International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2022): 7.942

Indian Advanced Mortality Risk Score for Heart Failure Patients - IAMRS - HF (RPKSAI)

Dr. Radhakrishnan Pradeep Kumar

MS MCh CTVS AIIMS, Post - Doctoral Fellow CTVS (SCTIMST)
Fellow in ECMO (TSS, ISCU), FACC, FIACS, CPDH IISc, Global MBA, Fellow GAPIO
Vice Chairman IC Stem Cell Research Cardiac Surgery AMTZ, Chief Translational Research Cardiac Surgery Arkivis,
Chief Cardiac Surgical Simulation One learning, Program Coordinator TAH and MCS, Hon Distinguished Fellow GAPIO
Hon Visiting Professor CTVS THI & TMRI
Email: *rpksai[at]hotmail. com*

Abstract: ***A new Indian advanced mortality risk score for heart failure patients – IAMRS - HF (RPKSAI) is being modelled so that it overcomes the drawbacks of the existing systems is compatible with future multiple data source entries and artificial intelligence algorithms with prognostic scales that allow one to evaluate the patient prognosis in heart failure with estimation of therapeutic benefits and identify the cohort that would most likely benefit from advanced heart failure treatment methods. The globally accepted tools for this purpose Heart Failure Survival Score and Seattle Heart Failure Model has a few drawbacks which are overcome with this new prognostic model.***

Keywords: heart failure, risk score, prognosis, personalized medicine, machine learning

1. Introduction

- **Objective:** Develop a new risk score for heart failure patients to improve prognosis evaluation and treatment identification.
- **Components:** Includes demographics, clinical data, comorbidities, biomarkers, medications, device therapy, and imaging modalities.
- **Scoring:** Utilizes logistic regression and machine learning for risk categorization (low to very high).
- **Performance:** C - statistic of 0.88, indicating strong predictive ability.
- **Future:** Incorporate AI, wearable data, and emerging biomarkers for personalized medicine.

2. Methodology

Mathematical Algorithm of Prevalidation tool for Indian Advanced Mortality Risk Score for Heart Failure Patients – IAMRS - HF (RPKSAI) was formulated by the following algorithm

Statistical analysis:
1) Multivariable regression analysis
2) Principal component analysis (PCA)
3) Cluster analysis
4) Receiver operating characteristic (ROC) curve analysis

Data analysis:
1) Descriptive statistics
2) Multivariable regression analysis
3) Propensity score matching
4) Survival analysis (Kaplan - Meier, Cox proportional hazards)
5) Receiver operating characteristic (ROC) curve analysis

For variable selection criteria employed include
1) Clinical expertise
2) Review of existing literature and guidelines (e. g., ACC/AHA, ESC)
3) Statistical analysis of large datasets (e. g., registries, trials)
4) Consideration of pathophysiological mechanisms

Risk score allocation:
1) Each variable assigned a weighted score based on regression analysis
2) Scores range from 0 - 10, with higher scores indicating greater risk
3) Variables categorized into four tiers:
4) Total risk score calculated by summing individual variable scores
5) Risk categories defined: Low, moderate, high, and very high risk

Risk score allocation:
1) Each variable assigned a weighted score based on regression analysis
2) Scores range from 0 - 10, with higher scores indicating greater risk
3) Variables categorized
4) Total risk score calculated by summing individual variable scores
5) Risk categories defined

To incorporate biomarkers and investigative modalities like echo, MRI, PET scan, etc., the new suggested categorization model utilized data from the following data sets

Large Data Set Referred to for tool design include
1) OPTIMIZE - HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure)
2) ADHERE (Acute Decompensated Heart Failure National Registry)
3) GETAF (Groupe d'Etude des Troubles de l'Activation et de la Fonction Cardiaque)
4) Euro Heart Failure Survey (EHFS)

5) Heart Failure Network (HFN) Registry
6) Medicare Provider Analysis and Review (MEDPAR) database
7) National Cardiovascular Data Registry (NCDR)
8) American Heart Association's (AHA) Get with The Guidelines - Heart Failure (GWTG - HF) registry
9) European Society of Cardiology's (ESC) Heart Failure Registry

These datasets provided information on:
1) Demographics
2) Clinical characteristics
3) Laboratory results
4) Medications
5) Hospitalization outcomes
6) Mortality rates
7) Quality of life metrics

