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Author

Prasad, Sandhir B, Chan, Nicole Ivy, Krishnan, Anish, Martin, Paul, Stewart, Peter, Mallouhi, Michael, Vollbon, William, Atherton, John J

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Novel combined echocardiographic score comprising prognostically validated measures of left ventricular size and function to predict long-term survival following myocardial infarction: A proposal to improve risk stratification

Sandhir B. Prasad MBBS, PhD, FRACP[1,2,3] | **Nicole Ivy Chan MD**[1] | **Anish Krishnan MBBS, MClinEpi**[1] | **Paul Martin MBBS, PhD, FRACP**[1] | **Peter Stewart MBBS, FRACP**[1] | **Michael Mallouhi BSc**[4] | **William Vollbon BSc**[4] | **John J. Atherton MBBS, PhD, FRACP**[1,2]

[1]Department of Cardiology, Royal Brisbane and Women's Hospital, Herston, Australia

[2]Faculty of Medicine, University of Queensland, Brisbane, Australia

[3]Faculty of Medicine, Griffith University, Southport, Australia

[4]Statewide Cardiac Network, Ministry of Health, Brisbane, Queensland, Australia

Correspondence
A/Prof Sandhir B. Prasad, MBBS, PhD, FRACP, Department of Cardiology, Royal Brisbane and Women's Hospital, Herston Road, Brisbane, Queensland, Australia.
Email: sandhir.prasad@gmail.com

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Abstract

Background: While left ventricular ejection fraction (LVEF) is the primary variable utilized for prognosis following myocardial infarction (MI), it is relatively indiscriminate for survival in patients with mildly reduced (> 40%) or preserved LVEF (> 50%). Improving risk stratification in patients with mildly reduced or preserved LVEF remains an unmet need, and could be achieved by using a combination approach using prognostically validated measures of left-ventricular (LV) size, geometry, and function.

Aims: The aim of this study was to compare the prognostic utility of a Combined Echo-Score for predicting all-cause (ACM) and cardiac mortality (CM) following MI to LVEF alone, including the sub-groups with LVEF > 40% and LVEF > 50%.

Methods: Retrospective data on 3094 consecutive patients with MI from 2013 to 2021 who had inpatient echocardiography were included, including both patients with ST-elevation MI ($n = 869$ [28.1%]) and non-ST-elevation MI ($n = 2225$ [71.9%]). Echo-Score consisted of LVEF < 40% (2 points) or LVEF < 50% (1 point), and 1 point each for left atrial volume index > 34 mL/m^2, septal E/e′ > 15, abnormal LV mass-index, tricuspid regurgitation velocity > 2.8 m/s, and abnormal LV end-systolic volume-index. Simple addition was used to derive a score out of 7.

Results: At a median follow-up of 4.5 years there were 445 deaths (130 cardiac deaths). On Cox proportional-hazards multivariable analysis incorporating significant clinical and echocardiographic predictors, Echo-Score was an independent predictor of both ACM (HR 1.34, $p < .001$) and CM (HR 1.59, $p < .001$). Inter-model comparisons of model χ^2, Harrel's C and Somer's D, and Receiver operating curves confirmed the superior prognostic value of Echo-Score for both endpoints compared to LVEF. In the subgroups with LVEF > 40% and LVEF > 50%, Echo-Score was similarly superior to LVEF for predicting ACM and CM.

Conclusions: An Echo-Score composed of prognostically validated LV parameters is superior to LVEF alone for predicting survival in patients with MI, including the subgroups with mildly reduced and preserved LVEF. This could lead to improved patient risk stratification, better-targeted therapies, and potentially more efficient use of device therapies. Further studies should be considered to define the benefit of further investigation and treatment in high-risk subgroups.

KEYWORDS
echocardiography, myocardial infarction, prognosis

1 | INTRODUCTION

The importance of left ventricular (LV) size and function for predicting survival following myocardial infarction (MI) was established in a number of seminal studies.[1–4] While the left ventricular ejection fraction (LVEF), has become established as the primary echocardiographic variable for prognosis, it has a number of important limitations in this regard. Volpi et al showed that while LVEF was a strong predictor of survival in patients with an LVEF < 40%, it was relatively indiscriminate for survival in patients with an LVEF > 40% (mildly reduced or preserved LVEF).[3] Data from real-world patients with implantable cardioverter defibrillators (ICDs) shows that the majority of patients with primary prevention ICDs implanted on the basis of a moderate or severely reduced LVEF do not experience ventricular arrhythmia or device treatment, and in fact, the majority of sudden cardiac deaths occur in patients with mild to moderately reduced LVEF.[5] Furthermore, the coefficient of variation of the measurement is 11%, and there is significant intra- and inter-observer variability.[6] To circumvent some of these recognized limitations of LVEF, the prognostic utility of other prognostically validated echocardiographic variables can be exploited. An expert review on the prognostic role of echocardiography after MI has previously recommended adopting a comprehensive, multiparametric approach using other prognostically validated echocardiographic variables to supplement the existing prognostic utility of LVEF following MI.[7]

Accordingly, this study was designed to test the prognostic utility of a Composite Echo-Score composed of prognostically validated measures of LV size, geometry, and function in comparison to the LVEF alone, for predicting all-cause and cardiac mortality following MI, including prognostic utility in the subgroups with LVEF > 40%. The study hypothesis was that a Composite Echo-Score would be superior to LVEF alone for predicting survival following MI.

2 | METHODS

2.1 | Study overview

A total of 3464 consecutive patients with MI (ST-elevation MI [STEMI] and non-ST-elevation MI [NSTEMI]) during the study period between January 2013 and December 2021 at a single tertiary level referral center were considered for inclusion in this study. Exclusion criteria included significant hemodynamic instability (shock, acute pulmonary edema, requirement for mechanical ventilation, inotropes, intra-aortic balloon pump, and those with ventricular tachyarrhythmia), in-hospital death, limited or point-of-care echocardiograms, severe left-sided valve disease and incomplete echocardiographic, clinical, echocardiographic, or follow-up data. All clinical, angiographic and echocardiographic data were retrospectively collected from prospectively maintained institutional cardiac catheterization and echocardiographic databases. Outcomes data were obtained from the State Births, Deaths, and Marriages registry, where each patient is tracked through a unique identification number. The primary outcome measures were all-cause mortality and cardiac.

