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Original Article

Comparing the Modified Frailty Index with conventional scores for prediction of cardiac resynchronization therapy response in patients with heart failure

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Abstract

Objective: The aim of the study was to compare, Modified Frailty Index (mFI), EAARN (LVEF <22%, Atrial Fibrillation, Age ≥70 years, Renal function (eGFR <60 mL/min/1.73m^2), NYHA class IV), and ScREEN (female Sex, Renal function (eGFR ≥60 mL/min/1.73m^2), LVEF ≥25%, ECG (QRS duration ≥150 ms) and NYHA class ≤III) score for predicting cardiac resynchronization therapy (CRT) response and all-cause mortality. **Methods**: In this prospective, non-randomized, single-center, observational study we enrolled 93 patients receiving CRT from August 2016 to August 2019. Pre-implant scores were calculated, and patients were followed for six months. Performance of each score for prediction of CRT response (defined as ≥15% reduction in left ventricular end-systolic volume [LVESV]) and all-cause mortality was compared. **Results**: Optimal CRT response was seen in seventy patients with nine deaths. All the three scores exhibited modest performance for prediction of CRT response and all-cause mortality with AUC ranging from 0.608 to 0.701. mFI has an additional benefit for prediction of prolonged post-procedure stay and 30-day rehospitalization events. **Conclusion**: mFI, ScREEN and EAARN score can be used reliably for predicting all-cause mortality and response to CRT.

Keywords: Cardiac resynchronization therapy, Frailty, Heart failure, Risk score model

Introduction

Cardiac resynchronization therapy (CRT) has emerged as an effective treatment modality for patients having heart failure with reduced ejection fraction (HFrEF). This benefit is limited to a specific group of patients with QRS duration ≥130 milliseconds and who continues to be in New York heart association (NYHA) class II-IV of dyspnea[1]. However, one-third of patients receiving CRT have sub-optimal response despite adhering to strict selection criteria[2,3].

Such a high number of sub-optimal response warrants itself for a prediction model to identify patients at risk for poor outcome. Recently multiple risks predicting models based on demographic profile, electrocardiographic parameters, biochemical test results, and co-morbid conditions have been proposed and validated. Scores like ScREEN[4], EAARN[5], VALID CRT[6], L2ANDS2[7], CRT-SCORE[8], machine learning (ML) algorithms[9], and Modified Frailty Index (mFI)[10] have been studied to predict CRT outcome. The ScREEN, EAARN, and mFI scores are derived from easily available clinical and biochemical variables and have performed good for prediction of clinical outcome in their respective derivation cohorts[4,5,10], still which one to be used with most reliability is uncertain.

In this study, we aim to assess prospectively the performance of EAARN, mFI, and ScREEN scores for the prediction of outcome in patients receiving CRT.

The authors have no conflict of interest.

