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Risk Estimation in coronary Heart disease patients After cardiac rehaBilitation: development and validation of the REHAB score

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ABSTRACT

INTRODUCTION: The cardiovascular risk stratification represents one of the most interesting and charming challenge for physician and predictive scores are useful tools to do it.

We developed and validated a predictive model (REHAB score) of long-term mortality risk in patients who underwent coronary artery bypass graft (CABG) and completed a standard in-hospital rehabilitation program.

METHODS: we used the Cox proportional hazards model to estimate the predictive value of several risk factors (anamnestic, laboratory, echocardiographic and electrocardiographic data) included in a database of 1014 patients (80% derivation cohort, 20% validation cohort): with binary logistic regression analysis in the developmental dataset we looked for the beta coefficients necessary to estimate the overall and cardiovascular mortality risk using the REHAB score. Then we validated the models in the validation datasets.

RESULTS: during a mean 4-years follow-up 91 patients died. Mean REHAB score values in derivation dataset were 8.5% and 4.8% for overall and cardiovascular mortality risk, respectively. Goodness-of-fit (Hosmer Lemeshow Chi square) and area under the ROC curves analysis showed a satisfying calibration and discrimination power in derivation and validation datasets for both models.

CONCLUSION: REHAB score can predict overall and cardiovascular mortality risk in patients undergoing cardiac rehabilitation program after coronary artery bypass graft.

Key words: risk score, cardiovascular risk, coronary artery bypass graft, coronary artery disease, cardiac rehabilitation.

ABSTRACT IN ITALIANO

INTRODUZIONE: La stratificazione del rischio cardiovascolare rappresenta una delle sfide più interessanti e affascinanti per il medico e gli score di rischio sono strumenti utili per questo scopo.

Abbiamo sviluppato e validato un modello predittivo (REHAB score) di rischio di mortalità a lungo termine in pazienti sottoposti a intervento di bypass che hanno completato un programma di riabilitazione cardiovascolare.

METODI: Abbiamo utilizzato la regressione di Cox per stimare il valore predittivo di diversi fattori di rischio (anamnestici, laboratoristici, ecocardiografici ed elettrocardiografici)inclusi in un database di 1014 persone (80% coorte di sviluppo, 20% coorte di validazione): attraverso una regressione logistica binaria nel dataset di sviluppo abbiamo ottenuto i beta coefficienti necessari per stimare, utilizzando il REHAB score, il rischio di mortalità globale e cardiovascolare. Successivamente abbiamo validato i modelli nel dataset di validazione.

RISULTATI: durante un follow-up medio di 4 anni sono morti 91 pazienti. I valori medi di REHAB score nel dataset di sviluppo furono 8.5% e 4.8% rispettivamente per la mortalità globale e cardiovascolare. L'indice di bontà e l'analisi delle curve ROC hanno mostrato un soddisfacente potere di calibrazione e di discriminazione sia nel dataset di sviluppo che di validazione per entrambi i modelli.

CONCLUSIONI: Attraverso il REHAB score è possibile predire il rischio di mortalità globale e cardiovascolare nei pazienti sottoposti a riabilitazione cardiovascolare dopo intervento di bypass aorto-coronarico.

INTRODUCTION

The cardiovascular risk stratification represents one of the most interesting and charming challenge for physician. During last decades, many different scores have been developed and proposed in different guidelines to predict cardiovascular risk based on anamnestic data, clinical features, instrumental measurements, laboratory results and more.[1–4]

The Framingham risk score,[5] the European Society of Cardiology SCORE risk charts[6] and the Q-2 risk score[7] are widely used tools in clinical practice to predict long-term outcome in primary prevention population, thereby remaining cornerstones in this field despite the increasing number of cardiovascular risk factors routinely proposed in literature, such as psychosocial status[8-10], high-sensitivity C-reactive protein[11] or intima‐media thickness[12-16].

In secondary cardiovascular prevention several predictive models, such as TIMI and GRACE scores[17-19] for acute coronary syndrome (ACS), aimed to estimate early and mid-term mortality, mainly using data recorded during the acute phase of the event. Differently, the SMART risk score[20] has been developed and validated to predict long-term recurrent vascular events in patients with previous clinical manifestation of arterial disease.

In cardiac surgery patients EuroSCORE II[21] and STS score (Society of Thoracic Surgeons)[22–24] are used to predict early mortality; however, a risk score able to

stratify the long-term mortality in patients undergoing a cardiac rehabilitation program (CRP) after coronary artery bypass graft (CABG) is not yet available. We aimed to develop and validate a predictive model of long-term mortality risk in patients who underwent CABG and completed a standard in-hospital rehabilitation program.

