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The metabolic exercise test data combined with Cardiac And Kidney Indexes (MECKI) score and prognosis in heart failure. A validation study

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ABSTRACT

Background: The Metabolic Exercise test data combined with Cardiac and Kidney Indexes (MECKI) score is a prognostic model to identify heart failure (HF) patients at risk for cardiovascular mortality (CVM) and urgent heart

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transplantation (uHT) based on 6 routine clinical parameters: hemoglobin, sodium, kidney function by the Modification of Diet in Renal Disease (MDRD) equation, left ventricle ejection fraction (LVEF), percentage of predicted peak oxygen consumption (VO2) and VE/VCO2 slope.
Objectives: MECKI score must be generalizable to be considered useful: therefore, its performance was validated in a new sequence of HF patients.
Methods: Both the development (MECKI-D) and the validation (MECKI-V) cohorts were composed of consecutive HF patients with LVEF <40% able to perform a symptom-limited cardiopulmonary exercise testing. The CVM or uHT rates were analyzed at one, two and three years in both cohorts: all patients with a censoring time shorter than the scheduled follow-up were excluded, while those with events occurring after 1, 2 and 3 years were considered as censored.
Results: MECKI-D and MECKI-V consisted of 2009 and 992 patients, respectively. MECKI-V patients had a higher LVEF, higher peak VO2 and lower VE/VCO2 slope, higher prescription of beta-blockers and device therapy: after the 3-year follow-up, CVM or uHT occurred in 206 (18%) MECKI-D and 44 (13%) MECKI-V patients ($p < 0.000$), respectively. MECKI-V AUC values at one, two and three years were 0.81 ± 0.04, 0.76 ± 0.04, and 0.80 ± 0.03, respectively, not significantly different from MECKI-D.
Conclusions: MECKI score preserves its predictive ability in a HF population at a lower risk.

1. Introduction

Several predictive models of outcome in heart failure (HF) have been proposed, but few of them have been implemented in the clinical practice. Showing that a prognostic model predicts outcomes in the development data is not sufficient to demonstrate its validity; indeed it must prove to equally perform in different patient populations with the same diagnosis [1–2].

In 2012, the Metabolic Exercise test data combined with Cardiac and Kidney Indexes (MECKI) score was suggested, to identify the risk of cardiovascular mortality (CVM) and urgent heart transplantation (uHT) [3]: it relies on six variables, hemoglobin (Hb), sodium (Na+), kidney function by means of the Modification of Diet in Renal Disease (MDRD) equation, left ventricle ejection fraction (LVEF) by echocardiography, percentage of predicted peak oxygen consumption (ppVO2), and minute ventilation-carbon dioxide production (VE/VCO2) slope. The MECKI score has not as yet been validated.

Therefore, the present study was designed to validate MECKI score's prognostic capacity in a new, distinct HF cohort.

2. Methods

2.1. Study population

Two HF cohorts were considered: a derivation cohort (MECKI-D), extrapolated from the original MECKI score study [3], and a validation cohort (MECKI-V). Consecutive HF patients were prospectively recruited: demographics records, etiology of HF, laboratory, ECG (sinus rhythm versus atrial fibrillation), echocardiographic, CPET and medical treatment data were collected at enrollment in both MECKI populations. Inclusion and exclusion criteria were those of the original MECKI study [3]. Inclusion conditions were previous or present HF symptoms and former documentation of left ventricular systolic dysfunction (LVEF <40%), stable clinical conditions with unchanged medications for at least three months, ability to perform a symptom-limited CPET, and no major cardiovascular treatment or intervention scheduled. Exclusion criteria were history of pulmonary embolism, moderate to severe aortic and mitral stenosis, pericardial disease, severe obstructive lung disease, exercise-induced angina and significant ECG alterations or presence of any clinical comorbidity interfering with exercise performance. Clinical, laboratory and echocardiographic data were assessed and calculated, as previously stated [3]: glomerular filtration rate was calculated as MDRD by using the following formula: $186.3*(\text{crea})^{-1.154}*(\text{Age})^{-0.203}$ *0.75 for women [4]. The MECKI score was calculated in all patients: it was computed as follows = 10.3464 + (−.0262*ppVO2) + (.0472*VE/VCO2 slope) + (−.1086* Hb) + (−.0615* Na) + (−.0699*LVFE) + (−.0136*MDRD).

