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Permalink

https://escholarship.org/uc/item/2fs7g6sq

Journal

ESC Heart Failure, 9(1)

ISSN

2055-5822

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Publication Date

2022-02-01

DOI

10.1002/ehf2.13709

Peer reviewed

Identifying patients at increased risk for poor outcomes from heart failure with reduced ejection fraction: the PROMPT-HF risk model

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Abstract

Aims   We aimed to develop a risk prediction tool that incorporated both clinical events and worsening health status for patients with heart failure (HF) with reduced ejection fraction (HFrEF). Identifying patients with HFrEF at increased risk of a poor outcome may enable proactive interventions that improve outcomes.

Methods and results   We used data from a longitudinal HF registry, CHAMP-HF, to develop a risk prediction tool for poor outcomes over the next 6 months. A poor outcome was defined as death, an HF hospitalization, or a $\geq$20-point decrease (or decrease below 25) in 12-item Kansas City Cardiomyopathy Questionnaire (KCCQ-12) overall summary score. Among 4546 patients in CHAMP-HF, 1066 (23%) experienced a poor outcome within 6 months (1.3% death, 11% HF hospitalization, and 11% change in KCCQ-12). The model demonstrated moderate discrimination (c-index = 0.65) and excellent calibration with observed data. The following variables were associated with a poor outcome: age, race, education, New York Heart Association class, baseline KCCQ-12, atrial fibrillation, coronary disease, diabetes, chronic kidney disease, smoking, prior HF hospitalization, and systolic blood pressure. We also created a simplified model with a 0–10 score using six variables (New York Heart Association class, KCCQ-12, coronary disease, chronic kidney disease, prior HF hospitalization, and systolic blood pressure) with similar discrimination (c-index = 0.63). Patients scoring 0–3 were considered low risk (event rate <20%), 4–6 were considered intermediate risk (event rate 20–40%), and 7–10 were considered high risk (event rate >40%).

Conclusions   The PROMPT-HF risk model can identify outpatients with HFrEF at increased risk of poor outcomes, including clinical events and health status deterioration. With further validation, this model may help inform therapeutic decision making.

Introduction

Heart failure (HF) with reduced ejection fraction (HFrEF) affects ~13 million people worldwide.[1,2] Despite recent advancements in medical therapy, many patients with HFrEF continue to have a high burden of symptoms and are at increased risk for poor outcomes including death.[3,4] Routine risk assessment is recommended as part of standard of care

in the current HF guidelines, and identifying high-risk patients for appropriate interventions is an important aspect of high-quality care.[5]

Prior HF risk models have focused on describing the risk of HF hospitalization and all-cause mortality.[6–12] While these outcomes are certainly important, these models do not incorporate optimization of health status, including symptoms, functional status, and quality of life. From patients' perspec-

tives, optimizing their health status can be even more important than death, as almost a quarter of patients would have traded half of their remaining life to be alleviated of the symptoms, burdens, and quality-of-life impact of their HF.[13] Thus, expanding the outcomes of outpatient risk models is not only sensitive to patients' goals, but optimizing health status is also an essential component of high-quality HF care, and when patients consider new HF therapies, they prioritize the potential impact of the therapies on HF-related symptoms.[14]

To potentially aid in clinical decision making, we aimed to develop a risk prediction tool for outpatients with HFrEF at increased risk of poor outcomes—death, HF hospitalization, or a significant deterioration in their health status—over the next 6 months. We utilized data from CHAnge the Management of Patients with Heart Failure (CHAMP-HF) to develop a risk model for poor outcomes over the next 6 months among patients with at least fair functional status that incorporates both clinical outcomes and changes in health status.

Methods

CHAMP-HF was a prospective registry of outpatients in the USA with chronic HFrEF.[15] Eligible patients had a left ventricular ejection fraction of ≤40% and were receiving treatment with at least one pharmacotherapy for HFrEF. Patients were recruited and followed as part of routine outpatient care from 152 sites. This prospective cohort study was observational without any intervention, and there was no attempt to influence clinical practice. Patients participating in CHAMP-HF serially described their disease-specific health status by completing the 12-item Kansas City Cardiomyopathy Questionnaire (KCCQ-12) Short Form. The KCCQ-12 is a validated, multidomain, HF-specific tool with scores ranging from 0 (worst) to 100 (best).[16] In CHAMP-HF, KCCQ-12 data were collected in person at the enrolment visit and by telephone interviews or online surveys at the following time points: 30 days and 3, 6, 12, 18, and 24 months after enrolment. Clinical outcomes were reported by sites at the same follow-up intervals.

