Forecasting the Risk of Heart Failure Hospitalization After Acute Coronary Syndromes: the CORALYS HF Score

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The present study aimed to identify patients at a higher risk of hospitalization for heart failure (HF) in a population of patients with acute coronary syndrome (ACS) treated with percutaneous coronary revascularization without a history of HF or reduced left ventricular (LV) ejection fraction before the index admission. We performed a Cox regression multivariable analysis with competitive risk and machine learning models on the incideNce and predictOrs of heaRt fAiLure After Acute coronarY Syndrome (CORALYS) registry (NCT 04895176), an international and multicenter study including consecutive patients admitted for ACS in 16 European Centers from 2015 to 2020. Of 14,699 patients, 593 (4.0%) were admitted for the development of HF up to 1 year after the index ACS presentation. A total of 2 different data sets were randomly created, 1 for the derivative cohort including 11,626 patients (80%) and 1 for the validation cohort including 3,073 patients (20%). On the Cox regression multivariable analysis, several variables were associated with the risk of HF hospitalization, with reduced renal function, complete revascularization, and LV ejection fraction as the most relevant ones. The area under the curve at 1 year was 0.75 (0.72 to 0.78) in the derivative cohort, whereas on validation, it was 0.72 (0.67 to 0.77). The machine learning analysis showed a slightly inferior performance. In conclusion, in a large cohort of patients with ACS without a history of HF or LV dysfunction before the index event, the CORALYS HF score identified patients at a higher risk of hospitalization for HF using variables easily accessible at discharge. Further approaches to tackle HF development in this high-risk subset of patients are needed. **(Am J Cardiol 2023;206:320−329)**

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The burden of subsequent events after acute coronary syndrome (ACS) remains relevant because of the aging of the population, the increasingly complexity of patients from a clinical and an interventional point of view, and the detrimental impact on prognosis.[1,2]

Research has been mainly focused on the risk of recurrent myocardial infarctions and subsequent bleedings to tailor the length and kind of dual antiplatelet therapy. Several scores have been proposed, embedding the traditional regression model and machine learning (ML) approach, offering physicians useful tools to personalize a clinical and therapeutic approach for each patient.[3−5]

In this context, prediction of the development of heart failure (HF) remains an unmet need. A prompt recognition of the risk of HF after ACS may help physicians to tailor interventional strategies (i.e., completeness of revascularization),[6] focused therapies[7] and kind and timing of follow-up.[8,9]

Recently, an ML-based score from the Swedish Web system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART) registry has been published,[10] demonstrating a more than satisfactory accuracy to predict the risk of development of HF after myocardial infarction (MI). However, only 2/3 of the patients in the derivation cohort underwent coronary angiography and about 10% already reported a history of HF, potentially limiting the clinical translation of these findings.

Consequently, we aimed to develop a score to predict the risk of HF hospitalization after ACS in patients treated with percutaneous coronary intervention (PCI) who were included in the incideNce and predictOrs of heaRt fAiLure After Acute coronarY Syndrome (CORALYS) registry.

Methods

The CORALYS registry (NCT 04895176) is an international, multicenter, retrospective, observational study including consecutive patients admitted for ACS in 16 European Centers from 2015 to 2020. Where required, the study investigators received approval from their local institutional boards or ethic committees. Patients were considered eligible for inclusion in the registry if all the following criteria were met: (1) age >18 years; (2) confirmed diagnosis of ACS, including ST-segment MI (STEMI), non-STEMI (NSTEMI), or unstable angina at discharge; and (3) treatment of ACS with PCI.

Patients with a known history of congestive HF, previous HF hospitalizations, or reduced left ventricular (LV) ejection fraction (LVEF; <50%), evaluated with any imaging modality, before the index hospitalization for ACS were excluded. For the aim of the present study, which is a subanalysis of the main project, we excluded patients presenting with cardiogenic shock.

Demographic, clinical, and main angiographic characteristics were retrospectively retrieved and abstracted on prespecified electronic forms.

The presence of cardiovascular risk factors atrial fibrillation chronic obstructive pulmonary disease, malignancies, peripheral artery disease, and the history of previous MI or myocardial revascularizations and stroke was retrieved from medical records. Chronic kidney disease was defined as an estimated glomerular filtration rate <60 ml/min/1.73 m^2, according to Modification of Diet in Renal Disease equation. The diagnoses of STEMI, NSTEMI, and cardiogenic shock at admission were defined according to the current European Society of Cardiology guideline[11,12] definitions, and they were retrospectively assessed and retrieved from the patients' medical records and hospital discharge letters. Major bleedings were defined as Bleeding Academic research Consortium 3 to 5 bleedings.[13]

Multivessel disease was defined as more than 1 coronary vessel with a critical stenosis (≥70% diameter stenosis at angiographic evaluation or Fractional Flow Reserve ≤0.8/instantaneous wave-free ratio ≤0.89 at invasive physiologic assessment in nonculprit vessels). Complete revascularization was defined as no residual critical stenosis in any coronary vessel after PCI. LVEF was assessed by 2-dimensional transthoracic echocardiography and computed according to the bidimensional Simpson formula ([LV end-diastolic volume − LV end-systolic volume] ÷ LV end-diastolic volume]) and classified as moderate (between 35% and 45%).

