Prediction of outcomes in patients with heart failure

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Part I

Introduction

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

2 Depression and anxiety as predictors of mortality among HF patients: systematic review and meta-analysis

This article was published as "I. Sokoreli, J. J. G. de Vries, S. C. Pauws, and E. W. Steyerberg, "Depression and anxiety as predictors of mortality among heart failure patients: systematic review and meta-analysis", *Heart failure reviews*, vol.21, no.1, pp.49-63, 2016."

ABSTRACT

Aims: Several studies suggest that psychological factors are associated with negative outcomes and in particular higher mortality rates among Heart Failure (HF) patients. We aimed to evaluate the effect sizes of depression and anxiety on all-cause mortality in HF patients.

Methods and results: We conducted a systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methodology. We searched for studies on depression or anxiety effects on all-cause mortality among HF patients published up to June 2015. A number of 26 and 6 articles met inclusion criteria for depression (total 80627 patients) and anxiety (total 17214 patients) respectively. The effect estimates were pooled using random-effect meta-analysis.

Depression has significant and moderately heterogeneous effect on all-cause mortality (HR = 1.57; 95%CI 1.30 – 1.89, $P < 0.001$); adjustment for confounders led to a similar effect estimate (HR = 1.40; 95%CI 1.22 – 1.60; $p < 0.001$). Larger studies and higher study prevalence of depression were associated with smaller effect size. The effect of anxiety on mortality outcome was small and not conclusive given the low number of studies (n=6) (HR = 1.02; 95% CI 1.00 – 1.04, $P < 0.05$).

Conclusions: This systematic review and meta-analysis suggests that depression is an important and independent predictor of all-cause mortality among HF patients, while anxiety does not appear to have a strong effect. Further research is recommended towards the detection and treatment of depression.

INTRODUCTION

Heart Failure (HF) is defined as a clinical syndrome in which patients have typical symptoms such as breathlessness, ankle swelling, and fatigue and signs such as elevated jugular venous pressure, pulmonary crackles, and displaced apex beat, resulting from an abnormality of cardiac structure or function [1]. Approximately 1–2% of the adult population in developed countries has HF, with the prevalence rising to $\geq 10\%$ among persons 70 years of age or older [2]. HF is one of the most common causes of hospital readmission and mortality.

Psychological factors such as depression or anxiety are often reported with high prevalence and strong association with negative outcomes in patients with cardiovascular disease [3]. Many studies have reported high rates of depression among HF patients. A prior systematic review and meta-analysis published by Rutledge in 2006 [4] reported an overall aggregated depression prevalence rate of 21.6% among HF patients, while individual study prevalence estimates ranged from 9% to 60%. Moreover, in 2005 Konstam [5] reported that approximately 40% of HF patients may suffer from major anxiety, and overall anxiety levels are 60% higher than levels seen in the healthy population.

Depression has been linked to increased risk of negative outcomes, such as rehospitalization and mortality among HF patients. According to a previous meta-analysis, the aggregated risk estimate derived from 8 studies suggested a greater than 2-fold risk of death and secondary events for HF patients with heightened depressive symptoms or a depressive disorder [4]. A similar analysis was also published by Fan [6] in 2014 on 9 prospective studies, who reported a pooled Hazard Ratio of 1.51 for patients with depression compared to patients without depression. In both cases the result was strongly heterogeneous but no further analysis, such as meta-regression, was performed to examine the sources of this heterogeneity. On the other hand, there is, to the best of our knowledge, no meta-analysis published about the prevalence of anxiety among HF patients and the effect of anxiety on mortality outcome. Even though anxiety is usually correlated with depression, it has not extensively been studied among patients with HF.

Our aim is to provide an updated systematic review of prospective or retrospective studies and a meta-analysis of the effect of depression and the effect of anxiety on

mortality among HF patients. To reach this objective, we searched extensively for available studies investigating the impact of depression and anxiety on mortality of HF patients. Within these studies, we identified also the reported prevalence of depression or anxiety among HF patients.

METHODS

Search strategy and selection criteria

This systematic review and meta-analysis were conducted according to the guidelines introduced in the Preferred Reporting Items for Systematic reviews and Meta-analysis (the PRISMA Statement) [7]. The 27 checklist items of the PRISMA methodology followed are given in Appendix A. Three electronic databases (MEDLINE, BIOSIS and EMBASE) were searched for studies that investigated the relationship between depression or anxiety and mortality among Heart Failure (HF) patients. No publication time restriction was applied. All papers written in English and published before the 25th of June 2015 were included. Selected journals as well as the references of full-text papers were also hand-searched, when necessary, in order to identify studies that meet the inclusion criteria.

The database search string was created according to the PICO model (P, population/patient; I, intervention/indicator; C, comparator/control; and O, outcome). For the "P" in PICO the "HEART FAILURE" keyword was included. For the "I", the following keywords: "DEPRESS? OR STRESS OR ANXIETY OR PSYCHOLOG?". For the "C", no particular terms were used in our case. For "O", we used the following keywords: "MORTALITY OR DEATH". The complete query as used for the databases search is given in Appendix B.

Study selection

In our analysis, several inclusion and exclusion criteria were defined. All studies that met those criteria were included. The inclusion criteria were articles presenting studies focusing on the association between depression or anxiety and mortality in a HF adult population. All mortality outcomes such as all-cause or cardiac related mortality were included and studies focusing on inpatient, outpatient or both care settings were taken into account. On the other hand, publications analyzing data that had already been used before for the same purpose, studies introducing no quantitative assessment of the impact of depression or anxiety on the outcome or analyzing the use of antidepressants as primary focus were excluded from our analysis.

Review process and data collection

All titles and abstracts of studies identified by the electronic and hand search were screened by the reviewer (IS) to identify those meeting the inclusion/ exclusion criteria. Then, all the selected full texts were screened independently by two reviewers (IS, GJdV) to identify which articles should be included in the systematic review. Any disagreement between the reviewers was resolved by a third reviewer (SP). For each of the selected articles the reviewers extracted data about author, year of publication, follow-up period, outcome variable, location, study design, study population (size/ type), prevalence of depression or anxiety, assessment method of the psychological parameter, other parameters, statistical method and results.

Mendeley 1.13.8 software was used for organizing and managing of the articles.

Data analysis

All studies were categorized according to the psychological factor investigated (depression or anxiety). Information was extracted according to whether the analysis was adjusted for confounders such as age, gender, and clinical severity. For both groups the association between depression or anxiety and mortality was reported by collecting information of the hazard ratios/odds ratios, 95%CI and/or p-values.

Random-effects meta-analysis was applied to combine the results. We decided to pool not only the adjusted effect but also the unadjusted effects in order to avoid the bias of the different adjustments. For the few cases where Odds Ratios were reported, they were converted [8] into Hazard Ratios in order to be comparable with the other Hazard Ratios. In studies where results were presented for several periods of follow-up we selected the longest follow-up period to avoid bias of including multiple results on the same patient data.

Studies collected in our analysis were different with respect to patient population, locations and depression or anxiety assessment methods. The random-effects method allows for heterogeneity by assuming that the effects being estimated in the different studies are not identical, but follow a normal distribution. Heterogeneity across the studies was quantified by the I^2 statistic [9]. The I^2 statistic summarizes the fraction of the variation across studies due to heterogeneity relative to chance. Random-effect

meta-regression was used in an attempt to explain between-study heterogeneity and identify possible sources of bias. Meta-regression is a method to quantify the association between the estimated effect of depression and different study characteristics.

Meta analyses were presented in the form of forest plots created with the *metafor* package for R statistics version 3.0.3 (The R Foundation for Statistical Computing).

RESULTS

Search result

A total of 906 potentially relevant articles was identified from the electronic search and 5 from the hand search. After removing the duplicates and reviewing the titles and abstracts we ended up with 62 articles for a full text review. From these, 35 more articles were excluded, leaving 27 articles for the systematic review (Figure 2.1).

Characteristics of the selected studies

Depression and mortality

Among the identified studies, 26 reported on the effect of depression. The prevalence of depression varied from 10 to 79% in the identified literature studies. The unadjusted effect of depression is presented in Table 2.1, while the effect of depression after adjusting for several confounders in Table 2.2. The most common confounders, used in more than 10 studies, were age, gender, NYHA class and (left ventricular) ejection fraction. There were various techniques used among the studies to assess depression levels. We included all studies assessing for clinically significant depression. The most common scale used was the Beck Depression Inventory (BDI) [10], followed by the Patient Health Questionnaire (PHQ) [11].

FIGURE 2.1: Consort diagram

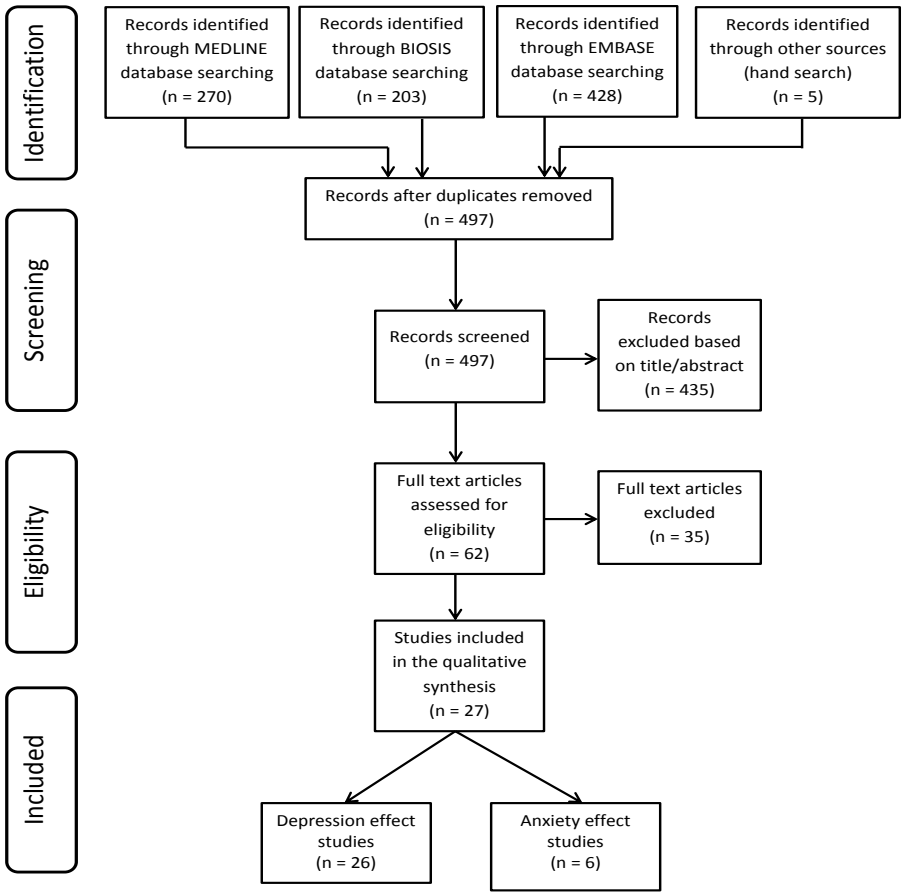

TABLE 2.1: Unadjusted effect of depression on all-cause mortality among HF patients

Author	Year	Assessment method	Population	Region	Study	Follow-up	Predicting period	Statistical method	HR/ OR	p-value	95% CI	Prevalence of depression
Adams [12]	2012	BDI ≥10	985 HF	US	Prospective cohort study	1792.3 days (mean)	–	Univariate Cox	1.35	<0.001	1.15– 1.57	30%
Albert [13]	2009	history of depression	48612 HF	US	OPTIMIZE-HF comprehensive registry	60-90 days	Inpatient	Univariate Cox proportional hazards model	1.36	0.027	1.04– 1.79	11%
Diez-Quevedo [14]	2013	GDS-4 ≥1	1017 HF	ES	Prospective cohort study	5.4 year (median)	Outpatient	Univariate Cox proportional-hazards model	1.39	0.001	1.15– 1.68	42%
Faller [15]	2007	PHQ-9	231 CHF	DE	Prospective cohort study	2.7 year (median)	Outpatient	Univariate Cox proportional-hazards model	3.3	<0.001	1.80– 6.10	13%
Faller [16]	2015	PHQ-9	863 HF	DE	Extended INH study	18 month	Outpatient	Univariate Cox proportional hazards model	1.07	<0.001	1.04– 1.09	-
Farisa [17]	2002	ICD-10	39 HF	UK	Retrospective cohort study	48 month (mean)	Outpatient	Univariate Cox proportional hazards model	2.1	0.0005	1.40– 3.20	21%
Friedmann [18]	2006	BDI-II	231 CHF	US	PFOS cohort study	23.6 month (mean)	Outpatient	Univariate Cox proportional hazards model	2.59	0.0177	0.23– 5.43	36%
Jiang [19]	2001	BDI ≥10	374 CHF	US	Prospective cohort study	1 year	Inpatient	Univariate logistic regression	2.26	0.04	1.04– 4.91	35%
Jiang [20]	2007	BDI ≥10	1006 HF	US	Cohort study	971 days (mean)	Inpatient	Univariate Cox proportional-hazards model	1.45	<0.001	1.19– 1.77	30%
Junger [21]	2005	HADS-D >6	209 CHF	DE	Prospective study	24.8 month (mean)	-	Univariate Cox proportional-hazards model	1.09	0.0071	1.02– 1.17	30%
Kato [22]	2009	CES-D ≥16	115 HF	JP	Prospective cohort study	2.1 year (median)	Outpatient	Univariate Cox proportional-hazards model	5.51	0.004	1.75– 17.39	23%

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Table 2.1 – *Continued from previous page*

Author	Year	Assessment method	Population	Region	Study	Follow-up	Predicting period	Statistical method	HR/ OR	p-value	95% CI	Prevalence of depression
Lesman-Leegte [23]	2009	CES-D $\geq$24	958 HF	NL	COACH prospective study	18 month	Inpatient	Univariate Cox proportional hazards model	1.18	0.172	0.93− 1.50	21%
Moraska [24]	2013	PHQ-9 $\geq$10	402 HF	US	Prospective cohort study	1.6 year (mean)	Inpatient/ outpatient	Univariate Cox proportional hazards model	3.37	<0.001	1.97− 5.75	15%
O'connor [25]	2008	history of depression	5791 HF	US	OPTIMIZE-HF Prospective cohort study	72.7 days (mean)	Inpatient	Univariate Cox proportional hazards model	1.56	0.0004	1.23− 1.97	14%
Sullivan [26]	2004	PRIME-MD interview/ HDRS/ SCL-20	142 HF	US	Prospective cohort study	3 year (mean)	Outpatient	Univariate Cox proportional hazards model	1.65	0.403	0.51− 5.28	29%

HR, hazard ratio; OR, odds ratio; CI, confidence interval; BDI, Beck depression inventory; GDS, geriatric depression scale; PHQ, patient health questionnaire; ICD, international classification of diseases; HADS-D, hospital anxiety and depression scale - depression; CES-D, center for epidemiological studies depression; HDRS, Hamilton rating scale for depression; SCL-20, Hopkins symptom checklist- 20-item depression scale; PRIME-MD, primary care evaluation of mental disorders; PFOS, psychosocial factors outcome study

TABLE 2.2: Adjusted effect of depression on all-cause mortality among HF patients

Author	Year	Assessment method	Population	Region	Study	Follow-up	Predicting period	Statistical method	Other parameters	HR/ OR	p-value	95% CI	Prevalence
Adams [12]	2012	BDI $\geq$10	985 HF	US	Prospective Cohort study	1792.3 days (mean)	-	Multivariate Cox proportional-hazards model	age, sex, race, marital status, NYHA, ischemic etiology of HF, history of CABG, diagnosis of diabetes	1.4	$<$0.001	1.16$-$ 1.68	30%
Albert [13]	2009	interviews/ medical records	48612 HF	US	OPTIMIZE-HF comprehensive hospital-based registry	60-90 days	Inpatient	Multivariate Cox proportional-hazards model	age, race, history of: ischemic heart disease, hypertension, liver disease and diabetes, any mechanical ventilation, any revascularization procedure, discharge medication: ACE, aldosterone antagonists, digoxin and lipid-lowering agentl discharge vital signs: SBP, DBP, HR; admission laboratory: serum sodium; discharge laboratory: serum creatinine	1.46	0.025	1.05$-$ 2.03	11%
Alhurani [27]	2015	PHQ-9 $\geq$10	1260 HF	US	HF Health-Related QoL Collaborative Registry	12 month	Outpatient	Multivariate Cox proportional-hazards model	age, gender, ethnicity, NYHA, combined anxiety/ depression	1.06	0.012	1.01$-$ 1.11	33%
Coyne [28]	2011	CES-D $\geq$16	706 HF	NL	COACH study randomized control trial	18 month	Inpatient	Multivariate Cox proportional-hazards model	BNP, type D	1.01	0.066	0.10$-$ 1.03	34%

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Table 2.2 – *Continued from previous page*

Author	Year	Assessment method	Population	Region	Study	Follow-up	Predicting period	Statistical method	Other parameters	HR/ OR	p-value	95% CI	Prevalence
Cully [29]	2009	ICD-9	12028 HF	US	Retrospective cohort study	12 month	Outpatient	Multivariate logistic regression	age,gender,race, married,income, comorbidities,combined depression/ anxiety	0.93	ns	0.71–1.15	18%
Diez-Quevedo [14]	2013	GDS-4 $\geq$1	1017 HF	ES	Prospective cohort study	5.4 year (median)	Outpatient	Multivariate Cox proportional-hazards model	Sex, age, months since HF diagnosis, ischemic etiology, LVEF, NYHA, DM, COPD, peripheral vasculopathy, CrC, BMI, ACE or ARB, BB	1.31	0.008	1.07–1.60	42%
Faller [15]	2007	PHQ-9	231 CHF	DE	Prospective cohort study	2.7 year (median)	Outpatient	Multivariate Cox proportional-hazards model	Age, sex, aetiology, NYHA, EF, syst./ non-syst. LV dysfunction, interaction term b/w LVEF and LV dysfunction	2.4	0.008	1.3–4.6	13%
Faller [16]	2015	PHQ-9	863 HF	DE	extended INH study	18 month	Outpatient	Multivariate Cox proportional-hazards model	age, sex, randomization status, NYHA, LVEF 30%, amino-terminal pro-BNP, SBP, HR, coronary artery disease, renal dysfunction, anemia, diabetes, ACE, ARB, BB, diuretics, and statins	1.04	0.017	1.01–1.07	-
Farisa [17]	2002	ICD-10	396 HF	UK	Retrospective cohort study	48 month (mean)	Outpatient	Multivariate Cox proportional-hazards model	demographics, social, medical history, baseline functional status and clinical severity	3	0.004	1.4–6.4	21%

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Table 2.2 – *Continued from previous page*

Author	Year	Assessment method	Population	Region	Study	Follow-up	Predicting period	Statistical method	Other parameters	HR/ OR	p-value	95% CI	Prevalence
Friedmann [18]	2006	BDI-II	231 CHF	US	PFOS cohort study	23.6 month (mean)	Outpatient	Multivariate Cox proportional-hazards model	treatment:ICD, amiodarone, afib, EF, depression score, social support amount	2.35	0.0222	2.354–4.743	36%
Jiang [19]	2001	BDI≥10/ positive DIS result	374 CHF	US	Prospective cohort study	1 year	Inpatient	Multivariate logistic regression	age, LVEF, NYHA, ischemic aetiology of CHF	2.12	0.07	0.94–4.81	35%
Jiang [20]	2007	BDI ≥10	1006 HF	US	cohort study	971 days (mean)	Inpatient	Multivariate Cox proportional-hazards model	age, LVEF, NYHA, ischemic aetiology of CHF, history of diabetes, marital status	1.4	0.003	1.12–1.74	30%
Junger [21]	2005	HADS-D >6	209 CHF	DE	Prospective study	24.8 month (mean)	-	Multivariate Cox proportional-hazards model	peakVO2, LVEF	1.08	0.02	1.01–1.15	30%
Kato [22]	2009	CES-D ≥16	115 HF	JP	Prospective cohort study	2.1 year (median)	Outpatient	Multivariate Cox proportional-hazards model	age, ACE, BNP	5.52	0.006	1.65–18.46	24%
Konstam [30]	1996	HRQL	3375 HF	US	Randomized clinical trial	36.5 month (mean)	-	Multivariate Cox proportional-hazards model	EF, age, treatment, NYHA	1.07	0.023	1.01–1.12	-
Lesman-Leegte [23]	2009	CES-D ≥24	958 HF	NL	COACH Prospective study	18 month	Inpatient	Multivariate Cox proportional-hazards model	age, gender, BNP level	1.43	0.04	1.02–2.02	21%

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Table 2.2 – *Continued from previous page*

Author	Year	Assessment method	Population	Region	Study	Follow-up	Predicting period	Statistical method	Other parameters	HR/ OR	p-value	95% CI	Prevalence
Moraska [24]	2013	PHQ-9 $\geq$10	402 HF	US	Prospective cohort study	1.6 year (mean)	In/ out-patient	Multivariate Cox proportional-hazards model	age, gender, CCI, incident vs. prevalent HF status	4.06	<0.001	2.35-7.01	15%
Murberg and Bru [31]	2001	SDS	119 CHF	NO	Prospective study	2 year	Outpatient	Multivariate Cox proportional-hazards model	age, NYHA, depressive symptoms, functional status	1.05	0.116	0.99–1.11	-
O'connor [25]	2008	history of depression	5791 HF	US	OPTIMIZE-HF prospective cohort study	72.7 days (mean)	Inpatient	Multivariate step-wise Cox proportional-hazards model	SBP, age, weight, reactive airway disease, sodium, SCr, liver disease, lower extremity edema, statin at discharge, BB at discharge	1.48	0.0034	1.14–1.93	14%
Rollman [32]	2012	PHQ-2	471 HF	US	Prospective study	up to 12 months	Inpatient	Multivariate Cox proportional-hazards model	sex,age$\geq$65, EF$\leq$30%, NYHA 3/4, anxiety, COPD, renal insufficiency, ACE-I or ARB, BB, Coumadin, hemoglobin<10, sodium<136, DBP, SBP	3.1	0.003	1.40–6.70	79%
Sherwood [33]	2007	BDI $\geq$10	204 HF	US	Prospective study	median 3 years	Outpatient	Multivariate Cox proportional-hazards model	NT-proBNP, antidepressant, age, HF etiology, and LVEF	1.05	0.06	1.00-1.10	46%

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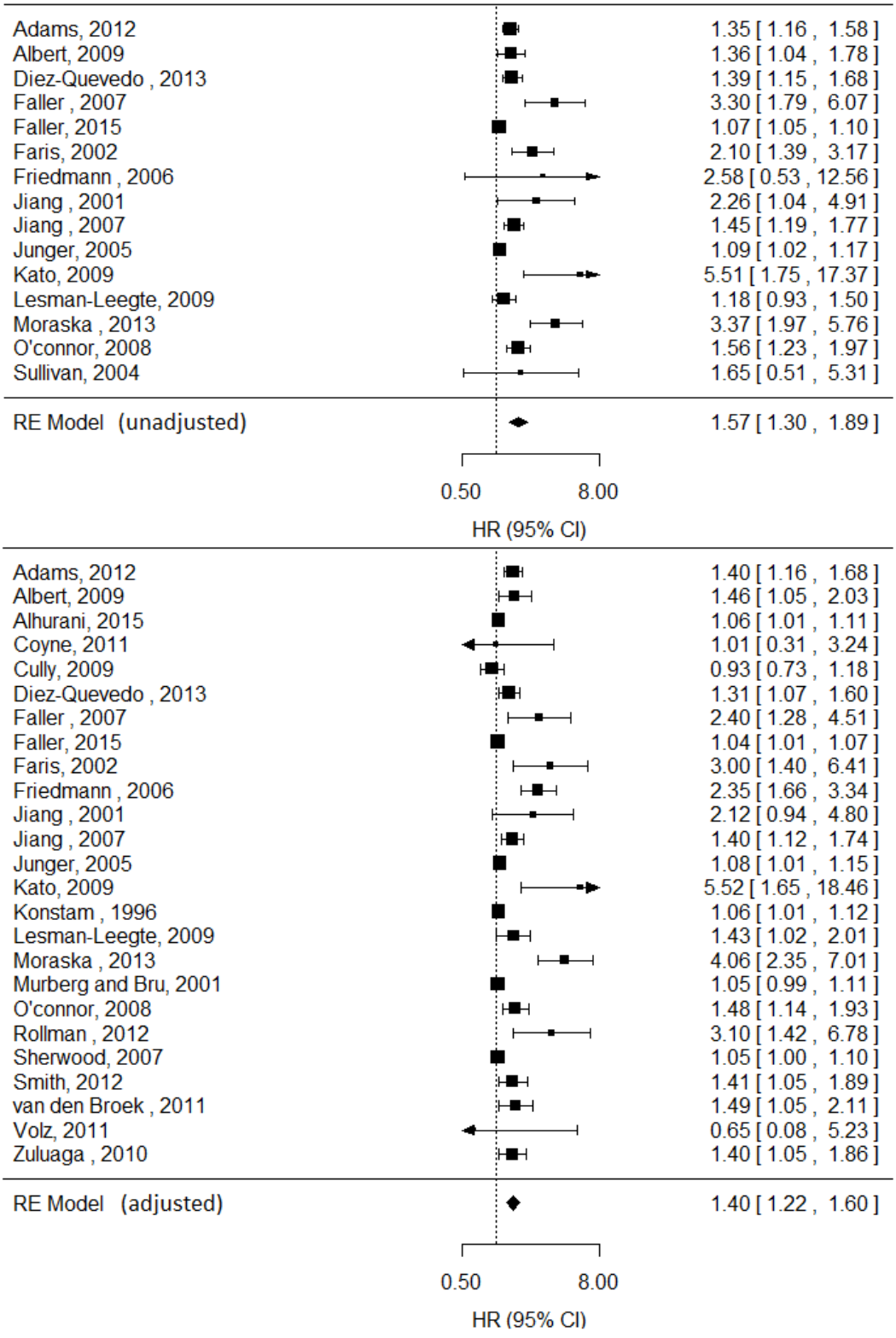
Table 2.2 – *Continued from previous page*

