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RESEARCH ARTICLE

MECKI score thresholds for heart transplantation referral of ambulatory heart failure patients

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† See Appendix.

Abstract

Introduction In heart failure (HF) patients, guidelines recommend scores for assessing outcomes and heart transplant (HTX) eligibility. However, scores use remains limited and cut-off values for HTX listing not well established.

Among the available tools, MECKI score is easy to calculate and likely offers the best prognostic accuracy. Compare MECKI score-based survival with that of HTX recipients and identify a MECKI threshold above which survival is inferior to that of HTX recipients at 5-year.

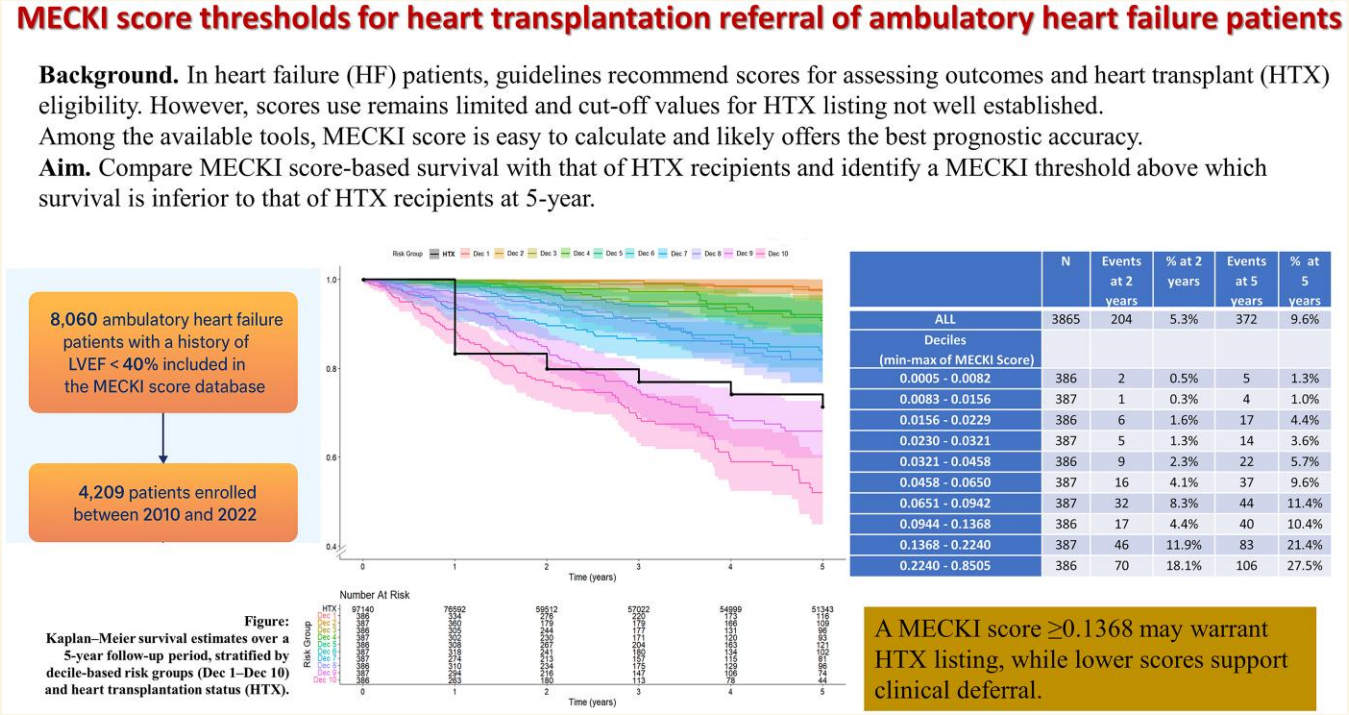
Methods Consecutive ambulatory HF patients enrolled in MECKI score programme between January 2010 and January 2022 were evaluated. Primary endpoint was a composite of cardiovascular death, HTX, or left ventricular assist device implantation. Heart transplant survival data were obtained from the International Society of Heart and Lung Transplantation registry updated through 2023. To identify the MECKI score threshold beyond which prognosis is worse than that of HTX recipients, patients were stratified by deciles of MECKI score.