2.2. Cardiopulmonary exercise test

Breath-by-breath analysis of expiratory gases and ventilation was performed. All CPETs were performed using either an electronically braked cycle ergometer or a treadmill; as in the original MECKI study [3], for a proper comparison, peak oxygen consumption (VO2) data measured on treadmill were reduced by 10% [5]. Ventilatory anaerobic threshold (VAT) was measured by V-slope analysis of VO2 and VCO2 [6], and it was confirmed by ventilatory equivalents and end-tidal pressures of CO2 and O2: VE/VCO2 slope was calculated as the slope of the linear relationship between VE and VCO2 from 1 min after the beginning of loaded exercise to the end of the isocapnic buffering period. Finally, predicted values of VO2 were calculated as: peak VO2 predicted =(Height-Age) *20 if male, =(Height-Age) *14 if female [6].

2.3. Patient follow-up and prognosis

Patient follow-up was carried out according to the local HF surveillance program, and end points were CVM or uHT in both populations. Patients who died of non-cardiovascular related causes or those who underwent non urgent HT were considered as censored at the time of the event. In agreement with the previous statistical procedure [3], all patients with a censoring time shorter than the scheduled follow-up thresholds (i.e. 1, 2 or 3 years) were excluded, while those with events occurring after those cutoff points were considered as censored.

2.4. Statistical analysis

Categorical variables, such as frequency and percentage, were compared by the chi-square test. Numerical variables were summarized as means ± SD. Student's unpaired t-test was used for group comparisons. Statistical significance was defined as $p < 0.05$. Survival was estimated by the product-limit Kaplan–Meier method, and differences between survival curves were tested with the log-rank $\chi 2$ statistic. The ability of MECKI score to correctly predict the occurrence of events was evaluated by receiver-operating characteristic (ROC) analysis. The equivalence of areas under the ROC curve (AUC) was tested according to Hanley et al. [5].

All analyses were performed using STATA data analysis and statistical software STATA/IC 11.1 (STATACorp LP, College Station, TX, USA).

3. Results

Although 2716 systolic HF patients were recruited in the original study, the MECKI-D consisted of 2009 patients, due to MECKI score missing records. Records were obtained from 13 and 17 Italian HF centers for MECKI-D and MECKI-V population, while the enrollment phase

lasted from March 1993 to June 2008 for the MECKI-D population, and from February 2002 to March 2013 for the MECKI-V cohort, respectively.

Age, BMI, MDRD and LVEF were higher in the MECKI-V cohort, as the percentage of patients with ischemic heart disease (IHD), and more patients were in NYHA I class, and less in NYHA III class (Table 1). A better exercise gas exchange profile was witnessed in MECKI-V patients: at the same peak respiratory exchange ratio (RER), patients showed a higher mean peak VO2 and ppVO2, while mean VE/VCO2 slope was reduced. Beta-blockers, loop diuretics, and anti-aldosteronic drugs were more prescribed in MECKI-V patients, while digitalis treatment was less recommended. Finally, more MECKI-V patients had an implantable cardioverter-defibrillator (ICD) (Table 1). Mean MECKI score was 0.105 ± 0.126 and 0.085 ± 0.101 ($p < 0.000$) in the MECKI-D and in the MECKI-V cohort, respectively.