Author	Year	Assessment method	Population	Region	Study	Follow-up	Predicting period	Statistical method	Other parameters	HR/ OR	p-value	95% CI	Prevalence
Smith [34]	2012	BDI	380 CHF	NL	-	2.3 year (median)	Outpatient	Multivariate Cox proportional-hazards model	male, age, LVEF, NYHA, smoking, exertion fatigue	1.41	0.02	1.05−1.88	-
van den Broek [35]	2011	CES-D ≥8	208 HF	NL	Prospective community based study	11 year (median)	Outpatient	Multivariate Cox proportional-hazards model	age, gender, race, SBP, cholesterol, DM, BMI, smoking, reduced physical activity, CHD at baseline, LVEF, left ventricular hypertrophy, NT-proBNP	1.49	-	1.05−2.11	36%
Volz [36]	2011	HADS >10	111 HF	CH	Prospective cohort study	2.8 year (mean)	Outpatient	Multivariate Cox proportional-hazards model	LVEF, peak oxygen uptake	0.65	0.7	0.08−5.17	10%
Zuluaga [37]	2010	GDS-10 ≥5	433 HF	ES	Prospective study	5.7 year (mean)	Outpatient	Multivariate Cox proportional-hazards model	age, gender, race, COPD, CCI, serum creatinine level, LVEF, NYHA, HF hospitalization in last year, ischemic cardiopathy, heart valve disease	1.4	<0 .01	1.05−1.86	24%

HR, hazard ratio; OR, odds ratio; CI, confidence interval; BDI, Beck depression inventory; PHQ, patient health questionnaire; CES-D, center for epidemiological studies depression; ICD, international classification of diseases; GDS, geriatric depression scale; HADS-D, hospital anxiety and depression scale - depression; HDRS, Hamilton rating scale for depression; SCL-20, Hopkins symptom checklist- 20-item depression scale; PRIME-MD, primary care evaluation of mental disorders; PFOS, psychosocial factors outcome study; NYHA, New York heart association; CABG, coronary artery mypass grafting; ACE, angiotensin converting enzyme; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; BNP, b-type natriuretic peptide; LVEF, left ventricular ejection fraction; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; CrC, creatinine clearance by Cockcroft formula; BMI, body mass index; ARB, angiotensin receptor blocker; BB, beta-blockers; CHD, coronary heart disease; CCI, Charlson comorbidity index

The pooled hazard ratio for the unadjusted effect of depression on mortality was strongly significant across 15 studies (HR = 1.57; 95%CI 1.30 – 1.89; $p < 0.001$). The pooled estimation was strongly heterogeneous as reflected by the I^2 statistic (I^2 = 94%, heterogeneity $p < 0.001$). The pooled adjusted Hazard Ratio was also significant (HR = 1.40; 95%CI 1.22 – 1.60; $p < 0.001$) and again heterogeneous (heterogeneity $p < 0.001$; I^2 = 97%, Figure 2.2).

FIGURE 2.2: Meta-analysis – Forest plot calculating the effect of depression (a) unadjusted effect, (b) adjusted effect



A random-effect meta-regression was performed to understand the sources of the higher than 90% observed heterogeneity between the studies. The potential study-level covariates analyzed were the study characteristics introduced in Tables 2.1, 2.2. There was no association found between heterogeneity and the depression assessment method, the adjusted or univariate analysis, the location where the study was conducted, the inpatient or outpatient predictive period, the year of the study, the type of the study and the follow-up period. On the other hand, significant heterogeneity was associated with the total population size (smaller effect in larger studies $p < 0.01$) and the prevalence of the depression in the study (smaller effect for prevalence $>29\%$; $p < 0.01$, Table 2.3).

Anxiety and mortality

Only 6 studies analyzing the effect of anxiety on mortality among HF patients were identified with a prevalence of anxiety varying from 9 to 53%. Table 2.4 shows the unadjusted effects reported in the studies and Table 2.5 the reported effects on mortality after adjusting for a group of confounders. Age, NYHA class and (left ventricular) ejection fraction were the most common confounders in the identified studies.

TABLE 2.3: Random-effect meta-regression; Univariate Analysis

	Estimated coefficient (SE)	**p-value**
Year	-0.0016 (0.0124)	0.8957
Assessment method		
BDI	0.0349 (0.1287)	0.7863
PHQ	0.2096 (0.1433)	0.1434
Other	-0.1571 (0.1117)	0.1596
Population size	**-0.0004 (0.0002)**	**<0.05**
Region		
EU	-0.1119 (0.1134)	0.3241
US	0.04355 (0.1140)	0.7555
Follow-up period	0.0014 (0.0269)	0.9599
Statistical method		
Unadjusted	0.1066 (0.1159)	0.3573
Adjusted	Reference	Reference
Study type		
Prospective	0.1453 (0.1134)	0.2003
Retrospective	0.0667 (0.2217)	0.7637
Other	-0.1756 (0.1178)	0.1359
Depression prevalence	**-0.0108 (0.0059)**	**<0.1**
Predicting period		
Inpatient	-0.1641 (0.1156)	0.1156
Outpatient	Reference	Reference

In order to estimate the unadjusted effect of each study-level factor, the studies with missing values were excluded in each case

TABLE 2.4: Unadjusted effect of anxiety on all-cause mortality among HF patients

Author	Year	Assessment method	Population	Region	Study	Follow-up	Predicting period	Statistical method	HR/ OR	p-value	95% CI	Prevalence of anxiety
Friedmann [18]	2006	STAI	149 CHF	US	PFOS cohort study	23.6 month	Outpatient	Univariate Cox proportional-hazards model	1.037	0.06	0.998-1.078	45%
Jiang [38]	2004	STAI	291 CHF	US	Prospective cohort study	1 year	Inpatient	Univariate Cox proportional-hazards model	State-A:1.017; Trait-A:1.010	State-A:0.12; Trait-A: 0.44	State-A:0.996 -1.039; Trait-A:0.98-1.03	29%

HR, hazard ratio; OR, odds ratio; CI, confidence interval; STAI, State-Trait anxiety inventor; PFOS, psychosocial factors outcome study

TABLE 2.5: Adjusted effect of anxiety on all-cause mortality among HF patients

Author	Year	Assessment method	Population	Region	Study	Follow-up	Predicting period	Statistical method	Other parameters	HR/ OR	p-value	95% CI	Prevalence of anxiety
Alhurani [27]	2015	BSI	1260 HF	US	Registry	12 month	Outpatient	Multivariate Cox proportional-hazards model	age, gender, ethnicity, NYHA, depression	1.07	0.652	0.79-1.45	-
Cully [29]	2009	ICD-9	12028 HF	US	Retrospective cohort study	12 month	Outpatient	Multivariate logistic regression	age, gender, race, married, income, comorbidities, combined depression/anxiety	1.01	ns	0.76 - 1.54	9%
Friedmann [18]	2006	STAI	149 CHF	US	PFOS cohort study	23.6 month	Outpatient	Multivariate Cox proportional-hazards model	NYHA, atrial fibrillation/ flutter, treatment group	1.03	0.12	0.989 - 1.072	45%
Jiang [38]	2004	STAI ≥ 40	291 CHF	US	Prospective cohort study	1 year	Inpatient	Multivariate Cox proportional-hazards model	BDI, age, LVEF, NYHA, ischemic CHF origin	State-A: 1.01; Trait-A: 1.00	State-A: 0.30; Trait-A: 0.97	State-A: 0.988-1.040; Trait-A: 0.971-1.031	-
Konstam [30]	1996	HRQL	3375 HF	US	Randomized clinical trial	36.5 month (mean)	-	Multivariate Cox proportional-hazards model	EF, age, treatment, NYHA	1.02	ns	-	-
Volz [36]	2011	HADS-A >10	111 HF	CH	Prospective cohort study	2.8 year (mean)	Outpatient	Multivariate Cox proportional-hazards model	LVEF, peak oxygen uptake	1.75	0.47	0.37-8.21	9%

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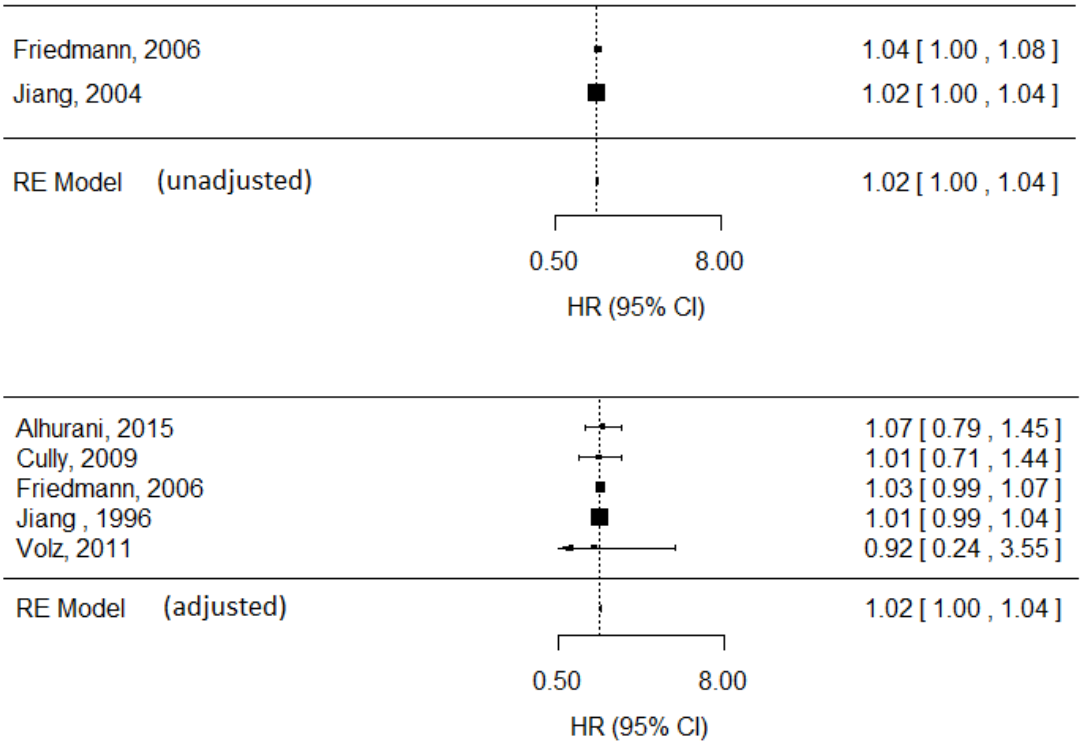
Table 2.5 – *Continued from previous page*

Author	Year	Assessment method	Population	Region	Study	Follow-up	Predicting period	Statistical method	Other parameters	HR/ OR	p-value	95% CI	Prevalence of anxiety

HR, hazard ratio; OR, odds ratio; CI, confidence interval; BSI, Brief symptom inventory; ICD, international classification of diseases; STAI, State-Trait anxiety inventor; HRQL, health related quality of life; HADS-A, hospital anxiety and depression scale - anxiety; PFOS, psychosocial factors outcome study; NYHA, New York heart association; BDI, Beck depression inventory; LVEF, left ventricular ejection fraction; EF, ejection fraction

There was no evidence found for anxiety as an independent predictor of mortality. The pooled hazard ratio for the unadjusted effect of anxiety on mortality, which was based on 2 studies, was 1.02 (95% CI 1.00 – 1.04; p = 0.24, heterogeneity p = 0.38; I^2 = 0%). The pooled hazard ratio for the adjusted effect of anxiety on mortality could be based on 5 studies and was identical (HR = 1.02; 95% CI 1.00 – 1.04; p = 0.09) and reasonably homogenous (heterogeneity p = 0.97; I^2 = 0%, Figure 2.3)).

FIGURE 2.3: Meta-analysis – Forest plot calculating the effect of anxiety (a) unadjusted effect, (b) adjusted effect



DISCUSSION

This systematic review was conducted according to the PRISMA guidelines to assess the evidence on the effect of depression (26 studies) and anxiety (6 studies) on all-cause mortality outcome among Heart Failure (HF) patients. <Key results: 1.6 for depression but very heterogeneous across studies; no effect for anxiety>. In contrast to other reviews, our study was not limited on follow-up duration or only in prospective studies reporting adjusted effects of the two parameters. We reviewed all studies published quantifying the effect of depression or anxiety.

The prevalence of depression varied among the 26 different studies with an average of approximately 29% ranging from 10 to 79%. The meta-analysis showed that the unadjusted risk of death among HF patients facing depression was 1.57 times higher than the risk among HF patients without depression and the pooled estimate of the adjusted Hazard Ratio was 1.40. In both univatiate and adjusted analysis, strong heterogeneity among the studies was found. Our findings are more conservative than previous reviews published [4, 6]. Rutledge et al reported a 2.10 higher adjusted risk of mortality and secondary events based on 8 studies and Fun et al reported a pooled adjusted Hazard Ratio of 1.51 based on 9 studies, both with substantial heterogeneity. From our attempt to explain heterogeneity we found that the effect of depression is weaker in larger studies; this suggests publication bias: small studies were published if they found relatively large effect estimates, while small studies with modest effect estimates were not. The weaker effect in studies with higher prevalence of depression may relate to the use of different cut-offs on an underlying, latent, scale for depression. If a more liberal cut-off was used, those labeled as depressed actually were milder than with a more strict definition of depression.

Our results for anxiety do not have the same weight as the results with respect to depression since anxiety was less studied in the literature. Anxiety had a similar prevalence to depression among the six identified studies (average 29%, range $9 - 45\%$), but patients with anxiety had no increased risk of death compared to those without anxiety. However, since anxiety is usually correlated with other factors such as depression, further research of anxiety as a covariate to other factors is recommended.

One limitation of our study is related to the variation in follow-up times. Follow-up

times varied from 30 days to a number of years; furthermore, there were studies covering different follow-up periods but in these cases we always selected the longest follow-up. Further analysis such as subgroup analysis would be recommended to investigate the effect variation in different follow-up periods, however limited information in some of the literature publications is restrictive towards this direction.

Moreover, we focused only on mortality. Nevertheless, there is evidence that depression and anxiety are also associated to other adverse events such as readmission. Further investigation in needed also towards this direction. One limitation of the meta-regression is that even though we tried to cover a broad selection of study-level covariates there are more that might also be related to the heterogeneity. Further research on different factors' interactions would be recommended.

The "gold standard" test of causality of a putative risk factor is a randomized clinical trial. Such a trial minimizes concerns about confounders [39, 40, 41]. To the best of our knowledge, there is no randomized clinical trial conducted for depression among a HF population. Based on our findings we strongly recommend such a trial in order to evaluate the causality of depression.

Finally, according to our findings from the meta-regression, depression should not be underestimated in clinical practice within HF population groups where prevalence is low. Furthermore, based on our overall findings on the effect of depression, we recommend further research on the recognition and management of depression in clinical practice which might improve patient outcomes. Further analysis such as subgroup analysis and interventional studies are required for stronger evidence towards this direction.

APPENDIX A: PRISMA CHECKLIST

TABLE 2.6: PRISMA checklist

Section/ topic	N	Checklist item	Page
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	15
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	17
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	18-19
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	20
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Appendix A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	20
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	20
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix B
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	20
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	21
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	20-22
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	21
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	21
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.	21

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Table 2.6 – *Continued from previous page*

Section/ topic	N	Checklist item	Page
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	21
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	21
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Fig. 2.1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Tables 2.1,2.2,2.4, 2.5
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	/
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Tables 2.1,2.2,2.4,2.5; Fig. 2.2 - 2.3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Fig. 2.2 - 2.3
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	34/ Table 2.3
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	34/ Table 2.3
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	40-41
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	40-41
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	40-41
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	/

APPENDIX B: DATABASE SEARCH QUERY

S (HEART(W)FAILURE)/TI AND ((DEPRESS? OR STRESS? OR ANXIETY OR PSYCHOLOG?) (S)(MORTALITY OR DEATH))/TI,AB.

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3 Depression as an independent prognostic factor for all-cause mortality after a hospital admission for worsening HF

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ABSTRACT

Background: Depression is associated with increased mortality among patients with chronic heart failure (HF). Whether depression is an independent predictor of outcome in patients admitted for worsening of HF is unclear.

Methods and results: OPERA-HF is an observational study enrolling patients hospitalized with worsening HF. Depression was assessed by the Hospital Anxiety and Depression Scale (HADS-D) questionnaire. Comorbidity was assessed by the Charlson Comorbidity Index (CCI). Kaplan-Meier and Cox regression analyses were used to estimate the association between depression and all-cause mortality.

Of 242 patients who completed the HADS-D questionnaire, 153, 54 and 35 patients had no (score $0-7$), mild (score $8-10$) or moderate-to-severe (score $11-21$) depression, respectively. During follow-up, 35 patients died, with a median time follow-up of 360 days amongst survivors (interquartile range, IQR $217 - 574$ days). In univariable analysis, moderate-to-severe depression was associated with an increased risk of death (HR: 4.9; 95% CI: 2.3 to 10.2; $P < 0.001$) compared to no depression. Moderate-to-severe depression also predicted all-cause mortality after controlling for age, CCI score, NYHA class IV, NT-proBNP and treatment with mineralocorticoid receptor antagonist, beta-blocker and diuretics (HR: 3.0; 95% CI: 1.3 to 7.0; $P < 0.05$).

Conclusions: Depression is strongly associated with an adverse outcome in the year following discharge after an admission to hospital for worsening HF. The association is only partly explained by the severity of HF or comorbidity. Further research is required to demonstrate whether recognition and treatment of depression improves patient outcomes.

INTRODUCTION

Psychosocial illness, including depression, is common in people with cardiovascular disease. Depression is particularly common in patients with heart failure (HF) [1]. Probably most patients with HF are depressed by their illness at some time but a meta-analysis suggests that depression affects about a 20% of patients at any time [2].

For patients with HF, depression is associated with an increased rate of adverse outcomes [2, 3], such as hospitalization and death. The aggregated risk-estimate derived from 26 studies was an approximately 1.5−fold risk of death in patients with HF if they had depression [3]. However, it can be difficult to disentangle whether depression causes a worse outcome, or merely reflects worse HF or more severe co-morbidity. We aimed to assess the prevalence and consequences of depression in patients admitted to hospital for worsening HF. We analyzed a prospective patient cohort and controlled for common covariates reflecting the severity of both the HF and any comorbidities.

METHODS

Study design

OPERA-HF is an ongoing prospective observational study, enrolling patients hospitalized with worsening heart failure (HF) to the Hull & East Yorkshire Hospitals NHS Trust, UK. The aim of the study is to gather a holistic view of the patients, their general condition and co-morbidities, and to identify predictors of mortality and re-admission to hospital. Clinical and psycho-social data were collected during hospital admission and just prior to discharge. The Charlson comorbidity index (CCI) was used to assess comorbidity (Appendix A).

Patients had to fulfill all of the following criteria to be included in the study: age $>$ 18 years; hospitalization for worsening HF; treatment with loop diuretics; and at least one of the following: left ventricular ejection fraction $\leq$ 40%, left atrial dimension $>$ 4.0 cm or NT-ProBNP $>$ 400 pg/ml (if in sinus rhythm) or $>$ 1200 pg/ml (if in atrial fibrillation). Patients unable to understand and comply with the protocol or unable or unwilling to give informed consent were excluded from the study. The study has full 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.

Depression assessment

Depression was assessed by the Hospital Anxiety and Depression Scale (HADS-D) questionnaire [4] (Appendix B). The HADS-D focuses on questions about depression. The response to each of the 7 questions is graded from 0 to 3, giving a total score that ranges between 0 and 21. A score of 7 or less implies that there is no depression; a score of 8-10 suggests mild depression; and a score of 11 or higher reflects moderate-to-severe depression [4]. Among 12 studies assessing the HADS-D questionnaire (total N = 2109 patients), a cut point of 8 for the diagnosis of depression had a mean specificity of 0.79 and a mean sensitivity of 0.83 when compared with a 'gold standard' diagnosis using DSM-III/IV or similar codes [5].

Mortality

All patients enrolled in the study are followed subsequent to discharge. Readmissions and all-cause mortality are automatically recorded in the hospital's IT system. For the present report, the primary outcome of interest was all-cause mortality.

Statistical analysis

We report the baseline characteristics of the patients who participated in the study between 14/10/2012 and 16/06/2015 and who completed the HADS-D questionnaire. Follow up was censored at 13/07/2015. The consort diagram is given in Appendix C.

Univariable and multivariable Cox proportional hazard regression models were used to estimate the association between depression and all-cause mortality. Univariable analysis was performed to assess the relation between variables and outcome, including demographics, clinical assessment, echocardiography and medication. In the multivariable model, we adjusted for all the variables found to predict outcome ($P \leq 0.1$) in the univariable analysis. Multiple imputation [6] was used to impute missing data when needed. The Kaplan-Meier method was used to estimate survival time and produce a survival curve [7]. All analyses were conducted using R 3.1.3 statistical software (The R Foundation for Statistical Computing, Vienna, Austria). In particular, the R package mice [8] was used for the multiple imputation and the R package survival [9] for the Kaplan-Meier method and the survival analysis.

RESULTS

Baseline characteristics of the study population

The baseline characteristics of the 242 participants who completed the HADS-D questionnaire are reported in Table 3.1. The median follow-up was 315 days (interquartile range, IQR 167 - 519) for all patients and 360 days (IQR = 217 - 574) amongst survivors. The mortality rate estimated from the Kaplan Meier curve was 15% [95% CI 10% - 20%] at one year.

