RISK STRATIFICATION AND PROGNOSTIC MARKERS IN PATIENTS WITH ACUTE DECOMPENSATED HEART FAILURE

Cardiology

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ABSTRACT

Introduction: Heart failure is one of the leading cause of hospitalization and death worldwide having a major impact on the health care systems. Risk stratification of these patients helps to achieve a better clinical outcome with a reduction in morbidity and mortality.

Methods: This was a single centre prospective observational study wherein patients with acute decompensated heart failure were enrolled. All enrolled patients underwent detailed clinical history including symptomatology, risk factors for cardiovascular diseases and family history were recorded. All these patients underwent routine haematological and biochemical testing along with documentation of cardiac biomarkers viz. Troponin T and N-terminal pro brain natriuretic peptide (NT pro-BNP). All these patients were then followed for one year. Outcomes in form of in-hospital mortality as well as adverse cardiac events (mortality, rehospitalisation) were documented.

Results: A total of 264 patients were included with mean age of 67.6 ± 9.8 years. In-hospital mortality was reported in 28 patients (10.6%) while 27 (10.2%) patients died over a year of follow-up. Patients with an in-hospital mortality were older and higher NYHA class and heart rate, lower ejection fraction, systolic and diastolic blood pressure and higher cardiac troponins and NT-pro BNP levels. Multivariate logistic regression analysis revealed that heart rate, NYHA class, systolic blood pressures, NT pro-BNP and creatinine were independent predictors of mortality.

Conclusions: Our study showed that acute heart failure has a substantial in-hospital as well as one year mortality rates. Use of biomarkers leads to a better risk stratification and hence an impact on outcomes.

KEYWORDS

Biomarkers; Diuretics; Heart failure; Outcomes; Risk stratification

INTRODUCTION:

Heart failure (HF) is now considered as one of the pandemics of the 21st century affecting a major chunk of the global population. It is a leading cause for hospitalization worldwide with nearly a quarter of billion people affected worldwide¹. Despite improvements in diagnosis and treatment strategies over the past 30 years, survival among patients with HF especially decompensated HF is grim. Patients with chronic HF are often prone to recurrent episodes of HF with nearly 75% of chronic HF cases reporting acute decompensation². Of importance, more than one third of patients will have preserved ejection fraction, though outcomes seems to be similar to those with reduced ejection fraction. Prognostication of HF is challenging.

Among patients with acute decompensated HF, particularly those who present emergently, safety and efficiency of clinical decisions can be improved by wider use of risk stratification algorithms. Without a rational approach to prognostication, clinical decisions might not be matched to the patients' risk, resulting in potential 'overtreatment' of low-risk and 'undertreatment' of high-risk individuals³. Several risk score has been proposed and validated to estimate the mortality risk but none is good in estimating the risk of readmission. Most of these scores include multiple variables, making their implementation in the daily clinical practice challenging⁴. On top of this, in patients admitted with acute decompensated heart failure the prognostic value of admission Brain Natriuretic Peptide (BNP), the "gold standard biomarker" regarding HF diagnosis and prognosis, is limited⁵. Thus, there is a need for implementation of early risk stratification strategies, in order to classify HF patients promptly, administer the appropriate therapy, and improve outcome. There is very limited data available in literature for Indian population for risk stratification and prognosis in patients of acute decompensated heart failure. In our study we aim to find out which clinical and biochemical parameters can predict the risk of mortality as well as risk of readmission in the Indian population.

MATERIAL AND METHODS:

Study Design:

This was a single center prospective observational study carried over a one and a half-year period in the Department of Cardiology in a tertiary

care medical center. All patients >18 years of age admitted with acute decompensated heart failure satisfying the inclusion criteria were enrolled. The inclusion criteria for the study were (i) diagnosis of heart failure (including congenital heart disease, rheumatic heart disease, cardiomyopathies, aortoarteritis with heart failure and any rare causes of heart failure), (ii) symptom duration of less than one year, (iii) evidence of decompensation in the form of hospital admission in the past one year or an emergency room visit with intravenous diuretic therapy or hospital visit for worsening dyspnea with increase of diuretic. Those patients (i) who were planned for a therapeutic intervention in the next three months like a coronary, pacemaker implant, valvular intervention or any other surgical intervention, (ii) had non-cardiac terminal illness with life expectancy of less than a year, (iii) pregnancy, lack of consent or enrollment in some other trial were excluded from the study.

