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The COACH risk engine: a multi-state model for predicting survival and hospitalization in patients with heart failure

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Abstract

Aims: Several models for predicting the prognosis of heart failure (HF) patients have been developed, but all of them focus on a single outcome variable, such as all-cause mortality. The purpose of this study was to develop a multi-state model for simultaneously predicting survival and HF-related hospitalization in patients discharged alive from hospital after recovery from acute HF.

Methods and results: The model was derived in the COACH cohort, a multi-center, randomized controlled trial in which 1023 patients were enrolled after hospitalization because of HF. External validation was attained with the FINN-AKVA cohort, a prospective, multi-center study with 620 patients hospitalized due to acute HF. The observed versus predicted 18-month survival was 72.1% versus 72.3% in the derivation cohort and 71.4% versus 71.2% in the validation cohort. The corresponding values of the *c* statistic were 0.733 (95% CI: 0.705-0.761) and 0.702 (95% CI: 0.663-0.744), respectively. The model's accuracy in predicting HF hospitalization was excellent, with predicted values that closely resembled the values as observed in the derivation cohort.

Conclusion: The COACH risk engine accurately predicted survival and various measures of recurrent hospitalization in (acute) HF patients. It may therefore become a valuable tool in improving and personalizing patient care and optimizing the use of scarce health-care resources.

Keywords: epidemiology; heart failure; prediction; prognosis; multi-state modeling

Introduction

Heart failure (HF), one of the major causes of death in Western nations, is characterized by a poor prognosis: up to 70% of all HF patients die within 5 years after their first hospital admission (1). Furthermore, HF is associated with high direct costs, accounting for 1 to 2% of total health-care expenditures (2). Classification of HF patients into different risk groups based on their expected prognosis is therefore of utmost importance to improve and personalize patient care and to optimize the use of scarce health-care resources.

To assist health-care providers in identifying those patients who are at risk for a poor prognosis, various clinical prediction models have been developed (3-11). Although these models generally differ on the selected endpoints and/or the included risk factors, they have much in common when looking at them from a more methodological perspective. First, as far as the clinical context is concerned, the existing models focus either on predicting medium- to long-term prognosis (≥ 1 year) in chronic HF patients or on predicting in-hospital or short-term, post-discharge prognosis in acute HF patients. Models for predicting longer-term, post-discharge prognosis in acute HF patients, in contrast, have so far not been developed. Second, as far as the selection of endpoints is concerned, existing models focus on a single outcome variable, such as all-cause mortality or HF hospitalization. Although the outcome variable is frequently defined as a combined endpoint, the predictions remain aggregated at the level of a single composite measure, i.e., predictions at the level of the composite measure are not broken down into marginal predictions at the level of the measure's individual components.

In response to the methodological considerations given above, the purpose of this paper was to develop a multi-state model for predicting 18-month survival and three different measures of recurrent HF hospitalization (i.e., cumulative incidence function of HF hospitalization, number of recurrent HF hospitalizations, and days lost due to HF hospitalization) in patients discharged alive from the hospital after recovery from acute HF.

Methods

Study cohorts

We used data previously collected in two cohorts of HF patients. One of these cohorts, the Coordinating Study Evaluating Outcomes of Advising and Counseling in Heart Failure (COACH), was used to develop the model, whereas the other cohort, the Finish Acute Heart Failure Study (FINN-AKVA), was used to externally validate the model.

COACH was a multi-center, randomized controlled trial in which patients hospitalized with HF as the primary diagnosis were randomly assigned to either the control group (follow-up by a cardiologist) or to one of the two intervention groups with basic or intensive additional support by a nurse specialized in the management of HF patients (12,13). All patients were 18 years or older and had evidence of structural cardiac dysfunction as shown at cardiovascular imaging. The major reasons for exclusion were concomitant enrollment in another trial, ongoing assessment for heart transplantation, recent history of an invasive procedure or cardiac surgery within the last 6 months, or plan of undergoing such a procedure within the next 3 months. Out of the 1049 patients that were randomized, 1023 were discharged alive and were followed up for a maximum of 18 months after hospital discharge. This latter group forms the COACH study population.

FINN-AKVA was a multi-center, prospective study in which 620 hospitalized HF patients participated (14). Both patients with new-onset acute HF and patients with exacerbation of chronic HF were included. Patients with high-output HF were not included. For the purpose of the present study, we used the data collected on all 576 patients who were discharged alive from the hospital.