TABLE 3.1: Baseline characteristics stratified by HADS-D group and total population. Characteristics are summarized by their count and fraction (N (%)) for categorical or their median and interquartile range (Median [25th − 75th]) for continuous variables, respectively; (∗) all variables are evaluated at admission apart from NT−proBNP and LVEF which are evaluated at discharge and (∗∗) NYHA class which was evaluated as the worst class during the last 7-days before admission (∗ ∗ ∗) Diuretics: loop diuretics or thiazide

Depression Score	**All (N=242)**		**0 − 7 (N=153)**		**8-10 (N=54)**		**11-21 (N=35)**	
Characteristics (*)	**Valid N**	**Summary**	**Valid N**	**Summary**	**Valid N**	**Summary**	**Valid N**	**Summary**
Women, %	242	76 (31%)	153	48 (31%)	54	18 (33%)	35	10 (29%)
Age, years	242	74 [64−80]	153	73 [64−81]	54	74 [67−78]	35	73 [63−80]
CCI, score	221	3 [2 − 5]	143	3 [2 − 4]	46	3 [2 − 6]	32	3 [2 − 5]
NYHA**: Class I/II, %	209	32 (15%)	132	23 (18%)	48	7 (15%)	29	2 (6%)
NYHA: Class III, %	209	135(65%)	132	87 (66%)	48	32 (67%)	29	16 (55%)
NYHA: Class IV, %	209	42 (20%)	132	22 (17%)	48	9 (19%)	29	11 (38%)
Hypertension, %	235	130 (55%)	150	82 (55%)	53	27 (51%)	32	21 (66%)
NT-proBNP, pg/mL	204	4792[1694 − 9784]	130	5022[1782 − 9668]	45	3188[1323 − 9445]	29	5368[2830 − 12290]
Heart Rhythm: Sinus, %	242	92 (38%)	153	50 (33%)	54	25 (46%)	35	17 (49%)
LVEF at discharge: $\leq$ 40%	216	128(59%)	142	89 (63%)	48	23 (48%)	26	16 (62%)
Main presentation:								
- Severe peripheral oedema, %	236	24 (10%)	149	19 (13%)	52	3 (6%)	35	2 (6%)
- Severe breathlessness at rest, %	236	76 (32%)	149	56 (38%)	52	12 (23%)	35	8 (23%)
- Increasing exertional breathlessness, %	236	106(45%)	149	53 (36%)	52	31 (60%)	35	22 (63%)
- Chest pain - cardiac, %	236	21 (9%)	149	14 (9%)	52	6 (11%)	35	1 (3%)
- Other symptom, %	236	9 (4%)	149	7 (5%)	52	0 (0%)	35	2 (6%)
HF Medication (on admission)								
ACE inhibitor, %	242	98 (40%)	153	54 (35%)	54	24 (44%)	35	20 (57%)
ARB , %	242	48 (20%)	153	30 (20%)	54	12 (22%)	35	6 (17%)
Beta-blocker, %	242	126(52%)	153	70 (46%)	54	32 (59%)	35	24 (69%)
Aldosterone Antagonist,%	242	51 (21%)	153	29 (19%)	54	11 (20%)	35	11 (31%)
Digitalis, %	242	35 (14%)	153	19 (12%)	54	9 (17%)	35	7 (20%)
Diuretics ***, %	242	128(53%)	153	71 (46%)	54	30 (56%)	35	27 (77%)

NYHA, New York Heart Association; CCI, Charlson comorbidity index; LVEF, Left ventricular ejection fraction; SOB, Acute shortness of breath;ACE, Angiotensin-converting enzyme; ARB: Angiotensin Receptor Blockers.

Depression assessment

The median HADS-D score amongst the 242 HF patients was 6 (IQR = 3 - 9); 153 patients had no (score 0-7), 54 had mild (score 8-10) and 35 had moderate-to-severe (score 11-21) depression, respectively. Patients with moderate-to-severe depression were, on average, in a worse NYHA class, had more likely sinus heart rhythm and were taking more HF medications than those with no depression (Table 3.1).

Patients were more likely to give high (i.e. worse) scores to the questions "I can laugh and see the funny side of things" and "I feel as if I am slowed down" (Table 3.2).

TABLE 3.2: Patients scoring of HADS-D questions; the score for each question ranges from 0 (as the most positive response) to 3 (most negative response). The aggregated scores are calculated based on the 242 HF patients answering the HADS-D questionnaire.

Question	**Score per answer**	**Number of patients**	**Aggregated score for 242 patients**
I still enjoy the things	Definitely as much - 0	58	294
I used to enjoy	Not quite so much - 1	109	
	Only a little - 2	40	
	Hardly at all - 3	35	
I can laugh and see	As much as I always could - 0	1	623
the funny side of	Not quite so much now - 1	18	
things	Definitely not so much now - 2	64	
	Not at all - 3	159	
I feel cheerful	Most of the time − 0	145	119
	Sometimes - 1	79	
	Not often - 2	14	
	Not at all - 3	4	
I feel as if I am slowed	Not at all − 0	12	472
down	Sometimes - 1	78	
	Very often - 2	62	
	Nearly all the time - 3	90	
I have lost interest	I take just as much − 0	117	194
in my appearance	care as ever		
	I may not take quite	65	
	as much care - 1		
	I don't take so much	51	
	care as I should - 2		
	Definitely - 3	9	
I look forward with	As much as ever I did - 0	94	224
enjoyment to things	Rather less than I used to - 1	85	
	Definitely less than I used to - 2	50	

Continued on next page

Table 3.2 – *Continued from previous page*

Question	Score per answer	Number of patients	Aggregated score for 242 patients
I can enjoy a good book or radio or TV program	Hardly at all - 3	13	126
	Often − 0	155	
	Sometimes - 1	59	
	Not often - 2	17	
	Very seldom - 3	11	

Effect of depression on mortality

The unadjusted rate for all-cause mortality was almost five times higher amongst patients with moderate-to-severe depression compared to patients without depression (HR: 4.9; 95% CI: 2.3 to 10.2; $P < 0.001$, Table 3.3a and Figures 3.1a). Increasing age (as a continuous variable), increasing NT-proBNP (continuous), NYHA class IV within 7 days before admission (compared with patients with Class I/II), increasing CCI score, and use of a mineralocorticoid receptor antagonist, beta-blocker and diuretic were all associated with increasing mortality. We therefore corrected for these characteristics in the multivariable analysis (Table 3.3b, Figure 3.1b). Moderate-to-severe depression remained a significant predictor of all-cause mortality (HR: 3.0; 95% CI: 1.3 to 7.0; $P < 0.05$) along with NT-proBNP (HR: 1.7; 95% CI: 1.1 to 2.8; $P < 0.05$) and NYHA class IV (HR: 1.2; 95% CI: 1.0 to 4.6; $P < 0.1$). Further details on the association between the covariates and the outcome are provided in Table 3.4.

TABLE 3.3: (a) Univariable analysis, (b) Multivariable analysis; (*) HR based on Cox proportional hazard models; (**) adjusted for age (continuous), CCI score (continuous), NYHA class IV (worst NYHA class during 7 days before admission - binary), log(NT-proBNP) (continuous), Aldosterone Antagonist (binary), Beta-blocker (binary) and diuretics (binary)

(a) Univariable analysis (N = 242 / events = 35) - Likelihood ratio test = 15.25 for 2 df, p<0.001			
Depression status at admission	**HR for all-cause mortality***	**95% CI**	**p-value**
None (reference)	1	–	–
Mild	1.54	0.63 – 3.80	0.34
Moderate-to-severe	4.86	2.30 – 10.25	<0.001
(b) Multivariable analysis (N = 242 / events = 35) - Likelihood ratio test = 41.5 for 9 df, p<0.001**			
Depression status at admission	**HR for all-cause mortality**	**95% CI**	**p-value**
None (reference)	1	–	–
Mild	1.44	0.58 – 3.63	0.44
Moderate-to-severe	2.97	1.26 – 6.99	<0.05

HR, Hazard Ratio; CI, Confidence Interval.

FIGURE 3.1: (a) Unadjusted cumulative incidence plot [analysis based on the imputed dataset], (b) Cumulative incidence plot adjusted for age (continuous), CCI score (continuous), NYHA class IV (worst NYHA class during 7 days before admission - binary), log(NT-proBNP) (continuous), Aldosterone Antagonist (binary), Beta-blocker (binary) and diuretics (binary) [analysis based on the imputed dataset]

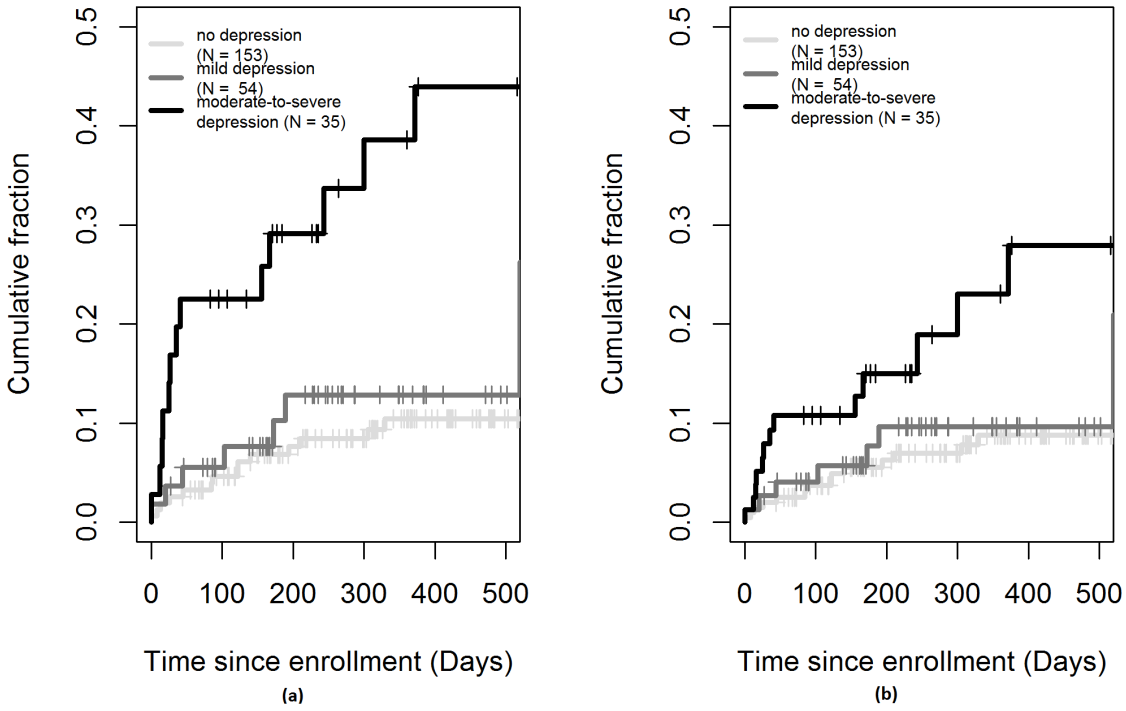

TABLE 3.4: Univariable/Multivariable analysis

	Univariable analysis (N = 242 / events = 35)			**Multivariable analysis (N = 242 / events = 35)**		
	HR	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Women, yes	0.78	0.37 – 1.67	0.52	-	-	-
Age at admission (10 year increase)	1.68	1.17 – 2.30	<0.01*	1.62	0.84 – 3.21	0.16
CCI at admission, score	1.13	1.00 – 1.29	<0.1*	1.08	0.93 – 1.26	0.39
NYHA**: Class I or II (reference)	1	–	–			
NYHA: Class III	0.72	0.26 – 2.02	0.52	-	-	-
NYHA: Class IV	2.62	0.95 – 7.27	<0.1*	2.15	1.00 - 4.59	<0.1*
Hypertension at admission, yes	0.85	0.43 – 1.65	0.63	-	-	-
$Log10$(NT-proBNP) at discharge, pg/mL	2.75	1.32 – 5.75	<0.05*	1.69	1.07 – 2.76	<0.05*
Sinus rhythm at admission, yes	1.17	0.60 – 2.28	0.65	-	-	-
LVEF $\leq$40 at discharge %	1.48	0.72 – 3.04	0.3	-	-	-
Main presentation:				-	-	-
- Severe peripheral oedema, yes	1	–	–			
- Severe breathlessness at rest, yes	0.42	0.15 – 1.14	0.11			
- Increasing exertional breathlessness, yes	0.48	0.18 – 1.25	0.13			
- Chest pain - cardiac, yes	0.26	0.05 – 1.31	0.11			
- Other symptom, yes	0.35	0.04 – 2.93	0.33			
HF Medication at admission						
- ACE inhibitor, yes	1.67	0.86 – 3.25	0.13	-	-	-
-ARB, yes	1.27	0.58 – 2.79	0.56	-	-	-
-Beta-blocker, yes	2.54	1.22 – 5.29	<0.1*	1.86	0.87 –3.99	0.15
-Aldosterone Antagonist, yes	2.27	1.13 – 4.58	<0.1*	1.69	0.79 – 3.62	0.18
-Digitalis, yes	1.36	0.56 – 3.27	0.5	-	-	-
-Diuretics, yes	2.44	1.17 – 5.09	<0.05*	1.1	0.48 – 2.53	0. 82

HR, Hazard Ratio; CI, Confidence Interval; NYHA, New York Heart Association;
CCI, Charlson comorbidity index; LVEF, Left ventricular ejection fraction;
ACE, Angiotensin-converting enzyme; ARB: Angiotensin Receptor Blockers.
*significance level of 0.1

DISCUSSION

Amongst patients admitted to hospital with worsening heart failure, the presence of moderate to severe depression is a strong predictor of mortality subsequent to discharge, even after correcting for potential confounders. This is consistent with evidence suggesting that depression predicts mortality amongst patients with chronic HF [2, 3] but the relationship may be even stronger for those admitted to hospital with worsening heart failure.

Whether the association between depression and mortality is causal and, if so, whether targeting this link could improve prognosis remains uncertain. Pessimism and depression may have biological effects that adversely affect prognosis [10]. Alternatively, depression may reduce adherence to lifestyle advice and heart failure medications leading to a worse prognosis [11, 12]. Health care professionals might be unconsciously less attentive to depressed patients. Finally, it is possible that we did not identify and measure some key prognostic variables; some patients may be depressed because they not only feel sicker but are indeed sicker. The clinical reality is that all of the above are probably relevant to different patients at different times. Teasing out which is the most important for an individual patient may be difficult.

It is unclear whether the recognition and management of depression might improve patient outcomes. Randomized trials of drug intervention with selective serotonin reuptake inhibitors have been disappointing [13, 14]. Interestingly, many patients admitted to hospital with worsening heart failure report good quality of life after discharge [15]. Maybe improving the patients' perception of their future and their enjoyment of their lives would have a positive feedback that improves outcome. Perhaps the focus should also be on serial assessment with intervention only when depression persists despite simple measures such as good treatment of the medical condition, social support and attention to health fears and loneliness. Trials of new interventions, such as cognitive behavioral therapy, use of self-management plans delivered by community health care teams or by tele-monitoring might be effective alternatives to drug therapy [16]. Tackling the problems that depression causes rather than depression itself could also be important; a diagnosis of depression should heighten awareness of the need for support, advice and encouragement of adherence.

Mild depression was not strongly associated with mortality in either the univariable

or multivariable models. This may reflect the attributes of the HADS score; several questions could reflect the severity of functional impairment due to HF itself rather than depression. For instance, one question asks the patient to rate this statement "I feel as if I am slowed down"; most patients gave themselves poor scores on this question, which could be interpreted as the inability to exercise due to heart failure: however, it leads to patients being given a HADS score suggesting mild depression.

Most patients gave themselves a worst-rank score for the statement "I can laugh and see the funny side of things". For other questions, there was a wider distribution of scores. It is not clear that the relatively complex questionnaires currently used to assess mood and quality of life are superior to single, simple, direct, intuitive questions in detecting important depression ("Are you depressed? If so, how badly does this affect you?") or assessing well-being ("On a scale of $1-10$ how well are you today?"); single questions are easy to administer and may be more efficient, although they may need to be interpreted in the context of the patients situation (for example, recent near-death experience, worsening heart failure or stable CHF) [17]. Indeed, responses to just two-questions (PHQ-2) appears to identify patients with depression fairly accurately compared to more complex instruments [18].

Other Limitations. The study is relatively small, with a modest number of events, but it is one of the first in patients hospitalized with worsening HF. The diagnosis of depression was made with a tool that does not give the same diagnostic certainty as DSM-III/IV or similar codes. The tool was only administered once, and we may have missed changes in mood during or after hospitalization. The HADS uses some colloquial language which may not be understood by patients from different backgrounds.

Conclusion. Moderate to severe depression is strongly associated with mortality in the year following discharge after a HF admission to hospital. The association is independent of HF severity and other comorbidity. New strategies are required to improve the recognition of depression and to target those with persistent problems who might benefit from intervention.

APPENDIX A: CHARLSON COMORBIDITY INDEX (CCI)

Comorbidity is assessed by Charlson Comorbidity Index (CCI) [19]. CCI is calculated during hospitalization by assigning to certain comorbidities a weighted value.

- 1 point: Myocardial infarction, congestive heart failure, peripheral vascular disease, dementia, cerebrovascular disease, chronic pulmonary disease, connective tissue disease, ulcer disease, mild liver disease, diabetes.
- 2 points: Hemiplegia, moderate or severe renal disease, diabetes with end organ damage, any tumor, leukemia, lymphoma.
- 3 points: Moderate or severe liver disease.
- 6 points: Metastatic solid tumor, AIDS.

APPENDIX B: HADS-D QUESTIONNAIRE ITEMS

In this analysis the depression related part of the HADS questionnaire is used. This part consists of the following seven questions and four possible answers per question.

1. I still enjoy the things I used to enjoy
   (a) Definitely as much
   (b) Not quite so much
   (c) Only a little
   (d) Hardly at all
2. I can laugh and see the funny side of things
   (a) As much as I always could
   (b) Not quite so much now
   (c) Definitely not so much now
   (d) Not at all
3. I feel cheerful
   (a) Not at all
   (b) Not often
   (c) Sometimes
   (d) Most of the time
4. I feel as if I am slowed down
   (a) Nearly all the time
   (b) Very often
   (c) Sometimes
   (d) Not at all
5. I have lost interest in my appearance
   (a) Definitely

(b) I don't take so much care as I should

(c) I may not take quite as much care

(d) I take just as much care as ever

6. I look forward with enjoyment to things

(a) As much as ever I did

(b) Rather less than I used to

(c) Definitely less than I used t o

(d) Hardly at all

7. I can enjoy a good book or radio or TV program

(a) Often

(b) Sometimes

(c) Not often

(d) Very seldom

APPENDIX C: CONSORT DIAGRAM

The consort diagram of the study is shown in Figure 3.2).

FIGURE 3.2: Consort diagram

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4 Prognostic value of psychosocial factors for first and recurrent hospitalizations and mortality in HF patients: insights from the OPERA-HF study

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ABSTRACT

Aims: Psychosocial factors are rarely collected in studies investigating the prognosis of patients with heart failure (HF), and only time to first-event is commonly reported. We investigated the prognostic value of psychosocial factors for predicting first or recurrent events after discharge following hospitalization for HF.

Methods and results: OPERA-HF is an observational study enrolling patients hospitalized for HF. In addition to clinical variables, psychosocial variables are recorded. Patients provide the information through questionnaires which include social information, depression and anxiety scores, and cognitive function. Kaplan-Meier, Cox regression and the Andersen-Gill model were used to identify predictors of first and recurrent events (re-admissions or death).

Of 671 patients (age 76$\pm$15 years, 66% men) with one-year follow-up, 291 had no subsequent event, 34 died without being readmitted, 346 had one or more unplanned readmissions and 71 patients died after a first readmission. Increasing age, higher urea and creatinine, the presence of co-morbidities (diabetes, history of MI, COPD), were all associated with increasing risk of first or recurrent event. Psychosocial variables independently associated with both the first and recurrent events were: presence of frailty, moderate to severe depression and moderate to severe anxiety. Living alone and the presence of cognitive impairment were independently associated only with an increasing risk of recurrent events.

Conclusion: Psychosocial factors are strongly associated with unplanned recurrent readmissions or mortality following an admission to hospital for HF. Further research is needed to show whether recognition of these factors and support tailored to individual patients' needs will improve outcomes.

INTRODUCTION

Patients with heart failure (HF) are at high risk of readmissions and death. About 25% of patients admitted with HF are readmitted within one month of leaving hospital [1]. In European studies, the readmission rate is up to 44% at 1 year after discharge [1]. Commonly, studies investigating risk factors for readmission only consider the first readmission. However, they are often recurrent, reflecting progression of the underlying disease or exacerbations due to co-morbidities and sub-optimal self-care and medication adherence. Understanding the causes, precipitants and risk factors for recurrent readmissions may help to prevent them. By focusing only on first event analysis, any subsequent events are ignored and the impact of potential risk factors can be greatly under- or over- estimated.

Several demographic or clinical variables, such as age, sex, the presence of co-morbidities, left ventricular ejection fraction, New York Heart Association class of symptoms and serum markers are important predictors of readmissions and death among patients with HF [2]. The impact of psychosocial factors on first readmission or mortality has also been studied [3]. The presence of psychosocial factors, such as depression, is significant predictor of mortality among patients with HF [4, 5]. The presence of frailty is also associated with increasing risk of first readmission or mortality [6, 7]. However, there is no report about the effect of depression, frailty and other psychosocial factors on recurrent events.

Accordingly, we explored the effect of psychosocial factors on first and recurrent unplanned readmissions or death in a cohort of patients discharged after a hospitalization for worsening HF.

METHODS

Study design

OPERA-HF is an ongoing 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. Additional assessments, including assessments of depression/anxiety and cognitive function, were performed during hospital admission using questionnaires completed by the patient.

Patients had to fulfill all of 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 [8] or NT-ProBNP $>$ 400 pg/ml (if in sinus rhythm) or $>$ 1200 pg/ml (if in atrial fibrillation) [9]. 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 full 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.

Depression and anxiety assessment

Depression and anxiety were assessed by the Hospital Anxiety and Depression Scale (HADS) questionnaire [10]. The HADS consists of two parts of 7 questions each, one focusing on depression and one on anxiety. For each part, the response to each of the 7 questions is graded from 0 to 3, giving a total score that ranges between 0 and 21. A score of 7 or less implies that there is no depression or anxiety; a score of 8-10 suggests mild depression or anxiety; and a score of 11 or more reflects moderate-to-severe depression or anxiety [10].

Cognition assessment

This assessment was based on the General Practitioner assessment of Cognition, [11] a brief screening tool for detecting cognitive impairment. It was designed for use by primary care practitioners. The cognitive test includes nine items focusing on time orientation, clock drawing, awareness of a current news event and recall of a name and an address. Each correct answer scores one point leading to a maximum score of 9. A score of 4 or lower indicates cognitive impairment.

Frailty

For frailty, a two-fold assessment was applied. First the patient was asked to respond to a question about having troubles bathing or dressing and then was assessed through the 'get up and go' test. The timed 'get up and go' requires patients to stand up from a chair, walk a short distance (3 m), turn around, return, and sit down again. The normal time to complete the task is less than 10 seconds and abnormal is more than 20 seconds [12]. Patients who reported either troubles in bathing or dressing or completed the 'get up and go' test in more than 20 seconds were defined as frail.

Readmission/Mortality

All patients enrolled in the study are followed subsequent to discharge. All-cause readmissions and mortality are automatically recorded in the hospital's IT system. For the present report, the primary outcome of interest was all-cause unplanned readmissions or mortality. Unplanned readmission is considered any type of emergency readmission such as emergency fast-track, through the Accident and Emergency department, or an urgent admission requested by the GP.

Statistical analysis

We report the baseline characteristics of the patients who participated in the study between October 2012 and July 2016. Follow up was censored at August 2016. We describe and compare the baseline characteristics of the patients by the number of their subsequent events. For the comparison among patients having no event with

patients having one or multiple readmissions or death after discharge, we used the chi-squared test to compare binary or categorical variables, and Kruskal-Wallis test for continuous variables. In order to avoid comparisons between groups of patients with unequal follow up times, we initially analysed events in patients for whom one year follow up data were available, including only those events which happened in the first year, in order to compare those with and those without an event.

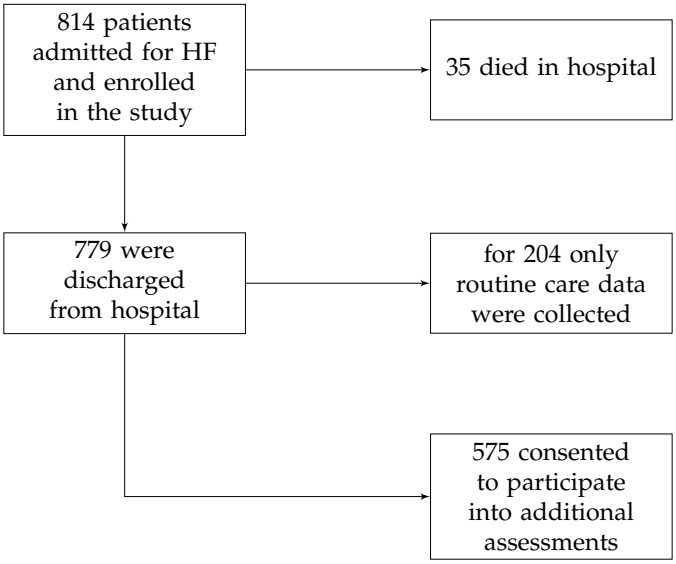
We subsequently included all patients in statistical modeling to determine the relation between a putative risk factor and outcome. The Kaplan-Meier method was used to estimate the cumulative incidence of events (readmissions and mortality) [13]. The event rate was calculated by taking into account all available recurrent events. We used univariable Cox regression to calculate the effect of potential risk factors on the first unplanned readmissions or death. The Andersen-Gill model was used to analyze the effect of the same factors when taking into account recurrent unplanned readmissions or death. The counting processes model of Andersen-Gill is a semiparametric model, and is a generalization of the Cox regression model [14]. It takes into account all the recurrent events along the time line, where the time to an event starts at the end of the previous event. All events are treated as being similar and independent of each other.

