ESC European Society of Cardiology

European Journal of Preventive Cardiology (2023) **30**, 1371–1379
https://doi.org/10.1093/eurjpc/zwad191

FULL RESEARCH PAPER
Heart failure and cardiomyopathies

International validation of the Metabolic Exercise test data combined with Cardiac and Kidney Indexes (MECKI) score in heart failure

Stamatis Adamopoulos[1], Dimitris Miliopoulos[1], Ewa Piotrowicz[2], Johan Aernout Snoek[3], Niki Panagopoulou[4], Serafim Nanas[5], David Niederseer[6], Reza Mazaheri[6], Jing Ma[7], Yundai Chen[8], Dejana Popovic[9,10], Petar Seferovic[9], Davide Girola[11], Ugo Corrà[12], Andrew J. S. Coats[13], Marco Metra[14], Giuseppe M. C. Rosano[15], Maurizio Volterrani[15], Anna Apostolo[16], Jeness Campodonico[16], Elisabetta Salvioni[16], Piergiuseppe Agostoni[16,17†], and Massimo Piepoli[18,19]*†

[1]Heart Failure and Heart Transplant Units, Onassis Cardiac Surgery Centre, Leof. Andrea Siggrou 356, Kallithea, 176 74, Attica, Greece; [2]Telecardiology Center, National Institute of Cardiology, Alpejska 42, 04-628 Warszawa, Poland; [3]Department of Sports Medicine and Cardiology, Dokter Van Heesweg 2, 8025 AB Zwolle, Netherlands; [4]Department of Cardiology, 'Helena Venizelou' Hospital, Elenas Venizelou 2, Athina 115 21, Greece; [5]Department of ICU, 'Evangelismos' Hospital, Ipsilantou 45-47, Athina 106 76, Greece; [6]Department of Cardiology, University Heart Center Zurich, University of Zurich, Rämistrasse 100, 8091 Zürich, Switzerland; [7]Department of Cardiology, First Medical Center of PLA General Hospital, 28 Fuxing Road, 100853 Beijing, China; [8]Department of Cardiology, Sixth Medical Center of PLA General Hospital, 6 Fucheng Road, Beijing, Cina, 100053; [9]Department of Cardiology, Clinical Center of Serbia, University Clinical Center of Serbia, Pasterova 2, 11000 BelgradE, Serbia; [10]Department of Cardiovascular Medicine, Mayo Clinic, 200 First street SW, Rochester, MN 55905, USA; [11]Capo Clinica, Clinica Hildebrand, Centro di riabilitazione Brissago, Via Crodolo 18, 6614 Brissago, Switzerland; [12]Istituti Clinici Maugeri, IRCCS, Via Revislate, 13 · 0322, Veruno, Italy; [13]Office of the CEO, Heart Research Institute, 7 Eliza St, Newtown NSW 2042, Sydney, Australia; [14]Cardiology, University of Brescia, Piazza del Mercato, 15, 25121, Brescia, Italy; [15]Cardio-Pulmonary Department, IRCCS San Raffaele La Pisana, Via della Pisana, 235. 00163 Roma, Italy; [16]Heart Failure Unit, Centro Cardiologico Monzino IRCCS, Via Parea 4, 20138, Milano, Italy; [17]Department of Clinical Sciences and Community Medicine, University of Milan, Via Festa del Perdono, 7, 20122 Milano, Italy; [18]Clinical Cardiology, IRCCS Policlinico San Donato, Via Morandi 30, 20097 Milan, Italy; and [19]Department of Biomedical Sciences for Health, University of Milan, Via Festa del Perdono, 7, 20122 Milano, Italy

Received 3 April 2023; revised 5 May 2023; accepted 1 June 2023; online publish-ahead-of-print 8 June 2023

Aims

Current European heart failure (HF) guidelines suggest the use of risk score: among them, the Metabolic Exercise test data combined with Cardiac and Kidney Indexes (MECKI) score has demonstrated to be one of the most accurate. However, the risk scores are still poorly implemented in clinical practice, also due to the lack of strong evidence regarding their external validation in different populations. Thus, the current study was designed as an external validation test of the MECKI score in an international multicentre setting.

Methods and results

The study cohort consisted of patients diagnosed with HF with reduced ejection fraction (HFrEF) across international centres (not Italian), retrospectively recruited. Collected data included demographics, HF aetiology, laboratory testing, electrocardiogram (ECG), echocardiographic findings, and cardiopulmonary exercise testing (CPET) results as described in the original MECKI score publication. A total of 1042 patients across 8 international centres (7 European and 1 Asian) were included and followed up from 1998 till 2019. Patients were divided according to the calculated MECKI scores into three subgroups: (i) MECKI score <10%, (ii) 10–20%, and (iii) ≥ 20%. Survival analysis comparison among the three MECKI score subgroups showed a worse prognosis in patients with higher MECKI score value: median event-free survival times were 4396 days for MECKI score <10%, 3457 days for 10–20%, and 1022 days for ≥20% ($P < 0.0001$). Receiver operating characteristic (ROC) curves and area under the ROC curves (AUC) were like those reported in the original internal validation studies.

* Corresponding author. Tel: +39 0252774966, Email: massimo.piepoli@unimi.it
† The last two authors contributed equally to the study.

Conclusion In patients diagnosed with HFrEF, the power of the MECKI score was confirmed in terms of prognosis and risk stratification, supporting its implementation as advised by the HF guidelines.