2.2 | Institutional protocol for MI

All patients with MI at the study institution were considered for an invasive approach unless significant contraindications existed. The default strategy for the management of STEMI was primary PCI with 24-h catheterization laboratory activation (mean door-to-balloon time 73 ± 12 min), and an early invasive approach for NSTEMI. The completeness of revascularization was at the discretion of the operator depending on the patient's condition, with an emphasis on culprit lesion PCI in primary PCI. All patients were started on evidence-based medical therapy for MI including aspirin, dual antiplatelet therapy, statins, angiotensin-converting enzyme inhibitors, and beta-blockers on admission unless contraindications existed. A comprehensive transthoracic echocardiogram was performed within 24 h of admission for all patients. All measurements obtained were in accordance with current ASE recommendations.[8]

2.3 | Echo-Score variable selection

The Echo-Score included LVEF < 40% (2 points) or LVEF < 50% (1 point), left atrial volume index (LAVi) > 34 mL/m^2 (1 point), septal E/e′ ratio > 15 (1 point), abnormal left ventricular mass index (using sex specific cut-offs) (LVMi) (1 point), tricuspid regurgitation velocity

(TRV) > 2.8 m/s and abnormal left ventricular end systolic volume index (using sex specific cut-offs) (LVESVi) (1 point). Simple summation was used to derive a score out of 7. The rationale for variable selection for composite score was as follows. A number of variables related to LV size, geometry and function measured on standard echocardiography were considered for inclusion in the composite score on the basis of the following criteria applicable to each measure: (i) available on standard 2D and Doppler echocardiography and hence widely applicable; (ii) highly feasible; (iii) robust prognostic validation in the published literature; (iv) avoidance of collinearity with other measurements; and (v) endorsed for routine measurement and clinical application in current American Society of Echocardiography (ASE)/European Association of Cardiovascular Imaging (EACVI) guidelines on chamber quantification and assessment of diastolic function.[8,9] A further over-riding principle was the need to minimize the number of variables to keep the score simple to promote ease of application in clinical practice. Based on these principles, the following variables were considered: LVEF, LVESVi, LVEDVi, WMSi, LVMi, tricuspid regurgitation velocity (TRV), E/e′ ratio, RFP (defined as E/A ratio > 2 as per current guidelines), LAVi, mitral annular plane systolic excursion (MAPSE) and deceleration time (DT). For the final score, LVEF, LVESVi, LVMi, septal E/e′ ratio, TRV, and LAVi were selected based on the above principles, with the reasons for excluding other variables listed below. LVEDVi was excluded as there was a suggestion of more robust prognostic data for LVESVi2, and due to collinearity with LVESVi. WMSi was excluded due to collinearity with LVEF. DT was excluded as it is not included in current ASE/EACVI algorithms for assessment of diastolic function.[9] MAPSE was excluded as this is not routinely measured on standard echocardiography. E/A ratio > 2 was not included due to collinearity with LAVI and E/e′ ratio.

2.4 | Echocardiogram protocol and measures

A comprehensive transthoracic echocardiogram was performed within 24 h of admission for all patients. All echocardiograms were performed on either a General Electric (GE) Vivid E9 machine (Horten, Norway) or a Phillips IE33 machine (Andover, Massachusetts, USA) with tissue Doppler imaging software and a 2.5–5 MHz variable frequency, phased array transthoracic transducer. The echocardiography protocol, performed by experienced clinical sonographers, followed a standard format with image acquisition from the parasternal, apical and subcostal acoustic windows, and included 2D, color flow mapping, continuous and pulse-wave Doppler, and tissue Doppler imaging. Left ventricular systolic function was assessed by LV ejection fraction (LVEF) obtained using Simpson's biplane method of discs from the apical 4 and 2 chamber views.[8] Left ventricular volumes were obtained from Simpson's biplane method of discs, and indexed to body surface area. Left ventricular mass was obtained using Devereaux's formula as recommended in current guidelines.[8] Mitral inflow Doppler was obtained by placing a 1 mm pulsed-wave (PW) sample box at the mitral leaflet tips in the apical 4-chamber view at end expiration using a sweep speed of 100 mm/s.[9] Tissue Doppler imaging (TDI) was obtained by placing a 2 mm PW sample box at the septal and lateral mitral annulus. E/e′ ratio was calculated using the early mitral inflow E wave velocity and septal e′ (E/e′ septal), lateral e′ (E/e′ lateral), and the average of septal and lateral e′ (E/e′ average).[9] LAVI was assessed using a Simpson's biplane method with an inbuilt disk summation algorithm on the echo machines used in this study, with the LA endocardium traced out in the apical 4 and 2 chamber views at ventricular end systole just prior to mitral valve opening, with the left atrial appendage, the area under the mitral valve annulus and the inflow of the pulmonary veins excluded from the tracing.[8] TRV was obtained from continuous wave Doppler signal of tricuspid regurgitation jets from either the RV inflow view, parasternal short axis at aortic valve level or apical 4 chamber view.

Echocardiographic data was retrospectively retrieved from the echocardiography laboratory archive, which is prospectively updated in real time at the completion of all echocardiogram reports. All echocardiograms done in the echocardiography laboratory, including limited studies and POCUS scans, have a report generated by a subspeciality-trained echo-cardiologist, which is archived with the images and measurements. Retrieved data from 100 randomly selected patients were manually audited against printed reports to verify the accuracy of echocardiographic data. All echocardiograms were performed individually by senior trained sonographers accredited for cardiac sonographers, or by trainee sonographers with one-on-one supervision by senior sonographers.