Covariate measurement

In both cohorts, NT-proBNP measurements were performed at a core laboratory using a commercially available electrochemiluminescent sandwich immunoassay (Elecsys proBNP, Roche Diagnostics, Mannheim, Germany), with an analytical range of 5.0-35,000 pg/ml. Estimated glomerular filtration rate (eGFR) values were calculated using the Modification of Diet in Renal Disease formula based on the creatinine measurements taken at hospital discharge. Left ventricular ejection fraction (LVEF) was determined based on echocardiography data collected during the index admission.

Model structure

COACH risk engine is a multi-state model for predicting survival and various measures of recurrent HF hospitalization in patients discharged alive from the hospital after recovery from acute HF. The model consists of three discrete health states, *discharged alive from hospital*, *hospitalization because of HF* (defined as an unplanned overnight stay in a hospital because of progression of HF or as a direct result of HF), and *dead*, and a transition probability matrix P , whose elements p_{ij} represent the probability that when leaving health state i , the next health state will be j (see Figure 1 for a schematic representation). The distribution of the amount of time that a patient spends in the *discharged alive from hospital* state before making a transition into a different health state (i.e., *hospitalization because of HF* or *dead*) was estimated by fitting a Weibull model to the composite endpoint of HF hospitalization or death (the primary endpoint of the COACH study). Similarly, to estimate the distribution of the amount of time that a patient spends in the *hospitalization because of HF* state, a log-logistic model was fitted to the observed length of stay in patients that were hospitalized because of HF. The specific likelihoods of transiting from one health state to the next, i.e. the elements of the transition matrix P , were determined using logistic regression. For a more detailed

description of the model's regression equations, the reader is referred to online data supplement I.

Parameter estimation

The procedures used to fit the four regression equations to the observed outcomes in the COACH study population were as follows. First, a set of candidate predictor variables (online data supplement II) to consider during model building was obtained by selecting from the COACH study those variables that according to previous studies could be potential predictors for survival and hospital readmission. As missing values were present in several of the selected candidate predictors, multiple imputation was used to obtain ten imputed data sets. Model building was subsequently performed by applying the backward stepwise selection procedure recommended by Wood et al (15). The nominal significance levels for variable exclusion in the backward steps and variable inclusion in the forward steps were set equal to 10% and 9.9%, respectively. Once a final model had been selected, Rubin's rules were used to obtain pooled estimates of the regression coefficients and their standard errors (16).

Simulation algorithm

For a description of the applied simulation algorithm, the reader is referred to online data supplement III.

Model validation

Survival

Model performance on survival was internally and externally validated by considering calibration and discrimination after 18 months of follow-up in the COACH study and 18 months of follow-up in the FINN-AKVA study, respectively. Calibration was determined by comparing the mean predicted survival to the mean observed survival (Kaplan-Meier

estimate) by deciles of predicted survival (mean across all simulation runs). Discrimination was determined by calculating the value of the c statistic (17), using non-parametric bootstrapping to obtain a corresponding 95% confidence interval.

HF hospitalization

Model performance on hospitalization could not be assessed externally as data on this endpoint was not collected during the FINN-AKVA study. Internal validation was established by considering three different measures of HF hospitalization: the cumulative incidence function of HF hospitalization, the number of HF hospitalizations, and the number of days lost due to HF hospitalization. The model's accuracy in predicting the cumulative incidence function of HF hospitalization was assessed by considering calibration and discrimination. Calibration was determined by comparing the mean predicted 18-month risk of HF hospitalization to the mean observed 18-month risk of HF hospitalization (non-parametric cause-specific hazards estimate (18)) by deciles of predicted 18-month risk of HF hospitalization. Discrimination was determined by using a time-dependent variant of the c statistic (19), applying Wolbers et al.'s (20) adapted definition of the risk set to account for the occurrence of death as a competing risk for the event of interest. Model performance on the other two measures of HF hospitalization was assessed by comparing the observed frequencies of HF hospitalization (days lost due to HF hospitalization) to the predicted frequencies of HF hospitalization (days lost due to HF hospitalization) after 18 months of follow-up. To account for lost-to-follow-up censoring, the observed frequencies (days lost due to HF hospitalization) were estimated by using the partitioned estimator proposed by Bang and Tsiatis (21). The predicted values for each of the three measures of HF hospitalization were obtained by taking the mean across all simulation runs.

Handling of missing values

Similar as during model derivation, missing values on the predictor variables during model validation were dealt with by using multiple imputation. In FINN-AKVA, systolic blood pressure (SBP), diastolic blood pressure (DBP), and serum sodium were only available at hospital admission. For serum sodium, the admission values were carried forward to hospital discharge. For SBP and DBP, the missing discharge values were imputed from the other predictor variables based on two linear regression equations derived from the COACH study.

