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Cardiac sympathetic innervation and mortality risk scores in patients with heart failure

Leonardo Bencivenga[1,2] | **Klara Komici**[3] | **Stefania Paolillo**[1] | **Carmela Nappi**[1] | **Paola Gargiulo**[1] | **Roberta Assante**[1] | **Giuseppina Gambino**[4] | **Fabio Santillo**[4] | **Grazia Daniela Femminella**[4] | **Grazia Maria Corbi**[4] | **Nicola Ferrara**[4] | **Alberto Cuocolo**[1] | **Pasquale Perrone-Filardi**[1,5] | **Giuseppe Rengo**[4,6]

[1]Department of Advanced Biomedical Sciences, University of Naples "Federico II", Naples, Italy

[2]Gérontopôle de Toulouse, Institut du Vieillissement, CHU de Toulouse, Toulouse, France

[3]Department of Medicine and Health Sciences, University of Molise, Campobasso, Italy

[4]Department of Translational Medical Sciences, University of Naples "Federico II", Naples, Italy

[5]Mediterranea Cardiocentro, Naples, Italy

[6]Istituti Clinici Scientifici Maugeri SpA Società Benefit, Telese Terme, Italy

Correspondence
Giuseppe Rengo, Department of Translational Medical Sciences, University of Naples "Federico II", Via Sergio Pansini 5, Naples, Napoli.
Email: giuseppe.rengo@unina.it

Abstract

Introduction: In the risk stratification and selection of patients with heart failure (HF) eligible for implantable cardioverter-defibrillator (ICD) therapy, ^{123}I-meta-IodineBenzylGuanidine (^{123}I-mIBG) scintigraphy has emerged as an effective non-invasive method to assess cardiac adrenergic innervation. Similarly, clinical risk scores have been proposed to identify patients with HF at risk of all-cause mortality, for whom the net clinical benefit of device implantation would presumably be lower. Nevertheless, the association between the two classes of tools, one suggestive of arrhythmic risk, the other of all-cause mortality, needs further investigation.

Objective: To test the relationship between the risk scores for predicting mortality and cardiac sympathetic innervation, assessed through myocardial ^{123}I-mIBG imaging, in a population of patients with HF.

Methods: In HF patients undergoing ^{123}I-mIBG scintigraphy, eight risk stratification models were assessed: AAACC, FADES, MADIT, MADIT-ICD non-arrhythmic mortality score, PACE, Parkash, SHOCKED and Sjoblom. Cardiac adrenergic impairment was assessed by late heart-to-mediastinum ratio (H/M) <1.6.

Results: Among 269 patients suffering from HF, late H/M showed significant negative correlation with all the predicting models, although generally weak, ranging from −0.15 ($p = .013$) for PACE to −0.32 ($p < .001$) for FADES. The scores showed poor discrimination for cardiac innervation, with areas under the curve (AUC) ranging from 0.546 for Parkash to 0.621 for FADES.

Conclusion: A weak association emerged among mortality risk scores and cardiac innervation, suggesting to integrate in clinical practice tools indicative of both arrhythmic and general mortality risks, when evaluating patients affected by HF eligible for device implantation.

Leonardo Bencivenga and Klara Komici equally contributed.

KEYWORDS
^{123}I-mIBG scintigraphy, cardiac adrenergic innervation, heart failure, mortality risk scores

1 | INTRODUCTION

Cardiac sympathetic nervous system (SNS) derangement represents a key feature of chronic heart failure (HF) and exerts a crucial role in the onset, progression and prognosis of this syndrome, which shows an increasing prevalence worldwide, especially among older adults.[1] Cardiac sympathetic dysfunction, more pronounced in the advanced stages of the disease, is due to the alteration of the complex molecular pathways involved in adrenergic signalling, whose chronic stimulation becomes detrimental over time and is responsible for the desensitization and downregulation of β-adrenergic receptors (βARs).[2]