METHODS

Study population

We created a database of 1321 consecutive patients referred to Cardiovascular Rehabilitation Unit of Fondazione Don Gnocchi (Parma) after CABG from January 2007 to June 2012. We excluded those subjects who could not complete the CRP due to clinical complications and patients with missing data, thereby considering a dataset of 1.014 subjects (78% male, mean age 68±10 years).

Baseline examination

All patients completed a standard in-hospital CRP, lasting approximately 2 weeks, consisting in supervised exercise sessions (60 minutes twice per day, each one comprehensive of 30 minutes of aerobic interval training using cyclette, warm up and cool down exercises), lifestyle and risk factors management, medical counselling and medical therapy optimization, in agreement with ESC guidelines.[25] The internal review board of Fondazione Don Gnocchi approved data collection.

We collected variables from medical record for each patient, including anamnestic findings, clinical and laboratory markers, electrocardiographic and echocardiographic measurements in order to select known and relevant predictors of outcome routinely used in clinical practice (all variables are showed in Table 1, column 1). We considered as cut-off for categorical variables values of normality routinely applied in clinical practice (see Table 1, column 3).

Echocardiographic parameters, electrocardiographic intervals duration, heart rate and laboratory data were collected at the end of CRP using as cut-off values those expressed in literature. A Left Ventricular Ejection Fraction (LVEF) >50% was considered normal[26] while, in terms of electrocardiographic intervals duration, PR and QTc were prolonged when >120 and > 440 msec, respectively[27]; for QRS duration we set the cut-off at 140 msec due to the low predictive power of the traditional one, 120 msec, in our population. Heart rate was calculated in the discharge 12-lead electrocardiography and, in agreement with literature[28], was considered as cut-off 70 bpm. Serum uric acid (SUA) level >6 mg/dl has been recently correlated with adverse outcome in our population[29] while, using the National Kidney Foundation (NKF) classification of chronic renal disease, we set a double cut-off for estimated Glomerular Filtration Rate (eGFR): < 60 ml/kg/min for mild impairment and < 30 ml/kg/min for severe reduction of renal function[30]. Similarly to QRS duration, we used a HDL cholesterol cut-off value of 30 mg/dl, instead of 45 mg/dl, to optimize the predictive value of this parameter in our population.

Systolic blood pressure (SBP) used in the model refer to the mean value of these parameters, recorded twice daily and it was measured by a restricted number of well-trained nurses with aneroid sphygmomanometer periodically calibrated (all the instruments were checked, standardized and calibrated by expert physicians) and auscultatory method. According to ESH/ESC guidelines for the management of arterial hypertension, day-by-day BP was measured in resting

supine position from 6:00 to 8:00 AM, within 1 hour after awaking and before breakfast for morning measurement, and from 4:00 to 6:00 PM for the afternoon, and a SBP cut-off value of 140 mmHg was used[31].

Lastly, we considered active smokers patients who stopped smoking due to the hospitalization or within 3 months before the intervention or acute event.

Follow-up

Follow-up data have been recorded by a medical doctor through a telephonic questionnaire, by collecting medical records and/or discussing with the general practitioner after an oral informed consent was obtained by the patient; outcomes were overall and cardiovascular mortality.

Model derivation

All the analyses were conducted with IBM SPSS Statistics 22.0 software.

We used the Cox proportional hazards model to estimate the predictive value of the risk factors included in the database.

The database was randomly divided into two subsets: 80% of subjects were included in the developmental dataset for the derivation of risk model, while the remaining 20% composed the validation subset and was used for testing and validating the model.

With a binary logistic regression analysis, we evaluated the multiparametric correlation between variables and overall mortality, with age as the only linear covariate.

In order to achieve the predictive overall mortality risk, we included the calculated β coefficients in the following formula:

$$\text{mortality risk ratio} = \frac{e^{(\beta_0 + \sum \beta_i X_i)}}{1 + e^{(\beta_0 + \sum \beta_i X_i)}}$$

where β_0 is the constant of the binary logistic regression analysis and β_i is the coefficient of the X_i variable. $X_i = 1$ if a categorical risk factor is present and $X_i = 0$ if it is not[32]; for age, X_i is the age of the patient expressed in years. (see Table 2).

The same statistical method was then used to create a predictive model of cardiovascular mortality (using correspondent β coefficients).

Validation

A goodness-of-fit testing (Hosmer Lemeshow Chi square) was applied in the developmental cohorts to evaluate how well the models were calibrated, reflecting the precision of how close the predicted probabilities are to the actual (observed) risks, while the area under the receiver operating characteristic (ROC) curves assessed how well the models could discriminate between alive and dead patients.