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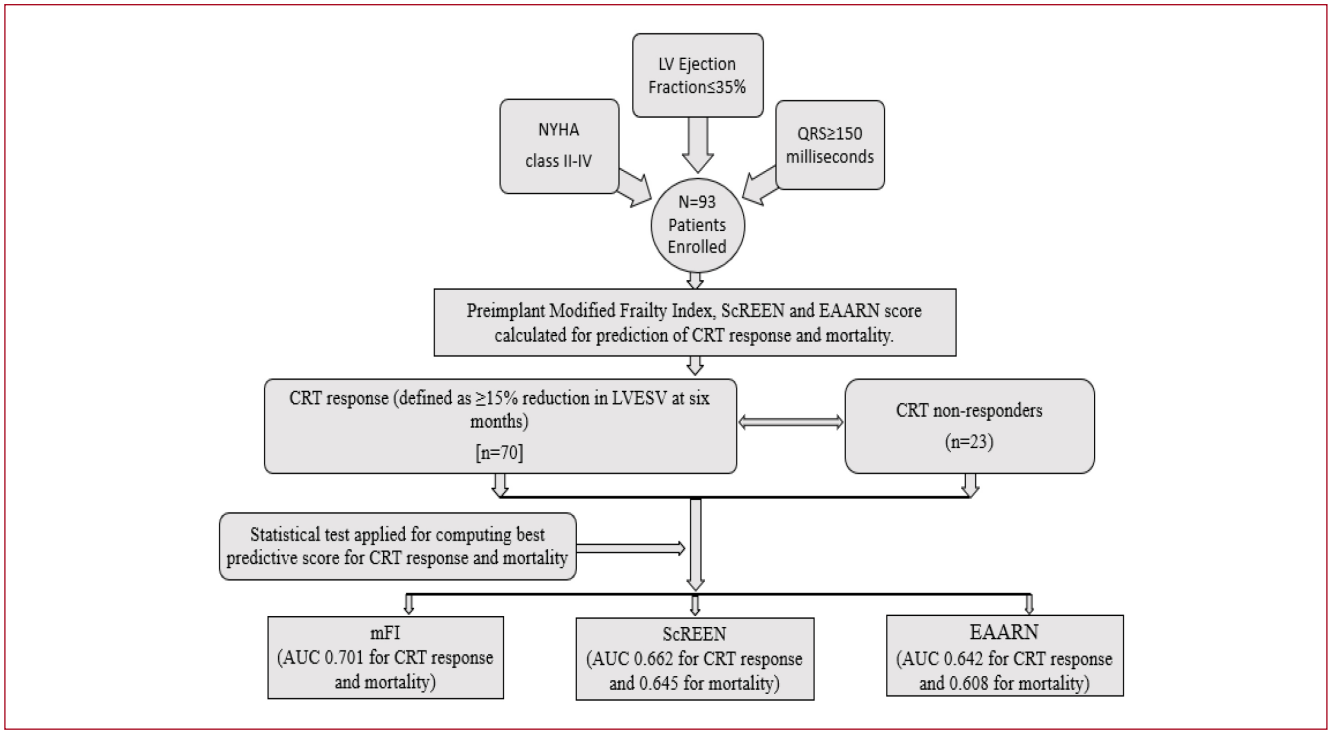

Figure 1. Study design.

Methods

Study Population

In this prospective non-randomized single-center observational study we enrolled patients who had undergone CRT with a defibrillator or pacemaker (CRT-D/P) in the Department of Cardiology at a tertiary care center in North India between August 2016 to August 2019. The sample size of 93 was obtained using the formula:

$$n=\frac{Z^2_{1-\alpha/2}p(1-p)}{\delta^2}$$

with 5% level of significance (α), 10% margin of error (δ) and prevalence of CRT response as 57% (p) according to the findings of a previous study done by Ypenburg et al.[11] ($Z\alpha$= Value of standard normal variate corresponding to α level of significance=1.96) Indication for CRT was New York Heart Association (NYHA) functional class II-IV symptoms despite optimal medical therapy, LVEF ≤35%, and QRS duration ≥150 milliseconds (ms) according to the ACA/AHA/HRS guidelines[12]. Figure 1 illustrates the study design. The outcomes were compared in terms of two variables:

1. All-cause mortality.
2. CRT response (defined as ≥15% reduction in LVESV at six months)[13,14].

All the patients enrolled were on maximum guideline-directed medical therapy (GDMT). Informed consent was taken from the participants and patients who did not consent were excluded from the study. The study protocol was passed by the Institutional Ethical Committee (letter no. IEC-Aug 2018-9406).

Data collection

Baseline data, including demographic profile, etiology of heart failure (HF), co-morbid conditions (diabetes, hypertension, and chronic kidney disease), type of device implanted (CRT D or P), NYHA (New York Heart Association) functional class of dyspnea (Class I - No symptoms and no limitation in ordinary physical activity; Class II - Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity; Class III - Marked limitation in activity due to symptoms, even during less-than-ordinary activity, comfortable only at rest; Class IV - Severe limitations. Experiences symptoms even while at rest) were recorded in standard proforma. Transthoracic echocardiography was performed using Philips Model Sonos 5500 machine (Phillips Medical Systems, Andover, MA, USA). Parameters in echocardiography evaluation were LV end-systolic volume (LVESV) and Left ventricular ejection fraction (LVEF) using modified Simpson's method as per standard guidelines[15].