These alterations parallel a progressive imbalance of cardiac sympathetic innervation, which is in turn associated with increased arrhythmic risk and cardiovascular mortality.[3] Accordingly, international societies' guidelines recommend therapy with implantable cardioverter-defibrillator (ICD) for primary prevention of sudden cardiac death (SCD) in selected HF patients.[4,5] Despite attempts to improve selection criteria to ICD therapy, the proportion of patients who actually benefit from this treatment, which is not free from complications such as infections and inappropriate shocks, remains low. Importantly, several reports indicate that the rate of non-cardiac deaths negatively impacts device effectiveness, especially in multimorbid patients.[6]

In recent decades, the scientific community has focussed its attention on the development of tools to ameliorate risk stratification and improve the accuracy of the selection of candidates for ICD therapy. ^{123}I-metaIodineBenzylGuanidine (^{123}I-mIBG) scintigraphy has emerged as a potentially effective non-invasive imaging method to assess cardiac adrenergic innervation, with an independent value in predicting HF decompensation, arrhythmic events, cardiac mortality and even appropriate ICD intervention.[7] Similarly, several clinical risk scores and models have been proposed to identify HF patients at the highest risk of all-cause mortality, for whom the net clinical benefit of ICD implantation would presumably be lower.[8]

Nevertheless, the comparison between the two classes of tools, one suggestive of significantly increased arrhythmic risk, the other of all-cause mortality, has not yet been adequately investigated. Therefore, the aim of the present study was to test the relationship between mortality risk scores and cardiac sympathetic innervation, assessed through myocardial ^{123}I-mIBG imaging, in a population of HF patients with left ventricle ejection fraction (LVEF) <50%.

2 | METHODS

2.1 | Study population

This is a secondary analysis on data obtained from individuals enrolled in previous studies.[9,10] Participants were recruited from patients referred to the Departments of Translational Medical Sciences and Advanced Biomedical Sciences of the University of Naples 'Federico II'. Inclusion criteria listed: adult patients able to understand study protocol and consent to participation; diagnosis of HF with LVEF <50%, at least 6 months before enrolment; stable clinical conditions during the month prior to inclusion; and optimal pharmacotherapy according to European Society of Cardiology (ESC) Guidelines.[5] Exclusion criteria were acute coronary syndromes and/or cardiac revascularization in the previous 6 months, congenital heart diseases and dialysis-dependent kidney failure.

All patients underwent medical history collection and accurate clinical examination with evaluation of the main demographic/clinical factors. The results of the main biochemical blood tests were also registered. All participants were carefully informed and signed a written consent to participate in the study. The research protocol was reviewed and approved by the Local Ethics Committee. Reporting of the study conforms to broad EQUATOR guidelines.[11]

2.2 | Models and scores for mortality risk after ICD

Eight risk stratification models were identified, through literature research, as applicable to the study population: AAACC,[12] FADES,[13] MADIT,[6] MADIT-ICD non-arrhythmic mortality score,[14] PACE,[15] Parkash,[16] SHOCKED[17] and Sjoblom.[18]

These scores were obtained and validated on populations of patients undergoing ICD therapy for primary and/or secondary prevention in different clinical settings, taking into account: demographic (age, gender and body mass index [BMI]) and clinical features (Cardiac Resynchronization Therapy [CRT-D], New York Heart Association [NYHA] functional class, smoking history); comorbidities (anaemia, atrial arrhythmias, chronic

kidney disease [CKD], chronic obstructive pulmonary disease [COPD], diabetes mellitus, peripheral arterial disease [PAD]); echocardiographic (LVEF), electrocardiographic (QRS duration) and laboratory variables (serum creatinine, blood urea nitrogen [BUN]).

Other scores were not considered, due to the unavailability of clinical variables necessary for the calculation (e.g. no data collected on active cancer, for the aCCI score[19]). Overview of the employed models, with list of variables and scores, is reported in Table 1.

TABLE 1 Overview of mortality risk models with individual variables and scores.