For this analysis, we included all patients in the CHAMP-HF registry with complete demographic, baseline KCCQ-12 scores, and follow-up data. We excluded patients with a KCCQ-12 overall summary score of <25 at baseline, representing poor to very poor health status. Not only is it already established that these patients are at very high risk for clinical events and that they should be considered for escalation of therapy or referral to HF specialists, but it also avoids mis-specifying the model if such patients could not deteriorate by more than 20 points.[17,18] This definition of poor baseline functional status was similar to prior analyses.[18–20]

The outcome of interest was a composite of all-cause mortality, HF hospitalization, a ≥20-point decrease in KCCQ-12 overall summary score, or any decrease in KCCQ-12 overall summary score below 25 from any starting value within 6 months of enrolling in the registry. A change in KCCQ-12 overall summary score of ~5 is considered clinically significant, and a change of 20 is considered a very large change.[21–24]

Study organization

Patients enrolled in the CHAMP-HF registry signed written informed consent prior to collection of study data, and institutional review board approval was obtained. The CHAMP-HF registry was sponsored by the Novartis Pharmaceuticals Corporation (East Hanover, NJ). Data were managed by the United BioSource Corporation (Blue Bell, PA), and the Duke Clinical Research Institute (Durham, NC) was the data analytic centre.

Statistical analyses

We first stratified patients by the composite poor outcome and described and compared baseline demographics, symptom burden, health status, medical history, medication use, and laboratory studies by study group using frequencies with percentages for categorical variables and means (standard deviations) or medians (inter-quartile range) for continuous variables. Tests for linearity of continuous variables were performed, and splines were used to handle non-linear relationships. To understand baseline characteristics associated with a poor outcome, we developed univariable Cox proportional hazard models to estimate the association between potential predictor variables and time to the composite outcome. All possible baseline characteristics were considered in the model including demographics, medical history, and laboratory values. Some variables had high rates of missing, including laboratory values such as amino-terminal pro-B-type natriuretic peptide, and were not included. Multilevel variables (e.g. race and household income) were examined to determine whether like categories could be grouped into binary variables. We then created a multivariable Cox proportional hazard model using backward selection with a statistical significance of $P < 0.05$ required to remain in the model. We then assessed the internal validity with a bootstrapping procedure for estimating the performance of the predictive model. We calculated the c-index and utilized bootstrapping to correct for optimism as well as calculated a decile plot of observed vs. expected probabilities of events by 6 months of follow-up. To create the simplified model, we included six of the variables with the strongest association with the composite outcome. We assigned point values to each variable and created a 0–10

score. All analyses were performed using SAS software (Version 9.4 SAS Institute, Cary, NC).

Results

Among 5040 patients in the registry, 4546 (90%) met the study eligibility criteria. The main reason that patients were excluded was a KCCQ-12 overall summary score of <25 at baseline (299 patients, 5.9% of the total cohort). Baseline patient characteristics are shown in *Table 1*. The average age of the cohort was 66 years. The majority of the patients were of White race and 18% were of Hispanic ethnicity. Patients with less education were more likely to have a poor outcome compared with patients with some college. Most of the patients (98%) had medical insurance, although there were notable differences in employment status. Patients that were unemployed because of a medical disability were more likely to have a poor outcome compared with those employed. In terms of medical history and baseline assessments, patients with a prior HF hospitalization within the last 12 months, a lower systolic blood pressure, and higher amino-terminal pro-B-type natriuretic peptide value were more likely to have a poor outcome compared with other groups.

Over 6 months of follow-up, poor outcomes were common. The frequency of the first event that occurred during follow-up is listed in *Table 2*. Among 4546 patients in the study, 11% had an HF hospitalization as a first event, 8.3% had a ≥20-point KCCQ-12 decrease in overall summary score, and 1.3% died.