After identifying predictors of outcome, we calculated the effect of each psychosocial variable whilst adjusting for all significant clinical ones. For the psychosocial variables we used only complete cases and for clinical variables we used multiple imputation to impute missing values [15]. Application of the technique requires three steps: imputation, analysis and pooling. Each missing clinical value was imputed 5 times following the predictive mean matching method, thus producing 5 imputed data sets; each one of these 5 imputed data sets was then analyzed by the aforementioned complete-data procedures. The 5 resulting analyses are then combined into one final analysis following Rubin's method. The means of these pools are reported in the result section [15, 16]. All analyses were conducted using R 3.3.2 statistical software (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Of 814 patients consented, 35 died during the index admission and 779 were discharged. (Consort diagram: Figure 4.1) The median follow up amongst survivors was 764 (interquartile range, IQR 411–1069) days. 671 patients either died during the first year or were still alive at one year. The remaining 108 patients were survivors who had not yet completed their first year follow up after discharge.

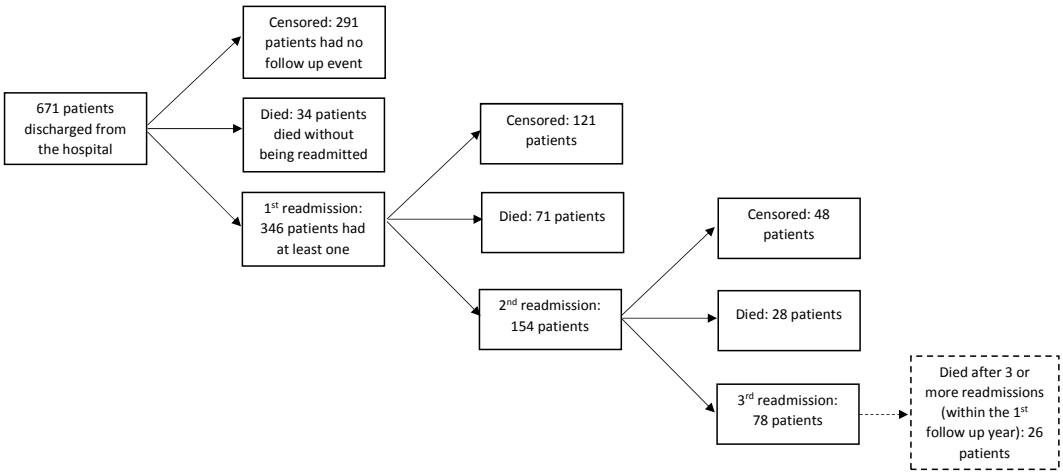
FIGURE 4.1: Consort diagram



First year follow up

Figure 4.2 shows the outcomes at one year for the 671 patients who had at least one year follow-up or who died within one year and consequently had known one year outcome. During the first year, 291 (43%) patients had no event; 34 (5%) patients died without being readmitted; 346 (52%) had at least one unplanned readmission and 125 (19%) died after one or more further admissions.

FIGURE 4.2: Diagram of events within first year of discharge, based on 671 patients surviving to index-admission discharge and with known outcome at one year



Of patients who agreed to complete the psychosocial assessments, 35% had all assessments completed and 54% had at least 4 of them completed. Patients who had no events in the first year were younger, and were less likely to have a history of MI or COPD (Table 4.1).

Patients with one or more follow up events were more likely to have moderate-to-severe depression or moderate-to-severe anxiety and were more likely to be frail; they were less likely to complete the "get up and go" test and were more likely to report difficulties in bathing or dressing.

All follow up

Figure 4.3 shows events for all 779 participants, including patients followed for less than one year and events that happened after the first year. Overall, 220 (28%) patients had no event; 41 (5%) died without being readmitted; 518 (66%) had at least one unplanned readmission and 228 (29%) died after one or more further admissions.

The incidence of unplanned readmission and mortality is shown in Figure 4.4, with a combined event rate of 70% [95% CI 68% - 72%] at one year.

FIGURE 4.3: Diagram of all events for 779 patients discharged after the index-admission (including those not censored at one year)

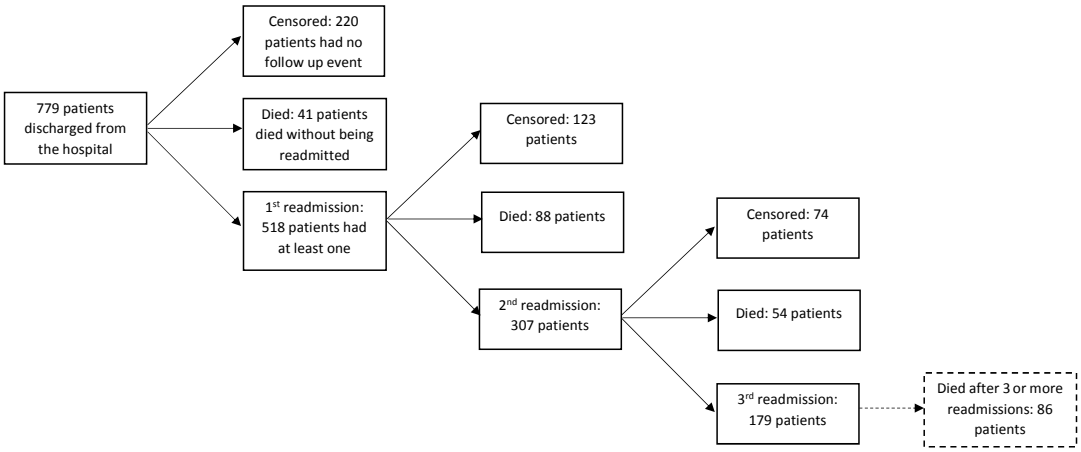
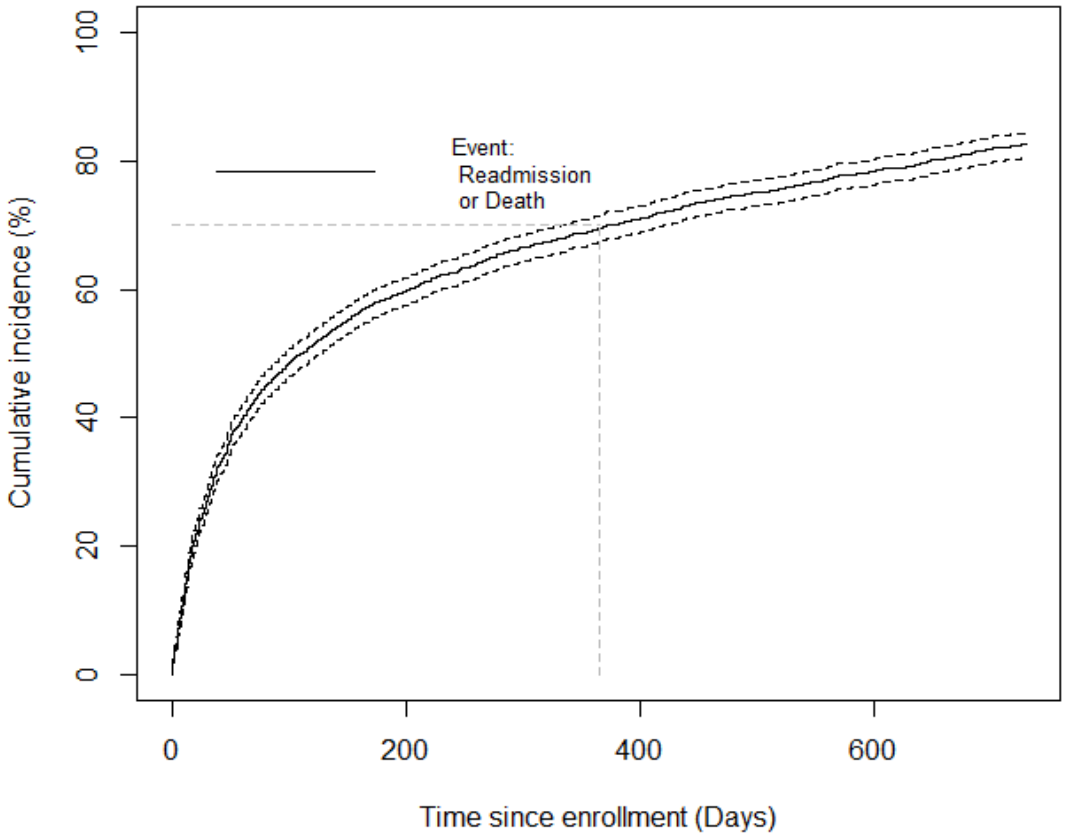


TABLE 4.1: Baseline characteristics for all study participants and all participants with follow up at one year stratified by number and type of events. Characteristics are summarized by their count and fraction (N (%)) for categorical or their median and interquartile range (Median [25th – 75th]) for continuous variables respectively; (*) 0.1 level of significance; (**) NYHA class which was evaluated as the worst class during the last 7-days before admission; (***) the closest measurement to discharge. N = number of patients with this variable available

	All patient data		**Patients with one year follow-up data**						
Event	**All**		**All**		**No Events**	**One re-admission**	**Death/ No re-admission**	**>1 event**	**Comparison**
	(N = 779)		(N = 671)		(N = 291)	(N=121)	(N = 34)	(N = 225)	
Characteristics	N		N						P-value*
Women, %	779	271(35%)	671	230(34%)	109(37%)	47(39%)	7(21%)	67(30%)	0.15
Age, years	779	75[67-82]	671	76[67-82]	73[64-80]	75[68-81]	79[73-86]	78[71-84]	<0.01
Diabetes, %	779	278 (36%)	671	243 (36%)	101 (35%)	45(37%)	14(48%)	83(37%)	0.53
History of MI, %	779	183 (23%)	671	163(24%)	57(20%)	34(28%)	12(35%)	60(27%)	<0.05
COPD, %	779	136(17%)	671	111(17%)	35(12%)	21(17%)	7(21%)	48(21%)	<0.01
Cancer, %	779	69(10%)	671	72(10%)	31(11%)	16(13%)	2(6%)	20(9%)	0.88
NYHA **:	672		569						
Class I/II, %		68(10%)		67(12%)	29(12%)	14(14%)	0(0%)	24(12%)	0.61
NYHA: Class III, %		427(64%)		365(64%)	163(67%)	70(71%)	20(74%)	112(56%)	
NYHA: Class IV, %		177(26%)		137(24%)	52(21%)	15(15%)	7(26%)	63(32%)	
Hypertension at ADM,%	726	359(58%)	622	359(58%)	163(59%)	64(55%)	17(55%)	115(57%)	0.48
NT-proBNP, pg/mL***	664	4300 [1803−9456]	570	4599 [1934-9553]	3931 [1894−7954]	4280 [1576-9023]	6369 [3884-16657]	5414 [2083-10843]	0.46
Sinus rhythm at DIS %	779	286(37%)	671	250(37%)	115(40%)	39(32%)	12(35%)	84(37%)	0.33
LVEF ≤40% at DIS, %	683	286(42%)	588	241(41%)	95(37%)	51(47%)	13(45%)	82(42%)	0.11
Main presentation:	768		660						0.48
-Severe peripheral oedema, %		59(8%)		50(8%)	20(7%)	6(5%)	5(16%)	19(9%)	
-Severe breathlessness at rest,%		225(29%)		204(31%)	94(34%)	36(30%)	8(25%)	64(29%)	
-Increasing exertional breathlessness, %		356(46%)		285(43%)	115(40%)	53(44%)	17(53%)	100(45%)	
-Chest pain-cardiac, %		72(9%)		67(10%)	28(10%)	16(13%)	2(6%)	21(9%)	
-Other symptom %		56(7%)		54(8%)	24(9%)	10(8%)	0(0%)	17(8%)	
Urea at DIS,	776	9[7-14]	669	9[6-14]	8[6 -11]	9[6-14]	18[11-25]	11[8-15]	0.17
Creatinine at DIS, μmol/L	774	106[84-141]	668	106[84-143]	97[80-125]	104[86-141]	161[111-210]	119[91- 157]	0.26
Depression HADS	371		300						<0.05
-None-to-mild, %		316(85%)		255(85%)	122(91%)	44(83%)	13(81%)	76(78%)	
-Moderate-to-severe, %		55(15%)		45(15%)	12(9%)	9(17%)	3(19%)	21(22%)	
Anxiety HADS	366		296						<0.01
-None-to-Mild, %		300(82%)		243(82%)	120(89%)	35(70%)	14(87%)	74(78%)	
-Moderate-to-severe,%		66(18%)		53(18%)	15(11%)	15(30%)	2(13%)	21(22%)	
GPCOG score≤4, %	380	28(7%)	315	25(8%)	7(5%)	2(4%)	3 (18%)	13(13%)	0.11
Living alone, %	660	218(33%)	566	184(33%)	74(30%)	32(30%)	9(36%)	69(33%)	0.29
Trouble bathing/ dressing, %	644	157(24%)	553	134(24%)	46(19%)	24(23%)	10(42%)	54(30%)	<0.05
Get up and go test:									
-Able to complete %	614	285 (46 %)	520	242 (46 %)	116 (51 %)	40 (42 %)	7 (29 %)	79 (45 %)	<0.1
Time to complete, sec	285	9 [6 - 15]	242	10 [6 - 16]	8 [6 - 12]	11 [8 - 20]	15 [4 - 22]	12 [8 - 20]	0.14

MI Myocardial infarction; NYHA New York Heart Association; ADM admission; DIS discharge; LVEF left ventricular ejection fraction; HADS Hospital Anxiety and Depression Scale; GPCOG General Practitioner assessment of Cognition.

FIGURE 4.4: Cumulative incidence plot of events; recurrent readmissions and mortality. For the plot gap times are used. That means that every recurrent event of a patient is taken into account as a new sample for the calculations starting from point zero. Dotted grey lines: incidence rate at 1 year; Dotted black lines: 95% confidence interval.



Risk factors for first event

There were 559 first events (41 deaths and 518 readmissions). Increasing age, a past history of MI or COPD, LVEF lower than 40%, and increasing urea and creatinine at discharge were all associated with increasing risk of first event. Amongst psychosocial

variables, moderate-to-severe depression, moderate-to-severe anxiety, worsening cognitive impairment and the presence of frailty were all associated with adverse events (Table 4.2a).

Risk factors for recurrent events

There was a total of 1600 events including 1041 events subsequent to the first. Increasing age, history of MI, the present of diabetes or COPD, and increasing urea and creatinine at discharge were all associated with increasing risk. Amongst psychosocial variables, moderate-to-severe depression or anxiety, cognitive impairment and frailty, assessed by a question on troubles with bathing/dressing and/or by the 'timed get up and go' test, were all also associated with adverse events. Patients living alone also had a significantly higher risk (although not facing an increased risk of first event alone) (Table 4.2b).

Impact of psychosocial factors adjusted for demographic and clinical variables

In the statistical models adjusting for the clinical variables found to be significant in the univariable analysis (age, diabetes, history of MI, COPD, urea and creatinine), moderate-to-severe depression, moderate-to-severe anxiety, cognitive impairment, the presence of frailty and living alone were significant predictors of adverse outcomes (Table 4.3).

Patients having troubles with bathing or dressing were 20% more likely to have one or more follow-up events compare to those not reporting troubles. Patients able to complete the "get up and go" test were 20% less likely to have a first follow up event than those who could not. Being unable to complete the test was a significant predictor of a first event, but not of recurrent events. Amongst those who did manage to complete the test, there was a 1% increase in risk of first or recurrent events for every extra second taken.

TABLE 4.2: (a) Univariable Cox regression model for first unplanned readmission or death (b) Univariable Anderson-Gill model for recurrent events. (*) 0.1 level of significance; (**) NYHA class which was evaluated as the worst class during the last 7-days before admission; (***) the closest measurement to discharge

	(a) First event only				**(b) Recurrent events**			
	(N/events)	**HR**	**95% CI**	**p-value***	**(N/events)**	**HR**	**95% CI**	**p-value***
Women, yes	(779/559)	0.97	0.82-1.15	0.7	(2110/1600)	1.06	0.88-1.27	0.53
Age, years	(779/559)	1.24	1.15−1.35	<0.001	(2110/1600)	1.29	1.16−1.43	<0.001
Diabetes, yes	(779/559)	1.1	0.93−1.30	0.28	(2110/1600)	1.34	1.12 − 1.59	<0.001
History of MI, yes	(779/559)	1.29	1.07−1.55	<0.01	(2110/1600)	1.33	1.10−1.62	<0.01
COPD, yes	(779/559)	1.43	1.14−1.79	<0.01	(2110/1600)	1.5	1.20−1.89	<0.001
Cancer, yes	(779/559)	0.97	0.74−1.27	0.83	(2110/1600)	1.04	0.78−1.40	0.77
NYHA **: Class I or II, yes	(672/468)	1	-	-	(1785/1343)	1	-	-
NYHA: Class III, yes		1.05	0.76−1.44	0.77		1.1	0.81−1.49	0.53
NYHA: Class IV, yes		1.19	0.85−1.68	0.31		1.29	0.92−1.81	0.14
Hypertension at ADM, yes	(726/515)	1.03	0.86 - 1.23	0.73	(1957/1477)	1.04	0.86-1.25	0.7
Log(NT-proBNP),pg/mL***	(664/477)	1.05	0.98−1.14	0.17	(1833/1396)	1.02	0.96−1.12	0.32
Sinus Rhythm at DIS, yes	(779/559)	0.91	0.76-1.08	0.28	(2110/1600)	0.95	0.79−1.13	0.57
LVEF $\leq$40% at DIS, yes	(683/479)	1.2	1.00−1.44	<0.05	(1845/1395)	1.17	0.97−1.41	0.1
Main presentation:	(768/548)				(2076/1571)			
-Severe peripheral oedema, yes		1	-	-		1	-	-
-Severe breathlessness at rest, yes		0.94	0.64 − 1.38	0.74		0.84	0.59−1.20	0.35
-Increasing exertional breathlessness, yes		1.07	0.74 − 1.56	0.71		1.02	0.73−1.45	0.89
-Chest pain - cardiac, yes		1.11	0.72−1.70	0.64		1	0.65−1.53	1
-Other symptom, yes		1.06	0.68−1.64	0.81		0.92	0.61−1.37	0.67
Urea at DIS, mmol/L	(776/557)	1.27	1.15−1.40	<0.001	(2099/1590)	1.25	1.15−1.36	<0.001
Creatinine at DIS, μmol/L	(774/556)	1.54	1.38−1.72	<0.001	(2094/1587)	1.54	1.39−1.72	<0.001
Depression HADS	(371/227)				(866 / 596)			
-None-to-mild, yes		1	−	−		1	−	−
-Moderate-to-severe, yes		1.73	1.24 − 2.41	<0.01		1.76	1.25 - 2.47	<0.001
Anxiety HADS	(366/222)				(848/581)			
-None-to-mild, yes		1	−	−		1	−	−
-Moderate-to-severe, yes		1.64	1.24−2.18	<0.001		1.37	1.03-1.84	<0.05
GPCOG score	(380/232)	1.7	1.06 − 2.71	<0.05	(903/628)	1.58	1.00−2.50	<0.1
Living alone yes	(660/465)	1.14	0.94 - 1.39	0.18	(1781/1341)	1.37	1.12−1.67	<0.01
Trouble bathing or dressing, yes	(644/453)	1.48	1.20−1.83	<0.001	(1736/1303)	1.27	1.02−1.57	<0.05
Get up and go test:								
-Able to complete, yes	(614/421)	0.72	0.59−0.87	<0.001	(1646/1229)	0.81	0.66−0.99	<0.05
-Time to complete, sec	(285/169)	1.02	1.01−1.03	<0.001	(701/495)	1.02	1.01−1.03	<0.001

N, number of patients with available data for this variable; HR, hazard ratio; CI, confidence interval, NYHA, New York heart association; ADM, admission; DIS, discharge; LVEF, left ventricular ejection fraction; HADS, hospital anxiety and depression scale; GPCOG, general practitioner assessment of cognition

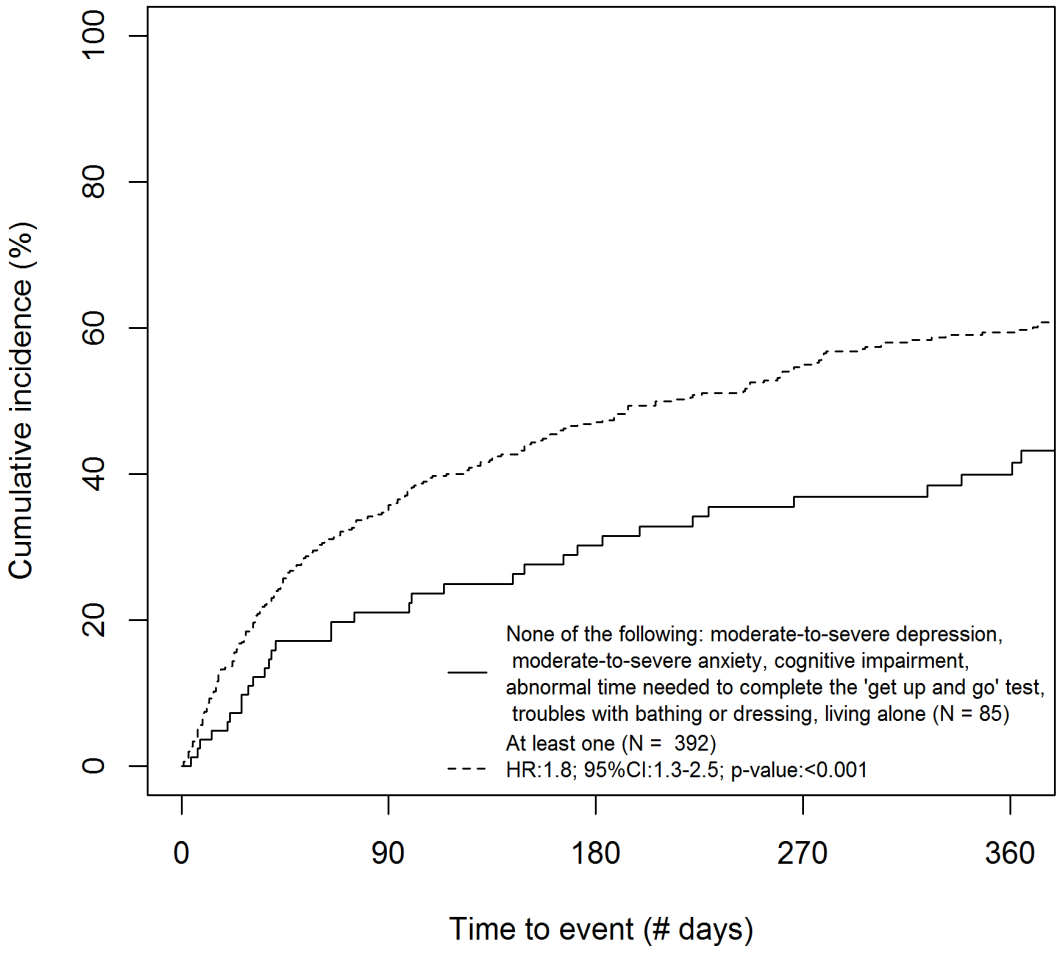
TABLE 4.3: (a) Adjusted Cox regression model for first unplanned readmission or death (b) Adjusted Anderson-Gill model for recurrent events. (*) 0.1 level of significance; (**) each variable is adjusted for the most significant (P<0.01) clinical variables including age, diabetes, history of MI, COPD, urea and creatinine at discharge (see Table 4.2)

	(a) First event only **			**(b) Recurrent events ****		
	HR	**95% CI**	**p-value***	**HR**	**95% CI**	**p-value***
Depression HADS						
-None-to-mild, yes	1	–	–	1	–	–
-Moderate-to-severe yes	1.74	1.24 - 2.44	<0.01	1.77	1.44 - 2.17	<0.001
Anxiety HADS						
-None-to-mild, yes	1	–	–	1	–	–
-Moderate-to-severe, yes	1.67	1.21 - 2.30	<0.01	1.35	1.11 - 1.65	<0.01
GPCOG score $\leq$ 4, yes	1.43	0.90 – 2.28	0.12	1.4	1.06 – 1.85	<0.05
Living alone, yes	1.04	0.85 – 1.27	0.71	1.24	1.11 – 1.39	<0.001
Trouble bathing or dressing, yes	1.33	1.07 – 1.65	<0.01	1.18	1.04 – 1.35	<0.05
Get up and go test:						
-Able to complete, yes	0.81	0.66 – 0.99	<0.05	0.95	0.84 – 1.07	0.38
-Time to complete, sec	1.02	1.01 – 1.03	<0.01	1.01	1.01 – 1.02	<0.001

HR, hazard ratio; CI, confidence interval; HADS, hospital anxiety and depression scale; GPCOG, general practitioner assessment of cognition.