2.5 | Statistical analysis

Continuous variables are expressed as mean ± SD and compared using an unpaired *t*-test if data was normally distributed or the Mann–Whitney *U*-test if data was not normally distributed. Categorical variables are presented as percentages and compared with Fisher's exact test. Associations between factors of interest and outcomes were tested with univariable Cox proportional-hazards analysis. Parameters significant at a level of .05 on univariate analysis were considered for inclusion in multivariable Cox proportional-hazards analyses. A series of nested models were constructed to examine the independence and incremental value of Echo-Score over significant clinical variables and LVEF for prediction of survival. Inter-model comparisons for increase in predictive power were performed by a comparison of the model χ^2 (chi squared) at each step by calculating change in overall log-likelihood ratio chi-square. Harrell's C-statistic and Somer's D statistic was also calculated for each model as an analogous overall measure of discrimination for predicting survival. Survival was also expressed using Kaplan–Meier Curves, with a log-rank test used to assess for statistical significance between curves. Receiver operator characteristic (ROC) curves were also generated for Echo-Score and LVEF as predictors of survival. A $p < .05$ was considered significant. All statistical analyses were carried out using SPSS version 23 (SPSS Inc, Chicago, Illinois). The study was approved by the institutional Human Research Ethics committee.

3 | RESULTS

Patient flow through inclusion and exclusion are shown in Figure 1. There were 3464 consecutive patients with MI that were considered for inclusion. There was a total of 370 exclusions, leaving a final study group of 3094 patients. Baseline clinical and angiographic data are summarized in Table 1. Echocardiographic data derived from index echocardiogram post-MI is provided in Table 2. Follow-up data were available for all patients. The mean age of patients was 63.0+12.5 years; 28.9% were females; and, 28.1% presented with STEMI. The risk factor profile was consistent with a cohort with established coronary artery disease: diabetes was present in 28.2%, hypertension was noted in 53.6%, dyslipidemia was present in 47.0% and 60.8% were either present or former smokers. The prevalence of renal dysfunction was low with 1.2% classified as having chronic kidney disease. On coronary angiography, 3 vessel disease was noted in 14.8%. In terms of management, 55.5% underwent percutaneous coronary intervention, 12.6% underwent CABG, and 31.8% had medical management only.

3.1 | Predictors of all-cause mortality

There was a total of 445 deaths (14.3%) over a median follow-up period of 4.5 years (range 1–9 years). Kaplan–Meier survival curves for Echo-Score 0–7 for all-cause mortality is shown in Figure 2A. There was a significant graded separation of survival curves for scores 0–7 as shown, with a score of 0 having the best survival and a score of 7 the worst (log rank $\chi 2$ 275.6 [p < .001]). Based on the separation of the survival curves and findings from ROC analysis, patients were further classified into low Echo-Score (0), intermediate Echo-Score (1–3) and high Echo-Score (4–7), analogous to LVEF cut-offs of > 50% (preserved LVEF), 41%–49% mildly reduced LVEF and < 40% (moderate to severely reduced LVEF). Kaplan–Meier survival curves for a low, intermediate and high Echo-Scores based on this classification is shown in Figure 2B. There was a significant graduated separation of survival curves, with patients with a high Echo-Score having the worst outcomes (log rank $\chi 2$ 204.2, p < .001). To place survival with Echo-Score in perspective, the Kaplan–Meier survival curves for LVEF stratified by a cut-offs of 50% (preserved LVEF), 41%–49% (mildly

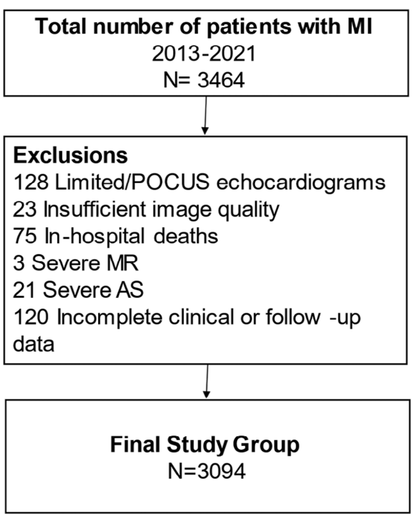


FIGURE 1 Patient flow data.

TABLE 1 Baseline clinical, angiographic, and echocardiographic data.

Characteristic	n = 3094
Clinical characteristics	
Age	63.03 ± 12.50
Male	2200 (71.1)
BMI	29.42 ± 9.07
CKD (eGFR < 90)	38 (1.2)
Diabetes	871 (28.2)
Dyslipidemia	1454 (47.0)
Family history of IHD	1143 (36.9)
Hypertension	1657 (53.6)
Smoking	1881 (60.8)
STEMI	869 (28.1)
Three vessel disease	459 (14.8)
Management strategy	
PCI	1718 (55.5)
CABG	392 (12.6)
Medical management	984 (31.8)
LV size and function	
LVEF (%)	52.79 ± 10.98
LVSepThickness (mm)	1.08 ± .22
LVPWThickness (mm)	.98 ± .19
LVEDD (mm)	47.20 ± 6.38
LVESD (mm)	33.33 ± 6.96
LVEDVi (mL/m^2)	52.39 ± 15.03
LVESVi (mL/m^2)	25.58 ± 12.21
LVMi	85.91 ± 23.72
Diastolic parameters	
E velocity	70.31 ± 22.89
A velocity	
E/A ratio	1.06 ± .48
Septal E/e′	12.60 ± 6.52
Lateral E/e′	9.83 ± 5.00
Average E/e′	11.15 ± 5.35
LA area	20.59 ± 5.29
LAVi (cm^3/m^2)	32.06 ± 10.72
Right heart parameters	
RVSP	32.06 ± 10.72
TR peak velocity	249.85 ± 44.58
RV S′ velocity (cm/s)	19.88 ± 283.62
RA pressure	5.72 ± 3.65