PCI was performed according to the standard local practice, in accordance with practice guidelines established by the European Society of Cardiology.[11,12] After PCI, all patients received dual antiplatelet therapy and were discharged on optimal medical therapy, including β blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, and mineralocorticoid receptor antagonists, if indicated. Follow-up data were obtained from electronic medical records of each participating center, clinical visit, telephonic contact, or formal query to the primary care physicians.

The area under the curve (AUC) for the risk of 1-year hospitalization for HF was the primary end point, whereas AUCs at 6 months and 2 years were the co-secondary end points. The end point of hospitalization was confirmed through a review of hospital records, consultation notes, discharge letters, and pertinent laboratory data.

Patients or the public were not involved in the design, conduct, reporting, or dissemination plans of our research.

Variables were expressed as mean ± SD, median and interquartile range, or counts and percentage, as appropriate. Comparisons between groups were made by the analysis of variance test on continuous variables using the Brown−Forsythe statistic when the assumption of equal variances did not hold or the nonparametric Mann−Whitney U test; the chi-square test or the Fisher's exact test were calculated for discrete variables.

A total of 2 different data sets were randomly created: 1 for the derivative cohort (80% of the patients) and 1 for the validation (20% of the patients); both of them were exploited for Cox regression and ML analysis.

The cause-specific Cox model was used to build the score for the risk of HF hospitalization, taking into account the risk of death. A restricted cubic spline transform was used when the association between the continuous covariates and the outcome was nonlinear. The assumption of proportional hazards was assessed by investigation of the Schoenfeld residuals. Because the disease diagnosis did not satisfy the assumption, a stratified cause-specific Cox model

was fitted by allowing a different baseline hazard for each level of the variable. To evaluate the importance of the predictors, the proportion of explained variance was used. In the final model, only significant covariates were retained. The formula of the score for the probability of having an HF hospitalization at time of interest was obtained using the nomogram. This probability refers also to the cumulative incidence function and it takes into account the competing risk of death. A $p < 0.05$ was considered statistically significant. Statistical analyses were performed in R version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria) packages "ggplot2," "survival," "RMS," "riskRegression," and "survminer."

A number of different ML models have been trained on the available data; to produce results comparable with the statistical analysis, all of them were based on the principles of competitive risk survival analysis. The investigated models were all based on recursive partitioning techniques, most commonly known as trees: survival tree, survival forest, and survival AdaBoost. These models differ from their more common classification version in that each node of the trees does not aggregate the samples based on the homogeneity of their class of belonging but on their survival outcome. Following this assumption, the splits in the trees were then calculated to increase, as much as possible, the purity of the obtained subset of samples based on their hazard. The competitive risks are taken into account by preprocessing the data set by way of the Fine−Gray model. AdaBoost was selected as the best model for this analysis because of its superior predictive performance with respect to the other investigated models while still being simple to train and interpret.

To evaluate the prediction performance of the score obtained using the 2 different methods, 2 metrics were used: the AUC as a measure of discrimination and the Brier score as a measure of calibration. The time horizons of interest used for the prediction were 6, 12, and 24 months from ACS. In the building phase of the score, the different methods were tested using 10 CV cross-validation of the derivative data set. The performance of the final ones was then evaluated on the validation data set.

Results

Among 14,699 patients available for the present analysis, at 1 year after index ACS presentation, 593 (4.1%) were admitted for development of HF (Supplementary Figure 1).

Those who developed HF in the first year after the index event (Table 1) were older, more likely to be female (37% vs 31%, $p = 0.004$), had higher rates of cardiovascular risk factors, and had a history of coronary revascularization.

Regarding admission diagnosis (Table 2) in patients developing HF, NSTEMI was the most frequent diagnosis (38%), followed by unstable angina (35%) and STEMI (27%). Patients who developed HF had more severe angiographic disease, with higher rates of multivessel disease (48% vs 34%, $p < 0.001$) and stenosis involving coronary bifurcations (12% vs 8%, $p = 0.002$), whereas complete revascularization was less frequently achieved (22% vs 33%, $p = 0.026$) than in those who did not develop HF.

As reported in the Methods section, for the purpose of the present analysis, 2 different data sets were randomly created: 1 for the derivative cohort including 11,626 patients (80%) and 1 for the validation including 3,073 patients (20%). No differences in the outcomes were found among the different data sets (Supplementary Table 1).

On the Cox regression analysis with competitive risk, hyperlipidemia, diabetes mellitus, smoking habit, history of previous PCI and of AF, chronic obstructive pulmonary disease, and anterolateral site of MI increased the risk of developing HF (Figure 1, Table 3, Supplementary Figure 1), whereas Killip I at admission and complete revascularization were protective. The importance of the predictors, with reduced renal function, complete revascularization, and LVEF as the 3 most relevant ones, are presented in Figure 2. AUC using 10-fold CV was 0.75 (0.72 to 0.78) at 1 year,