Results We analysed 3865 HF patients (mean age 62.4 ± 12.6 years). Peak VO_2 was 58.2 ± 18.3% predicted; VE/VCO_2 slope 33.2 ± 8.2, haemoglobin 13.5 ± 1.7 g/dL, Na^+ 139 ± 3 mmol/L, LVEF 33.7 ± 10.4%, and eGFR 73 ± 26 mL/min/1.73 m^2. Periodic breathing occurred in 15.8% of patients. At 5 years, mean survival was 83.7%.

The average 5-year survival of HTX recipients (71.2%) lies between the eighth and ninth MECKI score deciles suggesting a MECKI score value ≥0.1368 as the proper cut-off for HTX listing.

Conclusion MECKI score ≥0.1368 may warrant HTX listing, while lower scores support clinical deferral.

Graphical Abstract



	N	Events at 2 years	% at 2 years	Events at 5 years	% at 5 years
ALL	3865	204	5.3%	372	9.6%
Deciles (min-max of MECKI Score)					
0.0005 - 0.0082	386	2	0.5%	5	1.3%
0.0083 - 0.0156	387	1	0.3%	4	1.0%
0.0156 - 0.0229	386	6	1.6%	17	4.4%
0.0230 - 0.0321	387	5	1.3%	14	3.6%
0.0321 - 0.0458	386	9	2.3%	22	5.7%
0.0458 - 0.0650	387	16	4.1%	37	9.6%
0.0651 - 0.0942	387	32	8.3%	44	11.4%
0.0944 - 0.1368	386	17	4.4%	40	10.4%
0.1368 - 0.2240	387	46	11.9%	83	21.4%
0.2240 - 0.8505	386	70	18.1%	106	27.5%

Keywords Heart failure • Prognosis • Heart transplantation • Risk score

Introduction

Several reports and guidelines recommend the use of prognostic scores for assessing outcomes in patients with advanced heart failure (HF) and evaluating their eligibility for heart transplant (HTX) programmes.[1–3] This stems from the multifaceted nature of HF, which is better captured by composite scores than by individual parameters.[4] However, the systematic use of HF prognostic scores remains limited due to their complexity and the extensive data required for their calculation. Additionally, appropriate cut-off values for HTX listing are not well established.

