

# Correlation of mortality with Pro-BNP and precipitating factors of acute heart failure in patients presenting to a medical emergency of tertiary care hospital: an observational study from north India

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**Abstract.** – **OBJECTIVE:** Acute heart failure is a syndrome defined as the new onset *de novo* heart failure or worsening [acutely decompensated heart failure (ADHF)] leading to symptoms and signs of HF, mostly related to systemic congestion as based on the European Society of Cardiology (ESC) definition. India has a huge burden of heart failure patients. Several factors have been identified as precipitating acute HF hospitalizations. These include myocardial ischemia, no adherence to medications, arrhythmias, infection, uncontrolled hypertension (HTN), anemia, renal impairment, and diet. However, there is a dearth of studies assessing their effect on mortality in patients admitted with acute heart failure. Many previous studies have shown that BNP and NT-pro-BNP are independent predictors of mortality and other cardiac outcomes in patients with heart failure (HF) and ADHF. However, no studies have provided any clear direction with respect to the critical cut-off values that suggest high mortality. Comprehensive knowledge of the correlation of Pro-BNP and precipitating factors of heart failure with mortality can help in prognostication and clinical management of AHF patients.

**PATIENTS AND METHODS:** This was a prospective observational cross-sectional study conducted in the Emergency Department of the Postgraduate Institute of Medical Education and Research, Chandigarh which is a teaching and research hospital located in North India. Patients were enrolled from 1<sup>st</sup> August 2021 to 28<sup>th</sup> February 2022. Patients who met inclusion criteria were enrolled; they were followed for 5 days. After 5 days outcomes were recorded. Various precipitating factors for hospitalization were identified and their clinical impact on mortality was noted. Pro-BNP values were obtained at admission and their correlation with mortality and patient outcome after 5 days was noted. Values of Pro-BNP

were compared among those who survived after 5 days vs. those who had fatal outcomes.

**RESULTS:** The most common precipitating factor for AHF was poor medical compliance which did not affect mortality. It was followed by sepsis which significantly increases mortality in patients of AHF. ACS was also an important precipitating factor for AHF, though it had no effect on mortality. The mortality in the group of patients with very high Pro-BNP levels  $\geq 2000$  pg/ml was significantly higher than in the group of patients who had moderately elevated Pro-BNP  $< 2000$  pg/ml. The median value of Pro-BNP was significantly higher in patients who had fatal outcomes [3670 (IQR- 2745 to 3980)] as compared to patients who survived after 5 days of hospitalization [1340 (IQR- 987 to 1670)].

**CONCLUSIONS:** Poor compliance with medications and sepsis are the most common precipitating factors for acute heart failure in north Indian patients. Sepsis as a precipitating factor is a significant risk factor for in-hospital mortality in acute heart failure patients presenting to the emergency department. Pro-BNP values above 2000 pg/ml in patients with acute heart failure requiring emergency admission are associated with a poor prognosis.

#### Key Words:

Acute coronary syndrome, Heart failure with reduced ejection fraction, Heart failure with preserved ejection fraction, Myocardial infarction, Acute heart failure, B-type natriuretic peptide.

#### Abbreviations

ACS-Acute coronary syndrome, HFrEF-Heart failure with reduced ejection fraction, HFpEF-Heart failure with preserved ejection fraction, AF-Atrial fibrillation,

STEMI-ST-elevation myocardial infarction, NSTEMI-Non-ST elevation myocardial infarction, TLC-Total leucocyte count, AHF-Acute heart failure, BNP-B-type natriuretic peptide.

## Introduction

Heart failure is a complex clinical syndrome that results from the structural or functional impairment of ventricular filling or ejection of blood, which in turn leads to the cardinal clinical symptoms of dyspnoea and fatigue and signs of heart failure namely edema and rales. Acute heart failure is a syndrome defined as the new onset [de novo heart failure] or worsening [acutely decompensated heart failure (ADHF)] leading to symptoms and signs of HF, mostly related to systemic congestion as based on the European Society of Cardiology (ESC) definition<sup>1</sup>. Heart failure (HF) is a global pandemic affecting an estimated 26 million people worldwide and resulting in significant mortality, morbidity, and cost of care<sup>2,3</sup>. India has a huge burden of heart failure patients. An Indian study done in 2016 showed prevalence of heart failure was 1.2 per 1000 population which means around 10 million patients suffered from HF<sup>4</sup>. Despite the recent advance in the management of heart failure, symptomatic heart failure still carries a poor prognosis. In-hospital mortality estimates for AHF range from 4-6% in the US and up to 9% in the UK<sup>5,6</sup>. Several factors have been identified as precipitating acute HF hospitalizations<sup>7-9</sup>. These include myocardial ischemia, poor adherence to medications, arrhythmias, infection, uncontrolled hypertension (HTN), anemia, renal impairment, and diet<sup>10,11</sup>. However, there is a dearth of studies assessing their effect on mortality in patients admitted with acute heart failure. Many previous studies have shown that BNP and NT-pro-BNP are independent predictors of mortality and other cardiac outcomes in patients with heart failure (HF) and ADHF<sup>12-16</sup>. However, no studies have provided any clear direction with regards what are the critical cut-off values that suggest high mortality. Moreover, no studies from the Indian subcontinent looked at the correlation of Pro-BNP and precipitating factors of heart failure with mortality. Comprehensive knowledge of the correlation of Pro-BNP and precipitating factors of heart failure with mortality can help in prognostication and clinical management of AHF patients.