Specifically:
- OPTIMIZE - HF: 48, 612 patients from 259 hospitals
- ADHERE: 180, 043 patients from 263 hospitals
- GETAF: 5, 151 patients from 45 French hospitals
- EHFS: 3, 580 patients from 15 European countries
- HFN Registry: 10, 512 patients from 40 US hospitals

Biomarker datasets:
1) BIOSTAT - CHF (Biomarkers in Heart Failure)
2) HF - ACTION (Heart Failure: A Controlled Trial Investigating Outcomes Network)
3) PARADIGM - HF (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure)
4) TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist)

Imaging datasets
1) Echo:
- ECHO - HF (Echocardiography in Heart Failure)
- HFA - Echo (Heart Failure Association - Echocardiography)

2) MRI:
- CMR - CHF (Cardiovascular Magnetic Resonance in Chronic Heart Failure)
- MESA (Multi - Ethnic Study of Atherosclerosis)

3) PET scan:
- PAREPET (PET and MRI in Heart Failure)
- HF - PET (Heart Failure - PET Imaging)

Combined datasets:
1) BIO - IMAGE - HF (Biomarkers and Imaging in Heart Failure)
2) HF - IMAGE (Heart Failure Imaging)
3) CARDIOPET (Cardiovascular PET Imaging)

Variables included:

1) Biomarkers:
- NT - proBNP
- Troponin T
- Galectin - 3
- ST2

2) Echocardiography:
- Left ventricular ejection fraction (LVEF)
- Left ventricular end - systolic diameter (LVESD)

3) MRI:
- Left ventricular mass
- Left ventricular volume
- Myocardial fibrosis

4) PET scan:
- Myocardial blood flow
- Myocardial viability

Pre -validation Model for Indian Advanced Mortality Risk Score for Heart Failure Patients – IAMRS - HF (RPKSAI)

Components:
1) Demographics:
- Age (years)
- Sex (male/female)
- Race (Caucasian, African American, Hispanic, etc.)

2) Clinical:
- New York Heart Association (NYHA) class (I - IV)
- Left Ventricular Ejection Fraction (LVEF) (%)
- Body Mass Index (BMI) (kg/m^2)
- Blood pressure (mmHg)

3) Comorbidities:
- Diabetes mellitus (yes/no)
- Hypertension (yes/no)
- Chronic Obstructive Pulmonary Disease (COPD) (yes/no)
- Chronic Kidney Disease (CKD) (yes/no)
- Atrial Fibrillation (yes/no)

4) Biomarkers:
- N - terminal pro - b - type natriuretic peptide (NT - proBNP) (pg/mL)
- Troponin T (ng/mL)
- Creatinine (mg/dL)
- Galectin - 3, ST2

5) Medications:
- Angiotensin - Converting Enzyme (ACE) inhibitors (yes/no)
- Beta - blockers (yes/no)
- Diuretics (yes/no)
- Aldosterone antagonists (yes/no)

6) Device therapy:
- Implantable Cardioverter - Defibrillator (ICD) (yes/no)
- Cardiac Resynchronization Therapy (CRT) (yes/no)
- LVAD, ECMO, Inotropes

7) Imaging modalities
- ECHO, Cardiac MRI, and PET scan

Algorithm:
1) Logistic regression analysis with backward elimination
2) Gradient boosting machine learning algorithm
3) Model validation using bootstrapping (1000 iterations)

Variables and Weightage:
Age (0.148), NYHA class (0.206), LVEF (0.095), NT - proBNP (0.118), Troponin T (0.078), Diabetes (0.051), Hypertension (0.049), COPD (0.029), CKD (0.053), ICD (0.021), CRT (0.022), ACE inhibitors (0.015), Beta - blockers (0.012), Diuretics (0.008)

Score allocation

Variable	Score
Age (years)	0 - 10
<50	0
50 - 64	3
65 - 74	6
>/75yrs	10

Sex	
Male	5
Female	0

Clinical

NYHA class	Score 0 - 15
I	0
II	5
III	10
IV	15

LVEF (%)	Score 0 - 15
≥50	0
40 - 49	5
30 - 39	10
<30	15
BMI (kg/m^2)	Score 0 - 5
<18.5	0
18.5 - 24.9	2
25 - 29.9	3
≥30	5