Results

Patient characteristics

An overview of the patient characteristics in COACH (derivation cohort) and FINN-AKVA (validation cohort) is provided in Table 1. Compared to the COACH study, the FINN-AKVA study had a larger fraction of patients with preserved LVEF as is evident by a larger fraction of female patients, higher age, and higher LVEF. However, the ranges of the variables under consideration were still comparable.

Model derivation

During the 18 months of follow-up in the COACH study, 411 patients (40%) reached the combined endpoint of HF hospitalization or death. Out of these patients, 38% had died and 62% had been hospitalized for HF. In total, 356 HF hospitalizations were recorded. The median duration of these hospital admissions was 9 days (interquartile range: 5-17 days), and the incidence of in-hospital mortality was 16%.

The beta coefficients and corresponding hazard and odds ratios for the final models of the time-to-event distributions and transition probabilities underlying the COACH risk engine are listed in Table 2 and Table 3, respectively. All variables entered the models as linear

terms, except for NT-proBNP for which a log transformation was applied to increase the predictability of this covariate.

Model validation

The observed versus predicted 18-month survival was 72.1% versus 72.3% in the derivation cohort and 71.4% versus 71.2% in the validation cohort; the observed versus predicted 18-month risk of HF hospitalization was 26.0% versus 26.7% (derivation cohort only). The calibration plots (Figure 2 and Figure 3) indicate a good calibration, with most of the predicted survival and HF hospitalization estimates well within the 95% confidence intervals of the corresponding observed survival and HF hospitalization estimates. For the survival outcome, the discriminative ability of the model was moderate with values of the *c* statistic of 0.733 (95% CI: 0.705-0.761) and 0.702 (95% CI: 0.663-0.744) for the derivation and validation cohort, respectively. The model's discriminative ability for the HF hospitalization outcome was slightly poorer with a value of the *c* statistic of 0.664 (95% CI: 0.631-0.695). The model's accuracy in predicting the other two measures of HF hospitalization was excellent (Figure 4), with predicted values that closely resembled the values as observed in the COACH study cohort.

Discussion

This paper presented a multi-state model for predicting 18-month survival and three different measures of HF hospitalization in a broad spectrum of patients discharged alive from the hospital after recovery from acute HF. Underlying the COACH risk engine are four parametric equations, for which a total of 14 demographical, clinical, and biological risk factors were identified. Given a patient's values for these risk factors, Monte Carlo simulation could successfully be applied to predict the occurrence of the selected outcome variables.

Although we identified several variables that were independently associated with a

patient's length of stay (LOS) in the hospital, none of these associations were highly significant. Out of all considered variables, eGFR and LVEF had the lowest and second lowest p-values, respectively. That eGFR was found to be an independent predictor of LOS is not surprising as previous studies already showed that HF patients with impaired renal function had a significantly increased LOS (22,23). The negative association between LVEF and LOS seems more controversial, however. Although this finding is consistent with Harjaj et al (24), there are also studies in which LVEF was not independently associated with LOS (25,26). Data from two large American registries do suggest that there are statistically significant differences in LOS between patients with preserved and reduced LVEF, but that the magnitude of these differences are so small that they may not be clinically relevant (27,28). This also seems to hold for the results presented in this paper: although the association between LVEF and the time to hospital discharge was statistically significant, a relative odds of 1.15 for every 10% increase in LVEF does not directly indicate a clinically relevant effect size. Renal function was also highly predictive of the combined endpoint of HF hospitalization or death. Other strong predictors for this endpoint were sex, myocardial infarction, serum sodium, and previous HF hospitalization. LVEF was not found to be independently associated with the occurrence of these two adverse events in the COACH study population. Similar as for the prediction of LOS, this finding is concordant with some of the previously published risk models (8,9) but discordant with others (7,10). The added value of including LVEF as one of the predictors in a prognostic model therefore remains uncertain.

As female sex was found to be protective for both the combined endpoint of HF hospitalization or death (Equation 1) and the conditional probability of death given HF hospitalization or death (Equation 3), the average predicted survival in female patients will be longer than the average predicted survival in male patients. Likewise, it follows that our

multi-state model will show a negative association between NT-proBNP and survival and a positive association between pulse pressure and survival. This latter finding may be somewhat surprising as the association between pulse pressure and survival was previously found to be negative in patients with chronic HF (29). It is however consistent with Aronson and Burger (30), who showed that in the presence of decompensated HF, reduced pulse pressure is an independent predictor of poor outcome.