(Continues)

TABLE 1 (Continued)

Characteristic	$n = 3094$
Echo Score	
Low (0)	899 (29.1%)
Intermediate (1–3)	1726 (55.7%)
High (4–7)	469 (15.2%)

Note: Data expressed as mean ± SD or as number (percentage).
Abbreviations: BMI, body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CKD, chronic kidney disease; E/A, ratio of mitral E wave to A wave; E/e′, ratio of mitral E wave to e′; IHD, ischemic heart disease; LAVI, left atrial volume index; LV, left ventricular; LVEDVi, left ventricular end diastolic volume index; LVEF, left ventricular ejection fraction; LVESVi, left ventricular end systolic volume index; TR, tricuspid regurgitation.

reduced LVEF) and 40% (moderate or severely reduced LVEF) is shown in Figure S1; a comparison of the log rank χ^2 values shows a significantly superior prognostic value of Echo-Score compared to LVEF categories (log rank χ^2 204 vs. 109.6), and while there was a graded separation of curves with Echo-Score, there was significant overlap in the survival curves of preserved and mildly reduced LVEF.

On Cox proportional-hazards univariate analysis for clinical predictors of all-cause mortality (Table 3), the following clinical variables were found to have a significant association with death: age, sex, diabetes, hypertension, chronic kidney disease (CKD), family history of premature CAD, NSTEMI presentation and three vessel disease on coronary angiography. Amongst the echocardiographic variables, a high Echo-Score (HR 3.51, 95% CI 2.82–4.36, $p < .001$) was the most powerful predictor on univariate analysis. On Cox proportional-hazards multivariable analysis incorporating significant clinical predictors and Echo-Score (Table 3), Echo-Score was an independent predictor of all-cause mortality (HR 1.28(95% CI 1.22-1.34), $p < 0.001$). Inter-model comparisons of model χ^2 showed that the addition of Echo-Score resulted in a greater increment in model power compared to addition of LVEF (model χ^2 461.5 vs. 433.9, $p = .043$) (Table 3). Calculation of Harrel's C values showed that the model with Echo-Score had the highest absolute Harrel's C value (.783, $p < .001$). Furthermore, ROC analysis revealed that the area under the curve (AUC) for Echo-Score (0.69, 95% CI 0.66–0.71, $p < .001$) was superior to LVEF (0.60, 95% CI 0.57–0.63, $p < .001$) in predicting all-cause mortality (Figure 3). When a high Echo-Score (> 3) was entered into the multivariable equations as a binary variable, it was the strongest independent predictor of all-cause mortality (HR 2.23, 95% CI 1.85–2.79, $p < .001$) (Table 4).

3.2 | Predictors of cardiac mortality

There was a total of 130 cardiac deaths (4.2%) over a median follow-up period of 4.5 years (range 1–9 years). Kaplan–Meier survival curves for Echo-Score 0–7 for cardiac mortality is shown in Figure 4A. There was a significant graded separation of survival curves for scores 0–7 as shown, with a score of 0 having the best survival and a score of 7 the worst (log rank χ^2 235.6, $p < 0.001$). Kaplan–Meier survival curves for a low, intermediate and high Echo-Scores is shown in Figure 4B. There was a significant graduated separation of survival curves, with patients with a high Echo-Score having the worst outcomes (log rank χ^2 147.9, $p < .001$).

On Cox proportional-hazards univariate analysis for clinical predictors of cardiac mortality (Table 4), the following clinical variables were found to have a significant association with cardiac death: age, diabetes, hypertension, CKD, MI presentation, and three vessel disease on coronary angiography. Amongst the echocardiographic variables, a high Echo-Score (HR 6.25, 95% CI 4.43–8.82, $p < .001$) was the most powerful predictor on univariate analysis. On Cox proportional-hazards multivariable analysis incorporating significant clinical predictors and Echo-Score (Table 3), Echo-Score was an independent predictor of cardiac mortality (HR 1.48 (95% CI 1.35–1.62), $p < .001$). Inter-model comparisons of model χ^2 showed that the addition of Echo-Score resulted in a greater increment in model power compared to addition of LVEF (model χ^2 198.4 vs. 165.4, $p = .039$). Calculation Harrel's C values showed that the model with Echo-Score had the highest absolute Harrel's C value (0.829, $p < .001$). Furthermore, ROC analysis revealed that the AUC for Echo-Score (0.74, 95% CI 0.69–0.79, $p < .001$) was superior to LVEF (0.64, 95% CI 0.59–0.70, $p < .001$) for predicting cardiac mortality (Figure 3). When a high Echo-Score (> 3) was entered into the multivariable equations as a binary variable, it was the strongest independent predictor of cardiac death (HR 4.03, 95% CI 2.81–5.80, $p < .001$).

3.3 | Subgroup analysis in patients with mildly reduced and preserved LVEF (LVEF > 40%)

For the subgroup of patients with LVEF > 40% ($n = 2672$), there were 321 deaths (79 cardiac deaths). Echo-Score showed a significant association with both all-cause and cardiac mortality on Kaplan–Meier analysis (log-rank $\chi^2 = 151.2$, $p < .001$ for all-cause mortality and 110.7, $p < .001$ for cardiac mortality). On univariate Cox proportional-hazards analysis, Echo-Score had a significant association with both all-cause mortality (HR 1.49, 95% CI 1.39–1.60, $p < .001$) and cardiac mortality (HR 1.67, 95% CI 1.45–1.93, $p < .001$).