Table 1 Patient characteristics in all population and by MECKI score deciles

		All $n = 3685$	Dec 1 $n = 386$	Dec 2 $n = 387$	Dec 3 $n = 386$	Dec 4 $n = 387$	Dec 5 $n = 386$	Dec 6 $n = 387$	Dec 7 $n = 387$	Dec 8 $n = 386$	Dec 9 $n = 387$	Dec 10 $n = 386$	*P*	*P* trend
Age (years)	$n = 3865$	62 ± 13	58 ± 14	61 ± 13	61 ± 13	62 ± 12	62 ± 12	63 ± 12	64 ± 13	64 ± 13	64 ± 12	65	<.0001	<.0001
Weight (kg)	$n = 3865$	78 ± 15	82 ± 16	81 ± 16	82 ± 16	81 ± 16	80 ± 15	78 ± 16	76 ± 15	76 ± 15	75 ± 14	74 ± 13	<.0001	<.0001
LVEF (%)	$n = 3865$	34 ± 10	49 ± 10	41 ± 8	38 ± 8	35 ± 7	34 ± 7	32 ± 7	30 ± 7	28 ± 6	26 ± 6	22 ± 6	<.0001	<.0001
EDV (mL)	$n = 3543$	181 ± 73	130 ± 51	155 ± 56	162 ± 61	172 ± 62	173 ± 67	183 ± 65	187 ± 69	205 ± 71	212 ± 81	230 ± 84	<.0001	<.0001
PAPs (mmHg)	$n = 3130$	36. ± 13	29 ± 9	31 ± 10	32 ± 10	34 ± 10	33 ± 11	35 ± 12	38 ± 13	40 ± 13	42 ± 14	46 ± 13	<.0001	<.0001
Heart rate (bpm)	$n = 3846$	70 ± 12	68 ± 11	67 ± 11	70 ± 12	68 ± 11	69 ± 13	70 ± 13	69 ± 11	71.7 ± 13	71 ± 12	73 ± 12	<.0001	<.0001
VO_2 AT (mL)	$n = 3058$	802 (628;1031)	1124 (906;1420)	1004 (805;1213)	946 (771;1115)	900 (725;1060)	826 (668;1001)	782 (624;915)	703 (590;833)	683 (552;796)	618 (512;756)	553 (454;673)	<.0001	<.0001
Workload AT (Watt)	$n = 2873$	52 ± 24	75 ± 32	63 ± 23	59 ± 21	56 ± 21	52 ± 21	48 ± 19	43 ± 18	40 ± 17	39 ± 16	33 ± 17	<.0001	<.0001
VO_2 peak (mL/min)	$n = 3865$	1185 ± 453	1731 ± 556	1490 ± 439	1376 ± 402	1305 ± 352	1207 ± 346	1121 ± 320	1025 ± 279	952 ± 256	892 ± 248	755 ± 215	<.0001	<.0001
VE/VCO_2 slope	$n = 3865$	33 ± 8	27 ± 5	28 ± 4	29 ± 5	30 ± 6	31 ± 5	32 ± 6	349 ± 6	36 ± 6	39 ± 7	45 ± 9	<.0001	<.0001
RER	$n = 3807$	1.11 ± 0.12	1.11 ± 0.11	1.11 ± 0.11	1.11 ± 0.11	1.11 ± 0.11	1.11 ± 0.12	1.1 ± 0.12	1.11 ± 0.13	1.1 ± 0.12	1.11 ± 0.12	1.1 ± 0.14	0.8450	0.3195
Hb (m/dL)	$n = 3865$	13.5 ± 1.7	13.9 ± 1.6	14.0 ± 1.6	13.9 ± 1.7	13.9 ± 1.5	13.6 ± 1.6	13.5 ± 1.6	13.2 ± 1.7	13.2 ± 1.7	13.1 ± 1.7	12.6 ± 1.7	<.0001	<.0001
Na^+ (mmol/L)	$n = 3865$	139 ± 3	140 ± 23	140 ± 3	140 ± 3	140 ± 3	140 ± 3	139 ± 3	139 ± 3	139 ± 3	139 ± 3	138 ± 4	<.0001	<.0001
K^+ (mmol/L)	$n = 3853$	4.3 ± 0.5	4.2 ± 0.4	4.2 ± 0.4	4.3 ± 0.4	4.3 ± 0.4	4.3 ± 0.2	4.3 ± 0.5	4.4 ± 0.5	4.3 ± 0.5	4.3 ± 0.5	4.3 ± 0.5	<.0001	<.0001
BNP (pg/mL)	$n = 2105$	237 (91;631)	79 (40;135)	100 (53;186)	130 (70;296)	206 (87;428)	206.5 (100;476)	233.1 (150;487)	385.5 (171;798.5)	504 (269;1003)	641 ((345;1257)	992 (585;2180)	<.0001	<.0001
NT pro BNP (pg/mL)	$n = 1068$	1151 (481;2416)	199 (47;711)	411 (181;835)	598 (315;1138)	609 (373;1086)	750 (401;1576)	924 (502;1973)	1287 (613;2260)	1508 (778;2865)	2276. (1172;3866)	3558 (1925;5037)	<.0001	<.0001
MDRD (mL/min/ 1.73 m^2)	$n = 3865$	73 ± 26	92 ± 28	86 ± 24	82 ± 22	79 ± 22	77 ± 22	73 ± 23	67 ± 23	66 ± 22	59 ± 22	51 ± 20	<.0001	<.0001
VO_2 peak (mL/min/kg)	$n = 3865$	15.1 ± 5.1	21.3 ± 5.9	18.7 ± 5.0	16..9 ± 4.5	16.2 ± 4.0	15.2 ± 3.6	14.4 ± 3.5	13.5 ± 3.3	12.7 ± 3.1	12.0 ± 3.0	10.2 ± 2.6	<.0001	<.0001
VO_2 peak (%)	$n = 3865$	58 ± 18	83 ± 18	73 ± 15	67 ± 13	63 ± 12	59 ± 13	55 ± 12	52 ± 11	48 ± 11	44 ± 10	37 ± 10	<.0001	<.0001
MECKI score (%)	$n = 3865$	0.05 (0.02;0.11)	0.01 (0;0.01)	0.01 (0.01;0.01)	0.02 (0.02;0.02)	0.03 (0.02;0.03)	0.04 (0.04;0.04)	0.05 (0.05;0.06)	0.08 (0.07;0.08)	0.11 (0.1;0.13)	0.17 (0.15;0.2)	0.32 (0.26;0.43)	<.0001	<.0001

Patient baseline characteristics are presented for the entire study population (All) and stratified by MECKI score deciles (Dec, from 1 to 10). The table includes demographic, clinical, and laboratory variables to describe the cohort's profile across risk groups. Data are reported as mean ± standard deviation or median (interquartile range, IQR), as appropriate.