Factors associated with a poor outcome are displayed in Supporting Information, *Table S1*, results of a multivariable Cox proportional hazard model are displayed in *Table 3*, and a model calibration plot is displayed in *Figure 1*. Categorical variables associated with a poor outcome included Black race, lower than a high school education, baseline New York Heart Association class, and the presence of co-morbid medical conditions including coronary disease, diabetes mellitus, and chronic kidney disease. History of an HF hospitalization in the prior 12 months was also associated with a poor outcome [1 hospitalization vs. 0, hazard ratio (HR) 1.36, 95% confidence interval (CI) 1.18–1.57; ≥2 hospitalizations vs. 0, HR 1.77, 95% CI 1.50–2.10]. Continuous variables associated with a poor outcome included baseline KCCQ score, systolic blood pressure, and age. Baseline KCCQ-12 overall summary score was separated into three categories. Patients with lower baseline scores (25–60) had a decreasing hazard for a poor outcome as the score increased (HR 0.80, 95% CI 0.74–0.87). Patients with the middle category of scores (60–80) were associated with an increased hazard for poor outcome as the score increased (HR 1.23, 95% CI 1.09–1.38). Higher baseline systolic blood pressure was associated with a reduced hazard for a poor outcome. Age <70 years was asso-

ciated with a reduced hazard for a poor outcome, although age ≥70 years was associated with an increased hazard for poor outcome. The model's goodness of fit indicated an unadjusted c-statistic of 0.65 (95% CI 0.63–0.66). The model was then validated using bootstrapping methods, and the estimate of the bootstrapped optimism-adjusted c-index was calculated. The bootstrapped optimism-adjusted c-statistic was modest with an estimate of 0.64 (95% CI 0.62–0.65). For the simplified model, six of the original variables (New York Heart Association symptoms class, KCCQ-12 overall summary score, coronary disease, chronic kidney disease, prior HF hospitalization, and systolic blood pressure) provided the strongest association with the composite outcome (*Table 4*, *Figure 2*, and Supporting Information, *Figure S1*), uncorrected c-index = 0.63, R = 0.66. The bootstrapped optimism-adjusted c-statistic was also modest with an estimate of 0.62 (95% CI 0.61–0.64). Patients with a score 0–3 had an event rate <20% (low risk), 4–6 had a 20–40% event rate (intermediate risk), and 7–10 had an event rate >40% (high risk) (Supporting Information, *Table S2*).

Discussion

Supporting proactive, patient-centred care requires new approaches to identify those patients most at risk for adverse events so that timely interventions can be offered to potentially prevent these adverse events. This study used data from a large, prospective, multicentre registry, CHAMP-HF, to identify factors associated with a poor outcome in patients with HFrEF. In this contemporary ambulatory population of >4500 patients with HFrEF, we observed almost one in four patients experienced an adverse event within 6 months of follow-up. Importantly, the model was able to stratify risk such that the highest risk decile, with an estimated event rate of 45%, was almost five-fold greater than the lowest risk decile of 11%. Moreover, this short-term follow-up is a time interval that may be considered for a next routine follow-up visit for patients with HFrEF. We also identified a set of variables associated with poor outcomes and created the PROMPT-HF (identifying Patients at increased Risk for Poor OuTcoMes from HFrEF), a multivariable model that may be utilized to identify patients at high risk for poor outcomes. Many of the variables in our simplified model can be available as part of routine care: New York Heart Association symptom class, baseline KCCQ-12 overall summary score, history of coronary disease, history of chronic kidney disease, prior HF hospitalizations, and systolic blood pressure.