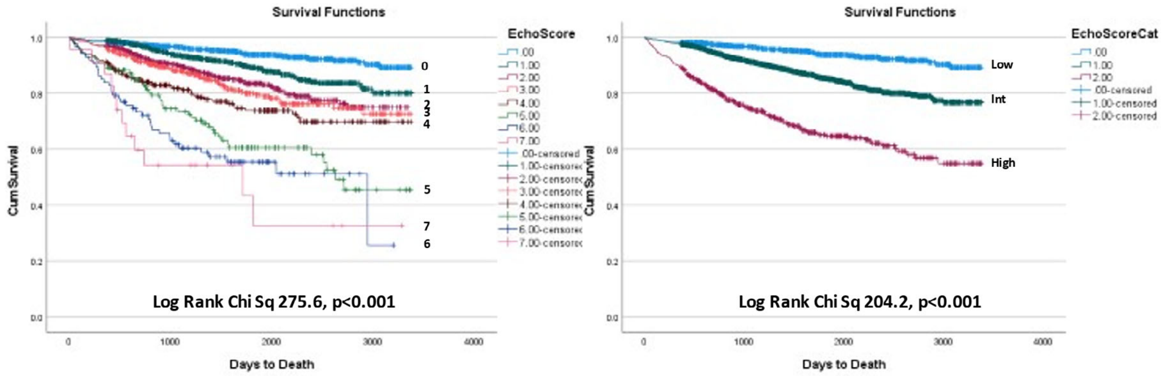
On Cox proportional-hazards multivariable analysis for all-cause mortality incorporating significant clinical predictors and Echo-Score, Echo-Score was an independent predictor of all-cause mortality (HR 1.30, 95% CI 1.20–1.41, $p < .001$). LVEF also remained a significant predictor when included in models with significant clinical predictors (HR 0.98, 95% CI 0.96–0.99, $p < .001$). Inter-model comparisons of model χ^2 for sequential models including LVEF then Echo-Score, however, showed that the addition of Echo-Score resulted in a greater increment in model power compared to addition of LVEF (model χ^2 310.8 vs. 281.1, $p = .041$). Calculation of Harrel's C values showed that the model with Echo-Score had the highest absolute Harrel's C value (0.771, $p < .001$) and Somer's D (compared to 0.542, $p < .001$). Furthermore, ROC analysis revealed that the AUC for Echo-Score (.65, 95% CI 0.60–0.67, $p < .001$) was superior to LVEF (0.52, 95% CI 0.49–0.56, $p = .163$) for predicting all-cause mortality.

TABLE 2 Univariate Cox proportional hazard analysis to identify significant predictors for all-cause mortality and cardiac mortality ($n = 3094$).

	Endpoint: All-cause mortality			Endpoint: Cardiac mortality		
	HR	95% CI	*p*	HR	95% CI	*p*
Clinical/Angiographic variables						
Age	1.06	(1.05–1.07)	<.001	1.06	(1.05–1.08)	<.001
Male	.81	(.66–.99)	.035	.92	(.63–1.34)	.671
CKD (eGFR <90)	2.49	(2.00–3.09)	<.001	2.90	(1.91-4.41)	<.001
Diabetes	2.34	(1.94–2.82)	<.001	3.23	(2.29–4.56)	<.001
Dyslipidemia	.87	(.72–1.05)	.149	.79	(.56–1.12)	.191
Family history of IHD	2.23	(1.77-2.81)	<.001	2.05	(1.36–3.10)	.110
Hypertension	2.22	(1.76–2.92)	<.001	2.78	(1.85–3.99)	<.001
Smoking	1.01	(.84–1.22)	.921	1.10	(.78–1.56)	.581
Previous MI	1.89	(1.22–2.93)	.004	1.86	(.82–4.17)	.136
MI presentation	.49	(.38–.63)	<.001	.52	(.33–.82)	.005
Three vessel disease	1.83	(1.46–2.29)	<.001	2.32	(1.58–3.44)	<.001
LV and RV size and function						
LVEF (%)	.96	(.95–.97)	<.001	.95	(.94–.96)	<.001
LVEF <40%	2.78	(2.25–3.44)	<.001	4.26	(2.97–6.11)	<.001
LVEF <50%	2.00	(1.66–2.41)	<.001	2.56	(1.81–3.61)	<.001
LVESVi (mLs/m2)	1.03	(1.02–1.04)	<.001	1.04	(1.03–1.04)	<.001
Abnormal LVESVi	1.80	(1.49–2.17)	<.001	2.04	(1.44–2.89)	<.001
LVEDVi (mLs/m2)	1.02	(1.01–1.02)	.005	1.03	(1.02–1.04)	<.001
Abnormal LVEDVi	1.62	(1.29–1.97)	.004			
LV Mass (g)	1.01	(1.00–1.02)	<.001	1.01	(1.00–1.01)	<.001
Abnormal LVMi	2.34	(1.90–2.89)	<.001	3.19	(2.22–4.59)	<.001
Diastolic parameters						
Septal E/e′	1.06	(1.05-1.07)	<.001	1.08	(1.07–1.09)	<.001
Septal E/e′ > 15	2.97	(2.46–3.57)	<.001	4.70	(3.32–6.67)	<.001
LAVi (mLs)	1.04	(1.03–1.04)	<.001	1.05	(1.04–1.06)	<.001
LAVi > 34	2.13	(1.77–2.58)	<.001	4.10	(2.80–6.00)	<.001
TRV (m/s)	1.01	(1.00–1.02)	<.001	1.02	(1.01–1.02)	<.001
TR peak velocity > 2.8	3.02	(2.37–3.84)	<.001	4.58	(2.96–7.10)	<.001
Echo-Score overall	1.53	(1.44–1.63)	<.001	1.67	(1.53–1.81)	<.001
Low Echo-Score (0)	.32	(.25–.43	<.001	0.24	(.13–.42)	<.001
Intermediate (1–3)	1.13	(.94–1.38)	.186	0.81	(.58–1.15)	.240
High Echo-Score (4–5)	3.51	(2.82–4.36)	<.001	6.25	(4.42–8.82)	<.001

Abbreviations: BMI, body mass index; DD2016, diastolic dysfunction by 2016 guidelines; E/A A, ratio of mitral E wave to A wave; E/e′, ratio of mitral E wave to e′; LAVI, left atrial volume index; LV, left ventricular; LVEDVi, left ventricular end diastolic volume index; LVEF, left ventricular ejection fraction; LVESVi, left ventricular end systolic volume index; MACE, major adverse cardiovascular events; STEMI, ST elevation MI; TR, tricuspid regurgitation.