CRT was implanted in the catheterization laboratory using standard technique, commercially available devices

Characteristic	Study cohort (n=93)	mFI Validation cohort (n=283)	EAARN Derivation cohort (n=600)	ScREEN Validation cohort (n=1959)
Age (years)	61.19±7.9	66±13	60.9±9.8	67.1±11.9
Male (%)	63(67.74) [B]	170 (59.9)	468 (77)	1417(72.3)
ICM (%)	44(47.31)	114 (40.1)	253 (42%)	948(49.6)
LBBB (%)	82 (88.17) [B]	N/A	N/A	1472(79.4)
CRT-D (%)	80(86.02) [B]	N/A	404 (68)	1122(57.3)
NYHA (mean)	2.67±0.54	2.63±0.8	N/A	2.8±0.6
II (%)	24(25.81)	N/A	135 (23)	N/A
III (%)	58(62.37)	N/A	406 (67)	N/A
IV (%)	11(11.83)	N/A	59 (10)	N/A
QRS duration (milliseconds)	163.87±10.32	157±36	164±22	65.9 [A]
LVEF (%)	27.82±2.88	26.1±7.2	28.52±7.71	27±9
eGFR (ml/m^2)	49.24±12	44.1±14	63.5±25.1	N/A
eGFR>60 ml/m^2	17(18.28)	N/A	332(55.3)	892(45.5)
Diabetes (%)	35(37.63)	140(49.46)	N/A	451(26.5)
LVESV (ml)	138.61±21.52 [B]	N/A	177.5±73.9	N/A

A=65.9% of patients in the ScREEN cohort had a QRS duration of ≥150 milliseconds. B=compared to other cohorts the statistically significant difference as per student t-test (p<0.05). CRT-D=cardiac resynchronization therapy with defibrillator; eGFR=estimated glomerular filtration rate; ICM=ischemic cardiomyopathy; mFI=Modified Frailty Index; ml=milliliters; LBBB=left bundle branch block; LVESV=left ventricle end-systolic volume; LVEF=left ventricle ejection fraction; N/A=not available; NYHA=New York Heart Association.

Table 1. Comparison of multiple baseline characteristics of the study population with cohort of mFI, EAARN, and ScREEN score.

were used. Left ventricle (LV) lead was selectively placed in the lateral branch of the coronary sinus, in-order to achieve activation of the lateral free wall of LV. The choice of LV lead used was as per coronary sinus anatomy and was decided by the operator firsthand.

Score computation

We calculated the ScREEN[4], EAARN[5], and mFI[10] risk scores during the pre-implantation phase of CRT to predict all-cause mortality and CRT response, for each patient as per the equations described in each score's original study.

For ScREEN[4] score five variables (female **S**ex, **R**enal function (eGFR ≥60 mL/min/1.73m^2), LV**E**F ≥25%, **E**CG (QRS duration ≥150 ms), and **N**YHA class ≤III) were assigned 1 point each, with a score ranging from 0-5. ScREEN score grouped the patients into 3 categories (0 and 1, lowest chances of CRT response; 2 and 3 intermediate chances of CRT response; 4 and 5 highest chances of CRT response).

EAARN[5] score was calculated using five variables (LV**E**F <22%, **A**trial Fibrillation (AF), **A**ge ≥70 years, **R**enal function (eGFR <60 mL/min/1.73m^2) and baseline **N**YHA class IV). Each additional predictor increased the mortality: one predictor, HR 3.28 (95% CI 1.37–7.8, *P*=0.008); two, HR 5.23 (95% CI 2.24–12.10, *P*<0.001); three, HR 9.63 (95% CI 4.1–22.60, *P*<0.001); and four or more, HR 14.38 (95% CI 5.8–35.65, *P*<0.001).