The primary objective is to study the correlation of pro BNP value with mortality in acute heart failure patients. The secondary objective is to study the prevalence of various precipitating

factors for hospitalization with acute heart failure in the north Indian population and their clinical impact on mortality.

## Patients and Methods

### *Study Design & Setting*

This was a prospective observational cross-sectional study conducted in the Emergency Department and emergency medical ward of the Postgraduate Institute of Medical Education and Research, Chandigarh which is a teaching and research hospital located in North India. Patients were enrolled from 1<sup>st</sup> August 2021 to 28<sup>th</sup> February 2022. The data from the observation file of patients in the Emergency Department was recorded and analysed.

### *Outcomes*

The patients were monitored for 5 days after receiving standard medical care. After 5 days the outcome of patients was evaluated as:

A) Identification of various precipitating factors for hospitalization with heart failure and their clinical impact on in-hospital mortality within 5 days of their hospitalization.

B) To study the relationship of Pro-BNP values in patients of AHF on in-hospital mortality within 5 days of their hospitalization.

### *Inclusion Criteria*

All patients admitted to the Emergency Department who were aged  $\geq 18$  and were diagnosed with acute heart failure were enrolled. Acute HF was defined as a syndrome with symptoms and signs of HF in either the new-onset [de novo heart failure (HF)] or worsening [acutely decompensated heart failure (ADHF)], mostly related to systemic congestion as based on the European Society of Cardiology (ESC) definition.

### *Exclusion Criteria*

Patients discharged from the emergency room without admission within six hours were excluded from the study. Patients who did not provide informed consent to participate in the study were also excluded.

### *Sample Size Calculation*

Sample size was calculated using Kelsey method for 95% two-sided confidence interval and 80% power with expected mortality of 25% in the very high pro-BNP group [ $> 2000$ ] and 5% in the mod-

erately high NT pro-BNP group [ $\leq 2000$ ]; and, ratio of patients in moderately high NT pro-BNP group to very high pro-BNP group of 4:1. The required sample size was 200, with 40 patients in very high NT pro-BNP group and 160 patients in the moderately high NT pro-BNP group.

### **Data Collection**

200 adult patients who presented to medical emergency from 1<sup>st</sup> August 2021 to 28<sup>th</sup> February 2022 who meet our inclusion criteria were enrolled in this study. Acute heart failure was broadly defined as a rapid onset of new or worsening signs and symptoms of HF. All the patients were asked about their detailed medical history, particularly regarding the previous CAD, DCM, HF, arrhythmias; any new medication recently started was also noted, if they were on any previous treatment, their compliance was enquired. Details regarding diet or any recent changes in the diet were enquired. Any recent history of fever or history suggestive of infection was noted. Any history suggestive of recent worsening of angina or new-onset angina was noted. Any history suggestive of arrhythmias like palpitations or missed beats was also noted. All patients enrolled were screened for Acute Coronary syndrome. Troponin T levels were measured in all patients. All patients were subjected to 2D Echocardiography to assess LV systolic function and look for valvular regurgitation. Pro-BNP levels at the time of admission were measured in all patients. A screen for any occult infection procalcitonin was measured in all the patients. They underwent all basic routine investigations like kidney function, liver function tests, and complete hemogram. They were given standard treatment. No form of treatment was denied to any patient. Patients were followed for 5 days. After 5 days outcomes were recorded. Various precipitating factors for hospitalization were identified and their clinical impact on mortality was noted. Pro-BNP values were obtained at admission and their correlation with mortality and patient outcome after 5 days was noted. Values of Pro-BNP were compared among those who survived after 5 days vs. those who had fatal outcomes.