Table 2 Number of events and event rates at 2 and 5 years in the all population and by MECKI score deciles

	At 2 years			At 5 years		
	N	Events	%	*N*	Events	%
ALL	2333	273	11.7%	933	105	11.3%
Deciles (min-max of MECKI score)						
0.0005–0.0082	258	12	4.7%	116	9	7.8%
0.0083–0.0156	245	12	4.9%	109	9	8.3%
0.0156–0.0229	237	19	8.0%	96	8	8.3%
0.0230–0.0321	234	17	7.3%	93	8	8.6%
0.0321–0.0458	267	25	9.4%	121	12	9.9%
0.0458–0.0650	242	30	12.4%	103	9	8.7%
0.0651–0.0942	213	22	10.3%	81	10	12.3%
0.0944–0.1368	242	38	15.7%	96	15	15.6%
0.1368–0.2240	216	54	25.0%	74	17	23.0%
0.2240–0.8505	179	44	24.6%	44	8	18.2%

This table summarizes the number of patients (*N*), number of events, and corresponding event rates (%) at 2-year and 5-year follow-up across the entire cohort (ALL) and stratified by deciles of the MECKI score. Each decile is labelled according to the minimum and maximum values of its MECKI score range, from the lowest risk (0.0005–0.0082) to the highest risk (0.2240–0.8505).

Among the available tools, the Metabolic Exercise Cardiac Kidney Indexes (MECKI) score is easy to calculate and likely offers the best prognostic accuracy. It has undergone multiple validations[1,5–8] and has been successfully compared with other scores, such as the Seattle Heart Failure Model, Meta-Analysis Global Group in Chronic Heart Failure, and Heart Failure Survival Score.[5,6,9] The MECKI score was developed using a Cox proportional hazards regression with stepwise variable selection and cross-validation, and it incorporates six parameters: peak oxygen uptake (VO_2), ventilatory efficiency measured by the ventilation over CO_2 production (VE/VCO_2) slope—both obtained from symptom-limited maximal cardiopulmonary exercise testing (CPET)—haemoglobin (Hb), serum sodium concentration (Na^+), left ventricular ejection fraction (LVEF), and estimated glomerular filtration rate (eGFR), calculated using the Modification of Diet in Renal Disease (MDRD) formula.[10]

In the present study we want to compare MECKI score-based survival with that of HTX recipients from the International Society of Heart and Lung Transplantation registry[11] and to identify a MECKI score threshold above which survival is inferior to that of HTX recipients at 5-year follow-up. This may allow a more precise allocation of ambulatory HF patients in the HTX list.

Methods

The study population belongs to the multicentre MECKI registry, which includes patients with previous or current heart failure symptoms (NYHA Class I–IV, ACC/AHA Stages B–C) and a documented LVEF <40%, clinically stable for at least three months, able to perform a CPET, and without major cardiovascular interventions planned.[10] From a population of 8060 ambulatory HF patients, we selected those enrolled between January 2010 and January 2022 ($n = 4209$). A total of 344 patients were excluded due to incomplete data required to compute the MECKI score. Inclusion and exclusion criteria have been described previously.[10] In brief major inclusion criteria were current or prior HF symptoms, history of prior or current LVEF <40%, and stable HF treatment for at least 3 months. Major exclusion criteria were history of pulmonary embolism, moderate-to-severe primitive valvular heart disease, pericardial disease, severe obstructive lung disease, exercise-induced angina, significant electrocardiographic abnormalities, or any clinical comorbidity that could interfere with exercise performance. A requisite for MECKI score data base inclusion was a cycle-ergometer symptoms limited CPET performed with a ramp exercise protocol. Cardiopulmonary exercise testing data were collected and analysed using standardized procedures.[12] Predicted peak VO_2 ($\%VO_2$) was calculated using Hansen *et al.*'s equations.[13]

In addition to CPET variables, the MECKI registry collects clinical, echocardiographic, ECG, therapeutic, and laboratory data at baseline. The primary endpoint was a composite of cardiovascular death, urgent HTX, or left ventricular assist device (LVAD) implantation. For patients who died outside the hospital, cause of death and medical documentation were reviewed. Treatments were updated during follow-up according to clinical need and guideline recommendations.