Table 1
Baseline features

	Patients developing HF (593, 4%)	Patients not developing HF (14106, 96%)	P
Age (years old)	71±10	65±12	<0.001
Female gender (%)	218 (37%)	4360 (31%)	0.004
Hyperlipidemia (%)	336 (57%)	8312 (69%)	0.223
Hypertension (%)	487 (82%)	10313 (73%)	<0.001
DM (both ID and not ID*, %)	274 (46%)	4142 (29%)	<0.001
Previous or current smoking (%)	220 (37%)	5528 (39%)	0.306
Previous MI† (%)	201 (34%)	3580 (25%)	<0.001
Previous percutaneous revascularization (%)	202 (34%)	4131 (30%)	0.013
Previous surgical revascularization (%)	103 (17%)	1406 (10%)	<0.001
Peripheral artery disease (%)	39 (7%)	377 (3%)	<0.001
Previous Atrial Fibrillation (%)	77 (13%)	722 (5%)	<0.001
Previous stroke (%)	19 (3%)	258 (2%)	0.016
Prior Barc 3-5 Major Bleedings (%)	9 (2%)	105 (1%)	0.052
Cancer (%)	140 (25%)	3700 (27%)	0.409
COPD (%)‡	60 (10%)	72 (5%)	<0.001

* Insulin- and not insulin-dependent.
† Myocardial infarction.
‡ Chronic obstructive pulmonary disease.

Table 2
In-hospital data

	Patients developing HF (593, 4%)	Patients not developing HF (14106, 96%)	P
Admission diagnosis (%)			0.003
1) STEMI*	160 (27%)	4172 (30%)	
2) NSTEMI*	226 (38%)	4599 (33%)	
3) Unstable angina	207 (35%)	5034 (37%)	
Anterior and anterolateral site of MI (%)	227 (39%)	2604 (22%)	0.002
Killip at admission more than 1(%)	73 (15%)	1104 (9%)	<0.001
Admission data:			
- Systolic blood pressure (mmHg)	138±18	137±12	0.065
- White blood cell count (10^9/L)	9±4	9±3	0.134
- Renal function (GFR†)	68±24	81±22	<0.001
ULM‡ (%)	27 (5%)	925 (7%)	0.126
Multivessel disease (%)	285 (48%)	4773 (34%)	<0.001
Coronary bifurcation (%)	73 (12%)	1259 (8%)	0.002
Complete revascularization (in-hospital or planned) (%)	130 (22%)	4596 (33%)	0.026
Ejection Fraction at discharge (%)	47±8	51±10	<0.001

* ST- and non−ST-elevation myocardial infarction.
† Glomerular filtration rate.
‡ Unprotected left main disease.