Finally, we employed the previous formula to validation datasets (using β-coefficients derived from developmental cohort analysis) in order to confirm the

calibration and discrimination power of our models with the tests already used in derivation cohorts.

RESULTS

Follow-up and baseline examination

During a mean follow-up of 48±24 months, 91 patients died (9%), 51 due to cardiovascular causes (5%).

One-third of population had diabetes mellitus and 201 patients (24%) were considered active smokers. One-hundred and eighteen subjects underwent coronary by-pass graft associated with cardiac valve replacement.

Clinical manifestation of coronary artery disease was mainly acute coronary syndrome (61%).

Most of patients were discharged with a normal left ventricular ejection fraction (mean 51.5%) and the absence of a severe kidney disease (mean eGFR 75 mL/Kg/min).

In terms of pharmacological therapy antiplatelet drug was taken by 93% and oral anticoagulant by 17.6% of patients; 95% of subjects were discharged with statin, 90.7% with beta-blockers and 70.2% with a rennin-angiotensin-aldosterone inhibitor.

All baseline characteristics and the cut-off values for each risk factor are reported in Table 1.

Model derivation

Table 2 shows the results of logistic regression analysis performed in our derivation dataset. The β coefficients represent the adjusted weight of each

variable in predicting outcome: the higher was the value, the heavier was the contribute of that factor in predicting mortality risks.

The highest β coefficients in our population were found for diabetes, atrial fibrillation and severe reduction of glomerular filtration rate (eGFR<30 mL/Kg/min). The history of acute coronary syndrome and the presence of PR or QTc intervals prolongation represent other significant risk factor in our predictive model; the low β coefficients of age were due to the analysis of this risk factor as linear variable in the binary logistic regressions.

The application of the REHAB score to the derivation dataset conducted to a mean value of 8.5% for overall mortality risk and 4.8% for CV mortality risk.

Validation

In terms of REHAB score mean values, the validation dataset showed a mean overall mortality risk of 7.8% and a mean CV mortality risk of 4.5%, both similar to those reported for the derivation dataset.

Goodness-of-fit test, performed in developmental and validation datasets, showed a good calibration for both overall and cardiovascular mortality risk predictive models.

Similarly, the area under ROC curves of developmental and validation datasets evidenced a satisfying discrimination power for both models (see Table 3).

DISCUSSION

From a registry of 1321 patients undergoing cardiac rehabilitation program after coronary artery bypass graft, we selected 1014 subjects to develop and validate the "Risk Estimation in coronary Heart disease patients After cardiac rehaBilitation" (REHAB) score, representing the first model created to estimate overall and cardiovascular mortality risk in this population.

The registries are a well-accepted research instrument helping physicians to evaluate cardiac rehabilitation programmes so as to improve their efficiency. In a recent systematic review, Poffley et al. analyzed the design and execution of these registries[33], with most of them collecting data on demographics, medical history, anthropometrics, clinical and psychosocial measures, and medication at cardiac rehabilitation enrollment and discharge. Apart from these similarities, these registries showed important limitations affecting their quality; service-level data and process methods were poorly reported, follow-up data were missing and evaluation of cardiac rehabilitation outcomes was limited[34], thereby lacking of data necessary to create predictive risk models.

From a secondary cardiovascular prevention prospective cohort study, such as the "Secondary Manifestations of ARTerial disease", Dorresteijn et al developed and validated the SMART score, largely employed to predict long-term recurrent events in subjects who suffered of various symptomatic arterial diseases[20]. Similarly, the current score evaluates the long-term mortality in secondary cardiovascular prevention; however, our predictive models have been tailored

to a more homogeneous population (CAD patients undergoing CABG) and all subjects completed an in-hospital CRP, a widely recognised approach able to reduce long-term mortality.

Moreover, our model adopted several well-known cardiovascular risk factors not included in the SMART score, such as serum uric acid levels, presence of atrial fibrillation and ECG intervals duration. Indeed, in secondary cardiovascular prevention, high SUA levels have been associated with adverse outcomes in post-myocardial infarction[35] and heart failure patients[36] and, in a recent paper, our group showed that high level of SUA was able to predict overall and cardiovascular mortality also in post CABG patients[29]. The presence of atrial fibrillation after cardiac surgery is a frequent finding. Recently, Gillinov et al. demonstrated no early mortality differences between rate versus rhythm control of AF in patients who underwent cardiac surgery[37]; differently, in our population the presence of AF at discharge represents a long-term mortality risk factor. Lastly, ECG intervals duration predictive role in CAD subjects has been largely demonstrated[38-40], although only pre-operative QTc prolongation has been correlated to mortality in CABG patients[41]; PR, QRS and QTc intervals prolongation showed to predict overall and cardiovascular death in our population, thereby usefully completing our model.