Keywords External validation heart failure • Prognosis risk score • Risk stratification

Introduction

Heart failure (HF) is a major public health issue with a current prevalence of over 23 million worldwide.[1] Despite major drug and device therapy advances, its prognosis remains still very poor. In the Olmsted County cohort for all types of HF patients, 1-year and 5-year mortality rates were 20% and 53%, respectively, between 2000 and 2010.[2] A study combining the Framingham Heart Study and Cardiovascular Health Study cohorts reported a 67% mortality rate within 5 years following diagnosis.[3]

Consequently, the number of HF patients who progress to end-stage disease requiring advanced mechanical circulatory support and/or heart transplant (HTx) is increasing which is in contrast with the limited number of available organs and with 20% 1-year mortality rate whilst on the waiting list.[4] Prioritization strategies aiming to mitigate the growing discrepancy between the number of available organs and potential recipients have been developed by healthcare authorities. The decision of listing appropriate candidates for HTx will be even more common and difficult for the physician dealing with HF. This is especially true for non–inotrope-dependent ambulatory patients, as avoiding delays in the listing of patients with higher risk needs to be carefully weighed against the deferral of less sick patients. Thus, there is a relevant need of a correct identification of the prognosis in the HF patients.

Over the last 3 decades, a number of scores combining several variables have been devised to aid the clinician in assessing patient prognosis. In 2013, the Metabolic Exercise test data combined with Cardiac and Kidney Indexes (MECKI) score was proposed by an Italian working group, to identify the risk of cardiovascular (CV) mortality and urgent heart HTx.[5,6] It relies on six variables: haemoglobin (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 (ppVO_2), and minute ventilation–carbon dioxide production (VE/VCO_2) slope. The above variables are well recognized prognostic markers, in HF, reflecting the complexity and the multi-organ involvement of this syndrome: they have been identified after multivariate analyses in large populations.[5,6]

The MECKI score was subsequently externally validated again by an Italian working group, based originally on 17 HF centres with a database of 2716 patients diagnosed with HF, followed up to 4 years.[7]

In recent comparisons, the MECKI score revealed good discriminative ability, higher than other common scores, such as Heart Failure Survival Score (HFSS), Seattle Heart Failure Model (SHFM), and Meta-analysis Global Group in Chronic Heart Failure (MAGGIC).[8,9] The Freitas *et al.* study[10] showed that the MECKI score can also be used with the advantage of being very well calibrated at 1-year intervals that might allow us to avoid the pitfalls of under- or over-estimation of the risk. However, still, few of the risk score are implemented in the clinical practice, also due to the lack of strong evidence regarding their external validation in different populations.[11]

The current study was designed as an external validation attempt of the MECKI score in an international multicentre cohort.

Methods

Study population

The study cohort consisted of consecutive patients diagnosed with HF from eight international centres (not Italian), retrospectively recruited between 1997 and 2019, and specifically analysed for the present study. Ethical Committee Approval was obtained by the coordinating centre (Onassis Cardiac Surgery Centre, protocol number 760/2022) and subsequently submitted in each centre. Inclusion criteria were (i) previous or present HF symptoms, (ii) history of reduced left ventricular systolic dysfunction (LVEF ≤ 45%), (iii) stable clinical condition without change in medication regimen in the last 3 months, (iv) no planned major CV treatment or intervention, and (v) performance of a maximal cardiopulmonary exercise testing (CPET), regardless of the respiratory exchange ratio reached with a ramp exercise protocol (steps no longer than 1 min) by treadmill or cycle ergometer with continuous respiratory gas and ventilation measurements. Exclusion criteria were history of pulmonary embolism, significant valve diseases, severe obstructive lung disease, exercise-induced angina, and significant electrocardiogram (ECG) alterations or presence of any clinical comorbidity interfering with exercise performance.

Clinical, laboratory, echocardiographic, and cardiopulmonary exercise testing data

Collected data included demographics, HF aetiology, laboratory findings, ECG, echocardiographic data, CPET results, and treatment. All measurements were taken within the same day. The included clinical, laboratory, and echocardiographic data were collected as described in the original MECKI score publication.[5] In this context, glomerular filtration rate (GFR) was calculated by the MDRD formula: estimated GFR (eGFR) = $186.3 \times (\text{creatinine})^{-1.154} \times (\text{age})^{-0.203}$ for male patients and $186.3 \times (\text{creatinine})^{-1.154} \times (\text{age})^{-0.203} \times 0.75$ for female.

Cardiopulmonary exercise testing was performed according to the protocols used in each centre without any adjustments for the current study. Predicted values of peak VO_2 were calculated according to the original study as follows: predicted peak VO_2 = (height−age) × 20 if male or (height−age) × 14 if female. For proper comparison, peak VO_2 data measured on treadmill were reduced by 10% as in the validation study.[3]

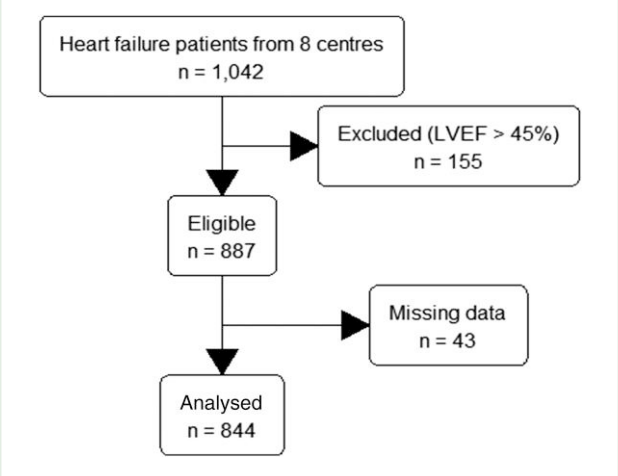

Figure 1 The study flowchart. Data from 1042 patients were collected. A total of 155 patients were excluded due to a reported LVEF > 45%, and a further 43 patients were excluded due to missing data. The analysed population consisted of 844 patients.

