Prediction of outcomes in patients with heart failure

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

This article has been submitted as "I. Sokoreli, A. Abdolahi, J. M. Riistama, S.C. Pauws, G. J. de Vries, P. J. Amelung, R. Nicholson, C. Veremakis, and E. W. Steyerberg, "Risk prediction of 30-day unplanned re-admission or mortality for HF patients: external validation of the OPERA model", 2019."

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

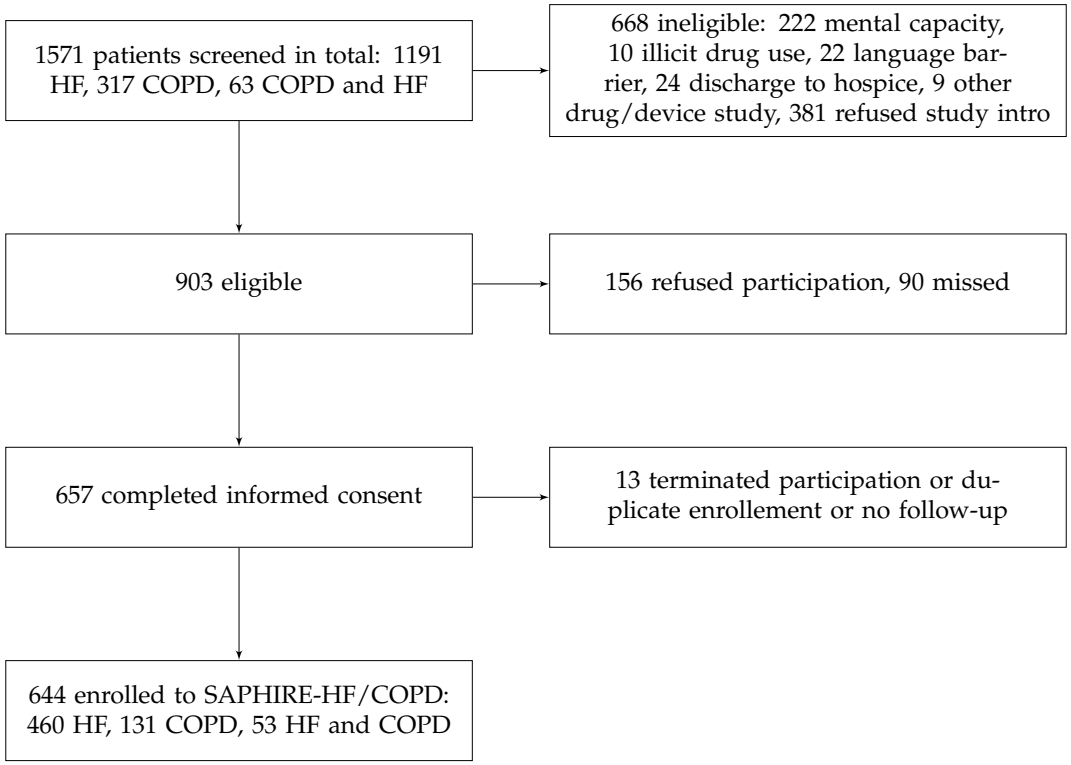

TABLE 6.1: Comparison of baseline patient characteristics and outcomes of SAPHIRE-HF with OPERA-HF.

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					

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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

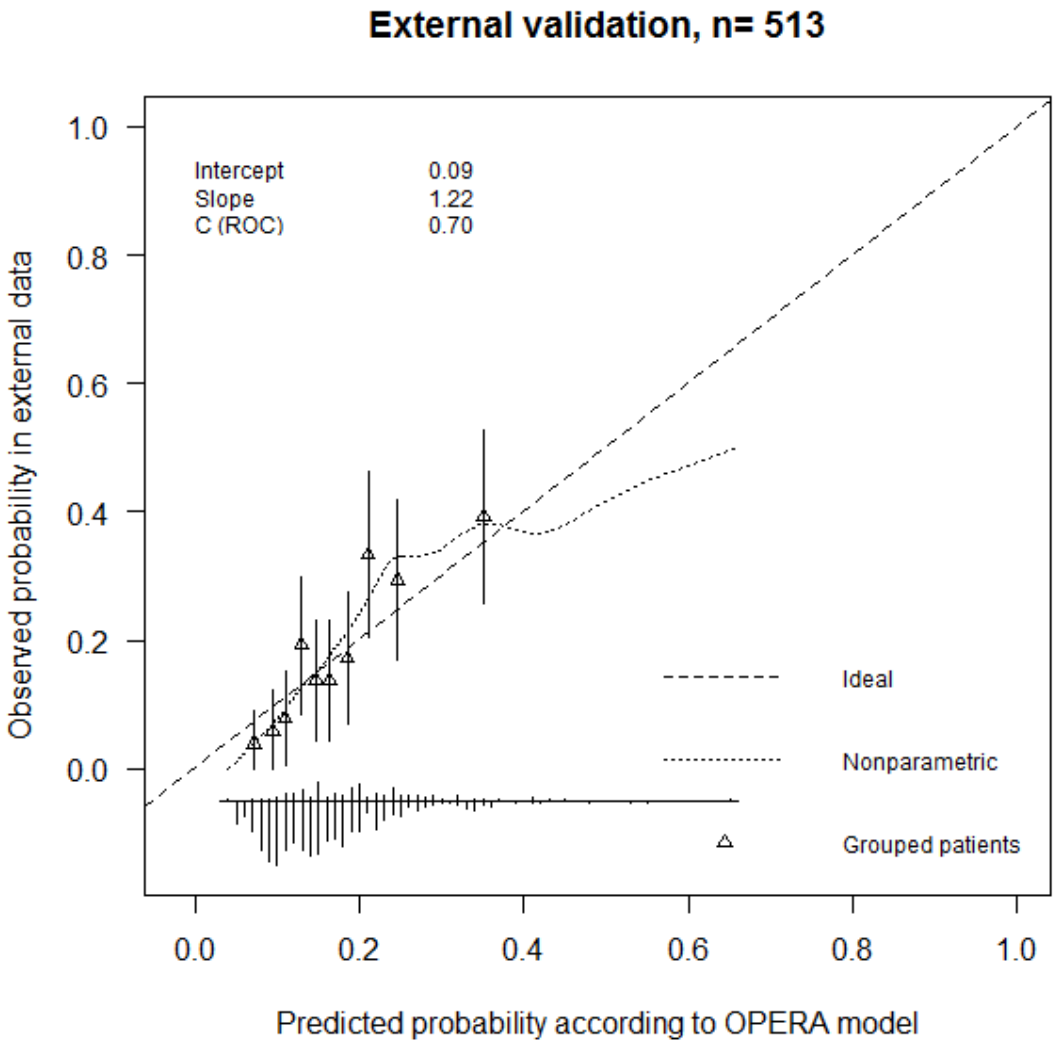

TABLE 6.3: Multivariate analysis and discrimination of 30-day unplanned readmission or mortality models.

	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