Risk models	Variables and scores
AAACC [12]	Age > 75 years (3 points) CKD (3) Anaemia (2) AF (1) COPD (1)
FADES [13]	65 < Age < 75 (0.5) or Age ≥ 75 years (2) NYHA ≥ III (1) Diabetes mellitus (1) LVEF ≤25% (1) Smoking (1)
MADIT [6]	NYHA ≥ III (1) Age > 75 years (1) BUN >26 mg/dl (1) QRS duration >0.12 sec (1) AF (1)
MADIT-ICD non-arrhythmic [14]	Age ≥ 75 years (2) BMI < 23 Kg/m^2 (2) LVEF ≤25% (2) AF (2) NYHA ≥ II (1) Diabetes mellitus (1) CRT-D (−1)
PACE [15]	Age ≥ 70 years (1) Serum creatinine ≥2.0 mg/dl (1) LVEF ≤20% (1) PAD (1)
Parkash [16]	NYHA ≥ II (1) Age ≥ 80 years (1) Serum creatinine ≥1.8 mg/dl (1) AF (1)
SHOCKED [17]	CKD (100) Age ≥ 75 (62) COPD (62) Diabetes mellitus (41) NYHA ≥ II (36) LVEF ≤20% (28) AF (27)
Sjoblom [18]	NYHA ≥ II (1) Age > 70 years (1) Serum creatinine >106 μmol (1) QRS duration >0.12 msec (1) Diabetes mellitus (1) AF (1)

Abbreviations: AF, atrial fibrillation; BMI, body mass index; BUN, blood urea nitrogen; COPD, chronic obstructive pulmonary disease; CRT-D, cardiac resynchronization therapy; CKD, chronic kidney disease; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association functional class; PAD, peripheral artery disease.

2.3 | Cardiac ^{123}I-mIBG imaging

Heart adrenergic innervation was assessed through a ^{123}I-mIBG cardiac scintigraphy, performed following previously described standards[20] and the recommendation provided by the European Association of Nuclear Medicine Cardiovascular Committee and the European Council of Nuclear Cardiology recommendations.[21] Early and late planar imaging of heart-to-mediastinum ratios (H/M) was computed through the mean counts per pixel within the myocardium divided by the mean counts per pixel within the mediastinum. Washout rate was calculated from the formula: ([early heart counts per pixel – early mediastinum counts per pixel] – [late heart counts per pixel decay corrected – late mediastinum counts per pixel decay corrected]) / (early heart counts per pixel – early mediastinum counts per pixel) × 100.[22] According to previously published imaging protocol, reproducibility was excellent both intra- and interobserver, and acquisition quality was adequate for all observations.[22]

Abnormal cardiac innervation was defined as late H/M < 1.6 based on previous literature.[23]

2.4 | Statistical analysis

Categorical data were shown as absolute observations with percentage, and continuous variables were described as mean ± standard deviation (SD) or median + interquartile range (IQR) based on the distribution of data. Comparisons in terms of cardiac innervation were performed between risk category groups (high vs. low) identified by the different cut-offs of all considered predicting mortality models, through Student's *t*-test. Pearson's *r* correlation coefficient was computed to assess the relationship between each risk score and the three ^{123}I-mIBG imaging parameters. ROC analysis was employed to quantify and compare the accuracy of the scores to discriminate cardiac innervation impairment as assessed by late H/M < 1.6 at ^{123}I-mIBG imaging.[24] Subgroup analyses based on HF aetiology (ischaemic and non-ischaemic) were also performed. As statistical significance threshold, a $p < .05$ was employed for all analyses, performed through the Stata17 software (StataCorp.).

3 | RESULTS

Participants' principal characteristics are reported in Table 2. Overall population consisted of 269 HF patients, predominantly male (227; 84.4%), with mean age 66.2 ± 10.8 years and LVEF 31.1 ± 7.0%; 163 (60.5%) participants showed significant cardiac denervation according to the late H/M cut-off, and 216 (80.3%) individuals were ICD carriers, of which 142 also with CRT function. The most prevalent comorbidities were represented by hypertension (197; 73.2%), ischaemic heart disease (IHD) (187; 69.5%) and diabetes mellitus (110; 40.9%). Data regarding anaemia were available on 238 participants.