Table 1 Patient demographics

Parameters	Units	Present study ($n = 844$)	MECKI-D ($n = 2009$)	MECKI-V ($n = 992$)
Age	Years	55.1 ± 13.1	61.0 ± 12.0****	62.0 ± 11.0****
Sex	Males (%)	692 (82%)	1681 (84%)	824 (84%)
BMI	kg/m^2	27.3 ± 4.7	26.5 ± 4.0****	27.0 ± 4.0
Aetiology	*n* (%)	Idiopathic: 317 (37.5)	Ischaemic: 975 (49)	Ischaemic: 522 (53)
		Ischaemic: 433 (51.3)		
		Valvular: 44 (5.2)		
		Other: 50 (5.9)		
NYHA class	*n* (%)	I: 95 (11.2)	I: 194 (10)	I: 205 (21)****
		II: 401 (47.5)	II: 1147 (57)*	II: 539 (54)
		III: 328 (38.8)	III: 668 (33)	III: 248 (25)****
		IV: 20 (2.3)	IV: -	IV: -
AF	*n* (%)	166 (19.6)	347 (17)	136 (14)**
Pacemaker	*n* (%)	86 (10.1)	—	—
ICD	*n* (%)	315 (37.3)	376 (19)****	418 (44)
CRT	*n* (%)	127 (15.0)	—	—
Beta-blockers	*n* (%)	754 (89.3)	1578 (79)*	888 (90)
ACE-I	*n* (%)	607 (71.9)	—	—
ARB	*n* (%)	133 (15.7)	332 (17)	179 (18)
Loop diuretics	*n* (%)	595 (70.5)	1603 (80%)	826 (83)*
MRA	*n* (%)	603 (71.4)	1048 (52)****	560 (57)**
Amiodarone	*n* (%)	174 (20.6)	527 (26)*	247 (25)
Digoxin	*n* (%)	146 (17.3)	577 (29)****	97 (10)****
LVEF	%	29.4 ± 8.3	31.0 ± 8.9****	33.0 ± 10.6****
Haemoglobin	g/dL	13.8 ± 1.6	13.5 ± 1.6****	13.6 ± 1.6***
Na^+	mmoL/L	139.1 ± 3.4	139.0 ± 3.4	139.0 ± 3.2
Creatinine	mg/dL	1.1 ± 0.4	1.2 ± 0.4*	1.1 ± 0.5
eGFR (MDRD equation)	mL/min	74.5 ± 25.6	69.3 ± 22.0****	72.9 ± 25.0
Peak VO_2	mL/kg/min	14.1 ± 4.9	14.2 ± 4.4	15.4 ± 4.7****
Peak VO_2	% predicted	64.3 ± 21.6	52.2 ± 15.5****	58.7 ± 16.3****
VE/VCO_2 slope		34.5 ± 9.6	33.0 ± 7.6****	31.9 ± 7.2****
MECKI score	%	4.7 (1.9–14.1)	10.5 ± 12.6**	8.5 ± 10.1**

Comparison of patient demographics, HF aetiology, and disease-related characteristics in the present study population and in the MECKI-D and MECKI-V populations described in Corrà *et al.* [7]

ACE-I, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter–defibrillator; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist.

*$P \leq 0.05$, **$P \leq 0.01$, ***$P \leq 0.001$, ****$P \leq 0.0001$ vs. present study.

The MECKI score was calculated in all patients as follows: $e^c/(1 + e^c)$ where $c = 10.3464 + (-0.0262 \times \text{predicted peak } VO_2) + (0.0472 \times VE/VCO_2 \text{ slope}) + (-0.1086 \times \text{haemoglobin}) + (-0.0615 \times \text{sodium}) + (-0.0699 \times \text{LVEF}) + (-0.0136 \times \text{eGFR})$ (https://www.cardiologicomonzino.it/en/mecki-score/#).

To quantify the outcome according to the MECKI score, the studied patients were categorized according to the calculated scores into three predefined subgroups: (i) MECKI score <10%, (ii) 10–20%, and (iii) ≥ 20%.

Patient follow-up and outcomes

Patient follow-up was carried out according to the HF programmes used in each centre. Endpoints were CV mortality, urgent HTx, or ventricular assist device (VAD) implantation. Patients were considered censored at the time of the endpoint event according to the methods of the original study.[3,4]

Statistical analysis

Continuous variables were examined by q-plots for normal distribution and described as means ± standard deviation (SD) or, in case of not normal distribution, as median and interquartile range (IQR). Categorical variables were described as frequency and percentage.

Comparisons between the here presented findings and the ones from the validation[7] studies in terms of patients' characteristics were analysed by unpaired *t*-test for normally distributed data, Wilcoxon test as a non-parametric alternative, and χ^2 test as appropriate. Differences between MECKI score groups were evaluated by ANOVA and χ^2 test along with post-hoc analysis when needed. The ability of the MECKI score to correctly predict the occurrence of events has been tested by receiver operating characteristic (ROC) and area under the ROC curve (AUC) analyses.

Kaplan–Meier curves are presented as part of the survival analysis, and their differences are tested with the log-rank test, whilst multiple comparisons were accounted with the Bonferroni method. Statistical significance was defined as $P \leq 0.05$.

All analyses were performed using R version 4.0.3 and RStudio version 1.3.1073 with packages survminer[12] for survival analysis and time ROC[13] for ROC analysis.