On Cox proportional-hazards multivariable analysis for cardiac mortality incorporating significant clinical predictors and Echo-Score, Echo-Score was an independent predictor for cardiac mortality (HR 1.46, 95% CI 1.26–1.69, $p < .001$). LVEF, however, was not an independent predictor when included in models with significant clinical predictors (HR 0.98, 95% CI 0.95–1.01, $p = .201$). Inter-model comparisons of model χ^2 for sequential models including LVEF and then Echo-Score, showed that the addition of Echo-Score resulted in a greater increment in model power compared to addition of LVEF (model χ^2 91.70 vs. 70.31, $p = .040$). Calculation of Harrel's C values showed that the model with Echo-Score had the highest absolute Harrel's C value (0.754, $p < .001$) and Somer's D (0.509, $p < .001$). Furthermore, ROC analysis revealed that the AUC for Echo-Score (0.68, 95% CI 0.62–0.74, $p < .001$) was superior to LVEF (0.51, 95% CI 0.42–0.55, $p = .707$) in predicting cardiac mortality (Figure 3). When a high Echo-Score (> 3) was entered into the multivariable



Days	0	1000	2000	3000
N at risk	3094	2152	981	316

Days	0	1000	2000	3000
N at risk	3094	2152	981	316

FIGURE 2 Kaplan–Meier survival curves for predicting all-cause mortality for raw Echo-Score (left) and categories of Echo-Score (right).

TABLE 3 Nested Cox proportional hazards models to identify independent predictors of all-cause mortality.

	Multivariate analysis					
	Model 1 (Base)		Model 2		Model 3	
	Clinical		Clinical + LVEF		Clinical + EchoScore	
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Age	1.06 (1.05–1.07)	<.001	1.06 (1.05–1.07)	<.001	1.05 (1.04-1.06)	<.001
Sex	1.05 (.86–1.30)	.621	1.13(.90–1.36)	.244	.97 (.78–1.17)	.793
Hypertension	1.29 (1.08–1.65)	.021	1.35(1.01–1.67)	.006	1.28 (1.03–1.59)	.024
Diabetes	1.98 (1.66–2.44)	<.001	1.79(1.49–2.20)	<.001	1.71 (1.40–2.07)	<.001
CKD	1.23 (.99–1.59)	.086	1.17 (.93–1.49)	.188	1.15 (.91–1.46)	.251
Previous MI	1.74 (1.12–2.70)	.016	1.61 (1.03–2.51)	.034	1.55 (.99–2.41)	.052
Family history of CAD	1.82 (1.44–2.30)	<.001	1.70(1.34–2.15)	<.001	1.69 (1.34–2.14)	<.001
3VD	1.33 (1.09–1.72)	.016	1.24(0.99–1.57)	.061	1.23 (.89–1.67)	.078
MI Subtype	1.36 (1.04–1.76)	.023	1.58(1.21–2.06)	<.001	1.48 (1.13–1.92)	.004
LVEF			**.97(.96–.98)**	**<.001**		
Echo-Score					**1.28 (1.22–1.34)**	**<.001**
Model Chi Sq	376.4		433.9		461.5	
Harrel's C	.757		.776			.783
Somer's D	.516		.553			.566

Abbreviations: CKD, chronic kidney disease, LVEF, left ventricular ejection fraction; MI, myocardial infarction.
Bold values represent results of interest.

equations as a binary variable in this subgroup, it was the strongest independent predictor of cardiac death (HR 3.39, 95% CI 1.99–5.76, $p < .001$).

3.4 | Subgroup analysis in patients with preserved LVEF (LVEF > 50%)

For the subgroup of patients with LVEF > 50% ($n = 2036$), there were 230 deaths (59 cardiac deaths). Echo-Score showed a significant association with both all-cause and cardiac mortality on Kaplan–Meier analysis (log rank $\chi^2 = 140.2$, $p < .001$ for all-cause mortality and 102.9, $p < .001$ for cardiac mortality). On univariate Cox proportional-hazards analysis, Echo-Score had a significant association with both all-cause mortality (HR 1.67, 95% CI 1.51-1.84, $p < .001$) and cardiac mortality (HR 1.96, 95% CI 1.63–2.34, $p < .001$).

On Cox proportional-hazards multivariable analysis for all-cause mortality incorporating significant clinical predictors and Echo-Score, Echo-Score was an independent predictor of all-cause mortality (HR 1.33, 95% CI 1.20–1.48, $p < .001$). LVEF was not a significant predictor