TABLE 2 Characteristics of the overall population

Variables	Overall population ($n = 269$)
Age (years)	66.2 ± 10.8
Gender (male)	227 (84.4%)
ICD	216 (80.3%)
CRT-D	142 (52.8%)
NYHA > II	83 (30.9%)
Anaemia[a]	50 (18.6%)
Atrial arrhythmias	56 (20.8%)
CKD	80 (29.7%)
COPD	81 (30.1%)
Diabetes mellitus	110 (40.9%)
Hypertension	197 (73.2%)
Ischaemic heart disease	187 (69.5%)
PAD	41 (15.2%)
Smoking	156 (58%)
LVEF mean	31.1 ± 7.0
QRS > 120 msec	74 (27.5%)
Serum creatinine (mg/dl)	1.16 ± 0.46
BUN (mg/dl)	53.99 ± 28.63
Cardiac denervation (Late H/M < 1.6)	163 (60.5%)
Early H/M	1.71 ± 0.24
Washout rate (%)	35.83 ± 19.85

Abbreviations: BMI, body mass index; BUN, blood urea nitrogen; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRT-D, cardiac resynchronization therapy; H/M, heart- to- mediastinum ratio; ICD, implantable cardioverter- defibrillator; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association functional class; PAD, peripheral artery disease; SD, standard deviation.

[a]Data available on 238 patients.

The population was stratified in high and low mortality risk groups according to each score cut-off value, to test for difference in ^{123}I-mIBG imaging parameters (Table 3). The lowest proportion of high-risk patients was identified by the PACE score (32; 11.9%), while the minimum disproportion in the number of patients assigned to the two risk categories group was established by the MADIT-ICD non-arrhythmic mortality score, whose number of high-risk patients was 112 (41.6%). Regarding cardiac innervation, early H/M ratio resulted to be significantly lower only in patients defined at higher mortality risk after ICD implantation by SHOCKED score (52 patients, 1.65 ± 0.29 vs. 1.73 ± 0.22; $p = .0155$). More pronounced statistically relevant differences emerged in late H/M ratio, since it was higher in

TABLE 3 Cardiac ^{123}I-mIBG imaging parameters in the study population stratified by low- and high-risk groups according to the eight predicting mortality scores.

Mortality risk scores			Early H/M			Late H/M			Washout rate		
Cut-offs and category		#obs.	Mean	SD	sig.	Mean	SD	sig.	Mean	SD	sig.
AAACC (>4)	Low	178	1.729	.227	0.086	1.553	.252	0.032	35.852	20.261	0.491
	High	91	1.687	.259		1.493	.241		35.799	19.121	
FADES (≥3)	Low	185	1.720	.223	0.301	1.565	.255	<0.001	34.146	20.092	0.019
	High	84	1.703	.272		1.460	.221		39.552	18.883	
MADIT (≥3)	Low	186	1.713	.218	0.450	1.556	.257	0.011	34.614	19.695	0.065
	High	83	1.717	.280		1.480	.225		38.570	20.031	
MADIT-ICD-NA (≥3)	Low	157	1.718	.204	0.392	1.567	.235	0.003	33.090	19.111	0.003
	High	112	1.710	.281		1.484	.262		39.681	20.300	
PACE (≥3)	Low	237	1.723	.222	0.058	1.541	.248	0.060	36.115	19.709	0.264
	High	32	1.652	.333		1.468	.254		33.755	21.048	
Parkash (≥2)	Low	223	1.717	.219	0.351	1.541	.246	0.112	35.748	19.719	0.437
	High	46	1.702	.320		1.492	.265		36.253	20.674	
SHOCKED (>202)	Low	217	1.730	.221	0.015	1.559	.250	0.001	35.792	19.894	0.471
	High	52	1.650	.294		1.422	.217		36.010	19.837	
Sjoblom (≥3)	Low	186	1.728	.226	0.084	1.565	.258	<0.001	34.313	20.067	0.029
	High	83	1.685	.263		1.459	.214		39.245	19.020	

Abbreviations: #obs, number of observations; NA, non-arrhythmic; SD, standard deviation.

TABLE 4 Relationship between cardiac ^{123}I-mIBG imaging parameters and all-cause mortality scores.