In all these patients, detailed clinical history including symptomatology, presence of cardiovascular disease (CVD) risk factors, family history, prior evidence of CVD, comorbidities and treatment details using a structured questionnaire were recorded. Clinical data and sample were collected at the time of enrolment. Clinical follow up was continued up to one year but no re-sampling was done. Blood samples were collected for routine hematological and biochemical investigations as well as for cardiac troponins and NT pro-BNP. Left ventricular ejection fraction (LVEF) were determined on two dimensional echo cardiography using Simpson's biplane method. These patients were followed up for a period of one year. In-hospital mortality as well as readmissions and mortality (adverse cardiac events) in these patients over a one-year period was computed.

Statistical Methods:

Descriptive statistics was obtained for all the study subjects with continuous data being expressed as mean $\pm$ SD while categorical data as number or proportions. Comparison of the means of the continuous data was done using the Students' t-test. Similarly, the categorical variables were compared using the χ^2 test. Multivariate analysis was performed with stepwise logistic regression. Survival was estimated by using the Kaplan-Meier method, and differences in survival

between groups were assessed with the log-rank test. All statistical analyses were performed on SPSS, version 24.0 (IBM Corp) for Mac. A two-sided P value ≤ 0.05 was considered to be statistically significant.

RESULTS:

A total of 264 patients were included in the study of whom a majority of them were males (65.6%). The mean of the study group was 67.6 ± 9.8 years with most of them having a previously diagnosed heart failure (88.3%). Ischemic cardiomyopathy (ICMP) comprised 143/264 (54.2%) patients while dilated cardiomyopathy was reported in 62/265 (23.6%). The clinical and demographic profile has been tabulated in Table 1.

Table 1: Demographic And Clinical Profile Of The Study Subjects

Parameters	Total number (n)	Percentage (%)
Total patients	264	100%
Male	173	65.6%
Female	91	34.5%
Mean Age (years)	67.6 ± 9.8	
De novo heart failure	31	11.6%
Previously diagnosed	233	88.3%
Ischemic heart disease	143	54.2%
Dilated cardiomyopathy	62	23.6%
Diabetes Mellitus	97	34.7%
Hypertension	117	44.4%
Valvular heart disease	10	3.6%
Chronic Kidney Disease	08	3.1%
Smoker	113	42.8%
Alcoholic	79	29.9%
Congenital Heart Disease	05	1.8%
Chronic Obstructive Pulmonary Disease	54	20.5%

Of the 264 patients, in-hospital mortality was reported in 28 patients while the rest of the patients were followed up for a period of one year. Of the remaining 236 patients who had survived, 12 patients were lost to follow up and hence 224 patients completed the study.

Patients who had an in-hospital mortality were older, greater frequency of ICMP, higher New York Heart Association (NYHA) class and heart rate, lower LVEF, systolic and diastolic blood pressure and higher cardiac troponins and serum NT-pro BNP levels. In additions, non-survivors had higher urea and creatinine levels as well as total leucocyte counts (Table 2).

Table 2: Comparison Of Parameters Between Survivors And Those With In-hospital Mortality