Modified Frailty Index (mFI)[10] used to assess the vulnerability of patients to adverse effects especially in the setting of medical intervention. The 11 variables of the mFI include non-Activities of Daily Living independent, diabetes mellitus, exacerbation of Chronic Obstructive Pulmonary Disease (COPD) or Congestive Heart Failure (CHF) in the last 30 days, myocardial infarction within 6 months, previous Percutaneous Coronary Intervention (PCI)/Coronary Artery Bypass Graft (CABG)/angina, hypertension, Peripheral vascular disease, impaired sensorium, and transient ischemic attack (TIA)/ Cerebrovascular Accident (CVA) with or without deficits.

Each variable was assigned 1 point and a composite score of ≥3 was used as the cut-off for defining frailty and predicting the poor outcome for CRT[10].

Follow up

All the patients were followed for six months, in the pacemaker clinic as per the pre-defined departmental protocol. Device interrogation and optimization using intrinsic device algorithms along with optimization of medical treatment were done at each follow-up visit.

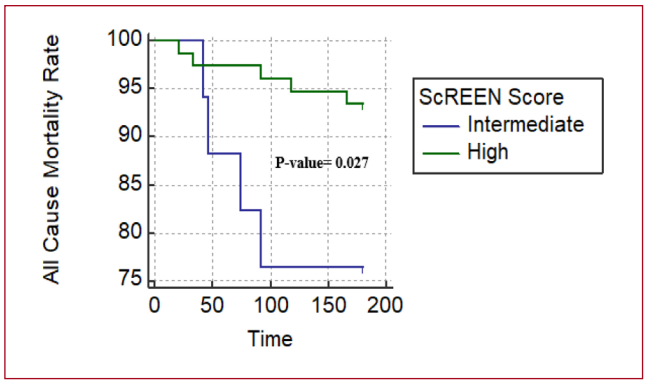

Figure 2. The plot of the Kaplan-Meier curve for the endpoint of all-cause mortality using the ScREEN score.

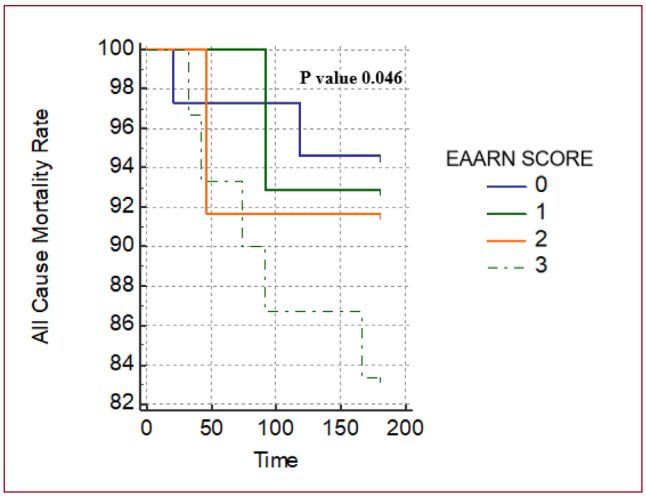

Figure 3. The plot of the Kaplan-Meier curve for the endpoint of all-cause mortality using the EAARN score.

Statistical analysis

All the data were analyzed using SPSS version 23.0 (SPSS, Chicago, IL, USA). Categorical data are presented as counts and percentages, whereas continuous data as mean ± standard deviation. Student's t-test was used for continuous variables and χ^2 test with Fisher's exact test for comparison of categorical variables between the two groups. For survival rate evaluation, the Kaplan-Meier method was used, and the difference was evaluated using the log-rank test.

As the ScREEN score and mFI were developed using logistic regression and EAARN using cox-regression, we plotted ROC (receiver operating characteristics) probability curve and used the area under the curve (AUC) to determine the better predictive model. AUC represents the degree or measure of separability and tells how much the model is capable of distinguishing between classes, the value ranges from 0.5 to 1.0 with higher values suggestive of a better predictive model. A two-sided p-value was calculated and a value <0.05 was taken to be statistically significant.

