International Validation of Metabolic Exercise test data combined with Cardiac and Kidney Indexes (MECKI) Score in Heart Failure

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Abstract

Background. Current European heart failure (HF) Guidelines suggests 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 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. 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, ECG, echocardiographic findings, cardiopulmonary exercise testing (CPET) results as described in the original MECKI score publication.

Results. 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 3 subgroups: (i) MECKI score <10%; (ii) 10–20%; (iii) ≥20%. Survival analysis comparison among the 3 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%; 1022 days for ≥20% ($p<0.0001$). ROC curves and the AUC curves were like those reported in the original internal validation studies.

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.

Key words. External validation Heart Failure; Prognosis; Risk Score, Risk stratification

Lay Summary

- In patients diagnosed with heart failure with reduced ejection fraction, the MECKI risk score underwent to an external validation
- MECKI Score prognostic power was confirmed in a large population of patients from Europe and Asia.
- These data support MECKI score implementation, as advised by the 2021 European Heart Failure Guidelines.

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 while 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 health care 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: 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 ($ppVO_2$), 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 seventeen HF centers with a database of 2,716 patients diagnosed with HF, followed up to 4 years.[7]

In recent comparisons, 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 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 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 8 international centers (not Italian), retrospectively recruited between 1997 and 2019, and specifically analyzed 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 center. 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 three months; (iv) no planned major CV treatment or intervention; (v) performance of a maximal CPET, regardless of the respiratory exchange ratio reached with a ramp exercise protocol (steps no longer than 1 minute) 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 ECG alterations or presence of any clinical comorbidity interfering with exercise performance.

Clinical, laboratory, echocardiographic and CPET data

Collected data included demographics, HF etiology, laboratory findings, ECG, echocardiographic data, CPET results and treatment. All measurement 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.

CPET 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 following: 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].

MECKI score was calculated in all patients as following: $e^c/(1 + e^c)$ where c = 10.3464 + (-0.0262 × predicted peak VO_2) + (0.0472 × VE/VCO_2 slope) + (-0.1086 × Hemoglobin) + (-0.0615 × Sodium) + (-0.0699 × LVEF) + (-0.0136 × eGFR). [https://www.cardiologicomonzino.it/en/mecki-score/#].

To quantify the outcome according to the MECKI score, the studied patients were categorised according to the calculated scores into 3 pre-defined subgroups: (i) MECKI score <10%; (ii) 10–20%; (iii) ≥20%.

Patient follow-up and outcomes

Patient follow-up was carried out according to the HF programs used in each center. 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 analyzed by unpaired t-test for normally distributed data, Wilcoxon test as a non-parametric alternative and chi-squared test as appropriate. Differences between MECKI score groups were evaluated by ANOVA and chi-square 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 by the 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 while 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.

Results

Study population

The flowchart of the study is shown in Figure 1. In total, 1,042 patients across 8 international centers (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. Supplemental Table s1 presents the distribution of study populations according to the participating centers. 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), higher VE/VCO_2 slope. Medical management was also different with more patients receiving mineralocorticoid receptor antagonists and fewer digoxin.

MECKI score subgroups

Patients were divided according to the calculated MECKI scores into 3 subgroups, whose characteristics of each subgroup are presented in Table 2. A progressive worsening of the clinical parameters (higher NYHA functional class, atrial fibrillation, VE/VCO_2 slope and lower LVEF, peakVO_2, 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 one, two and three 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 one, two and three years respectively. The median event-free survival time of the whole sample was 4,168 days (11.4 years) (Figure 2).

Survival analysis comparison among the 3 MECKI score subgroups showed a worse prognosis in patients with higher MECKI score value (Figure 3): median event-free survival times were 4,396 days (12 years) for MECKI score <10%; 3,457 days (9.5 years) for MECKI score 10–20%; 1,022 days (2.8 years) for MECKI score ≥20% ($p<0.0001$).

ROC analysis

ROC 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 to those reported in the original

(0.80±0.02, 0.79±0.01, 0.76±0.01 at 1, 2 and 3 years respectively) and validation study (0.81±0.04, 0.76±0.04, 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 six 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 to prove the applicability and efficacy of the model to the general population.

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 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-fiftyfive patients were excluded because at enrolment LVEF was >45%. This is different from what 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 to 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 MECKI score. It must be underlined that the recruitment of the present study population as well as that of the original MECKI score population were very long. This is 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 has finally acknowledged the value of the prognostic score (and in particular of the MECKI), where its use in clinical practice is advised.[17]

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, 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 analyzed 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 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 that the use of new HF drugs (ARNI and SGLT2 inhibitors) was limited due to enrollment timing.

Conclusion

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.

Data availability statement: data will be available upon request at www.zenodo.org

Figures

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

Figure 2. Kaplan-Meier survival curve of the analyzed 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%, ≥20%). The median event-free survival times were 4396 days (12 years) for MECKI score <10%; 3457 days (9.5 years) for 10–20%; 1022 days (2.8 years) for ≥20% ($p<0.0001$).

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

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

Authorship:

SA and DM contributed to the research protocol concenption and design, data collection, data analysis, manuscript preparation.