Mortality risk scores	Early H/M	Late H/M	Washout rate
AAACC	−0.075	−0.170	0.027
sig.	0.244	0.008	0.676
FADES	−0.120	−0.319	0.174
sig.	0.047	<0.001	0.004
MADIT	−0.011	−0.176	0.141
sig.	0.852	0.003	0.020
MADIT-ICD-NA	−0.024	−0.194	0.169
sig.	0.695	0.001	0.005
PACE	−0.099	−0.151	0.033
sig.	0.105	0.012	0.580
Parkash	−0.073	−0.152	0.078
sig.	0.231	0.012	0.199
SHOCKED	−0.155	−0.286	0.101
sig.	0.010	<0.001	0.097
Sjoblom	−0.082	−0.219	0.124
sig.	0.177	<0.001	0.041

Note: *p* Value corresponds to Pearson's *r* correlation coefficient.

TABLE 5 Discriminatory power of mortality scores on cardiac denervation assessed through cardiac imaging (late H/M < 1.6).

Mortality risk scores	AUC	SE	[95% conf. interval]
AAACC	0.590	0.036	0.519–0.662
FADES	0.621	0.033	0.555–0.688
MADIT	0.564	0.034	0.497–0.630
MADIT-ICD-NA	0.605	0.033	0.538–0.671
PACE	0.584	0.033	0.518–0.650
Parkash	0.546	0.033	0.482–0.611
SHOCKED	0.621	0.034	0.554–0.688
Sjoblom	0.574	0.033	0.507–0.640

low-risk groups stratified by all scores, except for PACE and Parkash. The two latter models did not show any significant difference between low- and high-risk groups for all ^{123}I-mIBG imaging variables. Washout rate was significantly reduced in low-risk patients according to FADES, MADIT-ICD non-arrhythmic mortality, and Sjoblom models.

Within all the examined relationships (Table 4), a weak, although significant, negative correlation was observed between early H/M ratio and FADES ($r = -.12$; $p = .047$) and SHOCKED ($r = -.15$; $p = .018$) scores. Late H/M ratio showed significant negative correlation with all the predicting models, ranging from $r = -.15$ ($p = .012$) for PACE to $r = -.32$ ($p < .001$) for FADES. Similar results were obtained for the washout rate, whose stronger positive association emerged with FADES score ($r = .17$; $p = .004$), and other significance thresholds reached with low coefficients for MADIT, MADIT-ICD non-arrhythmic mortality and Sjoblom scores.

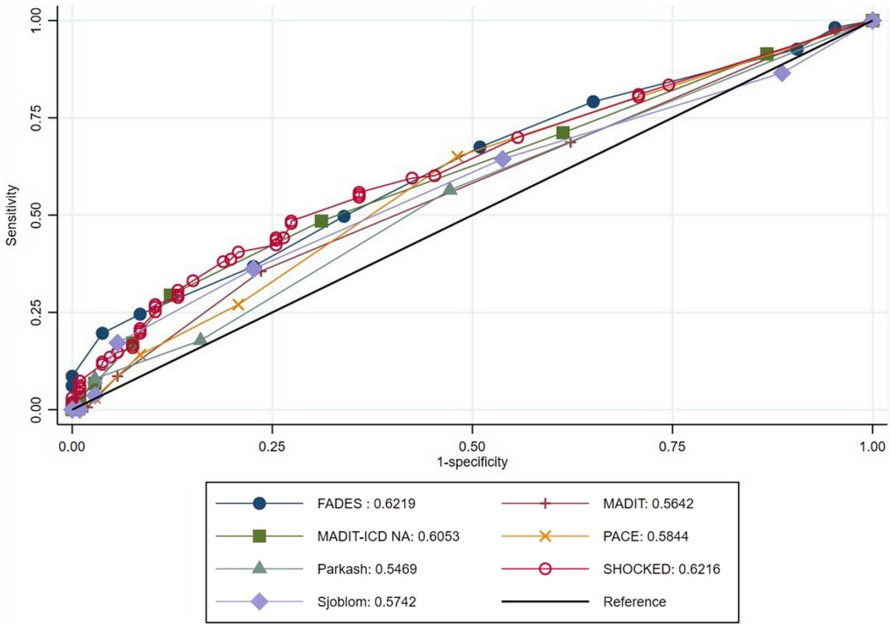

FIGURE 1 ROC curves of mortality risk scores for impaired cardiac innervation.