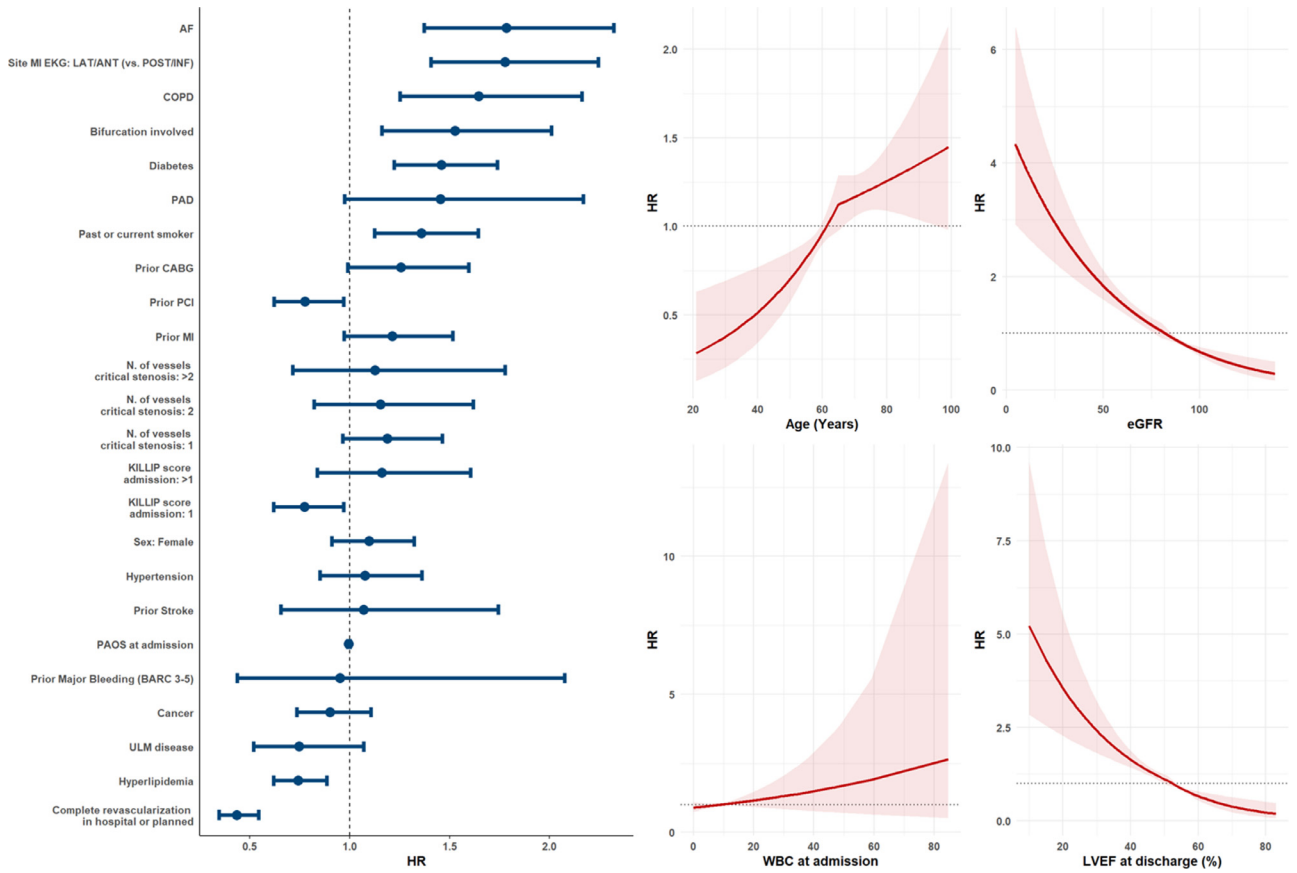

Figure 1. Cox regression analysis: impact of covariates. AF = atrial fibrillation; ANT = anterior; BARC = bleeding academic research consortium; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; EKG = electrocardiogram; INT = interior; LAT = lateral; N = number; PAD = peripheral artery disease; PAOS = Systolic Pressure; POST = posterior; ULM = unprotected left main; WBC = white blood cell.

Table 3
Cox regression model

Characteristic	HR	95% CI	p-value
Female gender	1.10	0.91, 1.32	0.3
Hyperlipidemia	0. 74	0.62, 0.89	0.001
Hypertension	1.08	0.85, 1.36	0.5
Diabetes	1.46	1.22, 1.74	<0.001
PAD	1.45	0.98, 2.17	0.066
Past or current smoker	1.36	1.13, 1.64	0.001
Prior MI	1.22	0.97, 1.52	0.085
Prior PCI	0.78	0.62, 0.97	0.027
Prior CABG	1.26	0.99, 1.60	0.060
AF	1.79	1.37, 2.32	<0.001
Prior Stroke	1.07	0.66, 1.75	0.8
Prior Major Bleeding (BARC 3-5)	0.95	0.44, 2.08	>0.9
Cancer	0.90	0.74, 1.11	0.3
COPD	1.65	1.25, 2.16	<0.001
More than 2 vessels with critical stenosis	1.13	0.72, 1.78	0.6
Anterior and Anterior/lateral site of MI	1.78	1.41, 2.25	<0.001
KILLIP score admission			
1	0.78	0.62, 0.97	0.026
>1	1.16	0.84, 1.61	0.4
Systolic blood pressure at admission	1.00	0.99, 1.00	0.3
ULM disease	0.75	0.52, 1.07	0.11
Bifurcation involved	1.53	1.16, 2.01	0.002
Complete revascularization in hospital or planned	0.44	0.35, 0.55	<0.001
WBC admission	1.05	0.97, 1.14	0.2

CI = confidence interval; HR = hazard ratio.