The impact of psychosocial variables on outcomes is plotted in Figure 4.5, with the patients grouped by having none or at least one of the following factors: moderate-to-severe depression; moderate-to-severe anxiety; cognitive impairment; more than 20 seconds needed to complete the 'get up and go' test; troubles with bathing or dressing; or living alone.

FIGURE 4.5: Cumulative incidence plot of events (recurrent readmissions and mortality) of patients having at least one psychosocial factor assessed negatively compared to those with none, adjusted for significant demographic and clinical factors. We used data of the 477 patents who had participated to at least one of the psychosocial assessments.



DISCUSSION

Our study is one of the first to evaluate the impact of psychosocial factors on the risk of subsequent events in patients hospitalized for heart failure (HF). We found a high event rate, with 70% of patients being re-admitted or dying at one year follow up. In common with previous studies, we have found that older patients with more co-morbidities, or higher urea or creatinine, are more likely to have one or more unplanned events. We also found that the presence of frailty, anxiety and depression were powerful predictors of outcome, both of first and of recurrent events.

We have previously reported that depression is strongly associated with increasing mortality in this cohort [4]. In the present study, we have found that patients with moderate-to-severe anxiety have a 1.7 times higher risk of a first event and a 1.4 higher risk of recurrent events compared to patients without anxiety. Patients with moderate-to-severe depression have a 1.7 times higher risk of a first event and a 1.8 higher risk of recurrent events compared to patients without depression. Patients living alone or with cognitive impairment have a 1.2 and 1.4 times higher risk of having multiple events after discharge compared to the patients not living alone or without cognitive impairment, respectively.

Psychological factors such as depression [17, 18] and other factors not directly related to the medical reason for an admission to hospital, such as cognitive impairment [19] or frailty [20], are associated with adverse events in older people. We have found that these are also powerful predictors of adverse outcomes amongst patients hospitalized with HF. We also showed that the presence of at least one adverse psychosocial factor was associated with 1.8 higher risk of one or more recurrent events compared to having none.

Frailty is increasingly recognized as an important factor in managing patients with long term conditions [21], but although it is easily recognized clinically, it can be difficult to define. Increasing age is an obvious risk factor for frailty, and around a quarter of patients admitted to hospital for HF are over 80 years of age [22]. Frailty is associated with poor nutritional status, itself associated with worse long-term outcome [23]. There are recent studies concluding that an indicator of frailty in routine care is related to first readmission or mortality in HF patients [7] or that amongst patients hospitalized for HF, worsening frailty measured by screening tools, such as the Derby frailty

index (DFI) or clinical frailty scale (CFS), is strongly related to increasing mortality [24]. The results of the present study show a strong association between the presence of frailty and the risk of follow up. Even the answer to a simple question about difficulties with daily activities has a similar predictive value as more elaborate screening tools. We also found that the 'get up and go' test, a simple test of mobility, is strongly related to outcome. For every extra second needed to complete the test the risk of recurrent events increased by 1%. As an indicator of "social frailty", living alone was also associated with a worse outcome.

Previous studies have not found an association between anxiety and mortality in HF although depression is associated with worse outcomes [4]. We found that both depression and anxiety are related to the risk of recurrent events. The mechanism is not clear, but may be related to the reduced self-care seen amongst patients with depression [25]. Further research is needed to see if any specific intervention targeted at psychological factors is helpful. Anti-depressant therapy in patient with HF does not affect mortality and morbidity [26] but psychotherapy in primary care has a limited beneficial effect on reducing depression in patients with a cardiac condition [27].

Cognitive impairment is a risk factor for adverse events in patients with HF [28]. We found that cognitive impairment is also associated with an increased risk of recurrent post discharge events. Cognitive impairment is also an impediment to HF patients' ability to self-care [29].

We have thus found that a range of related conditions not directly associated with the HF syndrome itself – frailty (both physical and social), cognitive impairment, depression and anxiety – are all associated with an increased risk of adverse outcomes following discharge from hospital after an admission for HF. The individual patient should always be treated within his or her individual social context, and proper management should always consider whole patient, something of which it can be easy to lose sight in a busy hospital.

It is not clear from the present study whether targeted interventions for the conditions we have identified as predictors of a poor outcome might have a beneficial effect. Multidisciplinary interventions have shown some evidence of benefit [30] and exercise therapy can also help in frail subjects [31]. Intervention trials are needed to see whether such interventions as providing extra help at home, day care or telemonitoring might be helpful.

Limitations. The Anderson-Gill approach assumes the recurrent events to be identically distributed and independent of each other, which might not always be the case. It also treats death as an event similar to readmission. Missing data is also a limitation in this study. However, there is evidence to support the method that we followed to impute part of the data [15]. Our analysis is based on patients hospitalized only in one location. Further external validation of the results is needed in order to support their generalizability.

Our methods have been developed for research and have not been extensively tested in routine practice for HF patients. The HADS survey will not give the same diagnostic certainty as ICD-9 or similar codes. The surveys were only administered once, and we may have missed changes during or after hospitalization or subsequent events. The questionnaires use some colloquial language which may not be understood by patients from different backgrounds.

Conclusion. Moderate-to-severe depression and anxiety, living alone, cognitive impairment and the presence of frailty are strongly associated with unplanned recurrent admissions and mortality in the year following discharge after a HF admission to hospital. Studies are needed to show whether strategies to support patients from a social perspective and to target those with persistent problems with appropriate non-clinical interventions help to reduce risk.

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Part III

Risk prediction models for early re-admission in HF

5 Added value of frailty and social support in predicting risk of 30-day unplanned re-admission or death for patients with HF: an analysis from OPERA-HF

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ABSTRACT

Aims: Models for predicting the outcome of patients hospitalized for heart failure (HF) rarely take a holistic view. We assessed the ability of measures of frailty and social support in addition to demographic, clinical, imaging and laboratory variables to predict short-term outcome for patients discharged after a hospitalization for HF.

Methods and results: OPERA-HF is a prospective observational cohort, enrolling patients with a discharge diagnosis of HF from a single center in Hull, UK. Variables were combined in a logistic regression model after multiple imputation of missing data to predict the composite outcome of death or readmission at 30 days. Comparisons were made to a model using clinical variables alone. The discriminative performance of each model was internally validated with bootstrap re-sampling.

1094 patients were included (mean age 77 [interquartile range 68 – 83] years; 40% women; 56% with moderate to severe left ventricular systolic dysfunction) of whom 213 (19%) had an unplanned re-admission and 60 (5%) died within 30 days. For the composite outcome, a model containing clinical variables alone had an area under the receiver-operating characteristic curve (AUC) of 0.68 [95% CI 0.64 – 0.72]. Adding marital status, support from family and measures of physical frailty increased the AUC ($p<0.05$) to 0.70 [95% CI 0.66 – 0.74].

Conclusion: Measures of physical frailty and social support improve prediction of 30-day outcome after an admission for HF, but predicting near-term events remains imperfect. Further external validation and improvement of the model is required.

INTRODUCTION

Patients with heart failure (HF) are often re-admitted to hospital shortly after discharge [1, 2, 3], although only 15-30% of such events are due to worsening heart failure. Repeated admissions to hospital are associated with substantial impairment in a patient's quality of life, high costs and increased mortality [4]. Some re-admissions are potentially avoidable and preventing them may benefit both patients and the health-care system. Outcome may be partly determined by the severity of cardiac dysfunction, but physical frailty, co-morbidity, anxiety and depression, cognitive dysfunction and poor social support might also contribute. Focusing only on cardiac dysfunction may reduce the ability to predict adverse outcomes and miss opportunities to prevent them.

Developing a holistic model that can predict which patients with HF are at high risk of early re-admission or death, and identify possible treatment targets, might improve management and reduce events. Currently there is no such model [5, 6]. Many predictive algorithms have been designed, but those aiming to predict short-term composite outcomes perform poorly compared to those designed to predict longer-term mortality [6, 7].

The OPERA-HF study was designed to collect a broad range of information on physical frailty, mood, cognitive function and social support amongst patients admitted for the treatment of worsening HF to find out whether such measures improve prediction of outcome compared to conventional clinical variables alone. The current analysis focuses on 30-day outcomes.

METHODS

Study design

OPERA-HF (An Observational registry to assess and PrEdict the in-patient course, risk of Re-Admission and mortality for patients hospitalised for or with Heart Failure) is a prospective observational study, enrolling consecutive, consenting patients hospitalized for HF in the Hull and 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. Data were collected during hospital admission and just prior to discharge. The Charlson co-morbidity index (CCI) was used to assess co-morbidity [8]. Psycho-social information including depression and anxiety, cognitive function and social support was collected during hospitalization using questionnaires (see below for details).

Patients had to fulfill the following criteria to be included: age >18 years; usual residence in the region served by the Hull and East Yorkshire Hospitals Trust; hospitalization for HF; treatment with loop diuretics; and at least one of the following criteria to confirm a diagnosis of HF: left ventricular ejection fraction (LVEF) $\leq$ 40%, left atrial dimension >4.0 cm [9] or NT-ProBNP >400 pg/ml if in sinus rhythm or >1200 pg/ml if in atrial fibrillation [10]. 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 was conducted in accordance with ICH-GCP, Declaration of Helsinki, the Data Protection Act 1998 and the NHS Act 2006.

Depression and anxiety

To assess depression and anxiety we used the Hospital Anxiety and Depression Scale (HADS) questionnaire [11], consisting of seven questions on depression and seven on anxiety, each graded from 0 to 3, giving a total score ranging from 0 to 21 for each emotional state. A score of 7 or lower, 8 to 10, and 11 or more, implies no, mild or moderate-to-severe depression or anxiety.

Cognitive impairment

We used the General Practitioner assessment of Cognition (GPCOG), a brief screening tool for detecting cognitive impairment [12]. The cognitive test includes nine items focusing on time orientation, clock drawing, awareness of a current news event and recall of a name and an address. Each correct answer scores one point leading to a maximum score of 9. A score of 4 or lower indicates cognitive impairment.

Physical frailty

Physical frailty was assessed by asking patients to complete a timed "get up and go" test, which asks patients to stand up from a chair, walk a short distance (3 m), turn around, return, and sit down again. Less than 10 seconds is normally needed to complete the task, while more than 20 seconds indicates poor functional independence of the patient [13, 14]. We defined patients as being frail if they were unable to complete the test or took more than 20 sec to complete it. Patients were also defined as being frail if they reported difficulties either bathing or dressing themselves.

There are several tools to assess physical frailty which have been extensively validated in the literature. There is, however, no consensus on the best performing tool for patients with HF [15]. We used the timed "get up and go" test because it is simple, easy to use in routine care, correlates well with functional independence and other reliable tools and has been proven to be reliable in patients with HF [14, 16].

Social support

We defined patients to have good social support when they were married, not living alone or when they self-reported perceiving good or excellent support from their family.

Outcomes

Re-admissions and mortality were automatically recorded in the hospital's IT system. For the present report, the primary outcome of interest was all-cause, unplanned re-admissions or mortality within 30-days of discharge. Unplanned re-admission was defined as any type of emergency re-admission (including emergency fast-track, admission via the Accident and Emergency department, or an urgent admission requested by the GP).

Statistical analysis

We analyzed data from patients who participated in the study between October 2012 and November 2016 excluding 51 patients who died during the index admission. Recommendations from the TRIPOD guidelines were followed for the model development and reporting [17]. We compared the baseline characteristics of the patients having and not having an event within 30 days of discharge. We used chi-squared testing to compare binary or categorical variables between groups, and the Kruskal-Wallis test for continuous variables.

We applied univariable and multivariable logistic regression analysis to relate patient characteristics to unplanned re-admission or death within 30 days of discharge. Odds ratios (OR) were calculated with 95% confidence intervals (CI). In both analyses, multiple imputation was used to impute missing data. This requires three steps: imputation, analysis and pooling. Each missing value was imputed five times following the predictive mean matching method, thus producing five imputed data sets; each one of these five imputed data sets was then analysed and the results were pooled into one final analysis following Rubin's method [18, 19].

After identifying the most important variables associated with the outcome in the univariable analysis ($p < 0.1$), we applied the least absolute shrinkage and selection operator (LASSO) technique [20] to select the set of predictors for the final multivariable model. LASSO uses a cross-validation procedure to select the optimal value for the shrinkage parameter λ. We developed and compared a holistic model including both clinical and other measures with a reference model based on clinical variables alone

[21]. Since multiple imputation was applied, we repeated all the analyses using a dataset of patients for whom data were complete, and compared the results.

Discrimination refers to the ability to distinguish patients experiencing an event from those who did not, and was quantified by the area under the receiver operating characteristic curve (AUC). An AUC of 0.5 indicates no discriminative ability at all while an AUC of 1 indicates perfect discrimination. Multivariable models were internally validated by a bootstrap procedure, by sampling with replacement for 200 iterations. For each imputed data set, full models were developed in bootstrap samples and evaluated in the original sample to estimate the statistical optimism in performance [22, 23].

Besides the composite outcome, we also assessed the model performance when taking into account readmission only or death only as an outcome. To evaluate the prediction of readmission only we excluded patients who died without being readmitted within 30-days from the analysis dataset. All analyses were conducted using R 3.3.3 statistical software (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline characteristics of the study population

Of the 1145 patients enrolled in the study, 51 died in the hospital and 1094 survived to discharge. (Figure 5.1) Median length of hospital-stay during the index admission was 10 [6 – 17] days. Of 1094 surviving to discharge, 33 died without being readmitted, 27 died after being readmitted and 186 did not die but had an unplanned re-admission within 30 days. 51% of the unplanned readmissions were related to heart failure, 25% to other cardiovascular reasons and 25% to non-cardiovascular problems. (Table 5.1)

At admission, 62% of patients were in NYHA functional class III and 30% in class IV. Only 41% were in sinus rhythm and only 22% had a Charlson co-morbidity index ≤ 1, while 30% had a score ≥ 5. Most patients (86%) were retired and 36% lived alone, 14% had moderate-to-severe depression, 17% had moderate-to-severe anxiety and 24% reported problems with bathing or dressing. Only 36% were willing and able to do a get-up-and-go test, although most who did the test managed it in < 20 seconds. The median number of tablets prescribed increased from 9 to 12 pills per day between admission and discharge.

TABLE 5.1: Baseline characteristics and outcomes of the study cohort (N = 1094). Characteristics are summarized by their count and fraction (N (%)) for categorical or their median and interquartile range (Median [25th – 75th]) for continuous variables, respectively

		All	**Re-admitted or died in 30 days**	**No events within 30 days**	**Compare with and w/o events**
Characteristics	**Valid N**	**(N = 1094) Summary**	**(N = 246) Summary**	**(N = 848) Summary**	**p-value***
Demographics					
Age, years	1094	77 [68 − 83]	79 [72 − 85]	76 [67 − 82]	<0.001
Women, %	1094	433 (40%)	100 (41%)	333 (39%)	0.75
Vital signs at hospital admission and other measurements					

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Table 5.1 – *Continued from previous page*

		All	**Re-admitted or died in 30 days**	**No events within 30 days**	**Compare with and w/o events**
Heart Rate, BPM	1067	88 [72−108]	84 [70−106]	89 [73−108]	<0.1
Systolic BP, mmHg	1083	129 [115−146]	125 [112−144]	130 [115−146]	<0.05
Diastolic BP, mmHg	1083	75 [63 − 86]	70 [60 − 82]	76 [64 − 87]	<0.001
Sinus Rhythm, %	1088	446 (41%)	84 (35%)	362 (43%)	<0.05
Weight, kg	987	82 [69 − 97]	79 [69 − 94]	82 [69 − 99]	0.19
BMI, kg/m^2	806	29 [25 − 34]	29 [25 − 34]	29 [25 − 34]	0.53
Medication at admission					
Total pill count	969	9 [5 − 13]	10 [6 − 14]	8 [5 − 12]	<0.01
HF related symptoms at admission					
NYHA(**): Class I or II, %	1052	81 (8%)	16 (7%)	65 (8%)	<0.01
NYHA(**): Class III, %		651 (62%)	126 (54%)	525 (64%)	
NYHA(**): Class IV, %		320 (30%)	91 (39%)	229 (28%)	
Co-morbidities					
CCI score:	1094				
≤ 1, %		235 (22%)	53 (22%)	182 (22%)	0.15
2, %		199 (18%)	36 (15%)	163 (19%)	
3, %		187 (17%)	40 (16%)	147 (17%)	
4, %		149 (14%)	30 (12%)	119 (14%)	
≥ 5, %		324 (30%)	87 (35%)	237 (28%)	
Diabetes, %	1094	380 (39%)	74 (35%)	306 (40%)	0.27
COPD, %	1094	188 (17%)	49 (20%)	139 (16%)	0.23
HF symptoms and vital signs at discharge					
Length of stay, days	1094	10 [6 - 17]	12 [7 − 21]	10 [6 − 16]	<0.01
Weight, kg	693	77 [65 − 91]	75 [64 − 88]	78 [66 − 92]	0.13
NYHA: Class I or II, %	907	743 (82%)	134 (71%)	609 (85%)	<0.001
NYHA: Class III, %		143 (16%)	45 (24%)	98 (14%)	
NYHA: Class IV, %		21 (2%)	10 (5%)	11 (2%)	
Dyspnoea at rest, %	932	60 (6%)	22 (11%)	38 (5%)	<0.001
Left ventricular	920				0.30

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Table 5.1 – *Continued from previous page*

		All	**Re-admitted or died in 30 days**	**No events within 30 days**	**Compare with and w/o events**
systolic dysfunction					
-None-trivial		254 (28%)	193 (27%)	61 (31%)	
-Mild-to-moderate		154 (17%)	27 (14%)	127 (18%)	
-Moderate-to-severe		512 (56%)	111 (56%)	401 (56%)	
Lab values at discharge					
NT-proBNP, pg/mL	905	4468 [1895−9889]	6121 [2013−12110]	4100 [1832−9210]	<0.01
Urea, mmol/l	1087	9 [7 − 14]	11 [8 − 16]	9 [6− 13]	<0.001
Creatinine, μmol/l	1085	105[83−140]	119[91−156]	102[82−136]	<0.001
Medication at discharge					
Total daily pill count	1044	12 [9 −16]	12 [9− 17]	12 [9 − 16]	<0.05
Prior hospitalization					
$\geq$ 2 EM in prior 6 month, %	1094	143 (13%)	46 (19%)	97 (11%)	<0.01
$\geq$ 1 EM in prior 1 month, %	1094	189 (17%)	61 (25%)	128 (15%)	<0.001
Social status/support					
Reported good or excellent support from family,%	1094	451 (41%)	87 (35%)	364 (43%)	<0.05
Living alone, %	962	349 (36%)	83 (41%)	266 (35%)	0.16
Married, %	1094	531 (49%)	102 (42%)	429 (51%)	<0.05
Retired, %	912	783 (86%)	176 (92%)	607 (84%)	<0.01
Mood and cognitive function					
Depression, HADS	391				<0.05
-None, %		257 (66%)	43 (61%)	214 (67%)	
-Mild, %		78 (20%)	11 (16%)	67 (21%)	
-Moderate-to-severe, %		56 (14%)	17 (24%)	39 (12%)	
Anxiety, HADS	384				0.7
-None, %		232 (60%)	44 (64%)	188 (60%)	

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Table 5.1 – *Continued from previous page*

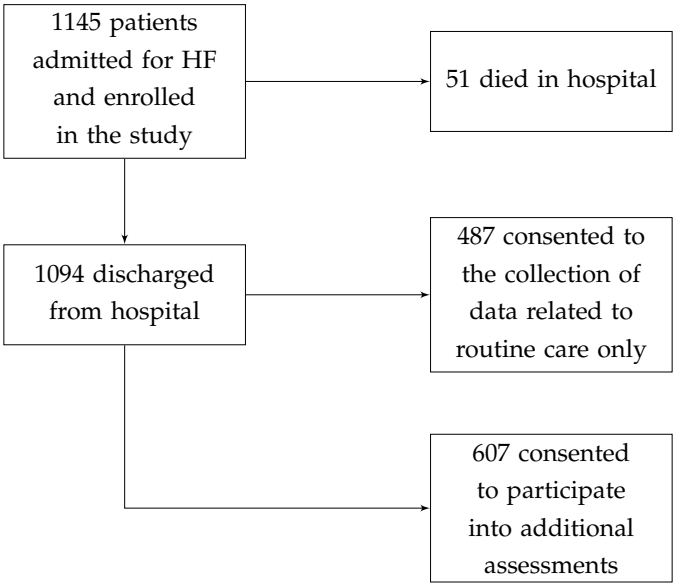
		All	**Re-admitted or died in 30 days**	**No events within 30 days**	**Compare with and w/o events**
-Mild, %		87 (23%)	13 (19%)	74 (24%)	
-Moderate-to-severe, %		65 (17%)	12 (17%)	53 (17%)	
GPCOG score ≤ 4	399	29 (7%)	8 (10%)	21 (7%)	0.44
Frailty and mobility					
Get up and go test: able or willing to participate, %	781	284 (36%)	52 (32%)	232 (38%)	0.46
Time for get up and go test, sec	295	9 [6 − 15]	12 [8− 20]	8 [6 − 14]	<0.01
Having trouble bathing or dressing, %	879	213 (24%)	57 (31%)	156 (23%)	<0.05
Outcomes					
30-day unplanned re-admission, %	1094	213 (19%)	-	-	-
30-day CV unplanned re-admission, %	1094	163 (15%)	-	-	-
30-day HF unplanned re-admission, %	1094	109 (10%)	-	-	-
30-day mortality, %	1094	60 (5%)	-	-	-

NYHA, New York heart association; CCI, Charlson comorbidity index; HADS, hospital anxiety and depression scale; GPCOG, general practitioner assessment of cognition

(*) 0.1 level of significance

(**) worst during the last 7-days

FIGURE 5.1: TRIPOD diagram



Univariable analysis

On univariable analysis (Table 5.2), patients who were re-admitted or died were on average older, had higher daily pill counts, worse NYHA class at admission and discharge, worse renal function, and were more likely to have had recent and/or multiple hospitalizations. They were also more likely to have evidence of physical frailty, problems with bathing and dressing, moderate-to-severe depression and cognitive impairment. They were less likely to be married and more likely to be single.