Prior HF risk models have focused on the important outcomes of HF hospitalization and all-cause mortality and identified similar variables associated with a poor outcome.[6–12] For example, the Meta-analysis Global Group in Chronic HF (MAGGIC) risk model identified 13 variables associated with

Table 1 Baseline patient characteristics stratified by outcome

	Overall N = 4546	Health status preserved and event-free N = 3480	Poor outcome N = 1066	P-value
Age (years), mean (SD)	66 (12.4)	66 (12.3)	66 (12.8)	0.81
Female sex (%)	1304 (29%)	9873 (28%)	317 (30%)	0.39
Race (%)				0.005
White	3365 (74%)	2617 (75%)	748 (70%)	
Black	781 (17%)	559 (16%)	222 (21%)	
Asian	76 (1.7%)	59 (1.7%)	17 (1.6%)	
Other	228 (5.0%)	171 (4.9%)	57 (5.3%)	
Hispanic ethnicity (%)	814 (18%)	641 (18%)	173 (16%)	0.10
Insurance status (%)				0.15
Private insurance	1203 (27%)	951 (27%)	252 (24%)	
Medicare	2576 (57%)	1951 (56%)	625 (59%)	
Medicaid	395 (8.7%)	299 (8.6%)	96 (9.0%)	
Other	270 (5.9%)	199 (5.7%)	71 (6.7%)	
Uninsured	102 (2.2%)	80 (2.3%)	22 (2.1%)	
Level of education (%)				<0.001
<High school	502 (11%)	357 (10%)	145 (14%)	
High school/GED	1548 (34%)	1164 (33%)	384 (36%)	
Some college	1439 (32%)	1125 (32%)	314 (30%)	
4 year college	622 (14%)	507 (15%)	115 (11%)	
Graduate/professional degree	435 (9.6%)	327 (9.4%)	108 (10%)	
Employment status (%)				<0.001
Full-time, ≥35 h/week	685 (15%)	552 (16%)	133 (13%)	
Part-time, <35 h/week	341 (7.5%)	277 (8.0%)	64 (6.0%)	
Medical disability	1103 (24%)	789 (23%)	314 (30%)	
Unemployed	2417 (53%)	1862 (54%)	555 (52%)	
NYHA class (%)				<0.001
I	501 (11%)	423 (12%)	78 (7.5%)	
II	2662 (60%)	2124 (62%)	538 (52%)	
III	1221 (28%)	822 (24%)	399 (39%)	
IV	64 (1.4%)	43 (1.3%)	21 (2.0%)	
KCCQ-OS, mean (SD)	68 (20.8)	69 (20.3)	64 (21.8)	<0.001
Medical history (%)				
HF hospitalization within 12 months	1690 (37%)	1169 (34%)	521 (49%)	<0.001
Ventricular arrhythmias	937 (21%)	701 (20%)	236 (22%)	0.16
Atrial fibrillation	1674 (37%)	1241 (36%)	433 (41%)	0.003
Coronary disease	2944 (65%)	2210 (64%)	734 (69%)	0.001
Hypertension	3813 (84%)	2892 (83%)	921 (86%)	0.012
Diabetes mellitus	1897 (42%)	1396 (40%)	501 (47%)	<0.001
CKD	947 (21%)	633 (18%)	314 (30%)	<0.001
Current smoking	906 (20%)	664 (19%)	242 (23%)	0.010
LVEF (%), mean (SD)	29 (7.9)	29 (7.7)	28 (8.2)	<0.001
Medical therapy				
Beta-blockers	4067 (92%)	3114 (92%)	953 (92%)	0.95
ACEI/ARB	2980 (67%)	2332 (69%)	648 (62%)	<0.001
ARNI	710 (16%)	536 (16%)	174 (16%)	0.46
Aldosterone antagonist	1617 (36%)	1225 (36%)	392 (37%)	0.33
Hydral-ISDN	511 (11%)	359 (10%)	152 (14.3%)	<0.001
CRT	350 (7.7%)	268 (7.7%)	82 (7.7%)	0.99
ICD	1876 (41%)	1419 (41%)	457 (43%)	0.23
Vital signs, mean (SD)				
Heart rate (b.p.m.)	74 (12.3)	73 (12.2)	75 (12.5)	0.005
Systolic BP (mmHg)	121 (17.9)	121 (17.7)	119 (18.3)	<0.001
Laboratory data, median (Q1, Q3)				
NT-proBNP (pg/mL)	1819 (718, 4318)	1646 (634, 4072)	2607 (1042, 5259)	<0.001
BUN (mg/dL)	20 (15, 28)	20 (15, 26)	22 (16, 32)	<0.001
Serum Cr (mg/dL)	1.1 (0.9, 1.4)	1.1 (0.9, 1.4)	1.2 (1.0, 1.5)	<0.001