The evaluation of cardiovascular risk is one of the most important and difficult assignment for physicians working in a rehabilitation unit; therefore, in the era of evidence-based medicine, a selected scores availability can help to better

estimate individual mortality risk in a population uniformly considered at high cardiovascular risk. To achieve this goal we decided to create the REHAB score, whose composing risk factors, available in worldwide cardiac rehabilitation setting, could make it applicable in clinical practice.

Although validation tests confirmed a good calibration and discrimination power, these models tend to underestimate the risks for low value of REHAB score and overestimate them when REHAB score is higher than 8% and 5% for overall and CV mortality risk, respectively. However, considering that the Youden index and the best correlation between observed and predicted death are both set near the REHAB score mean values of this population, our data suggest that a patient with an overall and CV mortality REHAB score value >8% and/or >5%, respectively, should be considered as a high-risk subject.

Perspectives

Even though the ratio between the number of patients and that of variables included can be considered adequate for the analysis proposed, we were forced to exclude several risk factors that could contribute to improve the predictive power of the REHAB score, in order to minimize the risk for over-fitting the model. With an higher number of subjects in the dataset, in fact, we could insert additional parameters, such as the 6-minute walk test, a simple test largely used to estimate exercise capacity in cardiac rehabilitation setting[42], useful to increase calibration and discrimination power of our models.

Limitations

Although our models did result well performing in our validation dataset, they would need external validation in other post-CABG cardiac rehabilitation datasets.

Table 1 Baseline characteristics

Variables	Developmental cohort	Risk factors cut-off used
Age (years)	68.5 (9.7)	
Male sex	654 (79)	Presence
Active smoking	201 (24.3)	Presence
Diabetes	270 (32.6)	Presence
ACS	504 (60.9)	Presence
Other than isolated CABG	118 (14.3)	Presence
HR (bpm)	69.8 (10.9)	≥ 80
SBP (mmHg)	119 (10.3)	≥ 140
LVEF (%)	51.5 (9.5)	< 50
eGFR (mL/Kg/min)	75.5 (28.4)	60-30
		< 30
Serum uric acid (mg/dL)	4.8 (1.7)	≥ 6.0
Serum HDL (mg/dL)	28.9 (7.7)	< 30
Atrial fibrillation	50 (6)	Presence
PR duration (ms)	172.1 (30.9)	≥ 200
QRS duration (ms)	103.7 (24.6)	≥ 140
QTc duration (ms)	433.9 (32.5)	≥ 440

Data are expressed in numbers of patients (percentage) or mean value (SD)

ACS = acute coronary syndrome; CABG = coronary artery bypass graft; HR = heart rate; SBP = systolic blood pressure; LVEF = left ventricular ejection fraction; eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein.

Table 2 Logistic regression model of REHAB score in developmental datasets

Variables	Overall mortality β coefficients	Cardiovascular mortality β coefficients
Age (linear)	0.0401259	0.0476693
Male sex	0.1880767	0.3220967
Active smoking	0.2776298	0.2247654
Diabetes	0.9228462	0.9011921
ACS	0.6012335	0.5918602
Other than isolated CABG	0.2699687	0.0629451
Heart Rate	0.4113417	0.1146633
Systolic Blood Pressure	0.1214225	0.4373221
LVEF	0.1818968	0.4668247
eGFR 30-60 mL/Kg/min	0.1467939	0.0024037
eGFR <30 mL/Kg/min	1.4166323	1.6669868
Serum uric acid	0.3367077	0.7433131
Serum HDL	0.3333651	0.4473445
Atrial fibrillation	0.8367261	1.3493564
PR duration	0.5066515	0.3245575
QRS duration	0.2158149	0.1077891
QTc duration	0.6699215	0.4846982
Costant β_0	-7.2335533	-8.6310098

ACS = acute coronary syndrome; CABG = coronary artery bypass graft; HR = heart rate; SBP = systolic blood pressure; LVEF = left ventricular ejection fraction; eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein.