TABLE 5.2: Univariable analysis of the imputed dataset (all subjects included using multiple imputation) for 30-day unplanned re-admission or mortality

	N	OR	95% CI
Age, years (*)	0	1.21	1.07 – 1.37
Women, yes	0	1.06	0.79 – 1.41
Heart Rate at admission, BPM (*)	27	0.95	0.90 – 1.00
Systolic BP at admission, mmHg (*)	11	0.94	0.88 – 0.99
Diastolic BP at admission, mmHg (*)	11	0.84	0.77 – 0.91
Weight at admission, kg	107	0.99	0.99 – 1.00
BMI at admission, kg/m^2	288	0.99	0.97 – 1.01
Sinus Rhythm at admission, yes	6	0.70	0.52 – 0.94
Total pill count at admission	125	1.05	1.02 – 1.07
NYHA Class IV at admission, yes (**)	42	1.70	1.26 – 2.28
CCI, score	0	1.04	0.98 – 1.10
Diabetes, yes	0	0.79	0.58 – 1.07
COPD, yes	0	1.27	0.88 – 1.81
Length of stay, (*)	0	1.15	1.04 – 1.27
Weight at discharge, kg	401	0.99	0.99 – 1.00
NYHA class III/IV at discharge, yes	187	2.44	1.76 – 3.37
Dyspnoea at rest at discharge, yes	162	2.97	1.83 – 4.80
Moderate-to-severe LVSD, yes	174	1.01	0.73 – 1.38
NT-proBNP at discharge pg/mL (log)	189	1.22	1.08 – 1.37
Urea at discharge, mmol/l (log)	7	1.99	1.54 – 2.58
Creatinine at discharge, micromol/l (log)	9	1.93	1.37 – 2.72
Total daily pill count at discharge	50	1.03	1.01 – 1.05
Number of prior EM hospitalizations in 6 months	0	1.36	1.19 – 1.56
Prior EM in 1 month, yes	0	1.85	1.31 – 2.61
Reported good or excellent support from family, yes	0	0.73	0.54 – 0.97
Living alone, yes	132	1.36	1.02 – 1.82
Married, yes	0	0.69	0.52 – 0.92
Retired, yes	182	1.43	0.95 – 2.24
Depression, HADS	703		
- None-to-mild, yes		1	-

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Table 5.2 – *Continued from previous page*

	N	OR	95% CI
- Moderate-to-severe, yes		1.65	1.13 – 2.39
Anxiety, HADS	710		
- None-to-mild, yes		1	-
- Moderate-to-severe, yes		1.18	0.81 – 1.70
Cognitive impairment GPCOG score $\geq$4, yes	695	1.83	1.18 – 2.80
Physical frailty, yes	249	1.77	1.13 – 2.88

N, number of imputed data points; OR, odds ratio; CI, confidence interval; LVSD, left ventricular systolic dysfunction; NYHA, New York heart association; CCI, Charlson co-morbidity index; EM, emergency; HADS, hospital anxiety and depression scale; GPCOG, general practitioner assessment of cognition

(*)10 unit increase

(**) worst during the last 7-days

Multivariable analysis

In the reference clinical model, the following variables were associated with a worse outcome: not being in sinus rhythm, a higher daily pill count, worse NYHA class, dyspnoea at rest, higher serum urea and plasma NT-proBNP at discharge, longer length of hospital-stay and more emergency hospitalizations in the previous 6 months. Additional predictors included in the extended model were: not being married, poor family support and being physically frail.

Data were missing for 20% of the patients for more than one of the variables included in this model (Table 5.3). Analyses using a dataset of 572 patients for whom data were complete showed similar results as imputed datasets (Appendix A tables 5.5 and 5.6).

TABLE 5.3: Multivariable models predicting 30-day unplanned re-admission or mortality in 1094 patients; reference model includes clinical characteristics; extended model adds physical frailty and social predictors

Variables	N	Reference model OR (95% CI)	Extended model OR (95% CI)
Number of daily pills at admission	125	1.03 (1.00 – 1.06)	1.03 (1.00 – 1.06)
Sinus rhythm	6	0.77 (0.56 – 1.05)	0.77 (0.57 – 1.06)
Urea, mmol/l (log) at discharge	7	1.57 (1.19 – 2.07)	1.61 (1.22 – 2.13)
NT-proBNP pg/mL (log) at discharge	189	1.09 (0.96 – 1.24)	1.07 (0.94 – 1.21)
NYHA class at discharge, 1-class increase	187	1.47 (1.14 – 1.90)	1.40 (1.08 – 1.82)
Dyspnoea at rest at discharge	161	1.50 (0.86 – 2.63)	1.72 (0.98 – 3.04)
Length of stay (10-day increase)	0	1.08 (0.97 – 1.19)	1.07 (0.96 – 1.20)
Number of prior EM hospitalizations in 6 months	0	1.27 (1.10 – 1.45)	1.26 (1.10 – 1.45)
Physical frailty	250		1.21 (0.73 – 2.00)
Married	0		0.72 (0.53 – 0.97)
Reported good or excellent support from family	0		0.74 (0.53 – 1.02)
AUC [95% CI]		*0.68 [0.64 – 0.72]*	*0.70 [0.66 – 0.74]*
(Bootstrap optimism-corrected AUC)		*(0.66)*	*(0.67)*

N, imputed data; NYHA, New York heart association.

Model performance

The reference clinical model had an area under the curve in ROC analysis of 0.68 [95% CI 0.64 – 0.72] in discriminating between patients who did or did not experience the primary outcome of all-cause unplanned re-admissions or death within 30 days. The extended model including physical frailty and social factors increased the AUC to 0.70 [95% 0.66 – 0.74]. Internal validation of the models by bootstrap provided a corrected AUC of 0.66 for the clinical model and 0.67 for the extended model, respectively.

The extended model for re-admission only or mortality only had AUC of 0.67 and 0.83, with internally validated estimates of 0.65 and 0.80, respectively (Table 5.4).

TABLE 5.4: Discrimination of reference clinical models and extended models for composite and single outcomes among HF patients; reported as AUC [95% CI] (Bootstrap optimism-corrected AUC)

	30-day composite outcome	**30-day unplanned re-admission**	**30-day mortality**
Reference model	0.68 [95% CI 0.64 – 0.72] (0.66)	0.65 [0.61 – 0.69] (0.63)	0.81 [0.76 – 0.87] (0.79)
Extended model	0.70 [95% CI 0.66 – 0.74] (0.67)	0.67 [0.63 – 0.71] (0.65)	0.83 [0.77 – 0.88] (0.80)
Incremental p-value	$<$0.05	$<$0.05	0.27

DISCUSSION

This study demonstrates the high prevalence of diverse aspects of frailty amongst patients admitted to hospital with worsening heart failure and their contribution to 30-day outcomes. Most clinical trials and registries of patients hospitalized for heart failure collect only clinical information thought useful by cardiologists. Only a few have collected data on other aspects of patient well-being and very few have investigated the importance of cognitive function or social support. Our study suggests that assessing diverse aspects of frailty, physical or social, improves prediction of near-term outcomes. However, prediction remains difficult especially for re-hospitalization. Future analyses will determine whether different aspects of frailty also predict longer-term outcomes.

We found that 1 in 5 patients hospitalized for heart failure will have an unplanned re-admission and 1 in 20 patients will die within 30 days of discharge. Not all events were related to HF and not all would have been preventable, although this was not evaluated for individual cases. Clinical trials focusing on treatments to improve cardiac function for patients with decompensated heart failure have met with a remarkable lack of success. This failure may be because one or more aspects of frailty, which will not respond to short-term pharmacological interventions, are key determinants of outcome. Indeed, measures of frailty, in particular physical and social, were strongly associated with outcome in our registry. In conventional prognostic models, age is usually a strong predictor of outcome, probably because of its association with multiple aspects of frailty and co-morbidity rather than merely chronological age. In the present multivariable analysis, age was not an independent predictor of outcome perhaps because chronological age is just a surrogate measure for frailty.

Published prognostic models focusing on clinical variables alone for the prediction of short-term outcome have reported relatively poor discrimination, especially for re-hospitalisation, which is consistent with our findings [5, 6, 7]. The performance of our model is amongst the highest for the composite end-point of all-cause re-hospitalisation or mortality within the first few weeks after discharge [7]; although the discrimination for re-hospitalisation is similar to other published models, we achieved a high discrimination for predicting mortality. Our model would be relatively simple to apply to routine care provided information from nursing as well as medical records.

Financial penalties are imposed on hospitals in some countries if a patient is re-admitted within 30 days, and therefore models predicting short-term events, especially if they are preventable, could be used to improve the quality of care. A high rate of re-admission may reflect a poor quality service that simply fails to prevent events. A high rate of re-admission may also occur in a high-quality service that only admits patients with advanced disease who cannot be managed in the community: such patients are consequently at a high risk of further events. Models can be used to compare predicted and actual outcome in different hospitals, taking case-mix, disease severity and diverse aspects of frailty into account. However, even with our extended model, variables shown in previous studies to be related to prognosis were not included in our final model. This may reflect inaccurate methods of collecting some data or the inherent unpredictability of some events. Our findings confirm prior evidence of the difficulty of predicting readmission. Further research is needed to explore the added value of other factors, such as evidence of decongestion, early scheduled post-discharge clinical evaluation or therapy at discharge.

It is important to note that many patients were sufficiently incapacitated that they felt unable to undertake tests of physical frailty, complete questionnaires manually or even provide consent to participate in a registry. Indicative of that is that only 278 patients in our cohort were able or willing to perform the timed "get up and go" test. Accordingly, our study underestimates the true burden of frailty amongst patients admitted to hospital with heart failure, which might only be properly assessed by clinical audits that do not require individual patient consent.

Physical frailty will be influenced by the severity of heart failure, co-morbidities and pre-morbid lifestyle and strongly associated with age. An extreme form of frailty is cardiac cachexia, leading to a loss of both fat and muscle mass [24]. Studies consistently show that patients with heart failure who have a high BMI (in the range of 30 to 35) have a better prognosis [25], although whether this reflects milder cardiac disease or is actually protective is controversial. There is a growing interest in both sarcopaenia and physical frailty as therapeutic targets [26]. Studies of exercise training have suggested improvements in quality of life but no clear reduction in hospitalization or mortality [27]. Studies of anabolic agents have been of modest size and clinical benefit is again uncertain [28].

Poor social support may be considered another aspect of frailty [29]. A patient receiving support from their family may be less likely to be admitted to hospital. Strong social bonds may also be an important motivation for self-help. They provide a network that reinforces advice on life-style and medication adherence and ensure that patients are well nourished. Companionship itself might improve prognosis, giving patients "something to live for" [30].

Two other aspects of frailty can be emotional frailty (anxiety or depression) or mental (cognitive dysfunction). Our univariable results suggest that depression and cognitive dysfunction should not be overlooked either. Several studies suggest a strong link between depression, functional status [31] and outcome [32, 33]. Many patients with heart failure appear to recover from depression if their condition is stabilized, suggesting it might often be a reaction to 'bad news', while antidepressants have not yet been shown to reduce re-hospitalization or death [28]. Mental frailty, in other words cognitive dysfunction, is a growing concern amongst older patients and therefore it is no surprise that it should be common in patients with heart failure [34]. There are many reasons why cognitive dysfunction should be associated with a worse outcome. It is associated with older age, co-morbidity and physical frailty.

Study limitations. One important limitation of our model is missing data. We addressed this by using multiple imputation and confirmed the robustness of our approach by repeating the analysis only on un-imputed data, which gave similar results. Another limitation is that the model was only internally validated. Further external validation for other hospitals in the UK and in other countries with different provision and organization of health-care is required. Some of our data-collection methods, for instance the HADS questionnaire, have been developed primarily for research and have not been extensively tested in routine practice for patients with heart failure. Questionnaires were only administered once; changes are likely to have occurred during or after hospitalization. Physical frailty was assessed by the timed "get up and go" test and by reported difficulties in bathing and dressing. These describe functional status and disability, which are part of a broader conception of "frailty", which, however, does include other elements, such as mental frailty [35]. The limited number of patients willing or able to perform the get up and go test limits the wider applicability of the frailty test. Finally, we restricted our analysis to 30 day outcome, while longer term patterns are also relevant.

Conclusions. Measures of frailty and social support improve the prediction of 30-day unplanned readmission or death to a modest extent compared to models including only conventional clinical risk predictors. However, prediction of events in the short-term, especially re-hospitalisation, remains difficult. Which aspects of frailty are most important and whether interventions to reduce frailty can improve outcome, requires more research.

APPENDIX A: COMPLETE CASES ANALYSIS

TABLE 5.5: Univariable analysis of original dataset (complete cases analysis) for 30 day unplanned re-admission or mortality; Only subjects with available data

	No.	OR	95% CI
Age, years (*)	1094	1.21	1.07 – 1.37
Women, yes	1094	1.06	0.79 – 1.41
Heart Rate at admission, BPM (*)	1067	0.95	0.90 – 1.00
Systolic BP at admission, mmHg (*)	1083	0.94	0.89 – 1.00
Diastolic BP at admission, mmHg (*)	1083	0.83	0.76 – 0.91
Weight at admission, kg	987	0.99	0.99 – 1.00
BMI at admission, kg/m^2	806	0.99	0.97 – 1.01
Sinus Rhythm at admission, yes	1088	0.71	0.53 – 0.95
Total pill count at admission	969	1.04	1.02 – 1.07
NYHA at admission: Class IV, yes (**)	1052	1.65	1.22 – 2.24
CCI, score	1094	1.04	0.98 – 1.10
Diabetes, yes	1094	0.78	0.57 – 1.06
COPD, yes	1094	1.27	0.88 – 1.81
Length of stay, (*)	1094	1.15	1.04 – 1.27
Weight at discharge, kg	693	0.99	0.98 – 1.00
NYHA class III/IV at discharge, yes	907	2.29	1.57 – 3.32
Dyspnoea at rest at discharge, yes	932	2.37	1.35 – 4.08
Moderate-to-severe left ventricular systolic dysfunction, yes	920	1.01	0.73 – 1.38
NT-proBNP at discharge pg/mL (log)	905	1.20	1.05 – 1.37
Urea at discharge, mmol/l (log)	1087	1.96	1.51 – 2.55
Creatinine at discharge, micromol/l (log)	1085	1.95	1.38 – 2.75
Total daily pill count at discharge	1044	1.03	1.01 – 1.05
Prior EM in 1 month, yes	1094	1.85	1.31 – 2.61
Number of prior EM hospitalizations in 6months	1094	1.36	1.19 – 1.56
Reported good or excellent support from family, yes	1094	0.73	0.54 – 0.97
Living alone, yes	962	1.27	0.92 – 1.74
Married, yes	1094	0.69	0.52 – 0.92
Retired, yes	912	2.20	1.29 – 4.02
Depression, HADS	391		

Continued on next page

Table 5.5 – *Continued from previous page*

	No.	**OR**	**95% CI**
- None-to-mild, yes		1	-
- Moderate-to-severe, yes		2.27	1.17– 4.25
Anxiety, HADS	384		
- None-to-mild, yes		1	-
- Moderate-to-severe, yes		1.04	0.50 – 2.02
Cognitive impairment GPCOG score $\leq$ 4, yes	399	1.55	0.62 – 3.52
Physical frailty, yes	845	2.05	1.21 – 3.69

NYHA, New York Heart Association; CCI, Charlson co-morbidity index; HADS, hospital anxiety and depression scale; GPCOG, general practitioner assessment of cognition

(*)10 unit decrease; (**) worst during the last 7 days

TABLE 5.6: Multivariable models developed on n=572 complete cases predicting 30-day unplanned re-admission or mortality; reference model includes clinical characteristics; extended model adds physical frailty and social predictors

	Reference model	Extended model
Variables	OR (95% CI)	OR (95% CI)
Number of daily pills at admission	1.04 (1.00 – 1.07)	1.04 (1.00 – 1.08)
Sinus rhythm	0.64 (0.41 – 0.99)	0.63 (0.40 – 0.98)
Urea, mmol/l (log) at discharge	1.63 (1.10 – 2.42)	1.61 (1.08 – 2.40)
NT-proBNP pg/mL (log) at discharge	0.97 (0.81 – 1.16)	0.95 (0.80 – 1.14)
NYHA class at discharge, 1-class increase	1.45 (1.01 – 2.42)	1.39 (0.96 – 2.01)
Dyspnoea at rest at discharge	2.06 (0.99 – 4.29)	2.27 (1.07 – 4.81)
Length of stay (10-day increase)	1.04 (0.88 – 1.23)	1.03 (0.86 – 1.23)
Prior EM hospitalizations in 6months	1.28 (1.07 – 1.53)	1.26 (1.05 – 1.51)
Physical frailty		1.37 (0.69 – 2.69)
Married		0.64 (0.41 – 0.99)
Reported good or excellent support from family		0.92 (0.59 – 1.43)
AUC (Bootstrap optimism-corrected AUC)	0.69 (0.67)	0.71 (0.68)

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6 Risk prediction of 30-day unplanned re-admission or mortality for HF patients: external validation of the OPERA model

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ABSTRACT

Aims: Chronic disease patients are at high risk of adverse events such as unplanned readmission or mortality. The aim of this study is to evaluate the generalizability of the previously developed OPERA-heart failure (HF) model for outcome prediction in another geography.

Methods and results: SAPHIRE is an observational prospective cohort study, consisting of patients hospitalized for HF or chronic obstructive pulmonary disease (COPD) in a tertiary care hospital in St. Louis, Missouri. Among 513 study participants diagnosed with HF, 72 (14%) had an unplanned all-cause readmission and 27 (5%) died within 30 days after discharge from the hospital. The risk prediction model based on the OPERA-HF study had an area under the receiver operating characteristic curve (AUC) of 0.70. When applied on SAPHIRE, the model showed similar discrimination (AUC 0.70 [95% confidence interval 0.65 – 0.76]) and provided accurate risk estimations (predicted 17%, observed 18%). By refitting the model to the SAPHIRE HF cohort, the performance was improved further (AUC 0.72 [95% CI 0.66 – 0.78]).

Conclusion: External validation demonstrated good calibration of the OPERA-HF model. Discrimination of those at low risk versus those at high risk remains modest, even upon refitting the model, implying a need for better predictors of poor outcome within 30 days after discharge.

INTRODUCTION

Nearly half of the adults in the US have at least one chronic condition, contributing to over 75% of hospital days, office visits, home health care and prescription drugs, and thus more than 80% of the total healthcare costs [1]. Re-admissions account for more than 30% of annual US healthcare expenditures [2]. This led to the Hospital Readmission Reduction Program, which was implemented by the Centers for Medicare and Medicaid Services (CMS) in 2012. This program imposes financial penalties on hospitals if their 30-day risk-adjusted readmission rates exceed national averages after an index hospitalization for several key discharge diagnoses, including heart failure (HF) [3]. Approximately 25% of the 1 million HF patients hospitalized annually in US are readmitted within 30 days of discharge [4, 5]. The multiple re-admissions of HF patients often reflect a substantial impairment in the patient's quality of life and are associated with increased mortality and high healthcare costs [6, 7].

Risk models have been developed that examine reasons of readmission and mortality in HF patients. However, these often are only internally validated and not tested in different geographies or healthcare systems. Only a few models have been externally validated, showing a poor performance [8]. Models predicting 30-day unplanned readmission tend to perform worse than models predicting mortality, all cause admissions or outcomes in longer time spans [8, 9]. 30-day readmission models usually include clinical factors and ignore psychosocial, healthcare utilization or patient frailty.

The OPERA-HF study included 1094 HF patients from the UK, where 213 (19%) experienced an unplanned readmission and 60 (5%) died within 30 days of discharge from index admission. A 30-day unplanned readmission or mortality prediction model was developed that included clinical factors (increasing daily pill counts at admission, being in sinus rhythm at admission, dyspnea at rest, NYHA class III or IV, increasing urea and NT-proBNP at discharge, length of stay in the hospital and number of prior emergency hospitalizations in 6 months) combined with physical frailty, not being married, and not perceiving family support. The aim of this analysis is to validate the generalizability of the OPERA-HF model in another geography and healthcare system.

METHODS

Study design

The SAPHIRE-HF/COPD study 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 aim of the study is to identify contributing factors to adverse outcomes for HF and COPD patients, to evaluate the additional value of non-clinical factors and to analyze the validity of prediction models. 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: observation unit admission only, part of another research study involving novel medications or devices, illicit drug use, or designated for transport to hospice at discharge. The study started in October 2014 and was approved by Mercy Health's Institutional Review Board. For the purposes of this report we focus only on the HF cohort of the study.

Data collection

Several variables known to be potential risk factors for adverse events in HF patients were collected by research nurses using automated electronic medical record (EMR) extractions and manual chart reviews. Information on depression and anxiety was also collected from the EMRs with no additional assessment conducted. Additional questionnaires were administered to the patients once during hospitalization about general demographics, socioeconomic issues, prior hospitalizations, functional limitations and ability to self-care.

Physical frailty

For frailty, a two-fold assessment was applied. Patients were asked to respond to a question about having trouble bathing or dressing and then they were asked to undergo the timed 'get up and go' test [10]. The timed 'get up and go' requires patients to stand up from a chair, walk a short distance (3 m) using any walking aids if needed, turn around, return, and sit down again. A time of less than 10 seconds to complete this task is considered normal for a healthy individual whereas a time of more than 20 seconds is considered abnormal. Patients who reported trouble with bathing or dressing, or patients who were not able to complete the 'get up and go' test in less than 20 seconds were defined as frail.

Endpoints

The primary study end-point was unplanned readmission. Mortality within 30 days of discharge from index admission was a secondary outcome. Outcomes were collected through EMR reviews of hospital encounters and national death records. Readmissions to healthcare systems other than Mercy Health may be missed using this method, though patients generally stay within the system for any follow-up care.

OPERA Model

The OPERA-HF study was an observational prospective study consisting of patients hospitalized for HF in Hull, UK. The OPERA model [11] is a logistic regression model developed based on the OPERA-HF cohort for prediction of 30-day unplanned all-cause readmissions or mortality. The predictors included in the model are a combination of clinical variables (increasing daily pill counts at admission, sinus rhythm at admission, dyspnea at rest, NYHA class III or IV and increasing urea and NT-proBNP at discharge), hospital utilization (length of stay in the hospital and number of prior emergency hospitalizations in 6 months), not being married, not perceiving family support and being physically frail. This combination demonstrated a discrimination (area under the receiver operating characteristic curve, AUC) of 0.70 [95% CI 0.66 – 0.74].

Statistical analysis

Data were analyzed from patients who participated in the study between October 2014 and January 2017. Baseline characteristics were compared between the HF cohort from this study and the OPERA-HF study sample using the χ^2 test for binary or categorical variables, and the Kruskal-Wallis test for continuous variables.

Univariable logistic regression analysis was applied to relate patient characteristics to unplanned readmission or mortality within 30 days after discharge. Odds ratios (ORs) were calculated with 95% confidence intervals (CIs). The results were compared with the univariable results from the OPERA-HF study. The OPERA model was then applied to the HF patients in this study. Multiple Imputation (MI) was used to impute missing data. MI technique requires three steps: imputation, analysis and pooling. Each missing value was imputed five times following the predictive mean matching method, thus producing five imputed data sets; each one of these five imputed data sets was then analyzed and the results were pooled into one final analysis following Rubin's method [12, 13]. For predictors not collected at all in our study, we used the mean values of the original data distribution when applying the model.

Discrimination and calibration were used to assess the external validity of the model [14, 15]. Discrimination refers to the ability to distinguish patients who will be readmitted from those who will not, and was quantified by the AUC. An AUC of 0.5 indicates no discriminative ability at all while an AUC of 1 indicates perfect discrimination [16, 17]. Calibration describes the agreement between observed and predicted outcomes. Calibration was assessed visually with a calibration plot. Groups of patients were created based on their predicted risk (deciles), which was plotted against the observed event rate for each decile. A majority of plotted risks being below the x=y line indicates overfitting, while a perfect model would coincide with the x=y line. Calibration-in-the-large was assessed by using the logit of the model predictions as input to a logistic regression model, which allows for inspection of the intercept as measure of structural overestimation of underestimation [14].

The model was further refitted to the SAPHIRE-HF patients and internally validated by a bootstrapping procedure, by sampling with replacement for 200 iterations [16, 18]. Bootstrapping was performed within each imputed data set. We planned to combine both cohorts and refit the model to derive a final model optimized for both sites.

All analyses were conducted using R 3.3.3 statistical software (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline characteristics of the study population

Of the 1571 patients approached, 644 consented and enrolled to the study (460 with a diagnosis of HF, 131 with a diagnosis of COPD, 53 with both diagnoses at enrollment as indicated by the hospital EMR, Figure 6.1). Thus, 513 patients had a primary or secondary diagnosis of HF and were included for analysis (Table 6.1). Participants had a median age of 73 years, 52% were women, 69% retired, 49% married, 34% had Left Ventricular Ejection Fraction (LVEF) $\leq$ 40% at discharge and median NT-proBNP was 3035 pg/mL at discharge. Their median length of stay in the hospital was 4.8 days and their Body Mass Index (BMI) was relatively high (median 31 kg/m^2). Depression and anxiety was prevalent in 13% and 11% of the sample, respectively. In the questionnaires, 13% reported trouble with bathing or dressing. Unplanned, all-cause readmission occurred in 72 (14%) participants within 30 days from index discharge while 27 (5%) died within the first 30 days after discharge.