No patient was lost to follow-up, and MECKI-V patients showed a better 3-year outcome (Fig. 1). According to the organization of the follow-up, 1756 and 825, 1406 and 591, and 1114 and 350 patients were evaluated in the MECKI-D and MECKI-V cohorts, respectively, at one, two and three-year follow-up. A higher percentage of devices (ICD) and beta-blocker treatment, mean LVEF, peak VO2 and ppVO2, and reduced VE/VCO2 slope were constantly observed in the MECKI-V population, as well as a higher percentage of patients in NYHA class I and a lower percentage of patients in NYHA class III (Table 2). A lower proportion of digitalis prescription was also constantly reported in the MECKI-V population, while mean MDRD, percentage of patients in atrial fibrillation (AF) and treated with amiodarone was lower in the MECKI-V cohort at one and two-year follow-up (Table 2). Survival was higher in MECKI-V vs MECKI-D cohort at all follow-up stages: study endpoints were registered in 83 (5%) vs 18 (2%) at one year ($p = 0.001$), 152 (11%) vs 30 (5%) at two years ($p < 0.000$) and 205 (18%) vs 44 (13%) at three years ($p < 0.000$), respectively. Of note, uHT was witnessed in 17, 29 and 43 patients, and 1, 4 and 4 patients, at one, two and three-year follow-up in MECKI-D and MECKI-V populations, respectively (NS). ROC curves AUC values of the MECKI-V cohort were similar those obtained in the MECKI-D, at the same follow-up period (Table 3), and ROC curves of the MECKI-V population are shown in Fig. 2.

Table 1
Patients' demographic, HF etiology and disease-related characteristics, medical and device therapy of the MECKI-D and MECKI-V cohorts.

Number of patients	MECKI-D	*p*	MECKI-V
	2009		992
Males (%)	1681 (84%)	0.673	824 (84%)
Age (years)	61 ± 12	0.021	62 ± 11
Body mass index (kg/m2)	25.6 ± 4	0.011	27.0 ± 4
Ischemic dilated cardiomyopathy (%)	975 (49%)	0.038	522 (53%)
NYHA class I (%)	194 (10%)	0.000	205 (21%)
NYHA class II (%)	1147 (57%)	0.152	539 (54%)
NYHA class III (%)	668 (33%)	0.000	248 (25%)
Atrial Fibrillation (%)	347 (17%)	0.014	136 (14%)
Implanted cardioverter defibrillator (%)	376 (19%)	0.000	418 (44%)
Angiotensin II receptor blockers (%)	332 (17%)	0.266	179 (18%)
Beta-blockers (%)	1578 (79%)	0.000	888 (90%)
Loop diuretics (%)	1603 (80%)	0.017	826 (83%)
Anti-aldosteronic drugs (%)	1048 (52%)	0.023	560 (57%)
Digoxin (%)	577 (29%)	0.000	97 (10%)
Amiodaron (%)	527 (26%)	0.550	247 (25%)
LVEF (%)	31 ± 8.9	0.000	33 ± 10.6
Hb (g/dL)	13.5 ± 1.6	0.501	13.6 ± 1.6
Na^+ (mmol/L)	139 ± 3.4	0.471	139 ± 3.2
Crea (mg/dL)	1.21 ± 0.40	0.123	1.18 ± 0.58
MDRD (mL/min)	69.3 ± 22	0.000	72.9 ± 25
Peak VO_2 (mL/kg/min)	14.2 ± 4.4	0.000	15.4 ± 4.7
Peak VO_2 (% of pred)	52.2 ± 15.5	0.000	58.7 ± 16.3
Peak RER	1.12 ± 0.12	0.121	1.11 ± 0.13
VO_2 at VAT (mL/kg/min)*	9.9 ± 3.1	0.000	10.4 ± 3.2
VE/VCO_2 slope	33.0 ± 7.6	0.000	31.9 ± 7.2
MECKI score	0.105 ± 0.126	0.000	0.085 ± 0.101

Abbreviations: MECKI = Metabolic Exercise test data combined with Cardiac and Kidney Indexes, MECKI-D = MECKI derivation cohort, MECKI-V = MECKI validation cohort, NYHA = New York Heart Association. LVEF = left ventricular ejection fraction. HB = serum hemoglobin, Na = serum sodium, Crea = serum creatinine, MDRD = Modification of Diet in Renal Disease, VO2 = oxygen consumption, RER = respiratory exchange ratio, VAT = ventilatory anaerobic threshold.

* When VAT has been identified.