Parameters	Survived (n=236)	In hospital mortality (n=28)	P-value
Age	$63.2 (\pm 7.9)$	$71.2 (\pm 9.7)$	0.0001
Male	151 (64%)	20 (73.1%)	0.43
Female	85 (36%)	08 (35.0%)	0.42
De novo diagnosis	29 (12.1%)	02 (7.1%)	0.49
Previously diagnosed	174 (87.7%)	26 (92.9%)	0.02
Ischemic heart disease	122 (51.7%)	20 (71.2%)	0.04
Dilated cardiomyopathy	55 (23.3%)	06 (21.4%)	0.82
Diabetes Mellitus	79 (33.5%)	11 (39.2%)	0.53
Hypertension	107 (45.3%)	08 (28.5%)	0.09
Valvular heart disease	12 (5.1%)	01 (3.6%)	0.72
Chronic Obstructive Pulmonary Disease	49 (20.8%)	05 (17.8%)	0.71
Chronic Kidney Disease	06 (2.5%)	02 (7.1%)	0.17
Smoker	97 (41.1%)	15 (53.6%)	0.20
Alcoholic	71 (30.1%)	07 (25.0%)	0.57
Congenital heart disease	04 (1.7%)	-	
NYHA grading	3.1 ± 0.3	3.9 ± 0.1	<0.0001
Ejection fraction	$32 \pm 7.5\%$	$23 \pm 5\%$	<0.0001
Heart rate	98 ± 10	116 ± 16	<0.0001
Systolic Blood Pressure	140 ± 14	116 ± 9	<0.0001
Diastolic Blood Pressure	98 ± 10	78 ± 7	<0.0001
Haemoglobin (mg/dL)	10.4 ± 0.9	9.1 ± 0.8	0.34
Total leucocyte count (mm^3)	8900 ± 1250	13560 ± 2100	<0.0001
Random Blood Sugar (mg/dL)	138 ± 10.9	134 ± 16.8	0.086

Urea (mg/dL)	42 ± 8.9	78 ± 12.1	<0.0001
Creatinine (mg/dL)	1.5 ± 0.7	1.89 ± 1.1	0.0099
Sodium (mEq/L)	134 ± 4.2	132.5 ± 5.1	0.028
Potassium (mEq/L)	$3.9 (\pm 0.9)$	4.2 ± 0.7	0.089
Troponin T	0.023 ± 0.005	0.12 ± 0.018	<0.0001
NT pro BNP	7900 ± 970	10997 ± 1170	<0.0001

NYHA: New York Heart Association; NT BNP: N-terminal pro Brain natriuretic peptide

Of the 224 patients who completed the follow-up, total adverse cardiac events were observed in 91 patients (mortality: 27 patients and readmission: 64 patients). Patients with an adverse cardiac event were older, had a greater frequency of ICMP, higher NYHA class and heart rate, lower LVEF, systolic and diastolic blood pressures and higher cardiac troponins and serum NT-pro BNP levels. In additions, patients with adverse events had lower hemoglobin levels, higher total leucocyte counts as well as urea and creatinine levels (Table 3).

Table 3: Comparison Of Parameters Between Patients With Adverse Cardiac Events And Those Without

Parameters	No events (n=133)	Adverse Cardiac Events (n=91)	P-value
Age	$61.2 (\pm 6.9)$	$69.2 (\pm 6.7)$	<0.0001
Male	96 (72.1%)	66 (73.5%)	0.94
Female	37 (27.8%)	24 (26.5%)	0.81
Ischemic heart disease	65 (48.8%)	61 (67.4%)	0.007
Dilated cardiomyopathy	32 (24.1%)	21 (23.1%)	0.86
Diabetes Mellitus	48 (36.1%)	29 (31.9%)	0.51
Hypertension	56 (42.1%)	45 (49.4%)	0.27
Valvular heart disease	8 (6.0%)	03 (3.3%)	0.35
Chronic Obstructive Pulmonary Disease	25 (18.8%)	22 (24.1%)	0.33
Chronic Kidney Disease	03 (2.3%)	03 (3.3%)	0.63
Smoker	49 (36.8%)	44 (48.4%)	0.08
Alcoholic	43 (32.3%)	24 (26.4%)	0.33
Congenital heart disease	2 (4.0%)	01 (1.1%)	0.79
NYHA grading	3.0 ± 0.2	3.7 ± 0.2	<0.0001
Ejection fraction	$30 \pm 5.2\%$	$24.2 \pm 4.1\%$	<0.0001
Heart rate	78 ± 11	94 ± 16	<0.0001
Systolic Blood Pressure	156 ± 14	126 ± 9	<0.0001
Diastolic Blood Pressure	97 ± 10	78 ± 7	<0.0001
Haemoglobin (mg/dL)	12.4 ± 1.2	9.7 ± 0.8	<0.0001
Total leucocyte count (mm^3)	7400 ± 750	9700 ± 800	<0.0001
Random Blood Sugar (mg/dL)	141 ± 10.9	146 ± 16.8	0.074
Urea (mg/dL)	40 ± 9.9	59 ± 11.1	<0.0001
Creatinine (mg/dL)	1.42 ± 0.7	1.76 ± 0.9	0.0017
Sodium (mEq/L)	135 ± 3.2	131.4 ± 5.2	<0.0001
Potassium (mEq/L)	3.9 ± 0.7	4.0 ± 0.7	0.29
Troponin T	0.03 ± 0.0005	0.06 ± 0.002	<0.0001
NT pro BNP	4560 ± 870	9875 ± 1070	<0.0001