Relative to OPERA-HF patients, SAPHIRE-HF patients were younger and more often female (Table 6.1). OPERA-HF patients were more likely complex HF patients with more comorbidities, significantly lower BMI, had longer hospital stays and higher average NT-proBNP value at discharge in comparison to the SAPHIRE-HF cohort. OPERA-HF patients also were less often in sinus rhythm and were more likely to experience a readmission.

FIGURE 6.1: Consort diagram

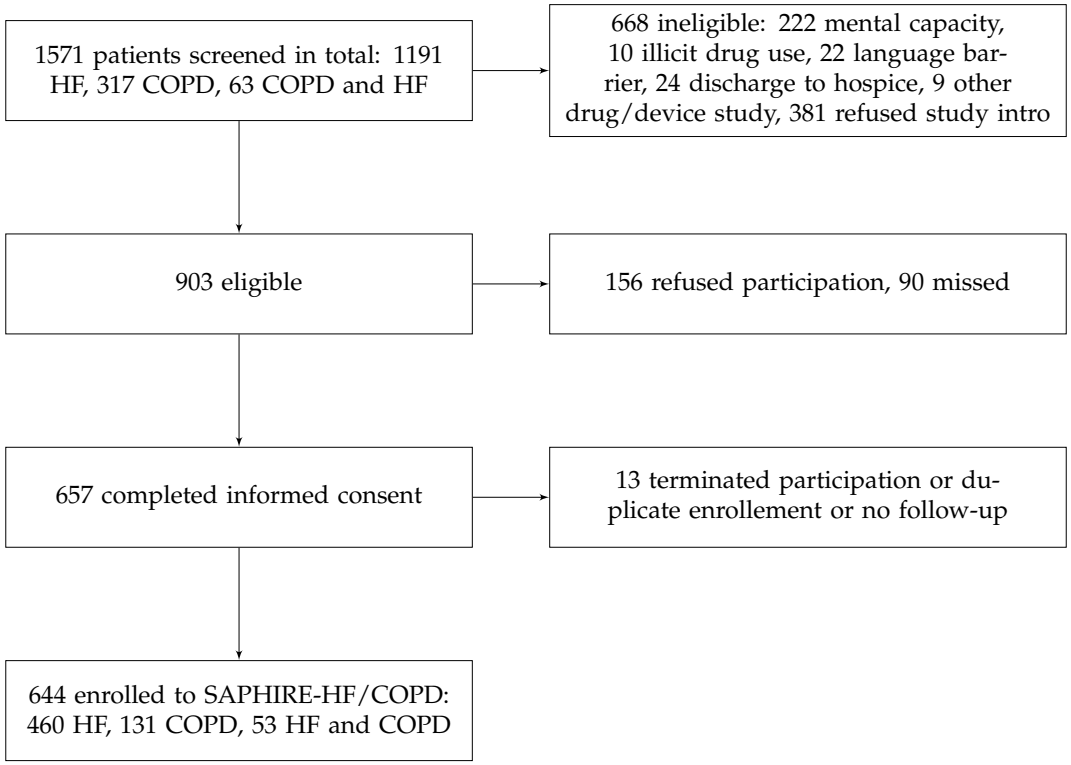

TABLE 6.1: Comparison of baseline patient characteristics and outcomes of SAPHIRE-HF with OPERA-HF.

Characteristics	N	SAPHIRE-HF (N= 513) Summary*	N	OPERA-HF (N= 1094) Summary*	p-value**
Demographics					
Age (years), median [IQR]	513	73 [62 – 82]	1094	77 [68 – 83]	<0.001
Women, n (%)	513	265 (52 %)	1094	433 (40 %)	<0.001
Vital signs at hospital admission and other measurements					
Systolic BP (mmHg), median [IQR]	NA	NA	1083	129 [115–146]	NA
Diastolic BP (mmHg), median [IQR]	NA	NA	1083	75 [63 – 86]	NA
Sinus Rhythm, n (%)	477	245 (51 %)	1088	446 (41 %)	<0.001
Medication at admission					
Total pill count, median [IQR]	512	7.5 [7.5 – 13]	969	9 [5 – 13]	<0.05
History Comorbidities					
Diabetes, n (%)	498	132 (27 %)	1094	380 (39 %)	<0.01
COPD, n (%)	498	76 (15 %)	1094	188 (17 %)	0.42
Cancer, n (%)	498	38 (8%)	1094	122 (11 %)	<0.05
HF symptoms and vital signs at discharge					
Length of stay (days), median [IQR]	513	4.8 [3.1 – 7.7]	1094	10.1 [6.0 – 17.0]	<0.001
BMI (kg/m^2), median [IQR]	512	31 [26 – 39]	587	27 [23 – 32]	<0.001
NYHA: Class III/ IV, n (%)	NA	NA	907	164 (18 %)	NA
LVEF $\leq$ 40 at discharge, n (%)	488	166 (34 %)	920	512 (56 %)	<0.001
Lab values at discharge					
NT-proBNP (pg/ml), median [IQR]	480	3035[1411–7117]	905	4468[1895-9889]	<0.001
Urea (mmol/l), median [IQR]	513	9 [7 – 14]	1087	9 [7 – 14]	0.22
Creatinine (micmol/l), median [IQR]	513	111 [84 – 154]	1085	105 [83 – 140]	<0.05
Bilirubin (mg/dl), median [IQR]	475	0.5 [0.4 - 0.9]	1085	0.9 [0.7 – 1.2]	<0.001
Prior hospitalization					

Continued on next page

Table 6.1 – *Continued from previous page*

Characteristics	N	SAPHIRE-HF (N= 513) Summary*	N	OPERA-HF (N= 1094) Summary*	p-value**
>2 prior EM in 6months, n (%)	513	18 (4 %)	1094	55 (5 %)	0.21
Social status/support					
Living alone, n (%)	NA	NA	938	324 (35 %)	NA
Married, n (%)	513	250 (49 %)	1094	531 (49 %)	0.98
Retired, n (%)	512	353 (69 %)	912	783 (86 %)	<0.001
Mood and cognitive function					
Depression, n (%)***	513	67 (13 %)	391	56 (14 %)	0.72
Anxiety, n (%)***	513	58 (11 %)	384	65 (17 %)	<0.05
Cognitive impairment, n (%)	NA	NA	399	29 (7 %)	NA
Frailty and mobility					
Time for get up and go test (sec), median [IQR]	207	17 [11 – 31]	295	9 [6 - 15]	<0.001
Having trouble bathing or dressing, n (%)	512	64 (13 %)	879	213 (24 %)	<0.001
Outcomes					
30-day unplanned re-admission, n (%)	513	72 (14 %)	1094	213 (19 %)	<0.05
30-day CV unplanned re-admission, n (%)	513	19 (4 %)	1094	163 (15 %)	<0.001
30-day HF unplanned re-admission, n (%)	513	18 (4 %)	1094	109 (10 %)	<0.001
30-day mortality, n (%)	513	27 (5 %)	1094	60 (5 %)	1

IQR, Interquartile range;N, available data; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; EM, emergency.

(*) summaries are based on patients with available data;

(**) 0.1 level of significance;

(***) in SAPHIRE-HF depression and anxiety were extracted by EMRs, while in OPERA-HF additional assessments were applied (by HADS questionnaires [19])

SAPHIRE-HF prognostic effects

In the univariable analysis of the 513 SAPHIRE-HF patients (Table 6.2), older age, longer length of stay in the hospital, higher urea and creatinine, history of one or more prior emergency admission during the last 6 months, and the presence of frailty were all associated with an increased risk of 30-day unplanned readmission or mortality. The estimated univariable effects were similar between studies.

TABLE 6.2: Univariable analysis for 30-day unplanned re-admission or mortality (SAPHIRE-HF, N = 513; OPERA-HF, N = 1094).

	SAPHIRE-HF		**OPERA-HF**	
	OR	**95% CI**	**OR**	**95% CI**
Age, years (10-unit increase)	1.19	1.00 – 1.43	1.21	1.07 – 1.37
Women, yes	1.14	0.73 – 1.78	1.06	0.79 – 1.41
Sinus rhythm, yes	0.61	0.39 – 0.96	0.70	0.52 – 0.94
Total pill count at admission	1.03	0.99 – 1.07	1.05	1.02 – 1.07
Diabetes, yes	1.29	0.78 – 2.11	0.79	0.58 – 1.07
COPD, yes	0.82	0.41 – 1.53	1.27	0.88 – 1.81
Cancer, yes	0.82	0.30 – 1.86	1.14	0.73 – 1.75
Length of stay, 10-day increase	1.73	1.14 – 2.61	1.15	1.04 – 1.27
BMI at discharge, kg/m^2	1.00	0.97 – 1.00	0.99	0.97 – 1.01
LVEF $\leq$40 at discharge, yes	0.93	0.57 – 1.49	1.01	0.73 – 1.38
NT-proBNP at discharge pg/ml (log)	1.24	1.05 – 1.48	1.22	1.08 – 1.37
Urea at discharge, mmol/l (log)	2.91	1.89 – 4.55	1.99	1.54 – 2.58
Creatinine at discharge, micmol/l (log)	1.92	1.23 – 2.99	1.93	1.37 – 2.72
Bilirubin at discharge, mg/dl (log)	1.32	0.92 – 1.88	1.12	0.83 – 1.56
Number of prior EM in 6months	1.32	1.05 – 1.64	1.36	1.19 – 1.56
Married, yes	0.86	0.55 – 1.35	0.69	0.52 – 0.92
Retired, yes	1.15	0.71 – 1.90	1.43	0.95 – 2.24
Depression, yes	1.63	0.87 – 2.93	1.65	1.13 – 2.39
Anxiety, yes	1.49	0.76 – 2.79	1.18	0.81 – 1.70
Physical frailty, yes	2.55	1.56 – 4.32	1.77	1.13 – 2.88

OR, Odds Ratio; CI, Confidence Interval; COPD, chronic obstructive pulmonary disease; BMI, body mass index; LVEF, left ventricular ejection fraction; CV, cardiovascular; EM, emergency.

OPERA model validation

At external validation, the OPERA model showed a similar discrimination to the original (AUC 0.70 [95% CI 0.65 – 0.76]) and good overall risk estimation (predicted 17%, observed 18%, p = 0.44). The plotted risks being close to the x=y line confirm that the probabilities of readmission were well estimated (Figure 6.2).

Multivariable analysis

Most effects of predictors were similar between cohorts. The effect of number of prescribed pills at admission and social support were stronger in OPERA, while the effects of higher urea and being frail were stronger in SAPHIRE (Table 6.3).

When refitting the model, we achieved a slightly higher performance of AUC 0.72 [95% CI 0.66 – 0.78] (corrected for optimism AUC 0.69).

When combining both cohorts, the effects of number of prescribed pills, urea, frailty and prior events were strongest. The discriminatory performance remained similar (AUC 0.71 [95% CI 0.68 – 0.74], with an optimism-corrected estimate of AUC=0.69) (Table 6.3).

FIGURE 6.2: Calibration plot for the external validation of the OPERA model on SAPHIRE-HF data; the triangles indicate the observed frequencies by deciles of predicted probabilities with 95% confidence intervals (vertical lines); the distribution of patients having vs not having an event is shown at the bottom of the graph

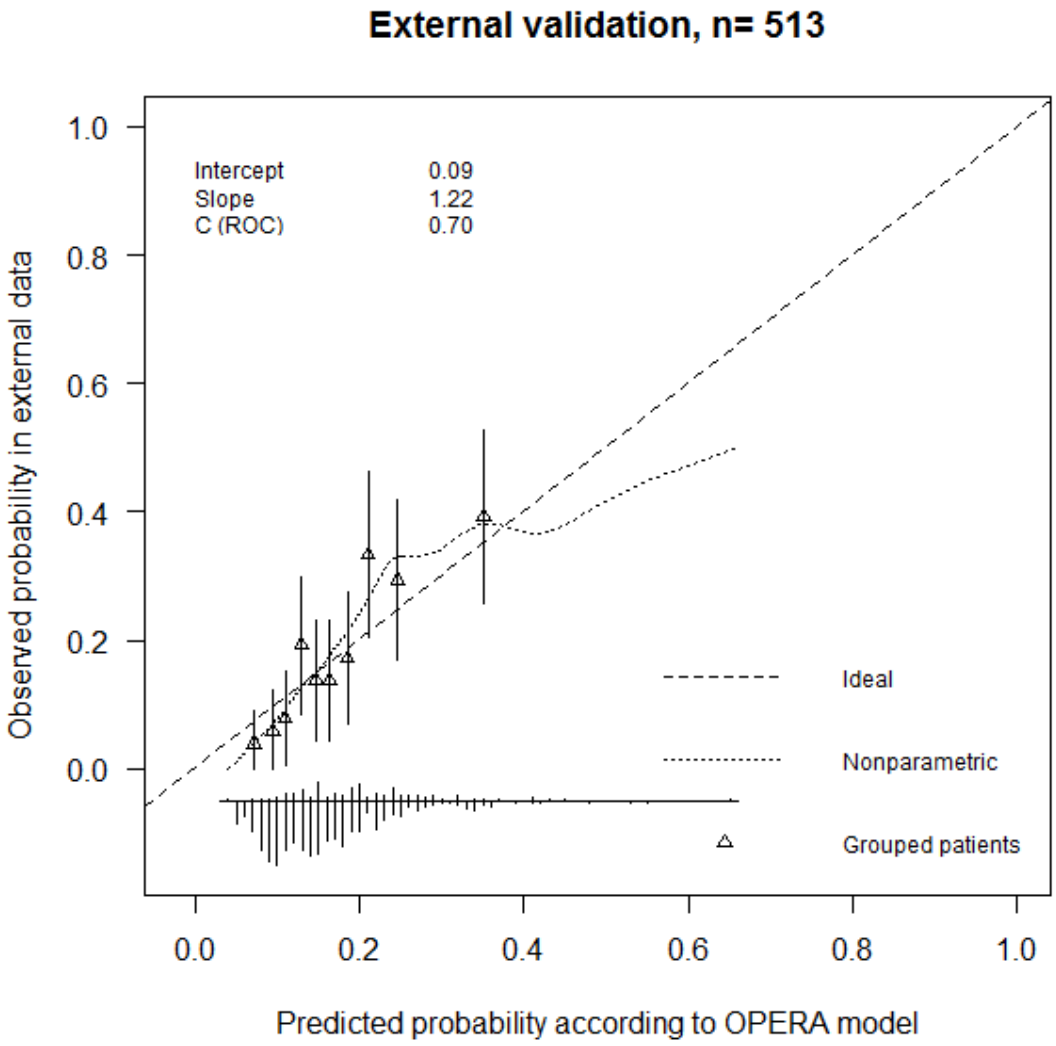

TABLE 6.3: Multivariate analysis and discrimination of 30-day unplanned readmission or mortality models.

	OPERA (N = 1094)		**Refitted model (N = 513)**	**Combined model (N = 1607)**
Variable	**OR (95 % CI)**		**OR (95 % CI)**	**OR (95 % CI)**
Number of daily pills at admission	1.03 (1.00 – 1.06)		1.01 (0.96 – 1.05)	1.02 (1.00 – 1.04)
Sinus rhythm at admission	0.77 (0.57 – 1.06)		0.65 (0.40 – 1.06)	0.75 (0.58 – 0.97)
Urea, mmol/l (log) at discharge	1.61 (1.22 – 2.13)		2.45 (1.55 – 3.88)	1.74 (1.37 – 2.20)
NT-proBNP pg/mL (log) at discharge	1.07 (0.94 – 1.21)		1.02 (0.85 – 1.23)	1.07 (0.97 – 1.19)
NYHA class at discharge, 1-class increase	1.40 (1.08 – 1.82)		Not available	1.48 (1.19 – 1.85)
Dyspnea at rest at discharge	1.72 (0.98 – 3.04)		Not available	1.37 (0.83 – 2.28)
Length of stay, 10-days increase	1.07 (0.96 – 1.20)		1.37 (0.88 – 2.13)	1.07 (0.97 – 1.18)
Prior EM hospitalizations in 6months	1.26 (1.10 – 1.45)		1.22 (0.96 – 1.54)	1.24 (1.10 – 1.40)
Physical frailty	1.21 (0.73 – 2.00)		2.24 (1.31 – 3.84)	1.73 (1.20 – 2.49)
Married	0.72 (0.53 – 0.97)		1.05 (0.63 – 1.73)	0.79 (0.61 – 1.02)
Perceiving support from family	0.74 (0.53 – 1.02)		0.64 (0.36 – 1.14)	0.80 (0.62 – 1.04)
Validation	**Original**	**External validation**	**Refitted**	**Combined**
AUC [95% CI] (Bootstrap optimism corrected)	0.70 [0.66-0.74] (0.67)	0.70 [0.65 – 0.76]	0.72 [0.66 – 0.78] (0.69)	0.71 [0.68 – 0.74] (0.69)

DISCUSSION

In this study, we externally validated an existing predictive model for early readmission or mortality in HF patients. We found good performance with discrimination similar to the original cohort and good calibration.

By comparing the two cohorts, we found that both studies had similar event rates and similar mortality rates, while the early, unplanned readmission rates were different between the US cohort (14%) and the UK cohort (19%). The difference in the readmission rate may partially be explained by the fact that in Hull all data were retrieved from the single institution providing hospital care in the area, making readmission elsewhere unlikely. On the other hand, in SAPHIRE there is a possibility of readmissions occurring to institutions outside of the network and hence not being captured. Other differences observed were that the US population was younger with less comorbidities. In spite of these differences and the differences in health care systems, we observed similar effects in both studies in the univariable analysis. Increasing age, not being in sinus rhythm, longer length of stay, increasing NT-proBNP, urea or creatinine, more prior events or being frail were all related to an increase risk of poor outcome.

The OPERA model performed well when tested in this geography supporting transportability of the model beyond one single site. By refitting the model in the external validation cohort, we improved the performance slightly. As a model update, we combined the cohorts and refitted the model on both such as to optimize the model for both geographies. Further external validation of the combined model in other geographies may assess the generalizability beyond the European and US settings considered so far.

In this analysis we confirmed the hypothesis that a combination of clinical and non-clinical variables provides better discrimination of the early outcomes compared to the known, purely clinical, models from the literature [8]. In the refitted model we achieved a significant improvement in the performance with a discrimination of AUC of 0.72. Although this level of discrimination is modest, we achieved a higher AUC than most HF models available in the literature [8, 20]. Predicting early readmissions with high accuracy remains challenging because of the multidimensional root causes of the events. Further research is needed to discover other predictors not yet studied that may improve the discrimination.

Frailty is an increasingly recognized factor affecting adverse outcomes in HF patients [21, 22]. As suggested by our analysis, taking frailty into account can improve prediction of outcomes following discharge from the hospital after an admission for HF. Physical frailty should not be overlooked in discharge plans for HF patients. Interventions to properly manage frail patients should be investigated that may improve the outcomes. Studies of exercise training have suggested improvements in quality of life but no clear reduction in hospitalization or mortality [23]. Studies of anabolic agents have been of modest size and clinical benefit is as yet uncertain [24].

As an indication of 'social frailty', marital status and support from family, should also not be overlooked. Our findings, suggest that a patient receiving support from their family may be less likely to be re-admitted to hospital. Perceiving social support may also be an important motivation for self-help for the patient [25]. Further research is recommended for interventions targeted at patients with poor social support that may improve their outcomes after discharge. One promising strategy is to send the patient home with high touch points or services to help the patient manage him or herself and stay out of the hospital.

An advantage of our model is that it is based on simple and easy to obtain variables either directly from the EMRs or by simple additional assessments. The output of the model is a risk score that is easily interpreted by clinicians. The simplicity of our model makes it easy to use as part of routine care due to commonly available variables. It can support the clinicians to optimize the post-discharge services provided to patients. Further research on model implementation in clinical practice and validation in other datasets is required.

Limitations. This study adds to the growing literature on predictors for HF early adverse events, but some limitations should be mentioned. The definitions of the collected data in SAPHIRE and methods of reporting were not identical to the OPERA-HF data points. However, this may be expected when considering two very different healthcare systems and geographies. Despite all these differences, discriminatory performance and calibration were adequate, supporting the transportability of the OPERA model. Missing data is a minor limitation in our study; we partially overcame this issue by using multiple imputation. In addition, the validated questionnaires use colloquial language that may not have been understood by patients from different backgrounds.

Conclusion. The OPERA model has good calibration in a different geography. Further research on other potential predictors and evaluation of the OPERA model in clinical practice is recommended.

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Part IV

Discussion and summary

7 General discussion

Heart failure (HF) patients have high hospitalization rates followed by high readmission rates with about 25% of them being readmitted within 30 days [1] leading to worse quality of life for the patient [2] as well as high financial implications for the health care systems [3]. Although clinical treatment is constantly being optimized [4], further optimization is needed with respect to community care, social care or psychological support provided to the patient. Identifying risk factors affecting adverse events in HF patients is important for the patients and the care providers, since new risk factors may lead to new methods to manage patients and optimize services. Tailored treatment to the specific needs of the patient including non-medical services, well-coordinated amongst multiple professional care disciplines could lead to better outcomes.

The aim of this thesis was to expand our knowledge on risk factors affecting recurrent readmissions or mortality in HF patients, develop a predictive model for early adverse events by taking into account the added predictive value of non-clinical factors and test the transferability of the model by externally validating it in a different geography. The specific research questions are listed in Table 7.1 along with some of the main findings.

TABLE 7.1: Research questions and findings

Research question	**Findings**
What is the impact of depression and anxiety on mortality in HF patients?	**Depression** - Prevalence: 29% - Unadjusted effect: HR = 1.6; 95%CI 1.3 – 1.9 - Adjusted effect: HR = 1.4; 95%CI 1.2 – 1.6 - Heterogeneous effect due to population sizes and prevalence - OPERA-HF: HR: 3.0; 95% CI: 1.3 to 7.0 (adjusted effect) **Anxiety** - Prevalence: 29% - No significant effect

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Table 7.1 – *Continued from previous page*

Research question	**Findings**
Which other psychosocial factors affect adverse outcomes in HF? What is their association with first and recurrent events?	Composite endpoint: readmission or mortality OPERA-HF: 70% event rate at 1 year follow up **Depression** - First event: HR = 1.7; 95%CI 1.2 – 2.4 - Recurrent events: HR = 1.8; 95%CI 1.4 – 2.2 **Anxiety** - First event: HR = 1.7; 95%CI 1.2 – 2.3 - Recurrent events: HR = 1.4; 95%CI 1.1 – 1.7 **Cognitive impairment** - First event: HR = 1.4; 95%CI 0.9 – 2.3 - Recurrent events: HR = 1.4; 95%CI 1.1 – 1.9 **Living alone** - First event: HR = 1.0; 95%CI 0.9 – 1.3 - Recurrent events: HR = 1.2; 95%CI 1.1 – 1.4 **Frailty (trouble bathing or dressing)** - First event: HR = 1.3; 95%CI 1.1 – 1.7 - Recurrent events: HR = 1.2; 95%CI 1.0 – 1.4 **Frailty (timed get-up-and-go test)** - First event: HR = 1.02; 95%CI 1.01 – 1.03 - Recurrent events: HR = 1.01; 95%CI 1.01 – 1.02
Can we predict early readmission or mortality with a model that is transportable to a different geography?	Improved discrimination by adding physical frailty and social support to clinical variables Discrimination still modest - Internal validation on OPERA-HF (AUC 0.7 – corrected for optimism: 0.67) Good calibration from EU to US - External validation on SAPHIRE-HF (AUC 0.7)

MAIN FINDINGS

Research question 1: What is the impact of depression and anxiety on mortality in HF patients?