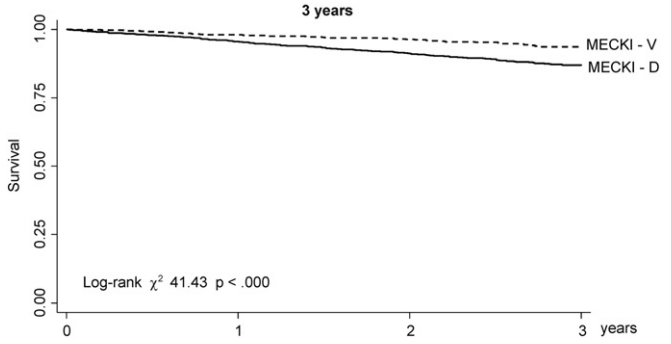

Fig. 1. Kaplan–Meier survival curves of MECKI-D and MECKI-V populations. MECKI-D = MECKI derivation population. MECKI-V = MECKI validation population.

4. Discussion

4.1. Study findings

The predictive power of MECKI score is evident in a HF population, with a better clinical, medical treatment and exercise profile, and a lower yearly event rate. This positive validation, together with the simplicity of MECKI score calculation, favors its utilization in daily HF routine practice.

4.2. Validation of a risk model

The performance of a risk score is typically overestimated in the original data [1], so validation is a crucial step to provide evidence about the performance in a different cohort [7]. Three validation strategies are recommended, separate or combined: internal, temporal and external validation [2]. Internal validation requires splitting the dataset randomly in two parts, developing the model using the first portion, and then verifying its predictive accuracy in the second portion: this approach tends to give optimistic results because the two datasets are very similar. In temporal validation, the model is tested on subsequent patients from the same center(s) [8–9]: temporal validation is a prospective assessment, independent of the original dataset and development process, and it is considered external in time [2]. External validation uses new data collected from a similar patient population gathered in a different center: fundamental design issues for external validation are sample selection and sample size [10–11].

4.3. Validation of a risk model in HF based on CPET data

Several CPET-based risk models have been recommended [12–16], mostly without validation. Myers et al. [15] developed a risk score based on 5 CPET variables — VE/VCO2 slope, oxygen uptake efficiency slope, resting end-tidal CO2 pressure (PET-CO2), heart rate (HR) recovery, and peak VO2 — to predict death, cardiac-related hospitalizations, HT, and left ventricular assist device (LVAD) implantation in HF patients. The optimal threshold was identified for each variable, then a "weighted" risk was assigned according to the hazard ratios: the resulting single-variable scores were summed to obtain the composite multivariable score. A summed score > 15 was associated with an annual mortality rate of 27%, whereas a score < 5 was associated with a mortality rate of 0.4% [14]. Myers's CPET risk model was validated in 2625

Table 2
Patients' demographic, HF etiology and disease-related characteristics, medical and device therapy of the MECKI-D and MECKI-V cohorts at one, two and three years follow up.