Table 2 Patient characteristics divided according to the calculated MECKI scores divided into three subgroups: (i) MECKI score <10%, (ii) 10–20%, and (iii) ≥ 20% (mean ± SD)

Parameters	Units	MECKI score < 10% (*n* = 573)	MECKI score 10–20% (*n* = 128)	MECKI score ≥ 20% (*n* = 143)
Age	Years	54.8 ± 13.0	56.6 ± 12.6	55.1 ± 14.0
Sex	Male (%)	464 (80.9%)	104 (81.3%)	124 (86.7%)
BMI	kg/m^2	27.7 ± 4.61	27.5 ± 4.86	25.9 ± 4.8***
HF aetiology	*n* (%)			
Idiopathic		210 (36.7%)	54 (42.2%)	53 (37.1%)
Ischaemic		301 (52.5%)	55 (43.0%)*	77 (53.9%)
Valvular		29 (5.1%)	8 (6.3%)	7 (4.9%)
Other		33 (5.7%)	11 (8.6%)	6 (4.2%)
NYHA class	*n* (%)			
I		86 (15.0%)	6 (4.7%)**	3 (2.1%)***
II		316 (55.2%)	47 (36.7%)***	40 (28.0%)****
III		163 (28.5%)	70 (54.7%)****	93 (65.0%)****
IV		8 (1.4%)	5 (3.9%)	7 (4.9%)
AF	*n* (%)	89 (15.5%)	28 (21.9%)	49 (34.3%)****
CRT	*n* (%)	72 (12.6%)	24 (18.8%)	31 (21.7%)*
LVEF	%	32.6 ± 7.62	24.5 ± 5.91****	21.4 ± 5****
Peak VO_2	% predicted	72.5 ± 19.7	53.5 ± 12.8****	41.1 ± 11.5****
Na^+	mmoL/L	140.0 ± 3.1	138.0 ± 3.4****	137 ± 3.6****
Hb	g/dL	14.1 ± 1.6	13.8 ± 1.5	12.9 ± 1.7****
eGFR	mL/min	80.5 ± 25.2	65.6 ± 21.6****	59.1 ± 21.6****
VE/VCO_2 slope	—	30.4 ± 5.5	39.4 ± 7.1****	46.9 ± 11.7****

eGFR, estimated glomerular filtration rate. For the remaining abbreviations, refer to *Table 1*.
*$P \leq 0.05$, **$P \leq 0.01$, ***$P \leq 0.001$, ****$P \leq 0.0001$ vs. MECKI score < 10% group.

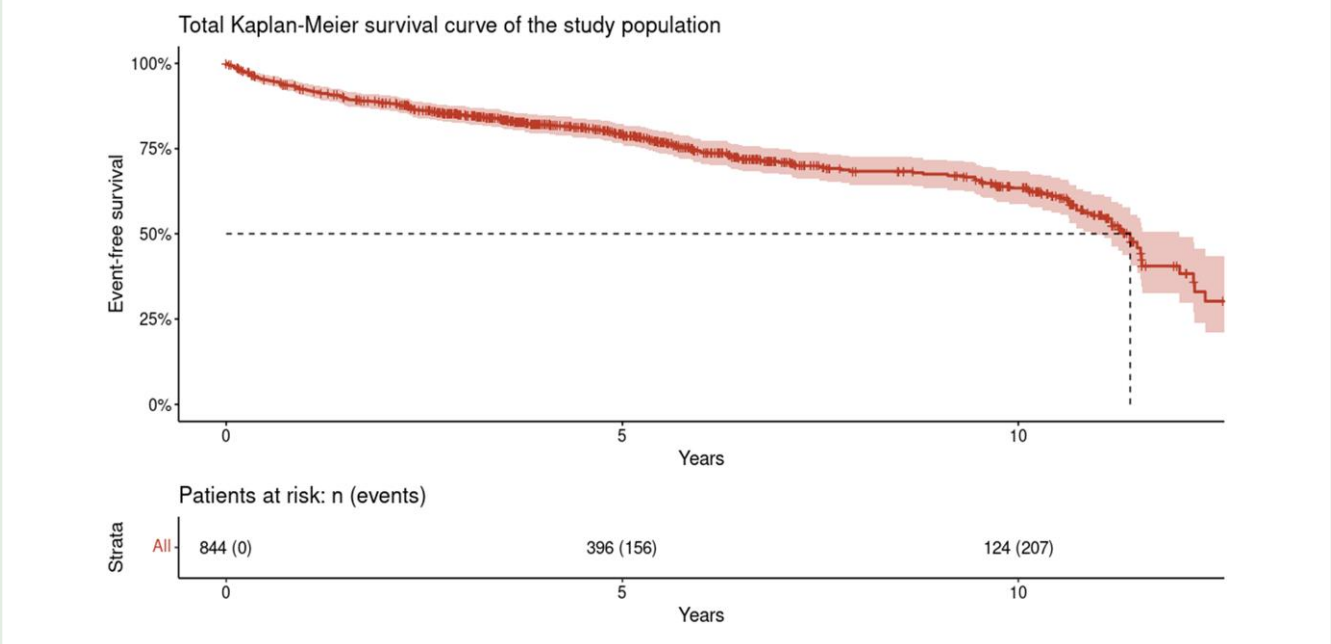

Figure 2 Kaplan–Meier survival curve of the analysed population. The median event-free survival time of the whole sample was 4168 days (11.4 years).