To address the first research question we followed a twofold approach. First, we conducted a systematic review and meta-analysis followed by the use of data from the OPERA-HF study to validate our findings from the systematic review on this cohort. In the systematic review, we identified 26 and 6 articles meeting inclusion criteria for depression and anxiety, respectively. The prevalence of both depression and anxiety in the identified studies was on average 29%. We found that depression is a significant and independent predictor of all-cause mortality among HF patients but with very heterogeneous effects reported across the different studies. For example, the adjusted effect of depression on mortality reported by Kato [5] was Hazard Ratio (HR) = 5.52, while the effect on the same outcome reported by Junger [6] was HR = 1.08. We performed a random-effect meta-regression to explore possible sources of this heterogeneity and we found that significant heterogeneity was associated with the total study population size and the prevalence of the depression in the study. The effect of depression was smaller in larger studies, which might reflect publication bias with small studies more often being published when reporting large effect estimates and less often published when reporting low effect estimates. Smaller effects were also observed in studies with higher prevalence of depression. That may relate to the use of different cut-offs on an underlying, latent, scale for depression. If a more liberal cut-off was used, those labeled as depressed actually were milder than with a more strict definition of depression.

The pooled unadjusted effect estimate from the literature for depression was 1.6 (HR = 1.6; 95%CI 1.3 – 1.9, $P < 0.001$) similar to the effect when adjusting for confounders (HR = 1.4; 95%CI 1.2 – 1.6; $p < 0.001$). On the other hand, there was no significant effect of anxiety on mortality identified.

In the OPERA study, we confirmed the strong association of depression with increased risk of mortality. Moderate-to-severe depression was independently associated to all-cause mortality in the year following discharge after an admission to hospital for HF when controlling for age, Charlson Comorbidity Index, NYHA class IV, NT-proBNP and treatment with mineralocorticoid receptor antagonist, beta-blocker and diuretics

(HR: 3.0; 95% CI: 1.3 to 7.0; P$<$ 0.05).

Research question 2: Which other psychosocial factors affect adverse outcomes in HF? What is their association with first and recurrent events?

HF studies mostly focus on demographics or clinical risk factors, such as increasing age, male, the presence of co-morbidities, reduced left ventricular ejection fraction (LVEF), increasing New York Heart Association class of symptoms and worse serum markers and ignore psychosocial or other non-clinical factors [7]. However, as we showed in the first part of the thesis, depression may have a strong impact on the outcomes. Other previous research has also proved the association of (physical) frailty with increasing risk of first readmission or mortality in heart failure [8, 9]. In Chapter 4 we confirmed that depression and frailty were some of the non-clinical factors independently associated with increased risk of unplanned readmissions or mortality. Also moderate-to-severe anxiety was independently associated with the combined outcome of readmission or mortality, even though it was not associated with mortality outcome alone [10].

Most HF studies are focusing on the impact on the first event; readmission or mortality. Most research, in particular, focuses on 30-day readmission as an outcome of interest because of the payment reform incentives pushed by policy makers / payers aiming to improve outcomes. However, HF patients are often experiencing recurrent hospitalizations reflecting progression of the underlying disease or exacerbations due to comorbidities and suboptimal self-care and medication. Taking into account more events will lead to more power and efficiency in estimating potential risk factors. Therefore, we extended our analysis to study the recurrent events. In the OPERA-HF study, there was an event rate of 70% of patients being readmitted or dying at 1-year follow-up. The 779 patients discharged from the hospital till July 2016 had 559 first events and 1600 recurrent events. Hence, there would have been 1041 events ignored if looking only into the first events that the patients experienced.

In the recurrent event analysis, psychosocial or other non-clinical variables independently associated with increasing risk of recurrent events in the year following discharge after a HF admission to hospital were: presence of frailty, moderate-to-severe

depression, and moderate-to-severe anxiety, living alone and the presence of cognitive impairment. Those remained significant predictors when adjusting for age, diabetes, history of myocardial infarction, chronic obstructive pulmonary disease, urea and creatinine at discharge. The effect of depression on the outcome was greater in the recurrent event analysis than in the first event analysis, while the effect of anxiety was smaller. Living alone and the presence of cognitive impairment were significant predictors of recurrent events but not of first event alone.

Research question 3: Can we predict early readmission or mortality with a model that is transportable to a different geography?

HF patients often experience adverse events early after being discharged from the hospital, with approximately 25% been readmitted within the first 30 days [1]. Readmissions within 30 days may be caused by worsening of clinical conditions of the patient but also due to other factors including lacking social support, being physically frail or having cognitive issues.

Available risk stratification algorithms for 30-day events (unplanned readmission or mortality) perform poorly [11] and include mostly risk factors reflecting the clinical profile of the patient. In Chapter 5, we used data from the OPERA-HF study to develop a 30-day composite outcome model, and we explored the added predictive value of non-clinical predictors to early outcomes: 30-day unplanned readmission or mortality within 30 days. The model containing clinical variables alone (not in sinus rhythm, worst symptoms, increasing urea and NT-proBNP at discharge, and higher daily pill count) and health care utilization (number of prior emergency hospitalizations in 6 month and length of stay) gave an area under the receiver operating characteristic curve (AUC) of 0.68 [95% CI 0.64 - 0.72]. By including in the model physical frailty and social support the AUC increased to 0.70 [95% CI 0.66 – 0.74] ($p<0.05$). In this model, we achieved an absolute increase in performance of 0.02 when taking into account non-clinical factors. The discrimination of the model remained modest reflecting the difficulty in early readmission or mortality prediction due to the diversity in the readmission root causes. However, we showed that by including less frequently evaluated patient characteristics (physical and social frailty), we can increase the discriminative value of the model. Another advantage is that our model is based on simple and easy to obtain variables, it can easily be used as part of the routine care practice and results

can be easily interpreted by the clinicians.

External validation. Most available risk stratification algorithms are only internally validated [12]. Internal validation is important to prove the reproducibility of the model on the original population [13]. This step is important but not enough when aiming to prove the validity of a model beyond the original population. It should be followed by external validation that proves the transportability of a model to a different 'plausibly related' population [13, 14, 15].

In the last part of this thesis we evaluated the transportability of the OPERA model to a different geography. The performance of the model was evaluated by discrimination and calibration. We used data from the SAPHIRE study, conducted in US, to externally validate the model. In SAPHIRE study, we collected similar data to the OPERA-HF. The external validation of the OPERA model was performed on 513 HF patients enrolled in the SAPHIRE study. Our results showed a good calibration and discrimination similar to the original. This means that the model can overcome any difference between the populations of two locations. It can be used in the new population to discriminate patients at risk of an early event with a performance equal to the one from the original derivation setting without any adjustment to the original model.

Early event prediction remains challenging, however, our findings suggest that non-clinical factors may improve the predictions. Further evidence towards this direction has been provided by another recent study demonstrating that causes of potentially preventable readmissions are mostly human-related caused by coordination and communication failures [16]. Furthermore, the generalizability of our model to a different geography indicates that the model designed for one setting can be used for another setting, as well.

METHODOLOGICAL CONSIDERATIONS

Study design

It is widely reported in literature that early outcomes and especially readmissions are generally hard to predict, due to the heterogeneity of the population characteristics, the reasons that might be causing a readmission, the short prediction window and the rare frequency of these events [17, 18, 19]. In the OPERA-HF study, we set up an intentionally broad protocol to explore different potential predictors. Our analysis showed that by taking into account frailty or lack of social support we can improve the discrimination for 30-day emergency readmission or mortality, while more psychosocial factors affect longer term outcomes. However, the discrimination of early events remains modest recommending further research on other important non-clinical predictors not yet identified. For instance, a recent study by van Galen et al. [20] reported that the patient reporting not feeling ready for discharge at index admission was significantly associated with the early readmission outcome.

Patient data

One limitation of the OPERA-HF study was that 20% of the patients had missing data for one or more of the predictors included in the model. The broad protocol requiring intense data collection, patient burden, collecting data for which diagnostic ground exists may be some or the reasons explaining the high missing data rates for some of the parameters. On the other hand, the SAPHIRE-HF/COPD study protocol was limited to the most important factors identified from the OPERA-HF study or other clinically significant factors indicated by domain experts. The difference in the size of the protocol may be one of the reasons explaining the smaller number of missing data in the SAPHIRE-HF/COPD study. In both studies, to overcome the missing data issue we used the multiple imputation technique [21].

With respect to follow-up data, we anticipated only a limited amount of outcome data missing in both studies. In both cases, we recruited study participants living in the local areas. However, there is still a possibility of missed events due to seeking care outside of the local areas that may result in an underestimation of readmission rates.

Additional assessment

In both studies, patients were asked to complete additional physical exams or psychosocial assessments via questionnaires in order to obtain a more holistic assessment of their status. These additional assessments are not part of the routine care provided to the patients.

There are different methods available that can provide assessments of depression, anxiety, social support, frailty or other characteristics of the patients. A limitation of some of the assessment methods used in our studies, for instance the HADS questionnaire for depression and anxiety [22], is that they have been developed primarily for research and have not been extensively tested in routine practice for patients with heart failure.

Another potential limitation of these assessments is that they may be subjective depending on the patient's physical or mental condition at the time of administration. They may rely on participant's perception of their own health and their ability to recall past experiences and events. Next to that, most of these assessments were performed once during patient's hospitalization. Hence, we may have missed significant changes of patient's status during or after hospitalization.

IMPLICATIONS AND FUTURE RESEARCH

The OPERA model takes into account frailty and social support next to healthcare utilization and clinical predictors to calculate a risk score of early adverse events for the patients. This risk score can be used by the discharge teams as part of the routine practice to identify patients at different risk levels. The model does not aim to replace but to assist clinicians or discharge teams to identify optimal care pathways for their patients. Some examples of interventions linked to different risk levels are given in Table 7.2. Further research is recommended to identify the optimal thresholds for the risk levels.

Patients with the highest risk scores are typically very complex, end stage heart failure patients who would benefit mainly from interventions such as palliative care. High risk patients usually require intense care and support by specialist, primary care and informal caregivers. One possible solution to support high risk patients effectively in their own home is telehealth [23]. HF patients in the medium risk levels, on the other hand could benefit by less intense interventions such as structured m-health support or lower intensity telehealth solutions [24]. HF patients with the lowest risk scores are usually well self-managed and they might only need clinical and social support with respect to health coaching and lifestyle management in order to maintain their risks low.

Often a multidisciplinary management approach is needed in order to identify the patients' needs and the interventions that would benefit them the most. The knowledge on the impact of specific factors on the outcomes can improve discharge management and explore interventions tailored to patient needs that may improve the outcomes. Our study recommends that non-clinical or non-disease specific factors should not be neglected when assessing a patient's status and needs. A holistic assessment of the patients' status with them also engaged in the process of deciding what is best for them (shared decision making) may help to optimize the care provided to the patients and identify avoidable hospitalizations. Depression or frailty are some of the factors that appear to be strongly related to the outcomes and it could be beneficial to include their assessment as part of the routine care provided to HF patients. The presence of certain non-disease specific factors should be taken into account while defining interdisciplinary treatment programs tailored to individual patient needs. The multidisciplinary management team may consist of HF specialist, physiotherapist, geriatrician,

rehabilitation physician, nurse and dietician depending on each patient's needs.

Cognitive Behavioral Therapy (CBT) or physical exercise are some of the interventions with positive effect on outcomes for patients with depression or frailty [24, 25, 26, 27, 28]. On the contrary, there is no evidence that antidepressants could positively affect the outcomes in patients with HF [29]. Multidisciplinary collaborative management to identify individual patients' needs, physical exercise or support groups are some of the interventions with positive impact on outcomes when the patient is lacking social support [28, 30]. Randomized controlled trials are recommended to evaluate the impact of these interventions on HF patients also in combination with other interventions such as telehealth.

In this thesis, we have reported a strong impact of psychosocial factors and frailty on several adverse outcomes of HF patients. There is evidence that many of these factors are affecting other groups of patients, as well. For example, frailty is increasingly recognized as an important factor in managing patients with long term conditions [31]. Major depression [32, 33] and cognitive impairment [34] have also been associated with high risk of death in older populations. Next to them, lack of social support is often associated with adverse follow-up outcomes in hospitalized patients [35]. Further research and evaluation of our findings on other patient groups is recommended.

TABLE 7.2: HF patient characteristics and managements in different risk levels

Risk level	**Patient profile**	**Possible interventions at discharge**
Very high risk	Terminal ill or very severe/ complex patients (e.g. transplantation or having other dominant (chronic) disease)	Nursing home, palliative care
High risk - complex needs	At risk of (recurrent) hospital emergency admissions or attendances to hospital. Unstable condition. Have difficulty following medication or treatment regimes.	Intense care (e.g. high intensity telemonitoring), community specialist nurse support, multidisciplinary management, social care
Medium risk - less complex needs	Lower chance to have unplanned readmissions within the next year, chance of deterioration.	Lower intensity telemonitoring, multidiciplinary management, Community specialist nurse support, social care, proactive care planning
Low risks	Well self-managed or early stage/ low severity HF patients. Able to maintain a good health management.	GP/practice nurse follow up in CDM clinics, primary care management, health coaching and lifestyle management, community activities

CONCLUSIONS

The research in this thesis aims to highlight new risk factors for HF adverse events and contribute in the improvement of predictive models for HF patients. We showed the strong effect of several psychosocial or non-disease specific factor with adverse outcomes in HF patients. Depression is strongly associated with increasing risk of recurrent hospitalizations or mortality in the year following discharge after an admission to hospital for HF. Other factors also related to increasing risk of recurrent events are the presence of frailty, moderate-to-severe anxiety, living alone and the presence of cognitive impairment. When looking into short-term outcomes, frailty and lack of social support both improved the discriminative power of a model predicting 30-day readmission or mortality.

These findings may enable researchers and health care providers to identify patients at risk of adverse events that are potentially avoidable and to adjust their decisions about patients' discharge to optimize the care provided them. Currently, the patient's status and post-discharge services are assessed by the professionals at the cardiology ward (cardiologists, nurses and/or the care managers) in an ad-hoc way, which may vary between professionals and institutions based on experience and knowledge. Our tool enables them to assess the patient's condition in a more systematic way from a holistic perspective, to stratify the patients in different risk levels and to recommend a multidisciplinary management or other interventions where needed.

RECOMMENDATIONS

The findings of our research allow for the following recommendations to health care professionals and researchers.

Recommendations for clinical practice

- Holistic assessment of the patient as part of routine care by a multidisciplinary team might be beneficial. The team may consist of HF specialist, physiotherapist, geriatrician, rehabilitation physician, nurse and dietician depending on each patient's needs.
- Do not neglect psychosocial aspects or frailty when assessing patients' condition.
- Use the OPERA model as part of routine care to identify patients at high risk of early events.

Recommendations for research

- Explore further non-clinical factors that may improve the prediction of outcomes for HF patients.
- Investigate the added value of frailty, social support and depression in predictive models for long-term outcomes.
- Validate our findings beyond HF patients on COPD or other chronic disease patients.
- Use the knowledge on impact of non-clinical factors to improve discharge management by involving a multidisciplinary team and next to the HF related interventions take into account interventions such as CBT, multidisciplinary management, physical exercise, counseling and education tailored to individual patient's needs.

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Part V

Appendices

Summary

The main aim of this thesis is to explore risk factors associated to an increased risk of adverse outcomes for heart failure (HF) patients and improve the early re-admission or mortality prediction in HF.

The first part of the thesis includes the general introduction. HF is a progressive disease and a major cause of morbidity and mortality worldwide. HF disease management can be difficult because besides medical treatment it requires significant lifestyle changes such as exercise, restricted fluid and salt intake and medication adherence. Therefore, despite the improvements in disease management, HF is often associated with poor quality of life and multiple hospital admissions. A portion of re-admissions can be prevented by predicting if they will occur and tailoring disease management interventions accordingly. Hence, identifying risk factors affecting adverse events in HF patients is important for patients and healthcare providers, because they may lead to new methods to manage patients and optimize services.

We designed the OPERA-HF study in the UK, to explore a wide range of variables as potential risk factors. In addition to demographic, clinical, imaging and laboratory variables, we explored non-disease specific and 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.

In the second part of the thesis, we study the impact of depression and other psychosocial factors on adverse outcomes. We conducted a systematic review and meta-analysis where we found that the prevalence of both depression and anxiety in the identified studies was on average 29%. We found that depression is a significant and

independent predictor of all-cause mortality among HF patients but with very heterogeneous effects reported across the different studies. The heterogeneity was associated with the total study population size and the prevalence of depression in the study. On the other hand, there was no significant effect of anxiety on mortality identified.

Subsequently we confirmed the strong association of depression with increased risk of mortality, in the OPERA-HF study. Moderate-to-severe depression was independently associated to all-cause mortality in the year following discharge after an admission to hospital for HF when controlling for age, Charlson comorbidity index, NYHA class IV, NT-proBNP and treatment with mineralocorticoid receptor antagonist, beta-blocker and diuretics. In the OPERA-HF study, moderate-to-severe depression was also significantly associated with recurrent events: unplanned readmission or mortality. Other psychosocial or non-clinical variables independently associated with increasing risk of recurrent events in the year following discharge after a HF hospital admission were: presence of frailty, moderate-to-severe anxiety, living alone and the presence of cognitive impairment.

In the third part of the thesis, we used data from the OPERA-HF study to develop a 30-day composite outcome model and we explored the added predictive value of non-clinical predictors to early outcomes: 30-day unplanned readmission or mortality within 30 days. A model containing clinical variables alone had an area under the receiver-operating characteristic curve (AUC) of 0.68. By including physical frailty and social support in the model the AUC increased to 0.70. The discrimination of the model remained modest reflecting the difficulty in early readmission or mortality prediction due to the diversity in the readmission root causes.

We then used data from the SAPHIRE study to externally validate the model. Our results showed a good calibration and discrimination similar to the original. This means that the model can overcome any difference between the populations of two locations. Early event prediction remains challenging, however, our findings suggest that non-clinical factors may improve the predictions and they should not be neglected when assessing a patient's status and needs.

In the last part of the thesis, the general discussion, we summarize the findings, we provide answers to the main research questions addressed in this thesis and present recommendations for future research.

Nederlandse samenvatting

Het hoofddoel van dit proefschrift is om risicofactoren te onderzoeken die geassocieerd zijn met een verhoogd risico op ongunstige uitkomsten voor patiënten met hartfalen en om de voorspelling van vroegtijdige heropname of sterfte van patiënten met hartfalen te verbeteren.

Het eerste deel van het proefschrift omvat de algemene inleiding. Hartfalen is een progressieve ziekte en een belangrijke oorzaak van morbiditeit en mortaliteit wereldwijd. De zorg van hartfalen is uitdagend omdat aanzienlijke veranderingen in leefstijl op het gebied van lichaamsbeweging, beperkte vocht- en zoutinname en therapietrouw noodzakelijk zijn voor een effectieve behandeling.

Ondanks de verbeteringen in de zorg, wordt hartfalen daarom vaak geassocieerd met een slechte kwaliteit van leven en meerdere ziekenhuisopnames. Een deel van de heropnames kan worden voorkomen door nauwkeurige voorspelling van deze opnames te doen en daarop het behandelplan met zorginterventies aan te passen. Het identificeren van risicofactoren gerelateerd aan heropnames en sterfte van patiënten met hartfalen is daarom belangrijk voor patiënten en zorgverleners, omdat het kan leiden tot nieuwe methoden voor betere zorg met betere interventies.

We hebben de OPERA-HF studie in het Verenigd Koninkrijk opgezet om een breed scala aan variabelen te verkennen als mogelijke risicofactoren. Naast demografische, klinische, beeldvormende en laboratoriumvariabelen, hebben we niet- ziektespecifieke en niet-klinische variabelen onderzocht en hun waarde geëvalueerd als voorspellers voor heropname of sterfte bij patiënten met hartfalen na een opname voor hartfalen. We wilden een klein aantal variabelen identificeren dat een zo goed mogelijk onderscheid zou geven voor de voorspelling van heropname of sterfte. Om onze bevindingen en hun generaliseerbaarheid buiten het ontwikkelingscohort te valideren, zijn de resultaten getoetst met de SAPHIRE studie, een patiëntencohort uit de Verenigde Staten.

In het tweede deel van het proefschrift bestuderen we de invloed van depressie en andere psychosociale factoren op ongunstige uitkomsten bij hartfalen. We hebben een systematisch literatuuronderzoek en meta-analyse uitgevoerd waarbij naar voren kwam dat de prevalentie van depressie en angst in de geïdentificeerde onderzoeken bij patiënten met hartfalen gemiddeld 29% was. Depressie als variabele bleek een significante en onafhankelijke voorspeller van algemene sterfte bij patiënten met hartfalen, maar met zeer uiteenlopende effectgroottes die in de verschillende onderzoeken zijn gemeld. De heterogeniteit was geassocieerd met de totale omvang van de onderzoekspopulatie en de prevalentie van depressie in het onderzoek. Aan de andere kant is er geen significant effect gevonden voor de relatie tussen angst en algemene sterfte.

Op basis van de analyse van de gegevens van de OPERA-HF studie is er een sterke associatie van depressie met verhoogd risico op sterfte gevonden. Matige tot ernstige depressie was onafhankelijk geassocieerd met algemene sterfte in het jaar na ontslag van een aan hartfalen gerelateerde opname in het ziekenhuis, waarbij gecorrigeerd is voor leeftijd, Charlson Comorbidity Index, NYHA klasse IV, NT-proBNP en behandeling met aldosteron-antagonist, bètablokker en diuretica.

In de OPERA-HF studie was matige tot ernstige depressie ook significant geassocieerd met herhaaldelijke heropnames of sterfte. Andere psychosociale of niet-klinische variabelen die onafhankelijk geassocieerd bleken met een verhoogd risico op recidive in het jaar na ontslag na een opname voor hartfalen in het ziekenhuis waren: aanwezigheid van ouderdomszwakte, matige tot ernstige angst, alleen leven en de aanwezigheid van cognitieve aandoeningen.

In het derde deel van het proefschrift zijn de gegevens uit de OPERA-HF studie gebruikt om een model te genereren gericht op het voorspellen van heropname of sterfte binnen 30 dagen na ontslag. Daarbij onderzochten we de toegevoegde voorspellende waarde van niet-klinische voorspellers voor de afzonderlijke uitkomsten. Een model met alleen klinische variabelen had een C-statistiek (AUC; oppervlakte onder de receiver operating characteristic curve) van 0,68. Door in het model ouderdomszwakte en sociale ondersteuning op te nemen, steeg de C-statistiek tot 0,70. Het onderscheidend vermogen van het model bleef bescheiden en illustreert de mate van complexiteit van het voorspellen van vroegtijdige heropname of sterfte vanwege de verscheidenheid aan mogelijke oorzaken.

Vervolgens hebben we gegevens uit de SAPHIRE-studie gebruikt om het voorspellend model extern te valideren in een ander cohort. Onze resultaten toonden een goede kalibratie en onderscheidend vermogen aan voor het model in dit nieuwe cohort, vergelijkbaar met de prestatie in het oorspronkelijke cohort. Dit betekent dat het model de mogelijke verschillen tussen de twee cohorten van de twee locaties kan compenseren. Het voorspellen van gebeurtenissen als vroegtijdige heropname en sterfte bij patiënten met hartfalen blijft een uitdaging, maar onze bevindingen geven aan dat niet-klinische factoren de voorspellingen kunnen verbeteren en overwogen zouden moeten worden bij het beoordelen van de toestand en behoeften van een patiënt.

In het laatste deel van het proefschrift, de algemene discussie, vatten we de bevindingen samen, geven we antwoorden op de belangrijkste onderzoeksvragen in dit proefschrift en worden aanbevelingen gedaan voor toekomstig onderzoek.

About the author

Ioanna Sokoreli was born in Patras, Greece on November 14th, 1986. In 2010, she obtained her Diploma in Electrical and Computer Engineering from the Technical University of Patras. In 2013, she obtained a Master degree in Business Information Systems from Eindhoven University of Technology in the Netherlands. She conducted a master thesis project in collaboration with Philips Research where she provided data analytics support for the HeartCycle European Project. Since 2013, she is working as a Research Scientist in the Chronic Disease Management group at Philips Research, Eindhoven. She has been involved in heart failure clinical trials' data collection and analysis, while in the last years, she has been working on several research topics on Population Health Management. In 2015, she started a PhD project on 'Prediction of outcomes in patients with heart failure', at Philips Research and Leiden University Medical Center, under the supervision of prof. dr. Ewout Steyerberg and prof. dr. Steffen Pauws, which resulted in this thesis.

List of publications

Journal publications

1. **I. Sokoreli**, J. J. G. de Vries, S. C. Pauws, and E. W. Steyerberg, "Depression and anxiety as predictors of mortality among heart failure patients: systematic review and meta-analysis", *Heart Failure Reviews*, vol.21, no.1, pp.49-63, 2016.

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