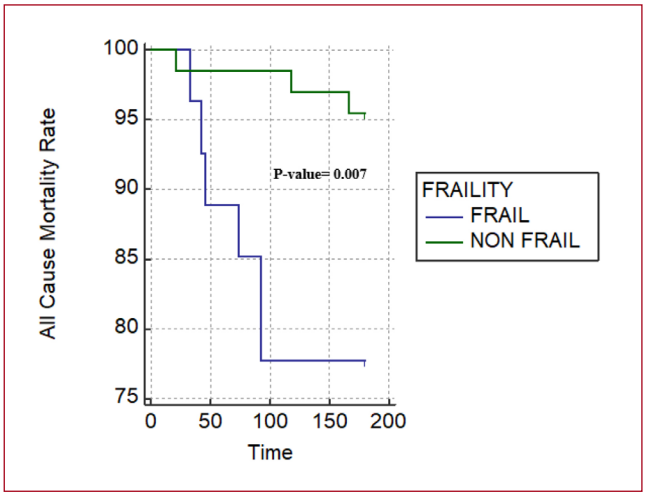

Figure 4. The plot of the Kaplan-Meier curve for the endpoint of all-cause mortality using Modified Frailty Index (mFI).

Results

Baseline characteristics

A total of 93 patients with HFrEF were enrolled in this study, who had undergone CRT implantation. The mean age of the study population was 61.19±7.9 years, with the maximum being male patients 67.74% (63/93). Ischemic cardiomyopathy (ICM) was present in 47.31% (44/93) and 86.02% (80/93) received CRT-D. Left bundle branch block (LBBB) morphology was present in 88.17 (82/93) and all were in sinus rhythm.

A comparison of baseline variables between the study cohort and cohorts in which mFI, EAARN, and ScREEN scores were validated is shown in Table 1. LVEF, renal function, QRS duration, and NYHA class distribution was similar among the four cohorts. However, study cohort patients were younger than the mFI and ScREEN cohort (p<0.001) with male preponderance, LBBB morphology was present in more patients (88.17%) and CRT-D was implanted more when compared to other cohorts (p<0.001). The echocardiographic parameter of LV remodeling (LVESV) was also less in the study cohort in comparison to the EAARN cohort (p<0.001).

Clinical endpoints during follow up

Over the follow-up of six months, CRT response as per the pre-defined criteria was seen in seventy patients, twenty-three patients had sub-optimal response and a total of nine deaths due to heart failure hospitalization. Each score was

	ScREEN Score			p-value
	Low (0-1)	Intermediate (2-3)	High (4-5)	
Non- Responder	0	8	15	0.018
Responder	0	9	61	

Table 2. Stratification of study cohort according to the ScREEN score for CRT response.

	EAARN Score				p-value
	0	1.0	2.0	3.0	
Non-Responder	2	5	7	9	0.042
Responder	6	32	20	12	

Table 3. Stratification of study cohort according to EAARN score for CRT response.

Parameter	Non-Frail (<3)	Frail (≥3)	p-value
Non-Responder	12	11	0.022
Responder	54	16	
No Hospitalization	59	13	<0.001
≥1 Hospitalization event	7	14	
Post procedural stay (mean days)	5.85	3.14	<0.001

Table 4. Stratification of study cohort according to mFI for CRT response, rehospitalization, and post-procedural stay.

used to predict mortality and CRT response on the study cohort, and a comparison was done among the scores for clinical endpoints.

The study cohort was stratified into three groups, Low (0-1), Intermediate (2-3), and High (4-5) as shown in Table 2 using the ScREEN score, as per the score of the patients. A high ScREEN score was associated with significantly better CRT response (p=0.018) and statistically lower mortality at six months (p=0.027) as per the Kaplan-Meier curve showed in Figure 2.