		1 Yr			2 Yrs			3 Yrs	
	MECKI-D	p	MECKI-V	MECKI-D	p	MECKI-V	MECKI-D	p	MECKI-V
Number of patients	1756		825	1406		591	1114		350
Males (%)	1467(84%)	0.864	687(84%)	1178(84%)	0.790	498(84%)	932 (84%)	0.864	295 (84%)
Age (years)	61.2 ± 12.2	0.051	62.2 ± 12.1	61 ± 12	0.021	62.5 ± 12	61 ± 12	0.003	63 ± 11
Body mass index (kg/m2)	26.6 ± 4.3	0.059	26.9 ± 4.4	26.5 ± 4.4	0.228	26.8 ± 4.3	26.4 ± 4	0.591	26.7 ± 4
Ischemic dilated cardiomyopathy (%)	864(49%)	0.481	431(52%)	691(49%)	0.489	305(51%)	560 (50%)	0.451	184 (53%)
NYHA class I (%)	168(10%)	0.000	164(20%)	133(9%)	0.000	111(19%)	105 (9%)	0.000	64 (18%)
NYHA class II (%)	1021(58%)	0.332	463(56%)	822(58%)	0.915	344(58%)	652 (59%)	0.332	205 (59%)
NYHA class III (%)	567(32%)	0.000	198(24%)	451(32%)	0.000	136(23%)	357 (32%)	0.002	81 (23%)
Atrial Fibrillation (%)	313(18%)	0.001	105(13%)	252(18%)	0.001	70(12%)	193 (17%)	0.001	47 (13%)
Implanted cardioverter defibrillator (%)	327(19%)	0.000	351(45%)	238(17%)	0.000	241(44%)	170 (15%)	0.000	151 (46%)
Angiotensin II receptor blockers (%)	288(16%)	0.519	143(17%)	227(16)	0.983	95(16%)	171 (15%)	0519	61 (18%)
Beta-blockers (%)	1365(78%)	0.000	737(90%)	1075(76%)	0.000	525(89%)	845 (76%)	0.000	316 (91%)
Loop diuretics (%)	1414(81%)	0.085	686(83%)	1147(82%)	0.444	489(83%)	936 (84%)	0.085	299 (86%)
Anti-aldosteronic drugs (%)	916(52%)	0.016	471(57%)	725(52%)	0.050	332(56%)	565 (51%)	0.076	196 (56%)
Digoxin (%)	542(31%)	0.000	81(10%)	475(34%)	0.000	56(10%)	411 (37%)	0.000	39 (11%)
Amiodaron (%)	476(27%)	0.073	195(24%)	380(27%)	0.010	126(21%)	294 (26%)	0.073	75 (21%)
LVEF (%)	31. ±8.9	0.000	32.6 ± 10.9	30.8 ± 8.9	0.000	32.7 ± 11.3	30 ± 8.8	0.000	33 ± 11.2
Hb (g/dL)	13.5 ± 1.6	0.817	13.5 ± 1.6	13.5 ± 1.6	0.503	13.5 ± 1.6	13.5 ± 1.6	0.817	13.6 ± 1.6
Na^+ (mmol/L)	139.5 ± 3.5	0.308	139.4 ± 3.1	139.4 ± 3.5	0.637	139 ± 3.2	139 ± 3.6	0.308	139 ± 3.3
Crea (mg/dL)	1.2 ± .4	0.229	1.18 ± .6	1.2 ± .39	0.638	1.19 ± .66	1.21 ± 0.40	0.229	1.23 ± 0.78
MDRD (mL/min)	69.4 ± 22	0.000	72.9 ± 23.8	69.4 ± 22.2	0.002	72.8 ± 23.5	69.5 ± 22	0.770	68.7 ± 24
Peak VO_2 (mL/kg/min)	14.2 ± 4.3	0.000	15.6 ± 4.8	14.1 ± 4.3	0.000	15.6 ± 4.9	14.2 ± 4.4	0.000	15.4 ± 4.7
Peak VO_2 (% of pred)	52.8 ± 15.5	0.000	59 ± 16.4	52.5 ± 15.4	0.000	58.7 ± 16.5	52.2 ± 15.5	0.000	58.0 ± 16.3
Peak RER	1.12 ± .13	0.707	1.12 ± .13	1.11 ± .13	0.320	1.12 ± .13	1.11 ± 0.10	0.707	1.12 ± 0.10
VO_2 at VAT (mL/kg/min)	10 ± 3.1	0.001	10.5 ± 3.2	10.1 ± 3.1	0.070	10.4 ± 3.17	10.2 ± 3.1	0.012	10.2 ± 2.7
VE/VCO_2 slope	33.1 ± 7.6	0.000	31.9 ± 7.2	33.4 ± 7.6	0.000	31.9 ± 7.1	33.7 ± 7.6	0.000	31.9 ± 7.0

Abbreviations: see Table 1. Yrs = years.

patients [16], 85% of whom were independent of the original sample: patients with both impaired and preserved LVEF were enrolled, and different type of adverse events were taken into account. Again, the summed risk score predicted outcomes with C indexes 0.70 for cardiac mortality and 0.72 for major events, respectively, and estimated one-year death rate of 12.2% in patients with a summed score of >15 and of 1.2% in those with a summed score < 5 [17].