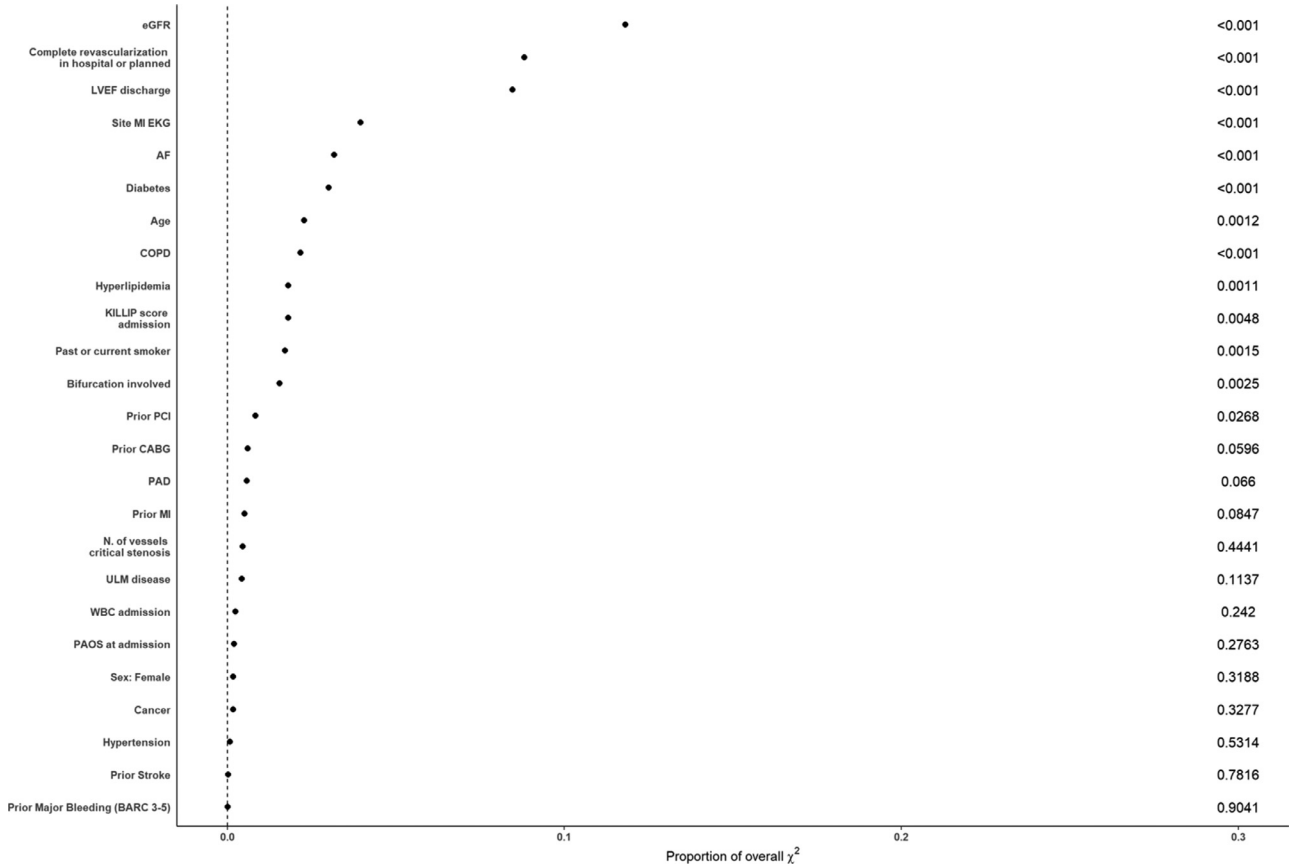

Figure 2. Cox regression analysis: importance of the predictors. AF = atrial fibrillation; ANT = anterior; BARC = bleeding academic research consortium; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; EKG = electrocardiogram; INT = interior; LAT = lateral; N = number; PAD = peripheral artery disease; PAOS = Systolic Pressure; POST = posterior; ULM = unprotected left main; WBC = white blood cell.

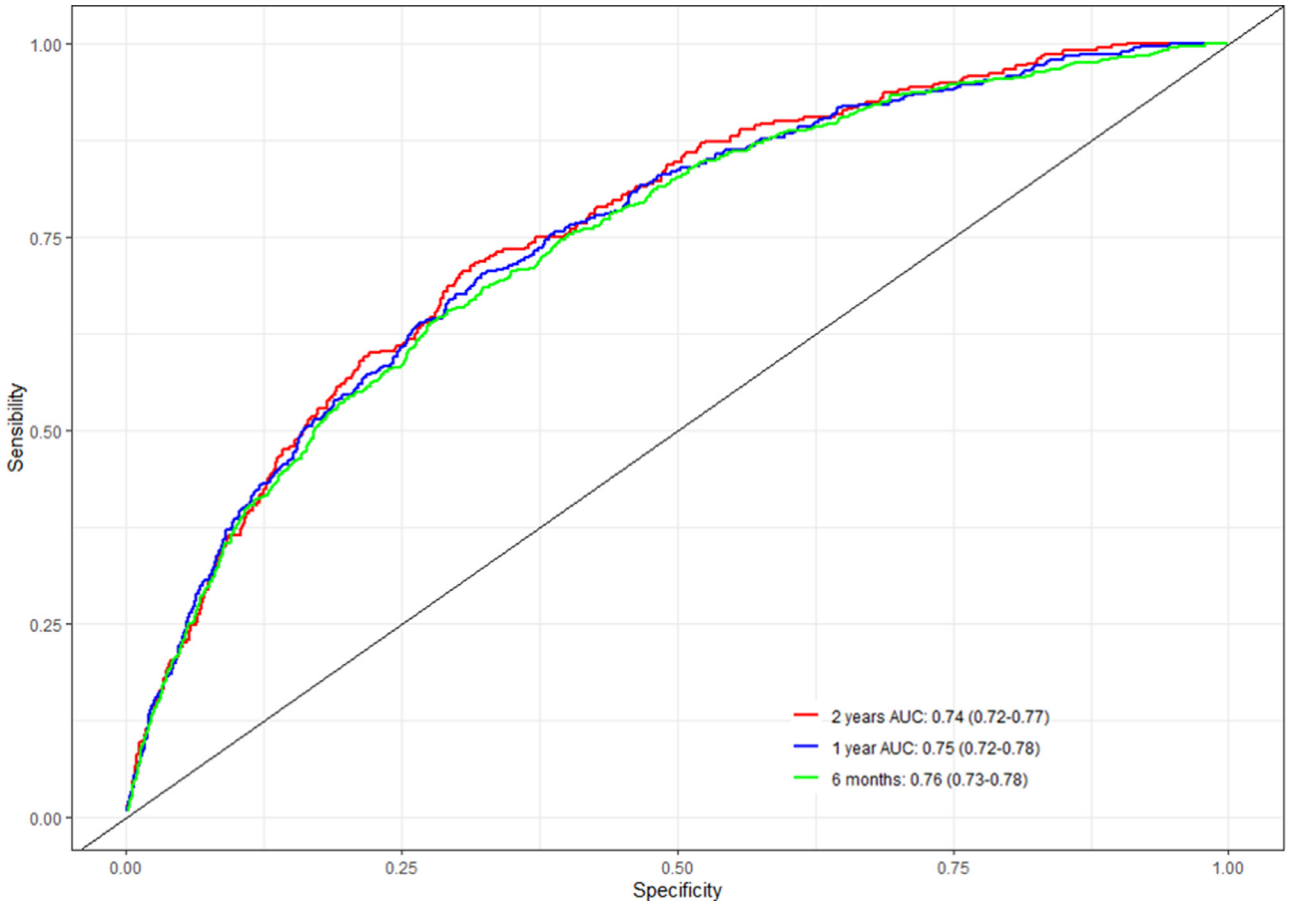

Figure 3. Cox regression analysis: AUC at 6, 12 and 24 months using 10-fold CV (internal validation). CV = cardiovascular.