The MECKI score was calculated using the formula:

$$e\hat{}c/(1 + e\hat{}c)$$

where:

$$c = 10.3464 + (-0.0262 \times \%\text{predicted peak } VO_2) + (0.0472 \times VE/VCO_2 \text{ slope}) + (-0.1086 \times Hb) + (-0.0615 \times Na^+) + (-0.0699 \times LVEF) + (-0.0136 \times eGFR)$$

Heart transplant survival data were obtained from the International Society of Heart and Lung Transplantation registry[11] updated through 2023. To identify the MECKI score threshold beyond which prognosis is worse than that of HTX recipients, patients were stratified by deciles of MECKI score. MECKI score was calculated at study run in.

The study was approved by the local ethics committee (protocol number: CCM04_21 PA).

Statistical analysis

Continuous variables were reported as mean ± standard deviation (SD) or median and interquartile range (IQR), as appropriate. Categorical variables were expressed as counts and percentages. Differences in continuous variables across MECKI score deciles were tested using one-way ANOVA or Kruskal–Wallis tests, as appropriate. Trends were assessed using linear regression or non-parametric equivalents. Kaplan–Meier curves were used for survival analysis. Heart transplant recipient survival curves were reconstructed from aggregate data using the 'KM_reconstruct' function from the reconstruct KM package in R (v4.3.1). Survival curves were compared using log-rank tests. All tests were two-sided, and *P*-values <.05 were considered statistically significant. Analyses were performed using SAS v9.4 (SAS Institute, Cary, NC, USA) and R v4.3.1.

Results

We analysed 3865 adult and Caucasian HF patients (mean age 62.4 ± 12.6 years; 81.1% male, NYHA class I = 16.1%, II 56.7%, III 25.9%, IV 1.3%) with reduced LVEF (HFrEF, $n = 2937$; 76%) or improved LVEF (HFimpEF, $n = 928$; 24%). At enrolment, most patients were treated with β-blockers (91.2%), ARNI/ACEi/ARBs (88.1%), MRAs (58.5%), and diuretics (80.1%). Mean peak VO_2 was 15.1 ± 5.1 mL/min/kg (58.2 ± 18.3% predicted); VE/VCO_2 slope, Hb, Na^+, LVEF, and eGFR were 33.2 ± 8.2, 13.5 ± 1.7 g/dL, 139 ± 3 mmol/L, 33.7 ± 10.4%, and 73 ± 26 mL/min/1.73 m^2, respectively. Periodic breathing occurred in 15.8% of patients; 43.4% had ICDs and 18.4% had CRT devices. Baseline characteristics of the entire population and clustered by decile are shown in *Table 1*.

Median follow-up was 2.59 (1.08–4.88) years. A total of 372 (9.6%) events occurred over 5 years: 286 cardiac deaths, 28 LVAD implantations, and 58 HTXs. Event rates by decile are reported in *Table 2*. Specifically, the event rate was calculated using as denominator the total number of subjects at risk at each yearly interval. A total of 933 cases were alive and actively followed at 5 years.

At 2 years, mean survival was 93.4% (ranging from 99.3% in decile 1 to 76.9% in decile 10). At 5 years, mean survival was 83.7% (from 97.5% in decile 1 to 52.0% in decile 10). Kaplan–Meier curves are presented in