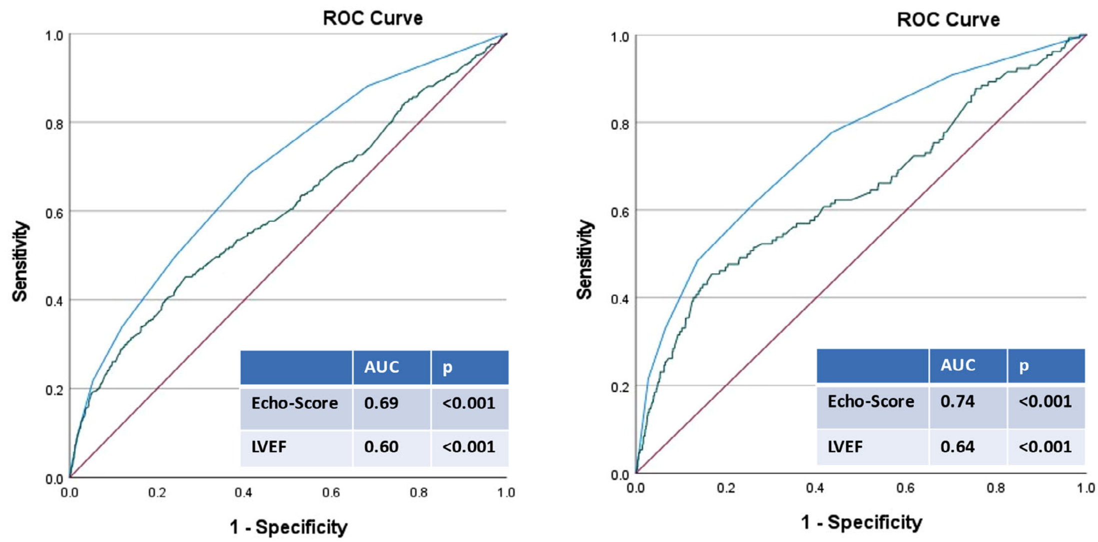


FIGURE 3 Receiver operating curves for Echo-Score and LVEF for predicting all-cause mortality (left) and cardiac mortality (right). LVEF, left ventricular ejection fraction.

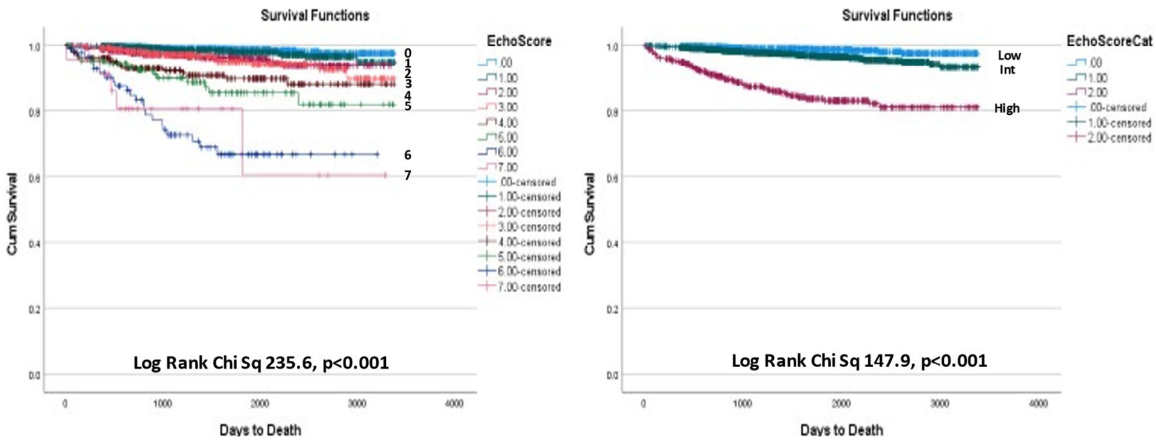
TABLE 4 Nested Cox proportional hazards models to identify independent predictors of cardiac mortality.

	Multivariate analysis					
	Model 1 (Base)		Model 2		Model 3	
	Clinical		Clinical + LVEF		Clinical + Echo-Score	
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Age	1.05 (1.04–1.07)	<.001	1.05 (1.03–1.07)	<.001	1.04 (1.02–1.06)	<.001
Hypertension	1.54 (1.01–2.33)	.043	1.65 (1.08–2.49)	.018	1.51(.99–2.28)	.053
Diabetes	2.62 (1.84–3.75)	<.001	2.27 (1.58–3.25)	<.001	2.05 (1.43–2.94)	<.001
CKD	1.46 (.93–2.31)	.101	1.34 (.84–2.12)	.216	1.30 (.82–2.06)	.268
MI Presentation	1.12 (.70–.89)	.629	1.39 (.86–2.23)	.176	1.26 (.79–2.03)	.334
3VD	1.65 (1.12–2.46)	.012	1.52 (1.02–2.25)	.039	1.52 (1.03–2.26)	.036
LVEF			**.96 (.95–.97)**	**.001**		
EchoScore					**1.48 (1.35–1.62)**	**<.001**
Model Chi Sq	129.6		165.4		198.4	
Harrel's C	.777		.807		.829	
Somer's D	.554		.614		.657	

Abbreviations: CKD, chronic kidney disease, LVEF, left ventricular ejection fraction; MI, myocardial infarction.
Bold values represent results of interest.

when included in models with significant clinical predictors (HR 0.99, 95% CI 0.97–1.01, $p = .378$). Inter-model comparisons of model χ^2 for sequential models including LVEF then Echo-Score, showed that the addition of Echo-Score resulted in a greater increment in model power compared to addition of LVEF (model χ^2 218.5 vs. 195.2, $p = .042$). Calculation of Harrel's C values showed that the model with Echo-Score had the highest absolute Harrel's C value (0.769, $p < .001$) and Somer's D (0.537, $p < .001$). Furthermore, ROC analysis revealed that the AUC for Echo-Score (0.67, 95% CI 0.63–0.71, $p < 0.001$) was superior to LVEF (0.49, 95% CI 0.45–0.5, $p = .705$) for predicting all-cause mortality. When a high Echo-Score (> 3) was entered into the multivariable equations as a binary variable, it was the strongest independent predictor of all-cause mortality (HR 2.57, 95% CI 1.65–4.00, $p < .001$).