0.76 (0.73 to 0.78) at 6 months, and 0.74 (0.72 to 0.77) at 24 months (Figure 3), whereas on the validation data set, they were 0.72 (0.67 to 0.77), 0.72 (0.66 to 0.77), and 0.70 (0.66 to 0.75 all CI 95%), respectively. A normogram was provided to visually depict the risk (Figure 4) and a web app (https://coralyshfscore.shinyapps.io/coralys_hfscore/) was created to easily calculate the CORALYS HF score for predicting the risk of the patients for developing hospitalization for HF at 1 year.

On the ADA boost analysis, renal function, LVEF, age, site of MI, systolic blood pressure, and white blood cell count were the most important predictors (Supplementary Figures 2 and 3).

On the derivative data set, AUCs were 0.75 (0.70 to 0.79) at 1 year, 0.75 (0.70 to 0.80), at 6 months and 0.75 (0.71 to 0.79) at 24 months (Figure 5), whereas on the validation data set, they were 0.75 (0.74 to 0.75), 0.75 (0.75 to 0.75), and 0.75 (0.74 to 0.75, all CI 95%), respectively. The calibration plots on the derivative and test data sets for the Cox regression and ML analysis are presented in Supplementary Figures 4 to 7.

Discussion

The CORALYS registry included a large real-world population of patients with ACS who were revascularized with PCI and without a history of HF or LV dysfunction before the index event. Given the ongoing contribution of HF to morbidity and mortality after ACS,[14] early risk stratification and preventive therapeutic strategies are required. Therefore, the present study aimed to identify early the patients at a higher risk of HF hospitalization after ACS revascularization.

The main findings of the present study are the following: (1) in the current era of ACS treatment, 4.1% of patients with ACS develop HF requiring hospitalization up to 1 year of follow-up, (2) among the several variables independently associated with HF hospitalization at 1 year, renal function, complete revascularization, and LVEF after revascularization are the most relevant factors associated with HF hospitalization, and (3) HF hospitalizations may be predicted with good discrimination, allowing the identification, through the CORALYS HF score, of patients at an increased risk of subsequent HF events and those who might benefit from a more tailored follow-up and more intensive medical therapy.

The importance of these findings is also based on the fact that we succeeded in identifying patients at risk of HF events after ACS in patients without a history of HF, thus excluding the potential role of previous HF on the outcomes. Although the use of clinical risk scores after PCI are recommended by the current international guidelines to estimate the risk of adverse events (mainly focused on the prediction of mortality), a risk score specific for the