EP. JAS, NP, SN, DN, RM, JM, YC, DP, and DG contributed data acquisition and manuscript critical revision,

PS, UC, AJSC,[12] MM, GMCR, and MV contributed to research protocol conception and design, manuscript critical revision.

AA, JC, and ES contributed to data interpretation and manuscript critical revision

PA and MP Research contributed to research protocol preparation, data interpreatations, manuscript preparation and final revision.

All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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Tables

Table 1. Patient demographics

Comparison of patient demographics, HF etiology and disease-related characteristics in the present study population and in the MECKI-D and MECKI-V populations described in[7]

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) Ischemic: 433 (51.3) Valvular: 44 (5.2) Other: 50 (5.9)	Ischaemic: 975 (49)	Ischaemic: 522 (53)
NYHA class	n (%)	I : 95 (11.2) II: 401 (47.5) III: 328 (38.8) IV: 20 (2.3)	I : 194 (10) II: 1147 (57)* III: 668 (33) IV: -	I: 205 (21)**** II: 539 (54) III: 248 (25)**** 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****
Hemoglobin	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**

Legends. * $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$; **** $p \leq 0.0001$ vs present study. 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, mineralcorticoid receptor antagonist.

Table 2.

Patient characteristics divided according to the calculated MECKI scores divided into 3 subgroups: (i) MECKI score <10%; (ii) 10–20%; (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 etiology	n (%)			
Idiopathic		210 (36.7%)	54 (42.2%)	53 (37.1%)
Ischemic		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****

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

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

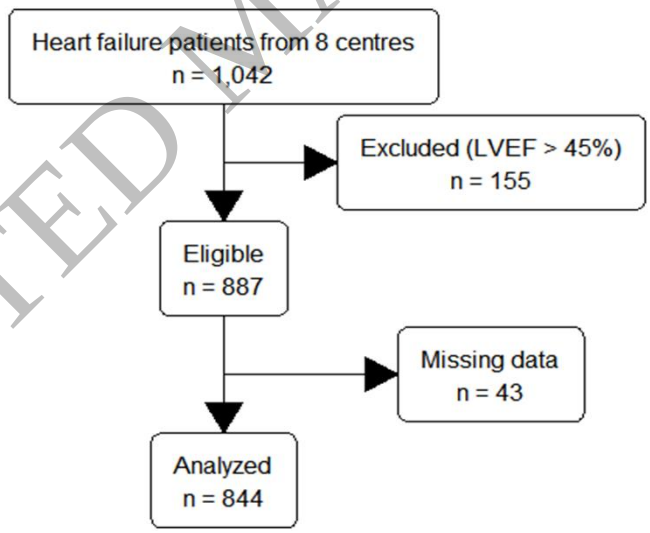

Figure 1
339x190 mm (x DPI)

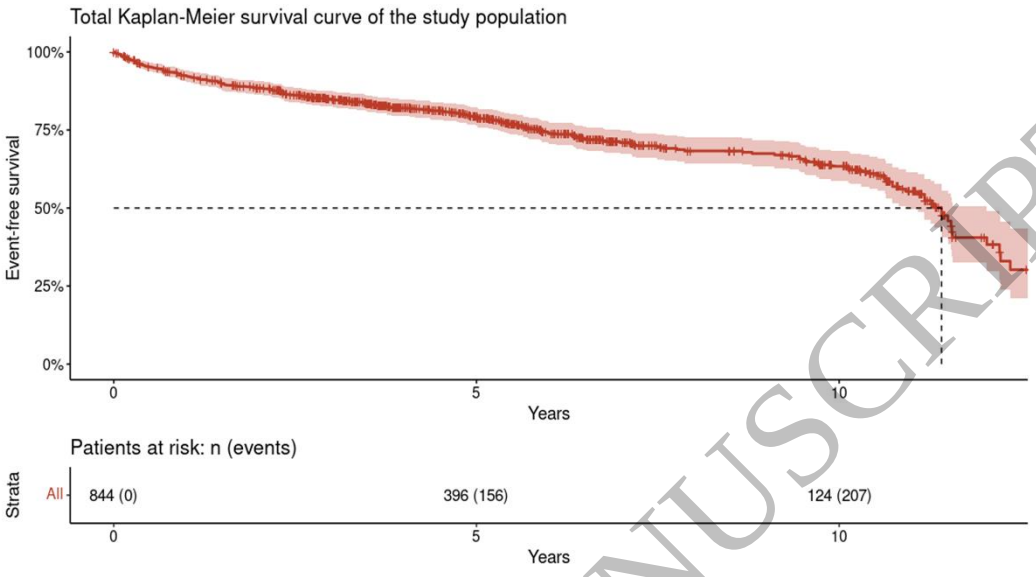

Figure 2
339x190 mm (x DPI)