On Cox proportional-hazards multivariable analysis for cardiac mortality incorporating significant clinical predictors and Echo-Score, Echo-Score was an independent predictor for cardiac mortality (HR 1.67, 95% CI 1.36–2.03, $p < .001$). LVEF, however, was not an independent predictor when included in models with significant clinical predictors (HR 0.99, 95% CI 0.94–1.03), $p = .534$). Inter-model comparisons of model χ^2 for sequential models including LVEF and then Echo-Score, showed that the addition of Echo-Score resulted in a greater increment in model power compared to addition of LVEF (model χ^2 70.31 vs. 38.80, $p = .033$). Calculation of Harrel's C val-



Days	0	1000	2000	3000
N at risk	3094	2051	972	304

Days	0	1000	2000	3000
N at risk	3094	2051	972	304

FIGURE 4 Kaplan–Meier Survival curves for predicting cardiac mortality for raw Echo-Score (left) and categories of Echo-Score (right).

ues showed that the model with Echo-Score had the highest absolute Harrel's C value (0.773, $p < .001$) and Somer's D (0.547, $p < .001$). Furthermore, ROC analysis revealed that the AUC for Echo-Score (0.70, 95% CI 0.62–0.77, $p < .001$) was superior to LVEF (0.50, 95% CI 0.43–0.57, $p = .966$) in predicting cardiac mortality. When a high Echo-Score (> 3) was entered into the multivariable equations as a binary variable, it was the strongest independent predictor of cardiac death (HR 6.01, 95% CI 3.06–11.83, $p < .001$).

4 | DISCUSSION

The main finding of this study is that a combined Echo-Score composed of prognostically validated measures of LV size, geometry, and function is superior to LVEF alone for predicting survival following MI. Furthermore, Echo-Score showed robust prognostic value in patients with mildly reduced LVEF (LVEF > 40%) or preserved LVEF (LVEF > 50%), where LVEF had attenuated utility, and where improved risk stratification has been an unmet need. This approach crystallizes the prognostic value of comprehensive echocardiography performed following MI into a simple score that can be easily translated into clinical practice, and captures the residual risk of mortality that is not captured by using LVEF alone. Only standard measures derived from comprehensive echocardiography were incorporated into Echo-Score, making this simple score more clinically applicable globally. The clinical significance of this finding is that it may allow improved risk stratification following MI, particularly in patients with mildly reduced LVEF (LVEF > 40%) or preserved LVEF (LVEF > 50%), subgroups in whom risk is currently under-estimated using LVEF alone.

The value of a comprehensive multiparametric approach to risk stratification has previously been proposed by experts, but a widely applicable risk score has not been developed to date.[7] Norris et al. proposed using a multiparametric approach with data derived from cardiac catheterization following MI in a classic study.[10] More recently, Prastaro et al proposed a comprehensive approach using echocardiography with particular emphasis on LVEF, WMSI and diastolic parameters including DT and E/e′ ratio as key variables.[7] A number of studies have demonstrated that the aggregate assessment of diastolic dysfunction based on key diastolic parameters was prognostically superior to the predictive ability of each of the individual parameters incorporated in the aggregate assessment,[11–13] illustrating the superior prognostic value of composite scores over individual parameters. While the interaction between the individual components of scores in medicine are inherently complex, simple scores have the potential to distil complex pathophysiological relationships into simple clinical tools.

The parameters included in the Echo-Score have all had robust prognostic validation following MI in previous studies utilizing echocardiography. The value of LV size and systolic function measured with LVEF, LVEDVi, and LVESVi have been demonstrated in multiple studies.[1–3,7,14] Verma et al demonstrated that LVMi was a powerful predictor of all-cause mortality at 24 months following MI.[15] The MERGE-AMI investigators demonstrated that restrictive filling pattern on mitral inflow (RFP) was a powerful predictor of survival following MI in a seminal meta-analysis that included > 3000 patients.[4] Hillis et al demonstrated the independent prognostic value of an elevated E/e′ ratio following MI, and a number of studies have demonstrated the powerful prognostic value of a dilated left atrium following MI.[16,17]

In summary, current clinical practices for prognosis following MI using LVEF has several shortcomings, and using multiparametric approaches to overcome these shortcomings is an attractive option. The main short-coming of using the LVEF as the single key criterion following MI is lack of prognostic utility in patients with mildly reduced or preserved systolic function, the subgroup with the largest number of patients and the greatest proportion of clinical events. In this context, the potential clinical impact of using the Composite Echo-Score includes improved patient risk stratification, better targeted therapies, and potentially more efficient use of device based therapies. A limited number of previous studies have attempted to use innovative approaches to combine multiple echocardiographic variables, including using machine learning/ artificial intelligence methods to image analysis, and the emerging data suggests that using combination approaches may be superior to LVEF alone, but further validation and proof of concept is required.[21,22] The emergence of new technology such as machine learning and artificial intelligence as a tool to improve both image analysis but also multiparametric risk assessment makes a more comprehensive approach to using echocardiography more feasible but also an attractive option moving forward.

4.1 | Limitations

This study has a number of limitations. Measurement of systolic function in the early phase following MI may underestimate LVEF due to myocardial stunning. Data on novel strain based parameters such as global longitudinal strain, early diastolic strain rate, and left atrial strain which have been correlated with outcomes following MI previously, and which have been shown to improve risk prediction relative to LVEF, were not available.[18-20] However, these novel parameters are not currently incorporated into standard clinical algorithms, and therefore not uniformly available, and were, a priori, not considered for inclusion in the composite score. Pre-existing echocardiographic abnormalities prior to the index MI represent an important confounder.

In conclusion, this study establishes the concept that a combined Echo-Score composed of prognostically validated measures of LV size, geometry, and function, is superior to LVEF alone for predicting survival following MI. This approach crystallizes the total prognostic value of comprehensive echocardiography into a simple score that can be easily translated into clinical practice. It is inherently a simple score comprised of standard echocardiographic measures that is clinically applicable globally. This approach can help address and overcome the prognostic limitations of LVEF following MI, particularly in patients with mildly reduced or preserved LVEF. Ultimately, improved risk stratification following MI may allow improved application of secondary prevention strategies that may improve prognosis following MI, although further studies are required to confirm this.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

ORCID

Sandhir B. Prasad MBBS, PhD, FRACP https://orcid.org/0000-0002-8681-9425

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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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