As reported in Table 5, the scores showed poor discrimination for cardiac denervation, with areas under the curve (AUC) ranging from 0.546 for Parkash to a maximum of 0.621 for FADES score (Figure 1).

Subgroup analyses on the study population divided according to ischaemic or non-ischaemic HF aetiologies are shown in Tables S1–S4. In patients suffering from IHD, no correlation emerged with early H/M, only FADES was associated with washout rate ($r = .18$; $p = .01$) and for late H/M the strongest correlation was detected with FADES ($r = -.27$; $p < .001$) (Table S1). The lowest and highest AUC for cardiac adrenergic impairment was registered with Parkash (0.531) and MADIT (0.609), respectively (Table S2). With regard to the 82 patients without IHD, significant negative correlation emerged for early H/M with SHOCKED ($r = -.26$; $p = .01$) and PACE ($r = -.25$; $p = .02$), while only MADIT-ICD non-arrhythmic mortality score related with washout rate ($r = .244$; $p = .02$). Late H/M did not show correlation with MADIT, PACE, and Parkash and ranged from the minimum value of $r = -.26$ ($p = .03$) with AAACC to the maximum of $r = -.386$ with FADES ($p < .01$) (Table S3). MADIT (0.463) and MADIT-ICD non-arrhythmic mortality score (0.698), respectively showed the lowest and highest discriminatory power for cardiac denervation in this group (Table S4).

4 | DISCUSSION

In a population of HF patients, a very weak correlation emerged between the risk of all-cause mortality and that of arrhythmic events, respectively, assessed through eight validated scores based on patient's global assessment, and non-invasive myocardial ^{123}I-mIBG imaging. This result is in line with previous evidence and stimulates the discussion on the opportunity to combine the employment of these two risk assessments for clinical management of HF patients. The prevalence of HF is increasing globally, especially in the older adults, and despite the great progresses in the therapeutic management of patients suffering from this complex syndrome, the prognosis is still poor.[25] Moreover, the cost of implantable devices is quite high, also imposing socioeconomic considerations, alongside the awareness of the possibility of malfunction and procedural complications, especially inappropriate shocks and infections.[26] To the best of our knowledge, this is the first study that seeks to determine the association between risk scores most employed in clinical practice for predicting all-cause mortality and the risk of arrhythmic events cardiac, assessed through myocardial ^{123}I-mIBG imaging, in a population of HF patients.

Sympathetic nervous system hyperactivity constitutes a pillar of chronic HF, with a detrimental effect on the pathogenesis and progression of this syndrome. Importantly, it initially constitutes a compensatory mechanism to support cardiac output, but turns deleterious in the long term accelerating syndrome progression and determining the high burden of morbidity and mortality.[2] As a matter of fact, most deaths in patients with advanced HF are due to its progression over time, fatal arrhythmia and SCD. Therefore, implantable devices such as ICD for primary and secondary prevention of SCD improved the overall survival of afflicted patients. Nevertheless, several authors showed conflicting data regarding this therapeutic aid.[27,28]

Therefore, it is not surprising the search of the scientific community for tools and models of risk stratification

in patients with HF, to maximize the appropriateness of ICD therapy. Accordingly, beyond the main international guidelines recommending device positioning only in case of life expectancy superior to 1 year,[5] many clinical risk scores have been proposed to identify patients at high risk of all-cause mortality, whose benefit from ICD implantation is very unlikely, irrespective of cardiac intervention status.[8] A retrospective analysis from data on over 900 consecutive patients, referred to 15 Spanish hospitals for defibrillator implantation in primary prevention, found that MADIT, FADES and SHOCKED showed a significant gradual increase in the risk of all-cause mortality over 4 years, somewhat better than PACE. However, the authors also remarked that, taking into account the specific differences with the reference populations where the scores have been validated, especially regarding the lower number of events, it is not possible to generalize on the exclusion of patients from the therapeutic approach based exclusively on this evidence. Furthermore, they stated that the scores are aimed at predicting mortality, not ICD therapy efficacy.[29] More recently, Calvi and co-authors employed the large real-life Home Monitoring Expert Alliance (HMEA) database to retrospectively test the accuracy of 10 different risks score in predicting 12-month postimplantation mortality. Of note, the analysis considered 1911 HF patients who had undergone ICD and/or CRT positioning without following any algorithm/score to estimate 1-year mortality risk. Surprisingly, the probability to survive beyond the 12th month albeit ominous prediction by the scores was superior to 75%, indicating that more elaborated models, including further variables to better discriminate appropriate therapy, would be desirable in clinical practice.[8]