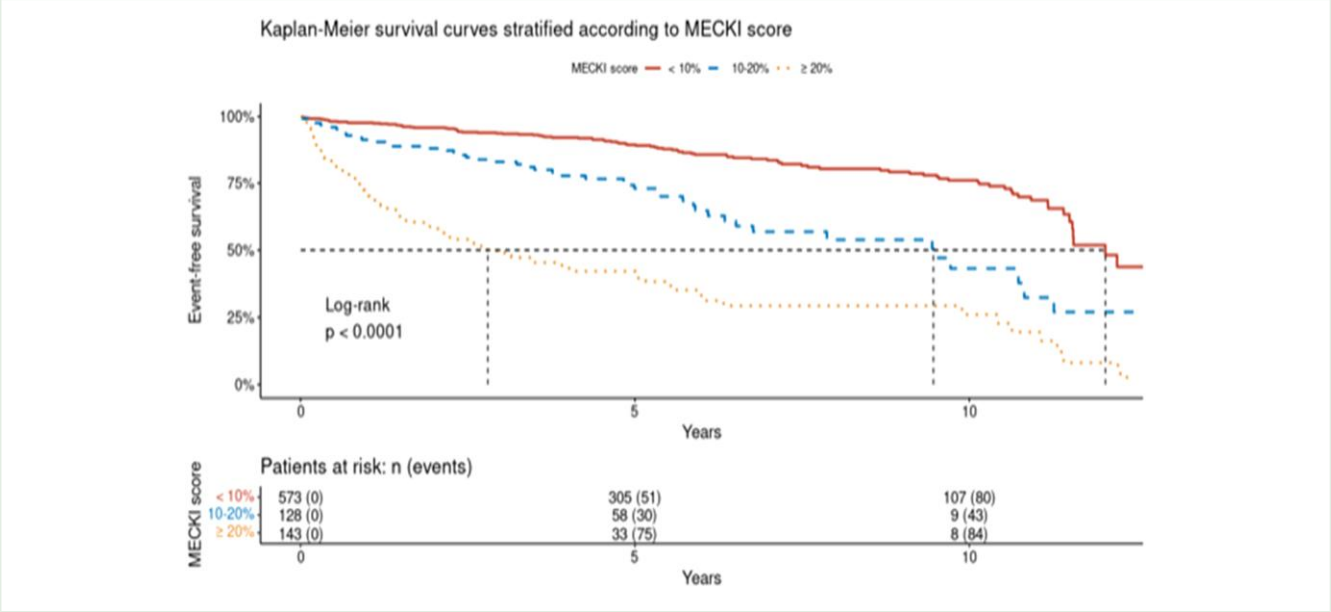

Figure 3 Subgroup Kaplan–Meier survival curves. The population was categorized according to MECKI score values (<10%, 10–20%, and ≥ 20%). The median event-free survival times were 4396 days (12 years) for MECKI score <10%, 3457 days (9.5 years) for 10–20%, and 1022 days (2.8 years) for ≥20% ($P < 0.0001$).

Results

Study population

The flowchart of the study is shown in *Figure 1*. In total, 1042 patients across 8 international centres (7 European and 1 Asian) were included in the study. Of them, 155 patients were excluded due to a reported LVEF > 45%. Of the 887 remaining eligible patients, 43 patients were excluded due to missing MECKI score variables, and finally, 844 were included in the study. Supplementary material online, *Table S1*, presents the distribution of study populations according to the participating centres. Patients were followed up from 1998 to 2019.

Patients' demographics, clinical, laboratory, echocardiographic, and CPET data are reported in *Table 1* along with the comparisons between this population and the two previous MECKI score populations reported by Corrà *et al.*:[7] on the average, the present study sample consists of younger population, but of comparable gender distribution, lower LVEF and peakVO_2 (but higher ppVO_2), and higher VE/VCO_2 slope. Medical management was also different with more patients receiving mineralocorticoid receptor antagonists and fewer digoxin.

Metabolic Exercise test data combined with Cardiac and Kidney Indexes score subgroups

Patients were divided according to the calculated MECKI scores into three subgroups, whose characteristics of each subgroup are presented in *Table 2*. A progressive worsening of the clinical parameters [higher New York Heart Association (NYHA) functional class, atrial fibrillation, and VE/VCO_2 slope and lower LVEF, peakVO_2, and eGFR] was associated with increasing MECKI score values.

Survival analysis

In total, there were 263 events: 234 were due to CV causes (89%: 101 deaths, 58 urgent HTx, and 75 VAD implantations), and 29 were due to non-CV causes (11%), the latter being censored at the time of the event.

Study endpoints were registered in 63 (7.5%), 95 (11.3%), and 122 (14.6%) patients at 1, 2, and 3 years, respectively: CV death occurred in 12 (1.4%), 19 (2.3%), and 30 (3.6%); HTx in 24 (2.8%), 37 (4.4%), and 43 (5.1%); and VAD implantation in 27 (3.2%), 39 (4.6%), and 49 (5.8%) at 1, 2, and 3 years, respectively. The median event-free survival time of the whole sample was 4168 days (11.4 years) (*Figure 2*).

Survival analysis comparison among the three MECKI score subgroups showed a worse prognosis in patients with higher MECKI score value (*Figure 3*): median event-free survival times were 4396 days (12 years) for MECKI score <10%, 3457 days (9.5 years) for MECKI score 10–20%, and 1022 days (2.8 years) for MECKI score ≥20% ($P < 0.0001$).

Receiver operating characteristic analysis

Receiver operating characteristic curves for the first 10 years of follow-up are presented on *Figure 4* and the AUC curve on *Figure 5*: AUC also remains > 0.77 for the 10-year period though with progressively increasing confidence intervals (*Table 3*). The AUC values are similar if not better compared with those reported in the original (0.80 ± 0.02, 0.79 ± 0.01, and 0.76 ± 0.01 at 1, 2, and 3 years, respectively) and validation study (0.81 ± 0.04, 0.76 ± 0.04, and 0.80 ± 0.03 at 1, 2, and 3 years, respectively).[7]

Discussion

The MECKI score was originally developed, based on a large (>2500 patients) Italian HF population who underwent symptom-limited CPET, through a multivariable Cox analysis including several variables of which only the aforementioned 6 were associated with prognosis for CV mortality and urgent HTx. However, a prognostic model is only representative of the population from which it was developed, regardless of how large it may be. Validation studies are necessary