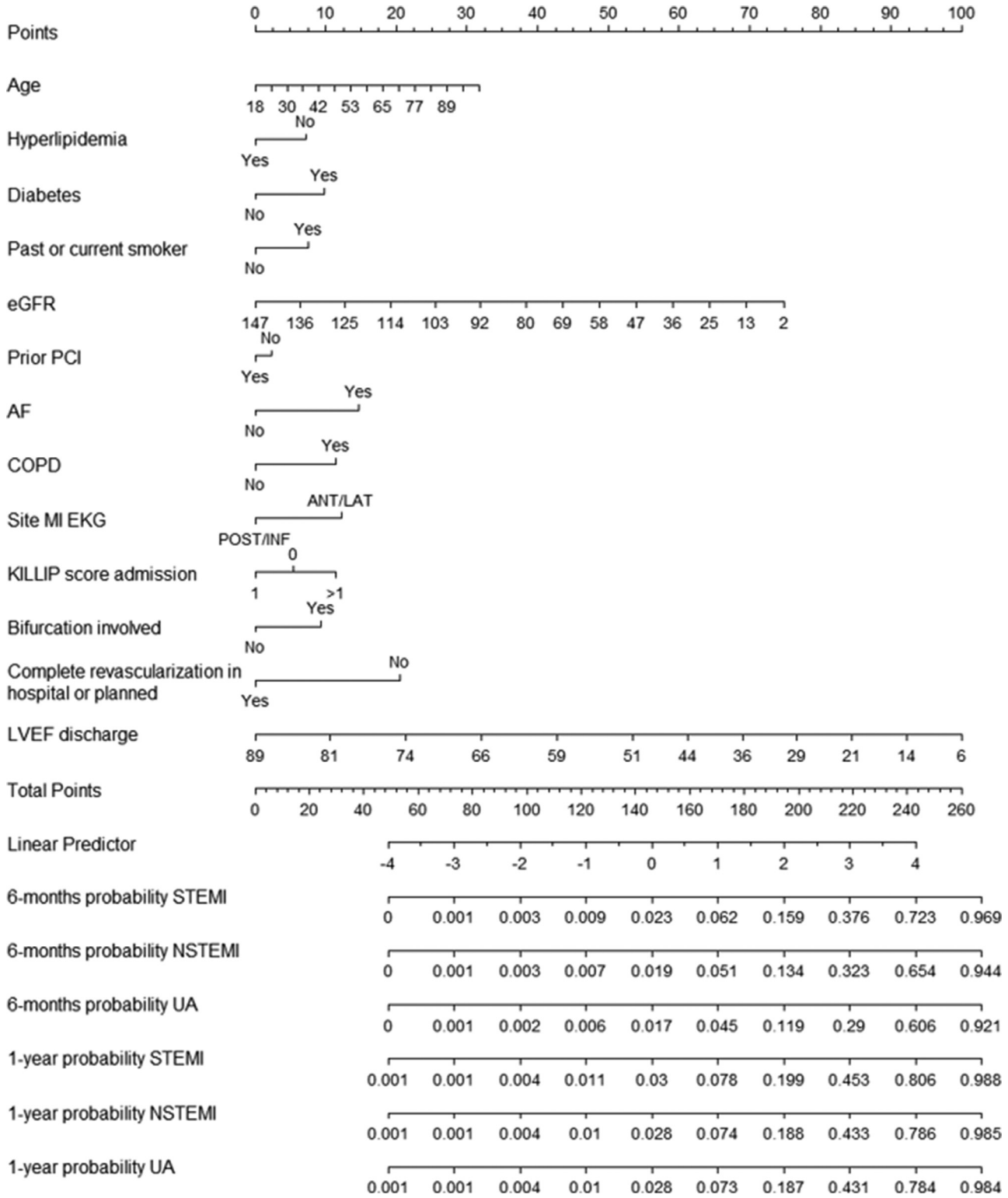

Figure 4. Cox regression analysis: normogram. COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; EKG = electrocardiogram; UA = unstable angina.

development of HF remains an unmet need. A contemporary dedicated score for HF prediction which integrates easily accessible variables may fill this gap and be of clinical value. Moreover, we included in the registry not only patients with MI presentation but also patients with unstable angina presentation, expanding the potential application of the risk score to all kinds of ACS presentation, thus maximizing the generalizability of our findings.