Thus, the rationale behind the present manuscript was to consider the risk of arrhythmic mortality as an essential component in determining the rates of deaths in patients with HF. At this regard, it is worth mentioning that ^{123}I-mIBG cardiac imaging has demonstrated to provide prognostic information in patients with HF, as typical impairment in cardiac innervation is related to increased risk of cardiovascular mortality, HF hospitalization and arrhythmic events.[23] Nevertheless, its use in clinical practice remains very restricted, due to some intrinsic limits of the imaging method.[30]

Reduced cardiac adrenergic innervation has been in patients suffering from several metabolic conditions such as obesity, diabetes mellitus and CKD.[10,31,32] Furthermore, ageing[19] also relates to impaired cardiac SNS, and notably, to further complicate the scenario, our group has shown that the absolute number of comorbidities does not impact on cardiac sympathetic innervation, thus confirming an alleged lower benefit from ICD therapy in very comorbid patients.[9] Indeed, a very low-grade correlation emerged between the mortality scores of all-cause mortality tested in our study and cardiac denervation measured by nuclear imaging, with FADES score showing the higher association with the most clinically relevant MIBG parameter, late H/M ratio. As expected, since the considered models to assess overall mortality share several variables, significant differences were not detected among different scores. In order to simplify the interpretation of the risk models employed from a clinical practice point of view, we decided to analyse the innervation in low- versus high-risk groups according to each score cut-off. Interestingly, statistically significant differences were detected between late H/M and all risk stratification models, except for PACE and Parkash, which did not show differences compared with all three MIBG parameters of cardiac adrenergic derangement. Small differences emerged from the subgroup analysis in patients with and without IHD, with the latter showing a higher, albeit still weak, significant correlation between some of the scores and MIBG parameters (especially SHOCKED and FADES with late H/M), as well as a better discriminatory power for cardiac denervation (in particular, MADIT-ICD-NA and FADES). Nevertheless, these results must be considered with extreme caution, due to the low number of patients included in the subgroups. Taken together, these results seem to support previous evidence suggesting a low overlap between the risk of all-cause and arrhythmic mortality in the population suffering from HF, confirming presumable lower benefit for ICD therapy in patients at higher comorbidity burden.

Nonetheless, it is worth mentioning that the assessment of the risk/benefit ratio is often particularly challenging in the clinical practice, even in areas in which the different factors contributing to outcomes intrinsically overlap, making it difficult to discriminate the relative contribution of each component. In this scenario, repeated evidence has shown that alterations in ^{123}I-MIBG imaging parameters represent independent prognostic factors, even when advanced age, comorbidities and chronic conditions (chronic kidney disease, diabetes and obesity) negatively concur to disease progression and outcome.[33] The ADMIRE-HF study included 964 patients with HF in NYHA class II–III to determine the independent predictive value of ^{123}I-MIBG imaging on all-cause mortality and on a composite endpoint of death/death-equivalent events. The authors demonstrated, through multiple multivariate risk modelling, the impact of cardiac sympathetic innervation on patient outcomes compared with other clinical measurements including brain natriuretic peptide (BNP) levels and LVEF.[34] Furthermore, Travin and collaborators showed incremental value of MIBG imaging over LVEF and BNP in the prediction of arrhythmic events, focussing on ischaemic HF patients included in

ADMIRE-HF study.[35] From another subanalysis of the same study, Ketchum and colleagues detected that the prognostic power of the Seattle Heart Failure Model, based on demographic data, imaging and laboratory tests, was complemented by the integration of MIBG imaging parameters.[36] A subanalysis of the PARAPET study was designed to explore whether PET parameters could improve SCD prediction and total cardiac mortality in patients with ischaemic cardiomyopathy, eligible to ICD therapy for the primary prevention. This analysis revealed that cardiac denervation, detected through adrenergic imaging, predicted arrhythmic events, while other routine clinical variables showed better performance in predicting non-arrhythmic death.[37] Despite the absence of follow-up data, our results are in the wake of these relevant evidence, highlighting the partial relationship between cardiac denervation and the risk of non-arrhythmic mortality. Our findings stimulate the discussion on the need to verify in larger studies the possibility to integrate the results of MIBG imaging with those derived from risk stratification models most employed in the clinical practice, to allow a complete risk assessment comprehensive of all its components.