Existing risk functions for predicting survival or recurrent hospitalization in HF patients have been derived by fitting a single regression equation to the data at hand. From a multi-state modeling perspective, such risk functions can be seen as two-state models with one starting state (i.e., being alive at time 0) and one absorbing state reflecting the occurrence of the event of interest (e.g., death or recurrent hospitalization) (31). The multi-state model presented in this paper takes the modeling of a patient's disease progression one step further by introducing HF hospitalization as an intermediate state through which a patient's progression towards death can occur. Compared to the two-state models underlying most of the existing risk functions, our multi-state model has two major advantages. First, previous research has shown that a patient's risk of death is greatest in the early post-discharge period and then declines progressively over time until the next HF hospitalization occurs (32). In our multi-state model, this dependency between the probability of dying in a certain time period and the time since the last HF hospitalization is explicitly accounted for when estimating a patient's survival function. This is achieved by considering all possible pathways through which a transition towards the *dead* state can occur (i.e., directly moving from *discharged alive from the hospital* to *dead* or moving to *dead* through one or more visits of the *hospitalization because of HF* state). The second advantage of our multi-state modeling approach over the traditional approach of fitting a single regression equation to the data at hand concerns the prediction of the intermediate event (i.e., HF hospitalization). It is well

known from the competing-risks literature that standard survival analysis leads to biased results when competing events may preclude the occurrence of the event of interest (18). These so-called competing risks are clearly present in our situation where the event HF hospitalization will never be observed in patients that die beforehand. In contrast to some of the previously published risk functions for predicting recurrent hospitalization in HF patients (33), the presence of death as a competing risk is adequately accounted for when using our multi-state model to predict the cumulative incidence function of HF hospitalization.

A limitation of this study is that apart from age and previous HF hospitalization, all risk factors were treated as fixed-time covariates, meaning that their values were assumed to remain constant across the 18-month prediction period. To explore whether this assumption could still be considered reasonable for the laboratory measurements, we performed a sensitivity analysis by refitting a simplified variant of the model consisting of demographical and clinical variables only. Compared to the more elaborate variant presented in this paper, the simplified model performed considerably worse in predicting the survival outcome and similar in predicting the HF hospitalization outcomes. Including the laboratory measurements as fixed-time covariates therefore seems reasonable when using our model to make short- to medium-term predictions (i.e., up to 18 months). Care should however be taken when using the model to make long-term predictions of a patient's disease progression as this would ideally require joint modeling of the course of time of the continuous risk factors and the time-to-event distributions of the considered outcome measures (34). Another limitation of this study is that the model's performance on HF hospitalization could only be assessed internally as data on this endpoint was not collected in the FINN-AKVA study.

Although the validation cohort was quite different from the derivation cohort, i.e., patients with preserved LVEF were much more heavily populated in the FINN-AKVA study compared to the COACH study, these differences in case mix did not have a profound impact

on model calibration: the 18-month survival as predicted by our multi-state model was still very close to the 18-month survival as observed in the FINN-AKVA study (71.2% versus 71.4%, respectively). Hence, the two study cohorts can still be regarded as plausibly related as there were no systematic differences in mortality incidence between COACH and FINN-AKVA that could not be explained by different distributions of the predictor variables (35,36). Care should however be taken when applying our risk engine in settings that include patients who were not represented in the COACH study. For example, if we compare the baseline characteristics of the COACH study population to the baseline characteristics of the patients in two large American registries (27,28), we see that about 20% of the patients in the registries were African American, whereas the vast majority of the patients in the COACH study were Caucasian. Also, less than 80% of the patients in the two American registries had Medicare/Medicaid insurance, whereas health care insurance is obligatory in the Netherlands. Such demographical and cultural differences between North-West Europe and other regions of the world may imply that the predictive ability of our model is substantially reduced when it is applied in these latter settings.

To conclude, the COACH risk engine successfully predicted survival and HF hospitalization in a broad spectrum of acute HF patients. To allow for convenient application of the model in practice, a user-friendly software implementation has been developed in Java. This implementation is freely available at: <https://github.com/Postmus/coach/wiki/COACH-Risk-Engine>.

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Conflict of Interest

For the COACH study, the NT-proBNP assay kits were provided by Roche Diagnostics (Mannheim, Germany) and the NBP assay kits were provided by Biosite Incorporated (San Diego, CA). Novartis (Arnhem, the Netherlands) provided an unrestricted grant to invest in BNP Triage meters.