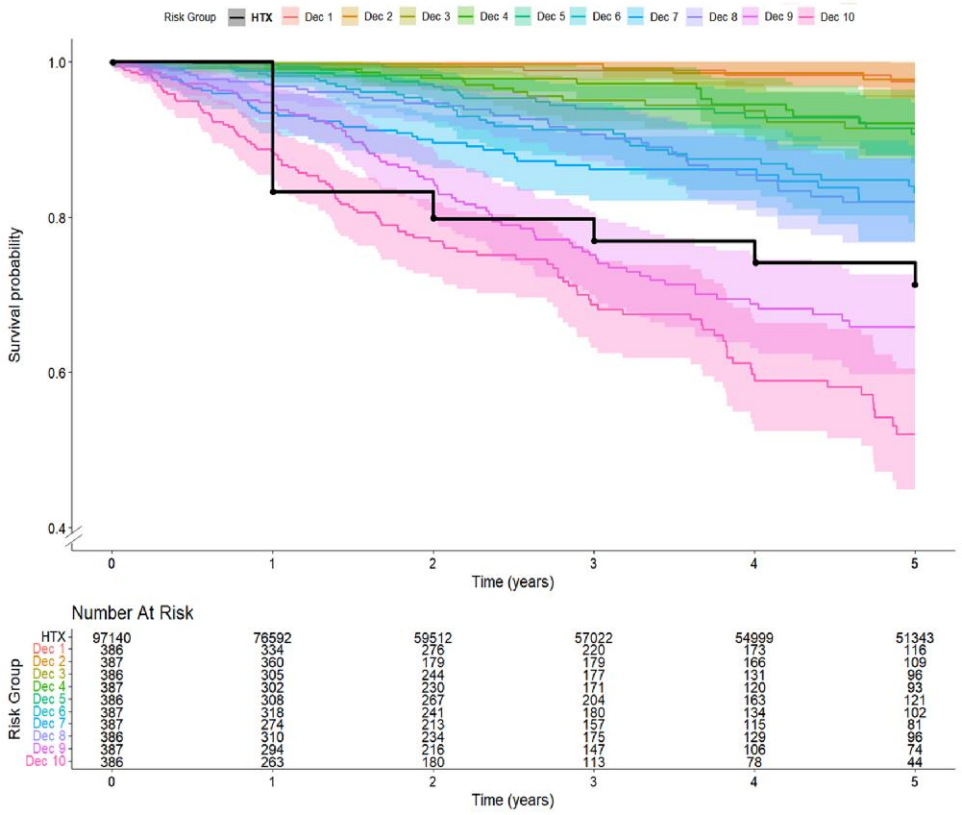


Figure 1 Kaplan–Meier survival curves by decile risk groups and heart transplantation recipients. Kaplan–Meier survival estimates over a 5-year follow-up period, stratified by decile-based risk groups (Dec 1–Dec 10) and heart transplantation status. Each colour corresponds to a specific decile group, ranging from the lowest (Dec 1) to the highest (Dec 10) predicted mortality risk. The survival curve for heart transplantation group was represented in red. Shaded areas represent 95% confidence intervals. The number of patients at risk at each time point is reported below the plot. A statistically significant difference in survival was observed across groups (log-rank test, $P < .0001$)

Figure 1. Heart transplant survival at 2 and 5 years was 79.8% and 71.2%, respectively.

Patients in the two highest MECKI score deciles had worse 5-year outcomes compared with HTX recipients. Specifically, patients with a median MECKI score of 0.17 (IQR: 0.15–0.20) had 2- and 5-year survival rates of 84.9% and 65.9%, respectively, and those with a median score of 0.32 (IQR: 0.26–0.43) had survival of 76.9% and 52.0%. Results were similar when excluding 928 cases with improved LVEF or after adjusting for the years of enrolment to take into account treatment strategy changes and guidelines evolution.

Discussion

In the present study we showed that a MECKI score ≥0.1368 may warrant HTX listing. Indeed, the average 5-year survival of HTX recipients (71.2%) lies between the 8th and 9th MECKI score deciles (score range: 0.11–0.17). Therefore, patients with a MECKI score ≥0.1368 (the upper bound of the 8th and lower bound of the 9th decile) should be considered for HTX listing. Conversely, HTX may be postponed in those with lower scores, if clinically appropriate. Given the dynamic nature of HF, regular reassessment of the MECKI score is essential.[14]