Table 3 REHAB score calibration & discrimination results

Datasets	Patients	Goodness-of-fit Chi square	Area under ROC curve
Developmental	828		
Overall mortality		7.45 (p= 0.49)	0.74 (p< 0.01)
CV mortality		12.62 (p= 0.13)	0.77 (p< 0.01)
Validation	194		
Overall mortality		5.91 (p= 0.66)	0.66 (p< 0.05)
CV mortality		6.93 (p= 0.54)	0.71 (p< 0.05)

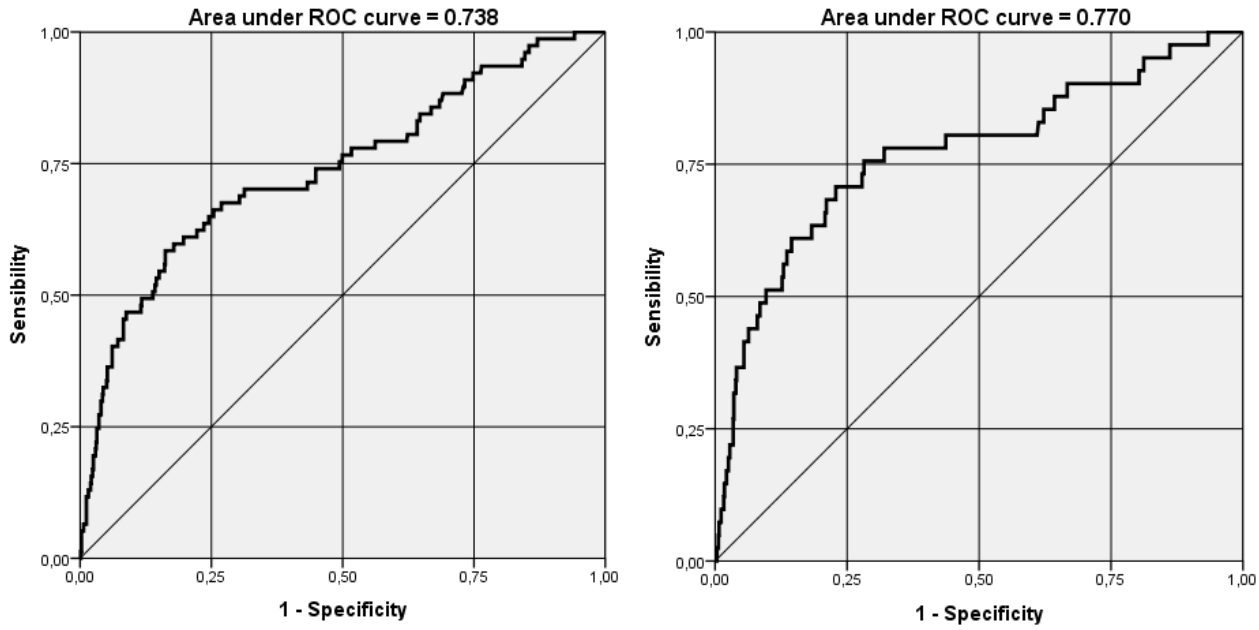

Fig. 1. **ROC curve graphs for overall (left) and cardiovascular mortality (right) developmental datasets.**

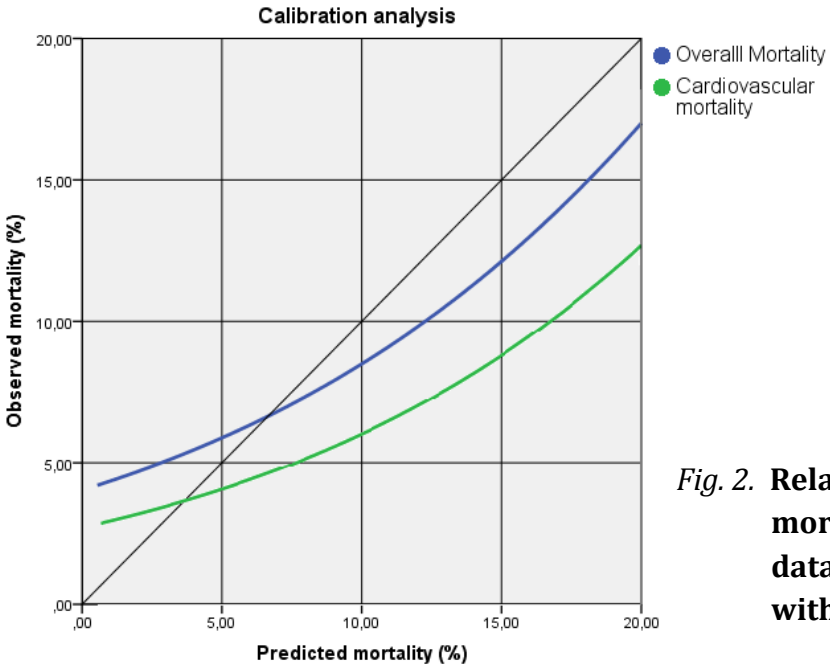

Fig. 2. **Relationship between observed mortality in developmental datasets and predicted mortality with REHAB score.**

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