Exercise variables were included in other prognostic models in HF [18–20], but only the Heart Failure Survival Score (HFSS) incorporated peak VO2: this score was evaluated in 268 ambulatory advanced HF patients (derivation sample), and it was prospectively validated in 199 similar patients [18]: outcome events were death without HT or urgent HT at 1 year. Freedom from events was significantly better in the derivation group than in the validation group (76 ± 3% versus 68 ± 4% at 1 year and 63 ± 3% versus 51 ± 5% at 2 years, respectively; p < 0.025), and, in the derivation cohort, the event-free survival rates at 1 year for the low, medium, and high-risk HFSS strata were 93 ± 2%, 72 ± 5%, and 43 ± 7%, respectively, while in the validation group they were 88 ± 4%, 60 ± 6%, and 35 ± 10% in the low, medium, and high-risk HFSS strata, respectively [18].

The MECKI score was developed in a large HF population, performing symptom-limited CPET [3]: at multivariable Cox analysis with subsequent cross validation, including more than 35 risk variables, only Hb, Na+, MDRD, LVEF, ppVO2, and VE/VCO2 slope resulted independently related to prognosis, and, on the basis of these 6 continuous variables, the MECKI score was defined to identify the risk of CVM and uHT. Moreover, an internal validation was performed, and a high concordance was detected between 2-year predicted and observed risk of event, stratified by decile of risk. The MECKI score AUC was 0.804 (0.754–0.852) at 1 year (1758 survivors and 83 events), 0.789 (0.750–0.828) at 2 years (1254 survivors and 152 events), 0.762 (0.726–0.799) at 3 years (1114 survivors and 205 events), and 0.760 (0.724–0.796) at 4 years (891 survivors and 246 events). It was concluded that the MECKI score is a simple, reliable, easy to calculate, personalized HF prognostic tool, with the high AUC values [3]. Albeit few reports have been generated from the MECKI score database, the MECKI score has not been validated, yet.

In the present study, the MECKI score model was validated in a new HF population, combining a temporal and an external confirmation process. The MECKI-V cohort was made up of 992 HF patients, prospectively enrolled, with inclusion/exclusion criteria and end-point events identical to those of the MECKI-D original study. Moreover, the statistical management of survival and event rate was analogous, as well [3]. MECKI-D and MECKI-V clinical and treatment features were significantly dissimilar, and, in particular, MECKI-V patients showed a higher LVEF, ppVO2 and MDRD, and a lower VE/VCO2 slope: accordingly, MECKI score was meaningfully divergent, lower in MECKI-V population. As regards outcomes, as expected, a lower occurrence of events was

Table 3
AUC values derived from receiver-operating characteristic (ROC) analysis with 95% interval of confidence in MECKI-D and MECKI-V cohorts. AUC were generated at one, two and three years.

	MECKI-D			MECKI-V			
	Patients observed	AUC	95% IC	Patients observed	AUC	95% IC	p AUC values
One year	1756	0.80 ± 0.02	0.75–0.85	825	0.81 ± 0.04	0.73–0.89	0.11
Two yrs	1418	0.79 ± 0.01	0.75–0.82	597	0.76 ± 0.04	0.68–0.84	0.29
Three yrs	1114	0.76 ± 0.01	0.72–0.80	350	0.80 ± 0.03	0.73–0.86	1.05

Abbreviations: see Table 1. Yrs = years. AUC = area under the curve, IC: interval of confidence.