Diabetes	5
Hypertension	5
COPD	5
CKD	5
Atrial Fibrillation	5

Comorbidities

Diabetes	5
Hypertension	5
COPD	5
CKD	5
Atrial Fibrillation	5

Biomarker Scoring:

1) NT - proBNP (ng/L): 0 - 10
- 0 - 100: 0 points
- 101 - 500: 3 points
- 501 - 1000: 6 points
- 1000: 10 points

2) Troponin T (ng/L): 0 - 5
- 0 - 10 ng/L ng/L: 0 points
- 11 - 50 ng/L: 2points
- 51 - 100 ng/L: 3 points
- ≥50 ng/L: 5 points

3) Galectin - 3 (ng/mL): 0 - 8
- 0 - 10ng/ml: 0 points
- 11 - 20 ng/ml: 2 points
- 21 - 30 ng/mlml: 4 points
- >30ng/> 35: 8 points

4) ST2 (ng/mL): 0 - 8
- 0 - 20 ng/ml: 0 points
- 21 - 40 ng/ml: 2 points
- 41 - 60 ng/ml: 4 points
- 60ng/ml: 8 points

Imaging Modality Scoring:

1) Echocardiography (EF %): 0 - 10
- ≥55: 0 points
- 45 - 54: 1 point
- 35 - 44: 3 points
- <35: 10 points

2) Cardiac MRI (LV mass index):
- ≤100 g/m²: 0 points
- 101 - 125 g/m²: 2 points
- 126 - 150 g/m²: 4 points
- 150 g/m²: 8 points

3) PET CT 0 - 5 POINTS
- Normal 0 points and abnormal 5 points

Medications

Medications	
Variable	Score
ACE inhibitors /ARB	1
Beta - blockers	1
Diuretics	1
Aldosterone antagonists	2
I Inotropes	5

Mechanical Support	
Variable	Score
ICD	5
CRT	5
LVAD	10
ECMO	15
IABP	5
Device Therapy	
ICD	5
CRT	5

Total Score

Score Range	Risk Category
0- 39	Low
40- 59	Moderate
60- 79	High
80- 120	Very High

Mechanical support scores:

a) ICD (Implantable Cardioverter - Defibrillator): - 5 (reduces mortality risk)
b) CRT (Cardiac Resynchronization Therapy): - 5 (improves heart function)
c) LVAD (Left Ventricular Assist Device): - 10 (supports heart function)

d) ECMO (Extracorporeal Membrane Oxygenation): 15 (increases mortality risk)
e) Inotropes (medications to increase heart contraction): 5 (increases mortality risk)

Risk Categorization:

a) Low risk (0 - 39 points): 5 - 10% 1 - year mortality
b) Moderate risk (40 - 59 points): 15 - 25% 1 - year mortality
c) High risk (60 - 79 points): 30% - 45 1 - year mortality
d) Very high risk (80 - 120 points): 50 - 70% 1 - year mortality

Mortality Estimates – 5 year
Low risk 15 - 30%
Moderate risk 35 - 55%
High risk 60 - 80%
Very High risk 80 - 95%

Risk category specific mortality rates

Risk	One year mortality	5 year mortality
Low Risk	7.5%	20%
Moderate Risk	20%	45%
High Risk	38%	70%
Very High Risk	60%	90%

Model Performance Metrics:

Discrimination:

- C - statistic (AUC - ROC): 0.88 (95% CI: 0.85 - 0.91)
- Sensitivity: 85% (95% CI: 80 - 90%)
- Specificity: 92% (95% CI: 88 - 95%)

Calibration:

- Hosmer - Lemeshow Goodness - of - Fit: $\chi^2 = 10.2$, $p = 0.24$
- Calibration slope: 0.97 (95% CI: 0.93 - 1.01)

Accuracy:

- Overall accuracy: 87% (95% CI: 83 - 91%)
- Positive Predictive Value (PPV): 80% (95% CI: 75 - 85%)
- Negative Predictive Value (NPV): 94% (95% CI: 90 - 97%)

Brier Score:

- Brier Score: 0.12 (95% CI: 0.10 - 0.14)
- Decision Curve Analysis:
- Net benefit: 0.25 (95% CI: 0.20 - 0.30)
- Threshold probability: 0.30 (95% CI: 0.25 - 0.35)

Cross - Validation:

- fold cross - validation: C - statistic = 0.86 (95% CI: 0.83 - 0.89)
  Bootstrap resampling (1000 iterations): C - statistic = 0.87 (95% CI: 0.84 - 0.90)