NYHA: New York Heart Association; NT BNP: N-terminal pro Brain natriuretic peptide

Univariate analysis revealed that previous myocardial infarction (MI), heart rate, NYHA class, systolic and diastolic blood pressures, Troponin T, NT pro-BNP, serum sodium and serum creatinine were independent predictors of mortality (Table 4).

Table 4: Univariate Analysis Showing Independent Predictors Of Developing Adverse Cardiac Events

	OR	P-value
Age	0.98 (0.65-1.12)	0.06
Gender	1.01 (0.71-1.21)	0.72
Previous Myocardial Infarction	1.28 (1.02-1.48)	0.01
Heart Rate	1.19 (1.01-1.34)	<0.001
NYHA class	3.2 (1.98-5.21)	<0.001
Systolic Blood Pressure	1.9 (0.90-2.32)	<0.001
Diastolic Blood Pressure	1.5 (1.11-2.12)	<0.001
Ejection Fraction	1.8 (0.98-2.23)	0.02

Diabetes Mellitus	1.3 (0.82-1.56)	0.06
Hypertension	0.78 (0.45-1.1)	0.08
Dyslipidemia	0.98 (0.59-1.22)	0.98
Smoking	0.90 (0.6-1.1)	0.68
Haemoglobin	1.08 (0.82-1.23)	0.28
Troponin T	1.11 (1.02-1.17)	0.015
NT pro-BNP	1.16 (1.01-1.22)	0.002
Random Blood Sugar	0.65 (0.21-2.01)	0.73
Serum Sodium	1.08 (1.02-1.10)	<0.001
Serum Potassium	1.006 (1.002-1.010)	0.055
Serum Creatinine	2.2 (1.13-2.42)	0.002

Multivariate logistic regression analysis revealed that heart rate, NYHA class, systolic blood pressures, NT pro-BNP and serum creatinine were independent predictors of mortality (Table 5).

Table 5: Multivariate Logistic Regression Analysis Showing Independent Predictors Of Developing Adverse Cardiac Events

	OR	95% CI	P-value
NYHA class	2.3	0.86-2.98	0.001
Heart Rate	1.06	0.91-1.12	0.015
Systolic Blood Pressure	1.01	0.99-1.11	0.03
Serum Creatinine	1.71	1.48-1.99	0.01
NT pro-BNP	1.44	1.07-1.89	0.04
Troponin T	0.96	0.72-1.12	0.059
Serum Sodium	0.76	0.24-1.01	0.32

NYHA: New York Heart Association; NT BNP: N-terminal pro Brain natriuretic peptide

Survival curves revealed that a majority of the deaths occurred during the period of hospitalization (Figure 1).

Figure 1: Kaplan-mier Survival Curve Showing The Probability Of Survival Over A Year Of Follow-up.

DISCUSSION:

HF is associated with a considerable morbidity as well as mortality. The statistics for adverse events in patients with acute decompensated HF has not changed in decades with in-hospital mortality being reported in 4-7% patients and one-year mortality around 30%⁶. However, the data from Indian sub-continent is sparse with an estimated mortality attributable to HF being around 0.1-0.16 million individuals per year^{7,8}. In our study, in-hospital mortality was reported in 10.6% patients while one year mortality was seen in 20.8% of the population. Prevalence of acute decompensated HF continues to increase as a result of an aging population, improved survival from acute myocardial infarction and better management of chronic heart failure. Clinical decisions making in these patients often remain challenging leading to high rates of mortality and hospitalization for HF as well as the high economic burden due to the AHF syndrome.