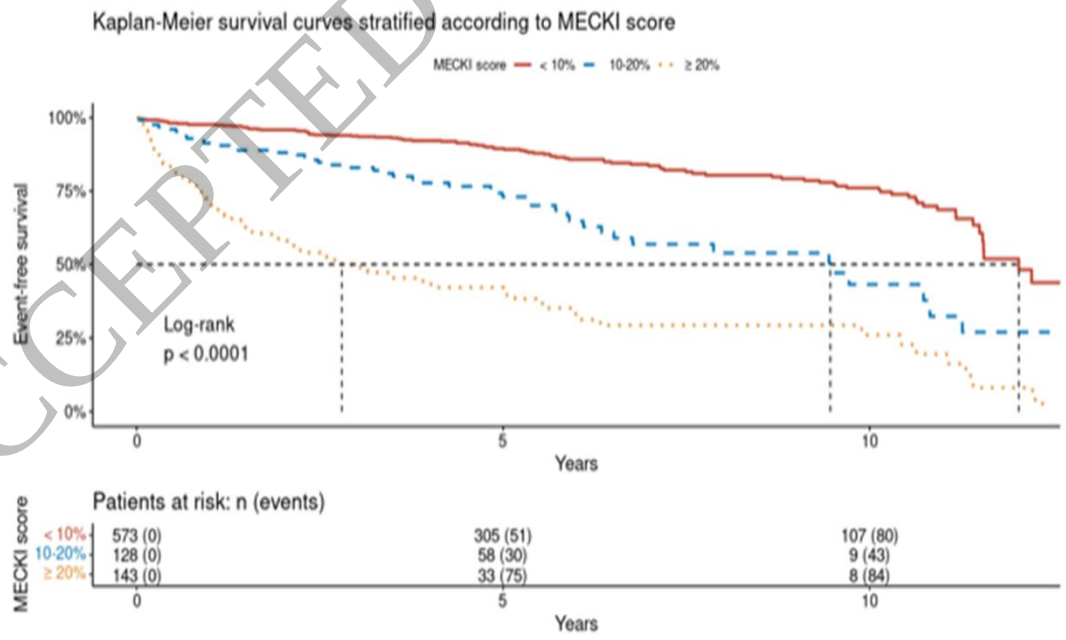

Figure 3
339x190 mm (x DPI)

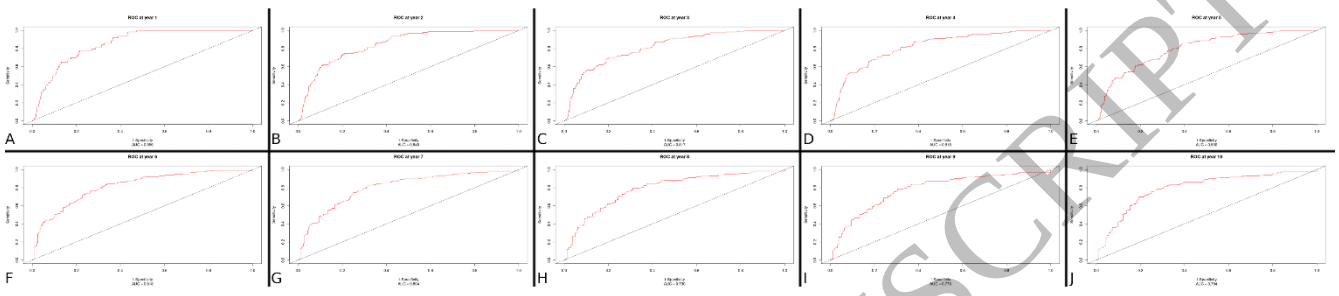

Figure 4
339x190 mm (x DPI)

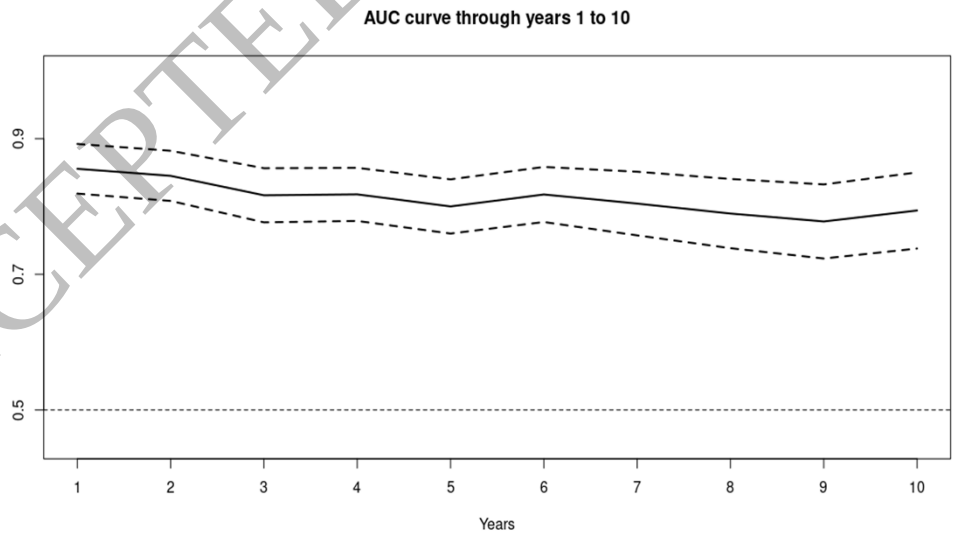

Figure 5
339x190 mm (x DPI)