into account data of patients enrolled till November 2016. Clinical and non-clinical data were collected during hospital admission and just prior

to discharge. Psychosocial information including depression and anxiety, cognitive function and social support was collected during hospitalization through questionnaires that the patient was asked to complete. Additional assessments including frailty assessment were also performed during hospitalization.

Patients had to fulfill the following criteria to be included in the present study: age > 18 years; usual residence in the region served by the Hull & East Yorkshire Hospitals Trust; hospitalization for HF; treatment with loop diuretics; and at least one of the following: left ventricular ejection fraction (LVEF) $\leq 40\%$, left atrial dimension > 4.0 cm [25] or NT-ProBNP > 400 pg/ml (if in sinus rhythm) or > 1200 pg/ml (if in atrial fibrillation) [26]. Patients who were unable to understand and comply with the protocol or unable or unwilling to give informed consent were not included in the study. The study has ethical approval from the South Yorkshire Research Ethics Committee (REC ref: 12/YH/0344) and is conducted in accordance with ICH-GCP, Declaration of Helsinki, the Data Protection Act 1998 and the NHS Act 2006.

SAPHIRE-HF/COPD

The observational study on clinical data to assess and predict the clinical, financial, and behavioral risk of re-admission or mortality of patients hospitalized for HF and COPD (SAPHIRE-HF/COPD) is a prospective cohort study consisting of patients aged 18 years and older who were admitted to Mercy Hospital in St. Louis, Missouri for HF and/or COPD. The study started in October 2014 and ended in January 2017. The aim of the study is to identify contributing factors to adverse outcomes for HF and COPD patients, to evaluate the added value of non-clinical factors and to analyze the validity and predictability of prediction models beyond a single disease population. All participants had to provide written informed consent and meet all of the following inclusion criteria: physically and mentally capable to cooperate based on clinical judgement of the care manager nurse, understand and speak the English language and willing to fill out the questionnaires during their hospitalization. Patients were excluded for any of the following reasons: only admitted to observation unit, part of another research study involving novel medications or devices, illicit drug use, or designated for transport to hospice at discharge. The study was approved by Mercy Health's Institutional Review Board.

AIMS AND OUTLINE OF THIS THESIS

The main aim of this thesis is to explore risk factors associated to an increased risk of adverse outcomes for HF patients and improve the early re-admission or mortality prediction in HF. In the first part of this thesis we study psychosocial factors. We explore the impact of depression or anxiety on mortality in HF patients by means of a systematic review of existing scientific literature. We then estimate the impact of depression on mortality in the OPERA-HF study. We extend our scope beyond depression or anxiety, by taking into account living status, cognitive impairment and frailty and we study the impact of these risk factors on the combined outcome of recurring re-admissions or mortality. In the second part of this thesis we use prediction model methods to develop and externally validate a risk prediction model for early re-admission or mortality taking into account new predictors. The aim of this thesis is reflected in the following research questions.

- What is the impact of depression and anxiety on mortality in HF patients?
- Which other psychosocial factors affect adverse outcomes in HF? What is their association with first and recurrent events?
- Can we predict early re-admission or mortality with a model that is transportable to a different geography?

This thesis consists of four parts. Part I (Chapter 1) includes the general introduction and the research questions. Part II (Chapter 2, 3 and 4) is addressing the first and second research questions. The third research question is approached in Part III (Chapter 5 and 6) where we report results on development and external validation of an early outcome risk model. These parts are followed by Part IV (Chapter 7), which includes the general discussion, summarizes the main findings of this thesis and provides answers to the aforementioned research questions and recommendations for future research.

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Part II

Impact of psychosocial factors and frailty on HF adverse outcomes