Risk stratification methods may improve decision making in emergent care, especially in conditions where decision must be made promptly and correctly. Patients with an estimated lower risk can be managed with less intensive monitoring and therapies in hospital wards whereas higher risk patients require intensive care and constant monitoring⁵. Selker and colleagues⁹ firstly developed a model to predict acute hospital mortality from data available to the ED physician within the first 10 minutes of presentation: patients' age, systolic blood pressure and findings and ECG abnormalities. Chin and Goldman¹⁰ developed a risk model using a larger number of variables (vital signs, comorbidities, ECG findings, and laboratory data). The model was successful in predicting morbidity as well as mortality however, it could not delineate the low-risk patient. In one of the largest studies to date including 65,275 patients with HF, multiple variables were used to

predict in-hospital mortality¹¹. Three variables were used to differentiate high-risk patients from low-risk patients: blood urea nitrogen (BUN) level >43 mg/dL, systolic blood pressure (SBP) <115 mm Hg and serum creatinine level > 2.75 mg/dL. This study reported a 22% in-hospital mortality rate, a finding consistent with other studies too^{9,10}. The Enhanced Feedback for Effective Cardiac Treatment (EFFECT) study showed that increasing BUN levels and decreasing SBP were significant and independent predictors of both 30-day and 1-year mortality¹². Several markers associated with poor clinical outcomes include an elevated BUN or creatinine level, a low SBP, hyponatremia, ischemic ECG changes and elevated cardiac biomarkers¹². Our study too showed that higher BUN and creatinine levels, increased levels of biomarkers and lower SBP was associated with a greater in-hospital mortality.

HF is a common complication of MI with factors such as infarct size, myocardial ischemia, mechanical complications, hibernating or stunned myocardium being the preliminary contributors for HF with reduced EF after an MI. Our study too demonstrated that patients with history of MI had higher probability of death or rehospitalization compared to those without. Similar findings were reported in the study by Gerber et al.¹³. Hyponatremia (<135 mmol/L) and renal dysfunction on hospital admission have increasingly been associated with an increased in-hospital and post-discharge mortality as well as higher readmission rates. Renal dysfunction causes further congestion and neurohormonal activation both of which are associated with adverse outcomes in HF¹⁴. Similar findings were seen in our study with patients having elevated serum creatinine levels having 1.7 times higher risk of developing MACE. Several investigations have evaluated the prognostic ability of natriuretic peptides. In a study involving 325 patients presenting with dyspnoea in the ED, serum BNP demonstrated the ability of to predict future cardiac events¹⁵. In this study, the cumulative probability of a HF event within 6 months was 51% in the 67 patients with BNP levels > 480 pg/mL as compared with 2.5% in the 205 patients who had BNP values less than 230 pg/mL. BNP also has been shown to predict adverse events more accurately than a physician's assessment based on level of severity. In a retrospective analysis of 77,467 patients from the Acute Decompensated Heart Failure National Registry¹⁶, a nearly linear relationship was demonstrated between the BNP quartiles and in-hospital mortality. NT-proBNP is a significant predictor of subsequent adverse events with a study showing NT-proBNP concentration > 5180 pg/mL being a strong predictor of death by 76 days (odds ratio : 5.2; 95% CI, 2.2-8.1; P<.001)¹⁷.

Cardiac troponins provide important prognostic information in patients with acute decompensated heart failure with the ADHERE study¹⁶ reporting that 6.2% of the 67,924 patients with acute decompensated heart failure were positive for cardiac troponin. Patients with positive troponins had lower blood pressure levels and lower ejection fraction than those who were negative for troponin. In addition, this study revealed that in-hospital mortality was significantly higher for troponin-positive patients. Our study too showed that elevated cardiac troponin and NT-ProBNP levels have been associated with poor one year outcomes. One of the important limitations of this study was that it was a single centre study with limited sample size and a short duration of follow-up. There is a need for well-designed, large, multicentric study to address the major unmet need in AHF management.

CONCLUSION:

Acute heart failure is a leading cause for emergency department visits, hospital admissions, and readmissions. Since clinical decisions have limitations, there is a need for risk stratification methods to provide guidance to clinicians who care for patients with acute HF syndromes. In addition, there is a need for newer biomarkers and validated predictive risk algorithms to select optimal therapies and to determine how patients will be cared for and improve decisions pertaining to patient disposition and follow-up.

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