EAARN score was calculated and the cohort was stratified in ascending order as per the individual score, with the minimum being score 0 (no risk factor) to a maximum of ≥4 (with 4 or more risk factors). It was observed that as there was an increase in EAARN score, the hazard ratio for the clinical endpoint of mortality increased: score of 1 HR 1.82 (95% CI 1.208 to 3.238; p=0.009) score of 2 HR 3.21 (95% CI 1.828 to 9.440; p=0.015) and a score of 3 HR 4.59 (95% CI 1.44 to 12.44; p=0.002). Similarly, a higher EAARN score was associated with significantly poor CRT response as shown in Table 3. When mortality was compared as per the Kaplan-Meier curve showed in Figure 3 there was significantly more mortality in patients with higher EAARN scores (p=0.046).

Using mFI, the study cohort was divided into two groups with a cut of ≥3 for defining frailty among the patients. A comparison between the frail and non-frail patients showed that the risk of suboptimal response to CRT was statistically significantly more with frail patients (p=0.022). As mFI also predicts the post-procedural stay and 30-day rehospitalization events of patients, we also calculated these parameters. Postprocedural stay and 30-day rehospitalization were also more with frail patients when compared with non-frail patients as shown in Table 4. A similar result with all-cause mortality was obtained using the Kaplan-Meier curve as showed in Figure 4.

Comparative performance of mFI, ScREEN, and EAARN score

Cox proportional hazards regression and logistics regression analysis were used to derive the predictive performance of EAARN, ScREEN, and mFI for the prediction

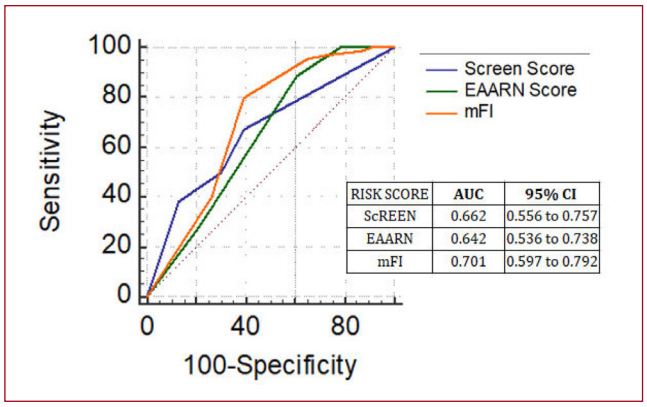

Figure 5. Comparison of area under the receiver operating curve (AUC) among mFI, ScREEN, and EAARN for CRT response over the follow-up.

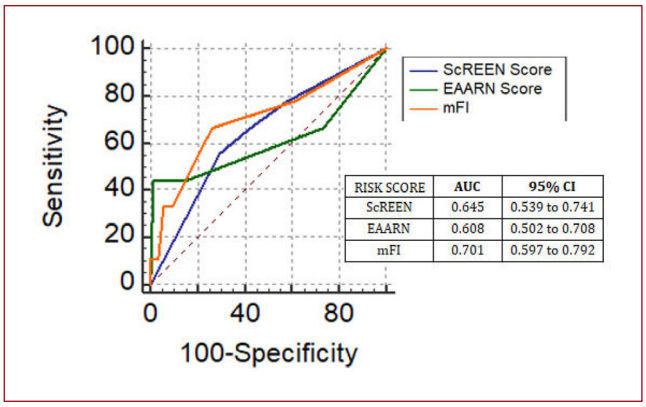

Figure 6. Comparison of area under receiver operating curve (AUC) among mFI, ScREEN, and EAARN for all-cause mortality.

of CRT response over time as shown in Figure 5, and mortality as shown in Figure 6. Among the three scores, mFI yielded the best predictive power for mortality when compared with ScREEN and EAARN, as the AUC was maximum for mFI 0.701 vs 0.645 and 0.608, respectively. Similarly, mFI yielded the best predictive power for CRT response also 0.701 vs 0.662 and 0.642, respectively.