In addition to the aforementioned issue, another critical aspect is represented by the clinical variables considered and the relative weight of each one in the risk stratification models, whose different composition might concur to explain the greater or lesser correlation with adrenergic innervation. Accordingly, considering the overall poor discrimination power showed by mortality scores for cardiac denervation, the integration of cardiac imaging into clinical practice may be very useful for physicians in specific borderline cases. Indeed, since the two classes of instruments contribute to the same decision on ICD implantation, when managing patients with a dubious assessment of the risk/benefit ratio only based on clinical risk scores, the decision may be facilitated by information regarding cardiac innervation status. In real-life clinical practice, the information added by MIBG imaging to the clinical assessment may facilitate the personalization of the therapeutic approach, overcoming the limits of each tool when considered individually.

Recent advances in imaging tools enable to better investigate cardiac adrenergic innervation, providing innovative perspectives in the risk stratification of HF patients. Nakajima and collaborators employed machine learning to create a model for predicting 2 years risk of fatal arrhythmia and syndrome death.[38] The authors included 13 indicators including late H/M, which was inversely correlated to HF mortality. Moreover, low-dose dual-isotope 123I/99mTc-acquisition protocol through a cadmium-zinc-telluride (CZT) SPECT camera enables simultaneous assessment of ventricular perfusion and innervation patterns, leading to improved characterization of cardiac function, with better quality, reduced examination time and shorter radiation exposure.[39]

In summary, in patients with HF, the results of the MIBG imaging, although somewhat related, differ sufficiently from the clinical risk stratification models to provide complementary prognostic information, reinforcing what has already been reported by other researchers. Future studies are needed to further explore the specific outcome risks predicted by imaging and clinical risk stratification models in order to better target specific therapies.

5 | LIMITATIONS

This is a secondary analysis of data derived from a monocentric study on a limited number of patients; further studies on larger populations are needed. Despite repeated evidence on the lack of gender-specific differences in the parameters of cardiac innervation, the disproportion between males and females in the study population contributes to the impossibility of establishing definitive conclusions. Similarly, the use of LVEF cut-off equal to 50% and the unavailability of some variables of potential interest (e.g., BNP and additional echocardiographic data) narrow the strength of our results and renew the need to confirm our findings in specifically designed protocols. Finally, the lack of follow-up data limits the possibility to verify the clinical relevance of our results on cardiovascular outcomes and the utility of the integration of risk scores and imaging findings to provide efficient predictive models for disease management, even in guiding the selection of patients for ICD implantation.

6 | CONCLUSIVE REMARKS

In a population of HF patients, a weak association has been observed between cardiac innervation, assessed through ^{123}I-mIBG parameters, and eight all-cause mortality risk scores. This study suggests a poor discriminatory power of the stratification models, validated for overall-mortality risk assessment, in the evaluation of altered cardiac adrenergic innervation. Thus, our results unveil the opportunity to integrate in the clinical practice tools assessing both arrhythmic- and overall mortality risks, especially in the management of HF patients with unclear eligibility for ICD implantation.

AUTHOR CONTRIBUTIONS

LB, GR, AC and PPF conceived this study. LB, KK and GG extracted the data. LB, KK and GDF designed and performed the statistical analyses. LB, SP, CN, PG, RA and FS wrote the first draft of the manuscript. GG and FS created

the graphical abstract. GMC, NF, AC, PPF and GR reviewed and modified the final manuscript. All authors read, critically reviewed and approved the final manuscript.

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CONFLICT OF INTEREST

None to declare.

ORCID

Leonardo Bencivenga https://orcid.org/0000-0002-9575-8337
Alberto Cuocolo https://orcid.org/0000-0003-3431-7658

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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