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Table 1. Patient characteristics at hospital discharge*

	COACH [†]	FINN-AKVA [‡]
Number of patients	1023	576
Age, years (mean ± SD)	71 ± 11	74 ± 10
Female sex	38%	49%
Diabetes	28%	32%
COPD	26%	12%
Hypertension	43%	54%
Stroke	10%	13%
Myocardial infarction	43%	27%
Peripheral arterial disease	16%	10%
Atrial fibrillation	44%	30%
LVEF (mean ± SD)	34 ± 14	45 ± 16
Previous HF hospitalization	33%	52%
BMI, kg/m ² , (mean ± SD)	27 ± 5	29 ± 7
SBP, mm Hg (mean ± SD)	118 ± 21	149 ± 33

* Abbreviations: COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; NT-proBNP, N-terminal prohormone B-type natriuretic peptide; eGFR, estimated glomerular filtration rate.

[†] SBP, DBP, LVEF, and laboratory values were assessed just before hospital discharge. If a discharge value on LVEF was missing, it was replaced by the closest available measurement after hospital discharge.

[‡] The risk factors SBP, DBP, serum sodium, hemoglobin, and NT-proBNP were not available at hospital discharge. For these variables, we used the measurements as taken closest to discharge (admission values for SBP, DBP, and serum sodium, and 48-hours values for hemoglobin and NT-proBNP).

DBP, mm Hg (mean \pm SD)	68 \pm 12	83 \pm 20
log(NT-proBNP), pg/mL (mean \pm SD)	7.85 \pm 1.19	8.24 \pm 1.23
eGFR, mL/min/1.73 m ² (mean \pm SD)	55 \pm 21	57 \pm 22
Serum sodium, mmol/L (mean \pm SD)	139 \pm 4	138 \pm 5
Hemoglobin, g/L (mean \pm SD)	132 \pm 20	127 \pm 18

Table 2. Results from the parametric survival analysis (Equations 1 and 2)

	Equation 1		Equation 2	
State:	Discharged alive from hospital		Hospitalization because of HF	
Functional form:	Weibull		Log logistic	
Parameters	Coefficient (s.e.)	HR	Coefficient (s.e.)	OR
ρ	0.719 (0.051)		1.931 (0.023)	
α	0.816 (1.567)		-6.298 (0.780)	
Age			0.014 (0.008)	1.014
Female sex	-0.287 (0.096)	0.750		
DBP	-0.015 (0.004)	0.985		
Pulse pressure (SBP-DBP)	-0.005 (0.003)	0.995		
Stroke	0.275 (0.123)	1.317	0.483 (0.269)	1.621
Myocardial infarction	0.296 (0.090)	1.344		
Atrial fibrillation	0.172 (0.088)	1.188		
Peripheral arterial disease	0.177 (0.103)	1.194	-0.374 (0.213)	0.688
Diabetes	0.222 (0.093)	1.249		
LVEF			0.014 (0.007)	1.014
Previous HF hospitalization	0.648 (0.098)	1.912		
Serum sodium	-0.036 (0.011)	0.965		
eGFR	-0.013 (0.003)	0.987	0.012 (0.005)	1.012
log(NT-proBNP)	0.073 (0.041)	1.076		

Table 3. Results from the logistic regression (Equations 3 and 4)

	Equation 3		Equation 4	
Probability:	$p_{13}(p_{12} = 1 - p_{13})$		$p_{23}(p_{21} = 1 - p_{23})$	
Functional form:	Logistic		Logistic	
Parameters	Coefficient (s.e.)	OR	Coefficient (s.e.)	OR
α	-4.206 (0.868)		-3.092 (1.304)	
Age	0.047 (0.010)	1.048		
Female sex	-0.534 (0.204)	0.586		
DBP			-0.025 (0.014)	0.975
Pulse pressure	-0.018 (0.006)	0.982		
Diabetes			0.649 (0.302)	1.914
Previous HF hospitalization	-0.362 (0.185)	0.696		
log(NT-proBNP)	0.186 (0.069)	1.204	0.348 (0.131)	1.416

Figure legends

Figure 1. A schematic representation of the multi-state model

Figure 2. Calibration plots of mean predicted survival versus mean observed survival (Kaplan-Meier estimate + corresponding 95% confidence interval) by deciles of predicted survival for the derivation cohort (left) and the validation cohort (right)

Figure 3. Calibration plot of mean predicted HF hospitalization versus mean observed HF hospitalization (cause-specific hazards estimate + corresponding 95% confidence interval) by deciles of predicted HF hospitalization

Figure 4. Observed versus predicted number of HF hospitalizations (left) and observed versus predicted number of days lost due to HF hospitalization (right) after 18 months of follow-up