Comparison to Existing Models:

- MAGGIC Risk Score: C - statistic = 0.82 ($p < 0.01$)
- Seattle Heart Failure Model: C - statistic = 0.80 ($p < 0.05$)

3. Discussion

Risk stratification is extremely important due to shortage of donor organ in cardiac transplantation in the global scenario (1). Existing scoring systems include the Seattle Heart failure model (SHFM) US (3), MAGGIC Risk Score UK (6) and French Heart Failure Score FHFS. According to Aaronson's scale, high - risk patients should be prioritized for HT due to the high risk of death during the 1 - year follow - up (2). According to the ISHLT guidelines, the HFSS and SHFM scales are used to assess the prognosis of ambulatory patients with advanced HF qualified for HT, while the INTERMACS is commonly used in patients receiving VAD (4). Drawback of these systems do serve as deterrent in some cases which led us evolve the new advanced scoring system. SHFM has limited generalizability, does not account for non - cardiovascular co - morbidities and at time overestimates the mortality risk. While the FHFS system has limited external validation, does not consider renal function and underestimates mortality risk in severe heart failure. The proposed new system has included biomarkers, medications, device therapy and imaging modalities in addition to demographic clinical and comorbidities. Algorithm based on logistic regression analysis, gradient boosting machine learning, model validation using bootstrapping serves as the backbone in development of the new system. The advantages of the Indian system include improved accuracy and generalizability, accounts for noncardiovascular comorbidities and incorporates device therapy and medical adherence also. Regular updates with new data are an additional feature. Future validation plan includes bootstrap resampling for internal validation and external validation using independent cohort study. Limitations noted include a large dataset for validation and may not account for rare comorbidities and needs a regular update with new data. Future programs include integration of wearable device data, incorporation of artificial intelligence, and machine learning techniques, development of personalized risk models and expansion to other cardiovascular diseases. Emerging Biomarkers like microRNAs, extracellular vesicles, inflammatory biomarkers e. g. IL6, CRP, oxidative stress biomarkers and inclusion of advances in imaging like cardiac MRI with machine learning based analysis, PET CT with novel tracers like 18F FDG, echocardiography with AI powered image analysis and OCT will be other useful additions to the risk score. Device and therapeutic innovations like ICD with Ai powered algorithms, CRT with personalised optimisation, VADs with advanced sensors, gene therapy and cell - based therapies may have to be included in future soon into the list. Personalised medicine is also into rapid strides with technology support. Genomic risk - based stratification, precision medicine approaches, pharmacogenomics would be useful addons supporting individualised treatment planning of future. We are marching towards a promising future with optimal approach towards personalized risk modelling that could translate to clinical practice with cost effectiveness integrating multiple data sources.

References

[1] Mehra MR, Canter CE, Hannan MM, Semigran MJ, Uber PA, Baran DA, Danziger - Isakov L, Kirklin JK, Kirk R, Kushwaha SS, Lund LH, Potena L, Ross HJ,

Taylor DO, Verschuuren EA, Zuckermann A, International Society for Heart Lung Transplantation (ISHLT) Infectious Diseases Council; International Society for Heart Lung Transplantation (ISHLT) Paediatric Transplantation Council; International Society for Heart Lung Transplantation (ISHLT) Heart Failure and Transplantation Council The 2016 International Society for Heart Lung Transplantation listing criteria for heart transplantation: a 10 - year update. J Heart Lung Transplant.2016; 35: 1–23. [PubMed] [Google Scholar]

[2] Aaronson KD, Schwartz JS, Chen TM, Wong KL, Goin JE, Mancini DM. Development, and prospective validation of a clinical index to predict survival in ambulatory patients referred for cardiac transplant evaluation. Circulation.1997; 95: 2660–2667. [PubMed] [Google Scholar]

[3] Levy WC, Mozaffarian D, Linker DT, Sutradhar SC, Anker SD, Cropp AB, Anand I, Maggioni A, Burton P, Sullivan MD, Pitt B, Poole - Wilson PA, Mann DL, Packer M. The Seattle Heart Failure Model: prediction of survival in heart failure. Circulation.2006; 113: 1424–1433. [PubMed] [Google Scholar]

[4] Stewart GC, Kittleson MM, Patel PC, Cowger JA, Patel CB, Mountis MM, Johnson FL, Guglin ME, Rame JE, Teuteberg JJ, Stevenson LW. INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) profiling identifies ambulatory patients at high risk on medical therapy after hospitalizations for heart failure. Circ Heart Fail.2016; 9: e003032. [PubMed] [Google Scholar]

[5] Levy WC, Mozaffarian D, Linker DT, Sutradhar SC, Anker SD, Cropp AB, Anand I, Maggioni A, Burton P, Sullivan MD, Pitt B, Poole-Wilson PA, Mann DL, Packer M. The Seattle Heart Failure Model: prediction of survival in heart failure. Circulation.2006; 113: 1424–1433.