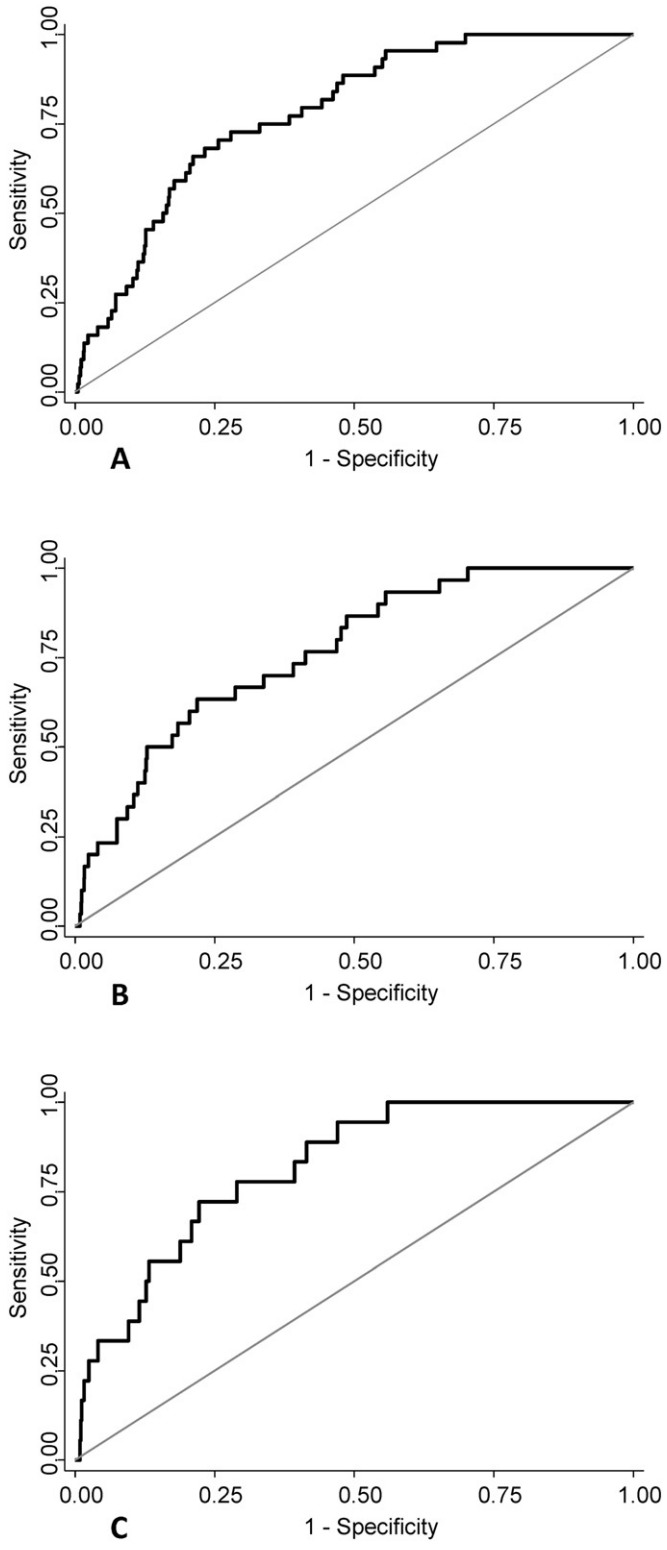

Fig. 2. Receiver-operating characteristic (ROC) analysis of the MECKI score at 1, 2, and 3 years for patients enrolled in the MECKI-V cohort. For abbreviations, see Table 3.

witnessed in the MECKI-V cohort at each of the 3 follow-up ending thresholds. Nonetheless, the MECKI score retained the predictive capacity to identify patients at risk of coming events. The AUC values generated by ROC analysis were good in the MECKI-V cohort at different follow-up closures, comparable to those observed in the MECKI-D cohort [3].

4.4. Limitations

At least two constraints should be mentioned. Due to technical motivations, i.e. the enrollment phase of MECKI-V, the sample size and the number of events observed later on, the follow up analysis was reduced to 3 years, so that a comparative analysis of MECKI score in MECKI-D and MECKI-V populations at 4 years was precluded. Moreover, MECKI score was validated to identify patients at risk, applying standard outcome events: different end points, such as LVAD implantation and cardiac-related hospitalizations, might have provided different results.

4.5. Conclusions

Guidance in efficient clinical decision-making requires accurate risk assessment; unfortunately, the paucity of validation studies justifies clinicians in not always trusting the probabilities provided by new risk models. The validation of MECKI score, together with the simplicity of the model with easy available measurements, legitimates its employment in daily HF routine as a prognostic tool.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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