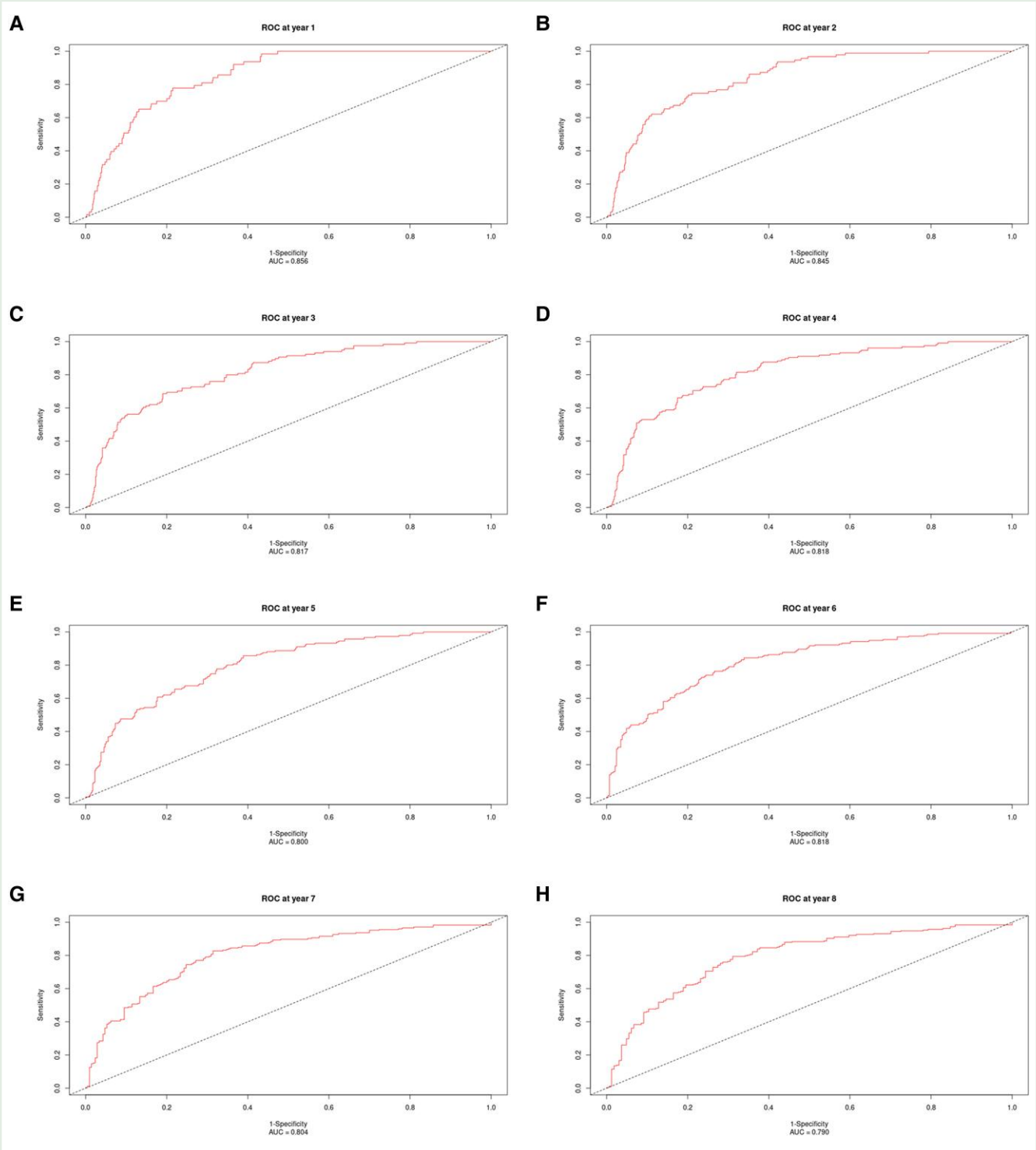

Figure 4 Receiver operating characteristic (ROC) curves for the first 10 years of follow-up.

to prove the applicability and efficacy of the model to the general population.

The MECKI score has been subjected to an internal (validated to a part of the original population which was not included in the model development)[7] and a temporal (usage of a different population in time by the same centre) validation with remarkable results, suggesting a predictive capability of at least 3 years.[14] However, these types of validation do not examine the generalizability of the model which is the role of external validation. External validation was here performed by researchers who do not have access to the original data but do have an

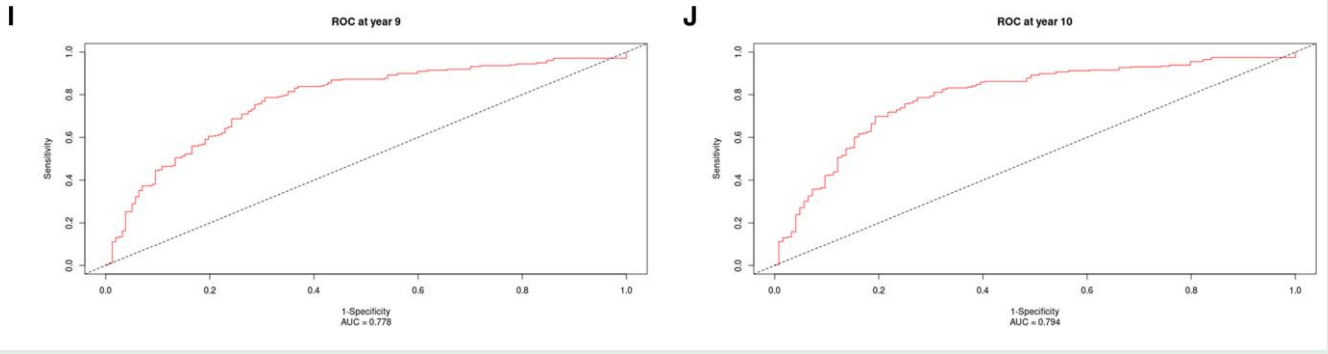

Figure 4 (Continued)