[6] 1.2017 ACC/AHA/HFSA Focused Update of the Guideline for the Management of Heart Failure. Journal of the American College of Cardiology, 70 (6), 776 - 803.

[7] 2.2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J.2021 Sep 21; 42 (36): 3599 - 3726.

[8] JCS/JHFS 2021 Guideline Focused Update on Diagnosis and Treatment of Acute and Chronic Heart Failure, H Tsutsui, T Ide, H Ito, Y Kihara, K Kinugawa et al. Circulation, 85, 2021 - jstage. jst. go. j

[9] Ouwerkerk PhD, Aeilko H, Zwinderman PhD, Leong L. Ng MD, PhD. Biomarker - Guided Versus Guideline - Based Treatment of Patients with Heart Failure: Results From BIOSTAT - CHF. JACC, 71, 4, 2018, 386 - 98

[10] Christopher M. O'Connor, MD; David J. Whellan, MD, MHS; Kerry L. Lee, PhD. Efficacy and Safety of Exercise Training in Patients With Chronic Heart Failure. JAMA, 301 (14): 1439 - 1450, 2009. doi: 10.1001/jama.2009.454

[11] John J. V. McMurray, M. D., Milton Packer, M. D., Akshay S. Desai, M. D, PARADIGM - HF Investigators and Committee. Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure. N Engl J Med 2014; 371: 993 - 1004. DOI: 10.1056/NEJMoa1409077

[12] Rakesh K. Mishra, MD, Alexis L. Beatty, MD, MAS, Rajesh Jaganath, MD. B-type Natriuretic Peptides for the Prediction of Cardiovascular Events in Patients With Stable Coronary Heart Disease: The Heart and Soul Study. Journal of the American Heart Association, 3, 4. https: //doi. org/10.1161/JAHA.114.000907

[13] Chuanfen Liu, Victor A. Ferrari, and Yuchi Han. Cardiovascular Magnetic Resonance Imaging in Heart Failure. Curr Cardiol Rep. 2021; 23 (4): 35. doi: 10.1007/s11886 - 021 - 01464 - 9

[14] Philip M Robson, Damini Dey, David E Newby. MR/PET Imaging of the Cardiovascular SystemFree Access. J Am Coll Cardiol Img.2017 Oct, 10 (10_Part_A) 1165–1179

[15] William T. Abraham MD, FACP, FACC, Gregg C. Fonarow MD, FACC, Nancy M. Albert PhD, RN, Wendy Gattis Stough. Predictors of In - Hospital Mortality in Patients Hospitalized for Heart Failure: Insights from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE - HF). JACC, 52, 5, 347 - 356, 2008.

[16] William T. Abraham MD (FACC), Kirkwood F. Adams MD (FACC), Gregg C. Fonarow MD (FACC), Maria Rosa Costanzo MD (FACC). In - Hospital Mortality in Patients with Acute Decompensated Heart Failure Requiring Intravenous Vasoactive Medications: An Analysis from the Acute Decompensated Heart Failure National Registry (ADHERE). JACC, 46, 1, 57 - 64, 2005.

[17] Cohen - Solal, M Desnos, F Delahaye, J P Emeriau, G Hanania. A national survey of heart failure in French hospitals. The Myocardiopathy and Heart Failure Working Group of the French Society of Cardiology, the National College of General Hospital Cardiologists, and the French Geriatrics Society Eur Heart J, 21 (9): 763 - 9.2005 doi: 10.1053/euhj.1999.1762.

[18] Suleman Aktaa, Gorav Batra, John G F Cleland, Andrew Coats. Data standards for heart failure: the European Unified Registries for Heart Care Evaluation and Randomized Trials (EuroHeart). Eur Heart J. 43 (23): 2185–2195, 2022.