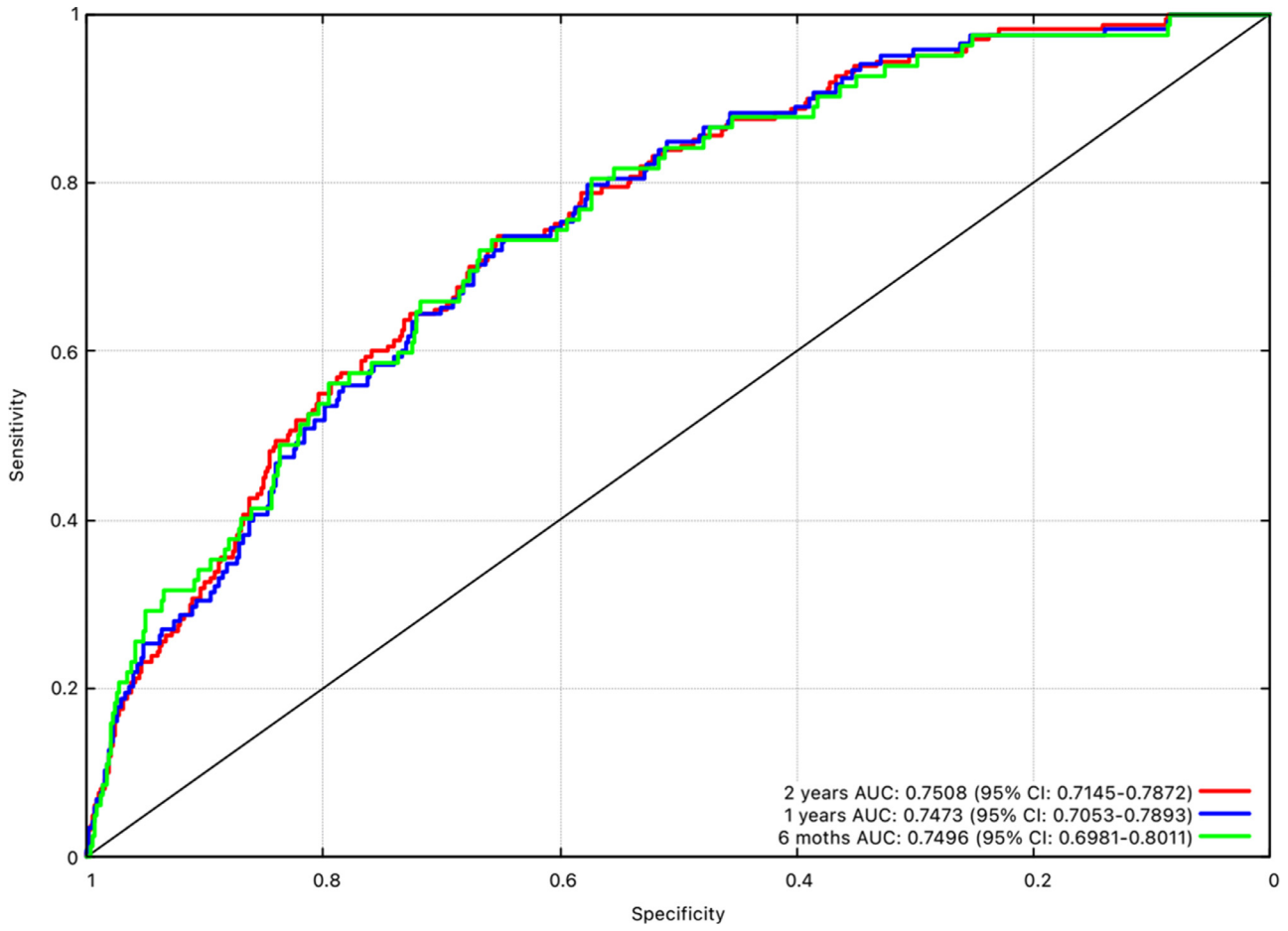

Figure 5. Ada boost analysis: AUC at 6, 12, and 24 months in the training data set.

Importantly, we analyzed the data using the "traditional" Cox regression analysis and the novel ML analysis, showing that both methods present similar performance in predicting HF risk. However, a web app for HF risk stratification based on the Cox regression may be more easily applied in the clinical context than the ML method because of the smaller number of variables required for predicting HF risk. Finally, we choose to focus on the Cox regression model because it showed the smallest confidence intervals on the main outcome (1-year development of HF in the validation cohort).

In the last decades, improvement in the pharmacologic treatment of patients with ACS and the increasing use of invasive treatment strategies may have contributed to the improvement of early survival of ACS.[15,16] Moreover, the current treatment of ACS, which includes timely and optimal revascularization of the jeopardized myocardium, may have contributed to the observed low rate (4.1%) of HF hospitalization up to 1 year after ACS in our population. Interestingly, in a recent analysis of the SWEDEHEART registry in which only 2/3 of patients with MI underwent coronary angiography and about 10% already reported a history of HF, the hospitalization rate for HF at 1 year after MI was reported to be up to 14.6%.[10] Conversely, in the external validation population, which had more coronary angiography and invasive treatment, the hospitalization rate for HF at 1 year was 4.2%, which is almost identical to the incidence of our population. Importantly, in our study, complete revascularization and higher LVEF after revascularization were the major protective factors for HF hospitalization at 1 year of follow-up. Because complete revascularization may have an impact on the risk of a first hospitalization for HF, although intuitive, it should be considered a novel finding which reinforces the importance of reducing the extension of myocardial necrosis, preventing recurrent ACS[17] (often associated with further myocardial impairment) and reducing the residual myocardial ischemic areas, preventing late ventricular dysfunction.[18] Therefore, when feasible, complete revascularization should be achieved in all patients with ACS and multivessel disease.

Patients with ACS with chronic renal disease may have more serious, complex, and calcified coronary artery lesions and more multivessel lesions.[19] This also has been largely documented in patients who underwent surgical revascularization; in the EUROScore 2 and in STS score renal function, this emerged as 1 of the most powerful predictors of prognosis.[20] In a similar way, renal function emerged as 1 of the most powerful independent variables for HF prediction. Therefore, patients with renal impairment should be considered at a very high risk for HF, irrespective of other

cardiovascular risk factors. This is in line with the fact that renal insufficiency is also common in patients with HF, with more than half of the patients exhibiting some impairment of kidney function.[21] Importantly, in patients with chronic renal disease, new therapies, such as the sodium-glucose cotransporter 2 inhibitors (SGLT2is), demonstrated a significant reduction in the clinical outcomes and kidney protective benefits.[22] Moreover, SGLT2is showed a profound reduction in the hospitalization for HF in patients with type 2 diabetes mellitus,[23–25] and in patients with a previous MI, SGLT2i reduced the composite of cardiovascular death or HF with a higher absolute risk reduction than in patients without a previous MI.[26] Considering the results of these molecules, the potential identification of patients at a higher risk of HF and who may derive the greatest benefit from novel therapy should be a matter of intense research in the future for a tailored and optimized therapy after ACS. Indeed, the identification of high-risk patients through the CORALYS HF score may not automatically translate to a higher probability of offsetting the future development of HF.

The findings of the present study should be considered in the context of some limitations. Our findings should be interpreted in light of the common limitations of a registry-based cohort study. Owing to the observational nature of the study, we provided only correlation with the explored outcome but not causation.

The participating centers were all located in Europe; therefore, our results may not be generalizable to non-European countries. Our study was not designed to evaluate the impact of pharmacologic treatments on HF incidence; however, we identified the patients who, at discharge, have a higher risk of subsequent HF at follow-up. The early identification of these high-risk patients may allow the targeted use of intensive monitoring and tailored therapy that may improve their outcomes.

In conclusion, in a large cohort of patients with ACS without a history of HF or LV dysfunction before index event, the CORALYS HF score identified patients at a higher risk of hospitalization for HF using variables easily accessible at discharge. Further approaches to tackle HF development in this high-risk subset of patients are needed.

Declaration of Competing Interest

The authors have no competing interests to declare.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2023.08.010.

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