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BP, blood pressure; BUN, blood urea nitrogen; CKD, chronic kidney disease; Cr, creatinine; CRT, cardiac resynchronization therapy; GED, General Educational Diploma; HF, heart failure; Hydral-ISDN, hydralazine and isosorbide dinitrate; ICD, implantable cardioverter defibrillator; KCCQ-OS, 12-item Kansas City Cardiomyopathy Questionnaire overall summary score; LVEF, left ventricular ejection fraction; NT-proBNP, amino-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SD, standard deviation.
A poor outcome was defined as a composite of all-cause mortality, HF hospitalization, a ≥20-point decrease in KCCQ-OS, or any decrease in KCCQ-OS below 25 from any starting value within 6 months of enrolling in the CHAMP-HF registry.

Table 2 Individual components of the composite outcome

	Frequency	Days to event, median (Q1, Q3)
Death	61	94 (49, 139)
Heart failure hospitalization	509	63 (28, 112)
≥20-point decrease in KCCQ-OS + KCCQ-OS < 25	47	45 (32, 100)
≥20-point decrease in KCCQ-OS	376	81 (32, 99)
KCCQ-OS < 25	73	34 (30, 92)

KCCQ-OS, 12-item Kansas City Cardiomyopathy Questionnaire overall summary score.

Table 3 Patient characteristics associated with poor outcome

	Hazard ratio (95% CI)	*P*-value
Age		
<70 years per 10 year increase	0.92 (0.85–0.99)	0.029
≥70 years per 10 year increase	1.17 (1.03–1.33)	0.020
Race		
Black vs. White	1.34 (1.14–1.57)	<0.001
Other vs. White	1.07 (0.86–1.32)	0.55
Education (<high school vs. ≥some college)	1.28 (1.07–1.53)	0.006
NYHA class		
II vs. I	1.22 (0.96–1.55)	0.11
III vs. I	1.75 (1.35–2.26)	<0.001
IV vs. I	1.68 (1.04–2.70)	0.032
KCCQ-OS		
25–60 per 10 unit increase	0.80 (0.74–0.87)	<0.001
60–80 per 10 unit increase	1.23 (1.09–1.38)	<0.001
>80 per 10 unit increase	0.89 (0.77–1.03)	0.11
Atrial fibrillation	1.15 (1.02–1.31)	0.034
Coronary disease	1.23 (1.07–1.42)	0.004
Diabetes mellitus	1.15 (1.02–1.31)	0.027
Chronic kidney disease	1.46 (1.27–1.67)	<0.001
Current smoking	1.20 (1.04–1.40)	0.015
HF hospitalization within 12 months		
1 vs. 0	1.36 (1.18–1.57)	<0.001
≥2 vs. 0	1.77 (1.50–2.10)	<0.001
SBP per 10 mmHg increase	0.93 (0.90–0.97)	<0.001

CI, confidence interval; HF, heart failure; KCCQ-OS, 12-item Kansas City Cardiomyopathy Questionnaire overall summary score; NYHA, New York Heart Association; SBP, systolic blood pressure.
A poor outcome was defined as a composite of all-cause mortality, HF hospitalization, a ≥20-point decrease in KCCQ-OS, or any decrease in KCCQ-OS below 25 from any starting value within 6 months of enrolling in the CHAMP-HF registry.