The MECKI score was first introduced in 2013[10] with ongoing data collection since 1993. This study focused on patients enrolled between January 2010 and January 2022, to avoid historical biases in survival while allowing for adequate follow-up.[15] It is acknowledged that, during this observation period, HF guidelines were progressively updated and introduced into clinical practice. Treatment reported refers to enrolment time but it was already with a great a percentage of β-blockers, ACE/AT1/ARNI, and MRA. In any case treatment of MECKI score population has progressively changed and updated. The MECKI score provides a holistic assessment of HF considering, LVEF, kidney function, Hb and Na^+ values, and two exercise-derived measurements (peak VO_2 and VE/VCO_2 slope), all of which are considered among the most powerful HF prognostic parameters. Kidney function, i.e. eGFR, in the original MECKI score report was calculated based on MDRD formula.[16] However, similar results are obtained using different formulas was eGFR calculations including Cockcroft-Gault (CG), Chronic Kidney Disease Epidemiology Collaboration, modified versions of the CG and MDRD (MDRDm) equations, as well as the European Kidney Function Consortium equation.[17–21] MECKI score prognostic capability at 2 years has been found to be in a range between 0.79 (first report) and 0.85 (international validation).[8,10]

The data we present provides actionable information to optimize timing of referral for HTX in ambulatory HF patients. However, it must be underlined that HTX recipient data were reconstructed based solely on published survival curves and the number of patients at risk at yearly intervals.[22] Due to the lack of additional patient-level clinical information, the reconstructed dataset may not fully account for the presence of high-risk individuals or comorbid conditions that could have significantly influenced outcomes. Moreover, the 0.1368 MECKI

score cut-off value should not be used to risk stratify HF patient populations who were not well represented in this cohort including patients with non-Caucasian ethnicity, patients with HF due to congenital heart disease, patients with preserved EF or with valvular HF. Similarly, the present data should be considered with caution in women who only represent 19% of our study population, albeit a recent report suggests the good performance of MECKI score in women.[23]

Further study limitations must be acknowledged: first, we can only provide an approximate MECKI score value above which patients survival is worst of that of the of HTX cases; indeed, the 0.1368 is the upper/lower limit of the eighth and ninth deciles, respectively and a definite cut-off cannot be assessed with the available data. Moreover, it must be emphasized that ≥0.1368 is a statistical boundary, not a validated clinical cut-off. Accordingly there is a need for a prospective validation of the present findings, Second, we arbitrarily selected 5 years as the time interval to define the appropriate HTX follow-up; however, from *Figure 1* shorter time intervals can be evaluated. Third, MECKI score value changes during the follow-up were not regularly assessed. Indeed, in HF trajectory events that influence patients prognosis including worsening HF or treatment changes may occur.[4] As a matter of facts, we previously reported the importance of re-evaluation of MECKI score at least yearly.[14] Fourth, SGLT2i were introduced by ESC guideline in 2021 and likely prescribed during the follow-up only in a limited number of patients within this cohort. Finally, we must re-emphasize that we studied a population of adult Caucasian low LVEF HF patients so that our findings cannot be extended to different HF population as paediatric patients, patients of different ethnicity or with preserved LVEF.

In summary, after a validation of the present data with a prospective study we believe that MECKI score must be implemented into the clinical practice and guide the HF decision making process. At present MECKI score can only help to guide patients referral, listing, or prioritization. Indeed, a MECKI score ≥0.1368 may warrant HTX listing, while lower scores support clinical deferral. Regular MECKI score assessment remains crucial.

Author contributions

A.P., A.L.: Conceptualization; Project administration; Supervision; Data interpretation; Writing-original draft; Writing—review and editing. G.A., S.E.: Data curation; Formal analysis; Writing-original draft; Writing—review and editing Visualization. M.M., E.M., P.M., P.A., S.G., M.D., P.S., P.A., C.J., C.U., R.R., C.A., I.A., S.A., B.R., S.M., P.F.P., C.M., P.E., M.M., V.C., C.M., B.N., C.G., G.M., L.G., P.G., P.B., W.R., P.P., A.A., M.M.V., B.F., B.M., R.F., S.A.B., S.S., G.D., P.C., L.V.F., P.F.: Writing—review and editing; Critical review of the manuscript; Critical discussion of results, revision of the text. All authors: Validation; Final approval of the manuscript; Agreement to be accountable for all aspects of the work.

Declarations

Disclosure of Interest

All authors declare no disclosure of interest for this contribution.

Data Availability

Repository of raw data will be available after acceptance at www.zenodo.org

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Ethical Approval

The study was approved by the local ethics committee (protocol number: CCM04_21 PA).

Pre-registered Clinical Trial Number

None supplied.

Appendix

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