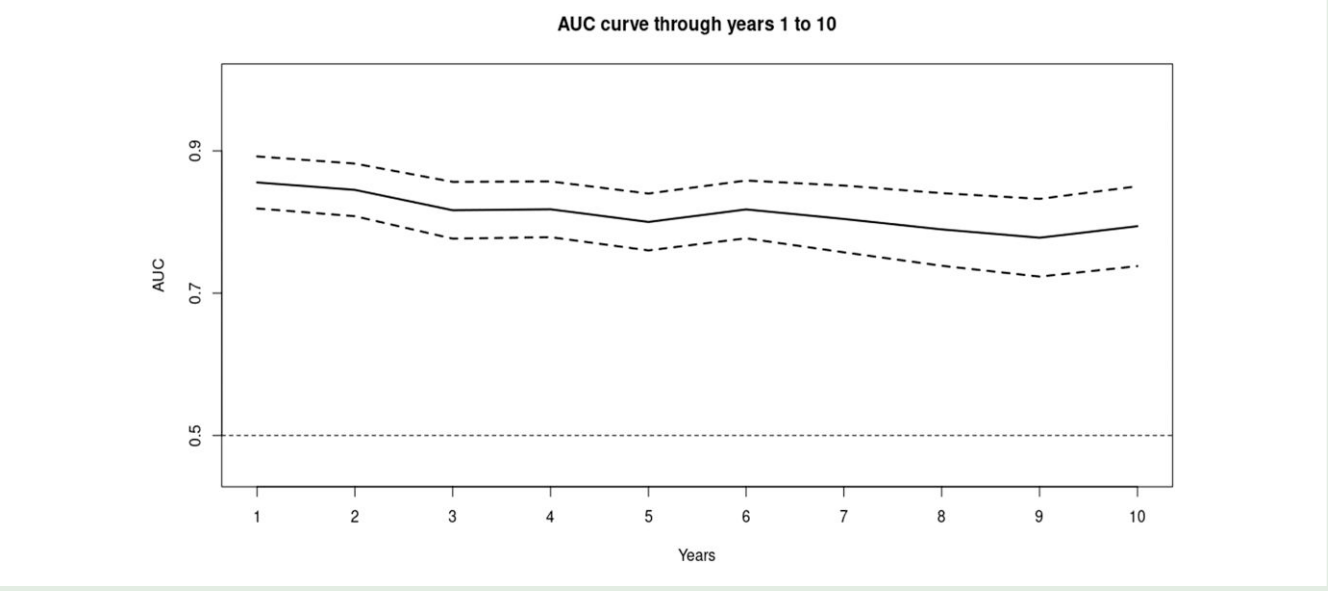

Figure 5 Area under the ROC curve (AUC) for the first 10 years of follow-up.

independent sample on which to evaluate the performance of the model.

Patients' demographics, clinical, laboratory, echocardiographic, and CPET data are reported in *Table 1* along with comparisons between this population and the ones from the original and validation[4] studies, proving its heterogeneity which is important in an external validation setting.

One hundred fifty-five patients were excluded because at enrolment LVEF was >45%. This is different from what was originally done in the MECKI score study. However, we introduced this further criterion to select a population with at least moderate HF. Indeed, in the present study, LVEF was lower compared with original MECKI score and to the validation study (*Table 1*) as reported by Corrà *et al.*[7]

Regarding the power of external validation studies, an adequate number of both patients and events should be achieved for adequate power. In general, as a rule of thumb, it is suggested to have at least 100 events and 100 non-events in the sample.[15] In our case, there were 263 events, more than enough to prove the validity of the MECKI score. It must be underlined that the recruitment of the present study population as well as that of the original MECKI score population was very long. This is the strength of the MECKI score which remains meaningful regardless the HF treatment strategies which have changed with time.

The prognostic stratification in patients with HF is fundamental to guide pharmacologic therapy and device implantation. It is also a very useful tool to guide HTx listing. In the past, the only scores that were recommended in this setting were the SHFM and the HFSS.[16] The over- and underestimation of risk (especially in the highest risk groups) which have been recently shown with the above scores can have a significant impact on treatment decisions, such as HTx listing. Accordingly, we recommend the implementation for HF prognostication of scores that include also findings from CPET, such as MECKI one, to better stratify this high-risk population.

The more recent European guidelines on HF diagnosis and treatment have finally acknowledged the value of the prognostic score (and in particular of the MECKI), where its use in clinical practice is advised.[17]

Table 3 Area under the ROC curve (AUC) values with 95% confidence intervals (CI) from year 1 to year 10

Years	Patients observed (*n*)	AUC (%)	95% CI
1	754	0.856 ± 0.02	0.819–0.892
2	705	0.845 ± 0.02	0.808–0.882
3	605	0.817 ± 0.02	0.777–0.856
4	475	0.818 ± 0.02	0.779–0.857
5	396	0.800 ± 0.02	0.760–0.840
6	286	0.818 ± 0.02	0.777–0.858
7	210	0.804 ± 0.02	0.757–0.851
8	164	0.790 ± 0.03	0.739–0.841
9	157	0.778 ± 0.03	0.723–0.833
10	124	0.794 ± 0.03	0.738–0.850

Limitations

This study has several limitations that should be acknowledged. First, due to its retrospective nature, the possible influences of confounders cannot be excluded. Secondly, natriuretic peptides were not regularly measured at patient enrolment. Indeed, BNP/NTproBNP would have helped the assessment of HF severity. However, in the present analysis, we took into consideration the peak VO_2, a reliable index of HF severity. Thirdly, MECKI score inclusion criteria include the capability and willingness to perform a maximal CPET. This is a relevant study factor, because the most severe HF patients were excluded: thus, only patients with moderate HF (average peak VO_2 64% of predicted value) were included in the present study. Further studies are needed with a larger population with moderate/severe heart failure since only 143 patients had a MECKI score >20%. Fourthly, we analysed patients with HFrEF, so that our findings cannot be extended to patients with preserved or mildly reduced LVEF or to patients with comorbidities that implied exclusion from the MECKI score database, such as severe chronic obstructive pulmonary disease (COPD), moderate-to-severe aortic and mitral stenosis, congenital heart diseases, recent myocardial infarction, exercise-induced angina or severe arrhythmias, or presence of any clinical comorbidity interfering with exercise performance. Consequently, the MECKI score population is not closely representative of a general HF population. Finally, it should be acknowledged that the sample size was limited (but this was at least partially compensated by the long follow-up), 5% of the study population had missing data (so unlikely it could have affected final findings), and the use of new HF drugs [angiotensin receptor–neprilysin inhibitor (ARNI) and sodium–glucose cotransporter-2 (SGLT2) inhibitors] was limited due to enrolment timing.