Figure 1 Model calibration plot. Calibration plot for prediction of poor outcome at 6 months of follow-up.
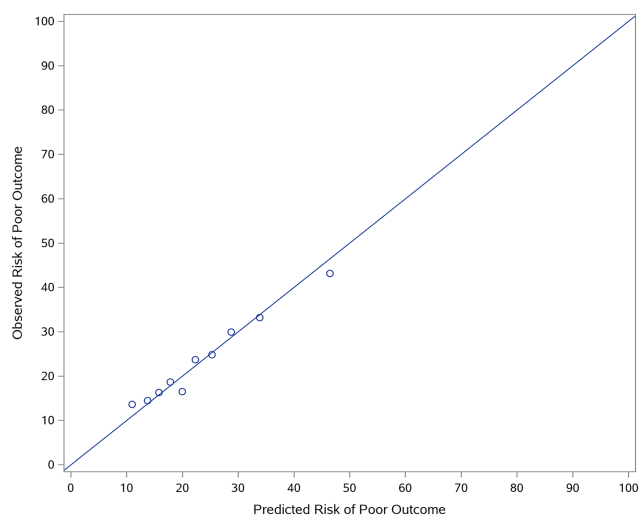
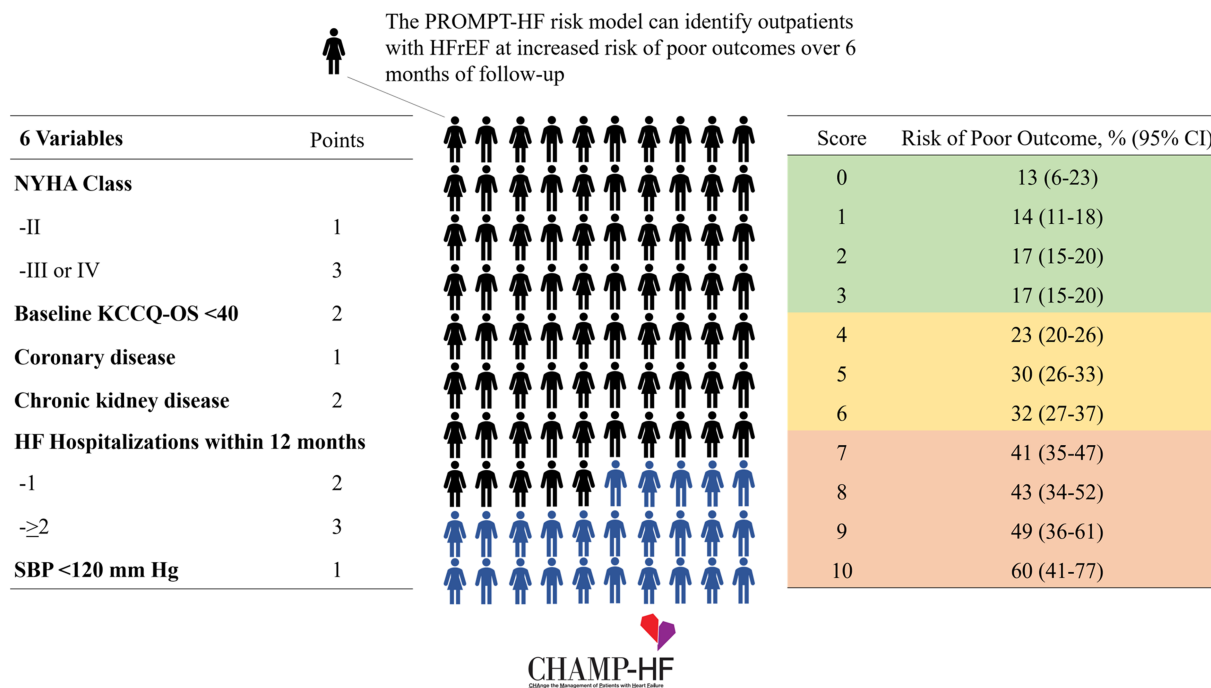**Table 4** Simplified model of patient characteristics associated with poor outcome

	Beta-coefficient (95% CI)	Score
NYHA class		
II vs. I	0.20 (−0.03 to 0.44)	1
III or IV vs. I	0.56 (0.32–0.81)	3
KCCQ-OS < 40	0.42 (0.26–0.58)	2
Coronary disease	0.16 (0.03–0.29)	1
Chronic kidney disease	0.40 (0.26–0.53)	2
HF hospitalization within 12 months		
1 vs. 0	0.33 (0.19–0.47)	2
≥ 2 vs. 0	0.63 (0.46–0.79)	3
SBP < 120 mmHg	0.16 (0.04–0.28)	1

CI, confidence interval; HF, heart failure; KCCQ-OS, 12-item Kansas City Cardiomyopathy Questionnaire overall summary score; NYHA, New York Heart Association; SBP, systolic blood pressure.
A poor outcome was defined as a composite of all-cause mortality, HF hospitalization, a ≥20-point decrease in KCCQ-OS, or any decrease in KCCQ-OS below 25 from any starting value within 6 months of enrolling in the CHAMP-HF registry.

