Prediction of outcomes in patients with heart failure

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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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		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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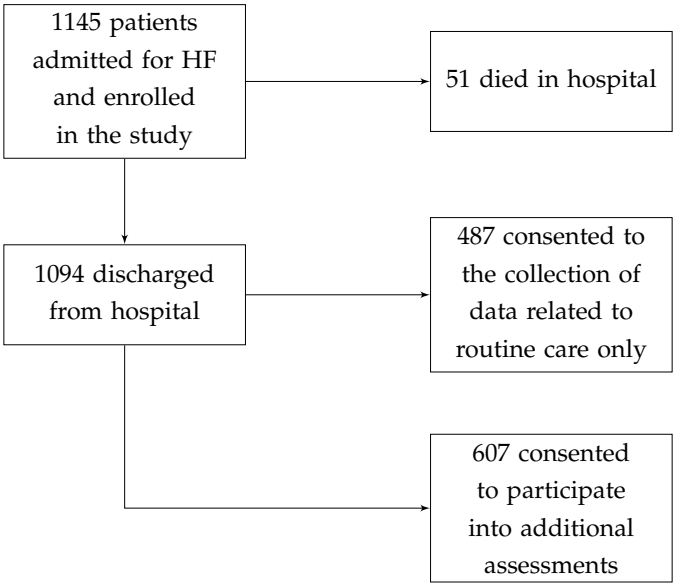
		All	Re-admitted or died in 30 days	No events within 30 days	Compare with and w/o events
-Mild, %		87 (23%)	13 (19%)	74 (24%)	
-Moderate-to-severe, %		65 (17%)	12 (17%)	53 (17%)	
GPCOG score ≤ 4	399	29 (7%)	8 (10%)	21 (7%)	0.44
Frailty and mobility					
Get up and go test: able or willing to participate, %	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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	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 ≥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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