Discussion

This study is the first to compare the predictive performance of these three scores, Modified Frailty Index (mFI), ScREEN, and EAARN. All these three scores were developed to predict the long-term outcome of CRT in patients with HFrEF. In this study, the 11-variable mFI based on easily available clinical characteristics and patient history yielded the best performance for CRT response and all-cause mortality as per the AUC (0.701). All the three scores performed equivalently well in our study for the prediction of CRT response (AUC ranging from 0.642 to 0.701) and all-cause mortality (AUC ranging from 0.608 to 0.701).

To the best of our knowledge, this is the first prospective study to compare the predictive performance of mFI, ScREEN, and EAARN scores. The indication for CRT implantation includes a strict selection of patients with LVEF≤35% with evidence of LV desynchrony on electrocardiogram (ECG QRS duration of ≥130 ms)[12]. Despite selecting patients as per the criteria, only 2/3rd of patients responds to CRT in the desired manner while the rest have a sub-optimal response[2,3].

As patients with HFrEF, undergoing CRT has a vulnerability to adverse health outcomes especially in the setting of medical interventions due to disease process, cachexia, advanced age, renal dysfunction, hemodilution, anemia, multiple drug therapies, and associated co-morbid conditions[16]. Along with the high cost of the CRT devices and inherent risk factors associated with its implantation, like perforation, dissections, pneumothorax, and pocket infection[17], hence identification of patients prone to sub-optimal response and complications that can increase the failure rate along with mortality is decisive[18].

Multiple scores for prediction of mortality in patients receiving CRT, such as EAARN[5], VALID-CRT[6], CRT SCORE[8], and HF CRT[19] have been studied. Several other risk scores like ScREEN[4], L2ANDS2[7], and mFI[10] were used to predict CRT response.

In our study ScREEN, EAARN and mFI score performed well for the prediction of CRT response (>0.60) and all-cause mortality (>0.60) which was in concordance with their validation cohorts[4,5,10]. However, comparing all three scores, mFI was associated with the best predictive power for both CRT response and all-cause mortality (0.70 respectively). This better response can be attributed to the prognostic design of the score as it includes most of the clinically relevant data like COPD/CHF in the last 30 days, MI within six months, history of CVA/TIA/PVD/Altered sensorium which was not included in rest of the two scores. And as it has been seen in prediction model studies that a score should include most of the relevant inclusions and variables should be easily obtained without the need for more sophisticated equipment's[20] which is obvious as variables included in mFI can be elicited in history itself without any biochemical lab results, unlike ScREEN and EAARN (both require eGFR, ECG and LVEF for computation). mFI proved to be superior as it does not include any arbitrary thresholds for continuous variables[21] as it leads to difficulty for the clinician to categorize a patient (example: eGR of 58 ml/m^2 confers a point in both the scores but an eGFR of 61 ml/m^2 lends a scoreless by 1 point, changing the stratified class of the patient and hence prognosis). Recently machine learning (ML) algorithms were proposed for prognostic prediction of echocardiographic CRT response and survival beyond

guidelines[9] with an AUC value of 0.70 which is comparable to our study (mFI 0.701) hence showing that the predictive performance of mFI is comparable to ML algorithms. Its simple structure makes it easy for the clinician to calculate the score and thus increasing the probability of it being used more often than one requiring data entry to a computer (ML algorithms) to make complex calculations[22].

Thus, our study shows that prognostic models can be used reliably for the prediction of CRT outcomes in a real-world scenario, and they will help us identify a group of likely non-responders patients with all the guideline-directed indications for CRT. It will also help us in reinforcing benefits for patients who are likely to have a high response rate. We can individualize our approach to patients who are likely to have a suboptimal response in form of regular algorithm optimization[23], medical therapy optimization with novel drugs[24], use of novel endocardial pacing modality[25], or early referral for heart transplant clinic.

Conclusion

All the three predictive scores Modified Frailty Index (mFI), ScREEN and EAARN can be used reliably to predict all-cause mortality and CRT response, reinforcing the guideline-directed indications for CRT in patients with HFrEF, to obtain a better CRT outcome.

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