all-cause mortality in chronic HF.[12] In our full model, we identified many overlapping risk factors for poor outcome including age, New York Heart Association symptom class, renal function, history of diabetes, smoking history, and systolic blood pressure. While many of the variables in our study have been previously identified to be associated with increased risk, to our knowledge, our study is the first in HF to specifically exclude those with poor baseline health status (i.e. KCCQ-12 overall summary score of <25) and include changes in KCCQ-12 overall summary score over time as part of a composite outcome.

We believe that incorporation of health status as an outcome for a risk model is essential as optimization of health status, including symptoms, functional status, and quality of life are primary goals in HF care. In prior research, there was an important gap between guideline recommendations and actual care provided for patients with HFrEF.[25–27] As new therapies for HFrEF become available,[28,29] identifying appropriate candidates for escalation of therapy and referral to advanced HF clinicians will be an increasingly important part of high-quality HF care. The results of the PROMPT-HF risk model may be a useful tool for clinicians, including non-HF specialists, and patients and families to determine timing of initiation of new HF medications, interventions, or referral to a specialist. Incorporating baseline health status into patient decision making seems especially important

Figure 2 The PROMPT-HF risk model. A poor outcome was defined as a composite of all-cause mortality, heart failure (HF) hospitalization, a ≥20-point decrease in 12-item Kansas City Cardiomyopathy Questionnaire overall summary score (KCCQ-OS), or any decrease in KCCQ-OS below 25 from any starting value within 6 months of enrolling in the CHAMP-HF registry. Patients with a score 0–3 are considered low risk (green), a score of 4–6 are considered intermediate risk (yellow), and a score of 7–10 are considered high risk (orange). In CHAMP-HF, nearly one in four patients (blue) experienced an adverse event within 6 months of follow-up. CI, confidence interval; HFrEF, heart failure with reduced ejection fraction; NYHA, New York Heart Association; SBP, systolic blood pressure.

The PROMPT-HF risk model can identify outpatients with HFrEF at increased risk of poor outcomes over 6 months of follow-up

6 Variables	Points
NYHA Class	
-II	1
-III or IV	3
Baseline KCCQ-OS <40	2
Coronary disease	1
Chronic kidney disease	2
HF Hospitalizations within 12 months	
-1	2
-≥2	3
SBP <120 mm Hg	1

Score	Risk of Poor Outcome, % (95% CI)
0	13 (6-23)
1	14 (11-18)
2	17 (15-20)
3	17 (15-20)
4	23 (20-26)
5	30 (26-33)
6	32 (27-37)
7	41 (35-47)
8	43 (34-52)
9	49 (36-61)
10	60 (41-77)

CHAMP-HF

given that prior research has identified that there is marked variability in the control of patients' symptoms and health status across practices in the USA.[20]

Our study should be considered in the context of the following potential limitations. For one, participation in CHAMP-HF was voluntary and may not be representative of patients with HFrEF in other settings. In addition, associations between baseline variables and outcomes may be confounded by other measured variables or unmeasured variables. While the calibration of the model was good, its discrimination was only modest. The applicability of the risk model is limited by the low use of patient-reported outcomes in routine practice, although this may improve over time.[30,31] Finally, future work should evaluate the PROMPT-HF risk model using patients outside of the CHAMP-HF registry to provide external validation.

Conclusions

The PROMPT-HF risk model is a clinical tool with moderate discrimination and excellent calibration that may be useful for clinicians to identify patients with HFrEF at increased risk for adverse outcomes including deterioration in health status

over the subsequent 6 months. This clinical tool uses 12 clinical variables that can be routinely assessed during an HF outpatient clinical visit. This tool requires additional evaluation but may be useful to inform therapeutic decision making including referral to advanced HF clinicians.

Conflict of interest

Funding

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Patient Characteristics Associated with Poor Outcome.
Table S2. Risk of Poor Outcome by Simplified PROMPT-HF Risk Score.
Figure S1. Simple Model Calibration Plot.

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