Conclusions

In conclusion, albeit with a retrospective analysis, in which we controlled some but not all the possible confounders, we provide strong evidence that, in patients diagnosed with HFrEF, MECKI score stratification power is confirmed, supporting its implementation in clinical practice, in patients with mild-to-moderate HF.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology*.

Author contributions

S.A. and D.M. contributed to the research protocol conception and design, data collection, data analysis, and manuscript preparation. E.P., J.A.S., N.P., S.N., D.N., R.M., J.M., Y.C., D.P., and D.G. contributed to data acquisition and manuscript critical revision. P.S., U.C., A.J.S.C.,[12] M.M., G.M.C.R., and M.V. contributed to research protocol conception and design and manuscript critical revision. A.A., J.C., and E.S. contributed to data interpretation and manuscript critical revision. P.A. and M.P. contributed to research protocol preparation, data interpretations, manuscript preparation, and final revision. All gave final approval and agree to be accountable for all aspects of work, ensuring integrity and accuracy.

Funding

Publication costs supported by Italian Ministry of Health (Ricerca Corrente).

Conflict of interest: None related to the present manuscript. Giuseppe Rosano received support from Menarini, Servier, Boheringer Ingelheim, and AstraZeneca and is President of the Heart Failure Association.

Data availability

Data will be available upon request at www.zenodo.org.

References

1. Bragazzi NL, Zhong W, Shu J, Abu Much A, Lotan D, Grupper A, *et al.* Burden of heart failure and underlying causes in 195 countries and territories from 1990 to 2017. *Eur J Prev Cardiol* 2021;**28**:1682–1690.
2. Gerber Y, Weston SA, Redfield MM, Chamberlain AM, Manemann SM, Jiang R, *et al.* A contemporary appraisal of the heart failure epidemic in Olmsted County, Minnesota, 2000 to 2010. *JAMA Intern Med* 2015;**175**:996–1004.
3. Tsao CW, Lyass A, Enserro D, Larson MG, Ho JE, Kizer JR, *et al.* Temporal trends in the incidence of and mortality associated with heart failure with preserved and reduced ejection fraction. *JACC Heart Fail* 2018;**6**:678–685.
4. Khush KK, Cherikh WS, Chambers DC, Harhay MO, Hayes D, Jr., Hsich E, *et al.* The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: thirty-sixth adult heart transplantation report - 2019; focus theme: donor and recipient size match. *J Heart Lung Transplant* 2019;**38**:1056–1066.
5. Salvioni E, Bonomi A, Re F, Mapelli M, Mattavelli I, Vitale G, *et al.* The MECKI score initiative: development and state of the art. *Eur J Prev Cardiol* 2020;**27**:5–11.
6. Agostoni P, Corra U, Cattadori G, Veglia F, La Gioia R, Scardovi AB, *et al.* Metabolic exercise test data combined with cardiac and kidney indexes, the MECKI score: a multiparametric approach to heart failure prognosis. *Int J Cardiol* 2013;**167**:2710–2718.
7. Corra U, Agostoni P, Giordano A, Cattadori G, Battaia E, La Gioia R, *et al.* The Metabolic Exercise test data combined with Cardiac and Kidney Indexes (MECKI) score and prognosis in heart failure. A validation study. *Int J Cardiol* 2016;**203**:1067–1072.
8. Agostoni P, Paolillo S, Mapelli M, Gentile P, Salvioni E, Veglia F, *et al.* Multiparametric prognostic scores in chronic heart failure with reduced ejection fraction: a long-term comparison. *Eur J Heart Fail* 2018;**20**:700–710.
9. Kouwert IJM, Bakker EA, Cramer MJ, Snoek JA, Eijsvogels TMH. Comparison of MAGGIC and MECKI risk scores to predict mortality after cardiac rehabilitation among Dutch heart failure patients. *Eur J Prev Cardiol* 2020;**27**:2126–2130.
10. Freitas P, Aguiar C, Ferreira A, Tralhao A, Ventosa A, Mendes M. Comparative analysis of four scores to stratify patients with heart failure and reduced ejection fraction. *Am J Cardiol* 2017;**120**:443–449.
11. Altman DG, Vergouwe Y, Royston P, Moons KG. Prognosis and prognostic research: validating a prognostic model. *BMJ* 2009;**338**:b605.
12. Kassambara A, Kosinski M, Biecek P. survminer: drawing survival curves using 'ggplot2'. 2020.
13. Blanche P, Dartigues JF, Jacqmin-Gadda H. Estimating and comparing time-dependent areas under receiver operating characteristic curves for censored event times with competing risks. *Stat Med* 2013;**32**:5381–5397.

14. Paolillo S, Veglia F, Salvioni E, Corra U, Piepoli M, Lagioia R, *et al.* Heart failure prognosis over time: how the prognostic role of oxygen consumption and ventilatory efficiency during exercise has changed in the last 20 years. *Eur J Heart Fail* 2019;**21**:208–217.
15. Vergouwe Y, Steyerberg EW, Eijkemans MJ, Habbema JD. Substantial effective sample sizes were required for external validation studies of predictive logistic regression models. *J Clin Epidemiol* 2005;**58**:475–483.
16. Mehra MR, Canter CE, Hannan MM, Semigran MJ, Uber PA, Baran DA, *et al.* The 2016 International Society for Heart Lung Transplantation listing criteria for heart transplantation: a 10-year update. *J Heart Lung Transplant* 2016;**35**:1–23.
17. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Bohm M, *et al.* 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur J Heart Fail* 2022;**24**:4–131.