### **Statistical Analysis**

The prevalence of various precipitating factors in including participants with acute failure was reported. The group of patients with AHF who died within 5 days of hospitalization were compared with patients who had good outcomes with respect

to precipitating factors and Pro-BNP. Categorical variables were compared using the chi-squared test and Fisher exact test. Continuous variables were compared using the Mann-Whitney U test.  $p$ -value  $<0.05$  was considered significant. We also pre-specified that included participants with AHF would be categorized into moderately elevated group Pro-BNP ( $\leq 2000$ ) and very high Pro-BNP values group ( $>2000$ ). The mortality in moderately elevated group Pro-BNP was compared with very high Pro-BNP values group.

### **Ethical Considerations**

Ethics approval was given by the independent Institute Ethics Committee of Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh (Ref. No.- NK/7678/Study/588). Consent to participate in the study was taken from all patients.

## **Results**

### **Participants**

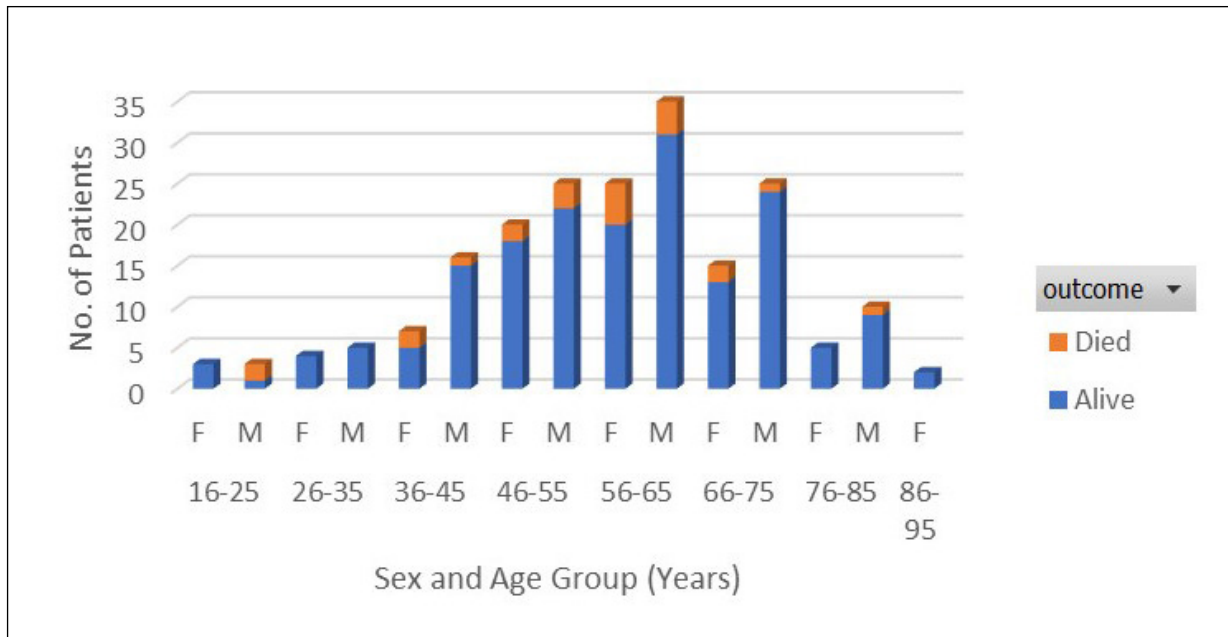
200 patients who presented with acute heart failure to a medical emergency during the study period were enrolled in the study. As shown in Figure 1, out of total 200 patients 59.5% ( $n=119$ ) were males and 40.5% ( $n=81$ ) were females. The mean age for males was 57.782 with (SD -13.56), the mean age for females was 57.691 with (SD-14.953).

### **Baseline Cardiac Illness**

As depicted in Figure 2, out of 200 patients 84% ( $n=168$ ) had HFrEF (left ventricular ejection fraction is 50% or less) and 16% ( $n=32$ ) had HFpEF (left ventricular ejection fraction  $\geq 50$  percent). Valvular heart disease was present in 30% ( $n=60$ ) and absent in 70% ( $n=140$ ). The mortality in patients with HFrEF (21 deaths out of 168) did not differ significantly from HFpEF (2 deaths out of 32) fisher exact test odds ratio of 2.136, 95% CI (0.479 to 19.768), and  $p=0.544$ . Deaths in patients with acute heart failure with valvular heart disease were significantly higher (14 deaths out of 60 patients) as compared to patients who did not have valvular heart disease (9 deaths out of 140) ( $X^2=11.793$ ,  $p<0.001$ ).

### **Comorbidities**

The most common comorbidity found in the study was diabetes. As depicted in Figure 3, it was present in 76% ( $n=153$ ) of the patients' the majority

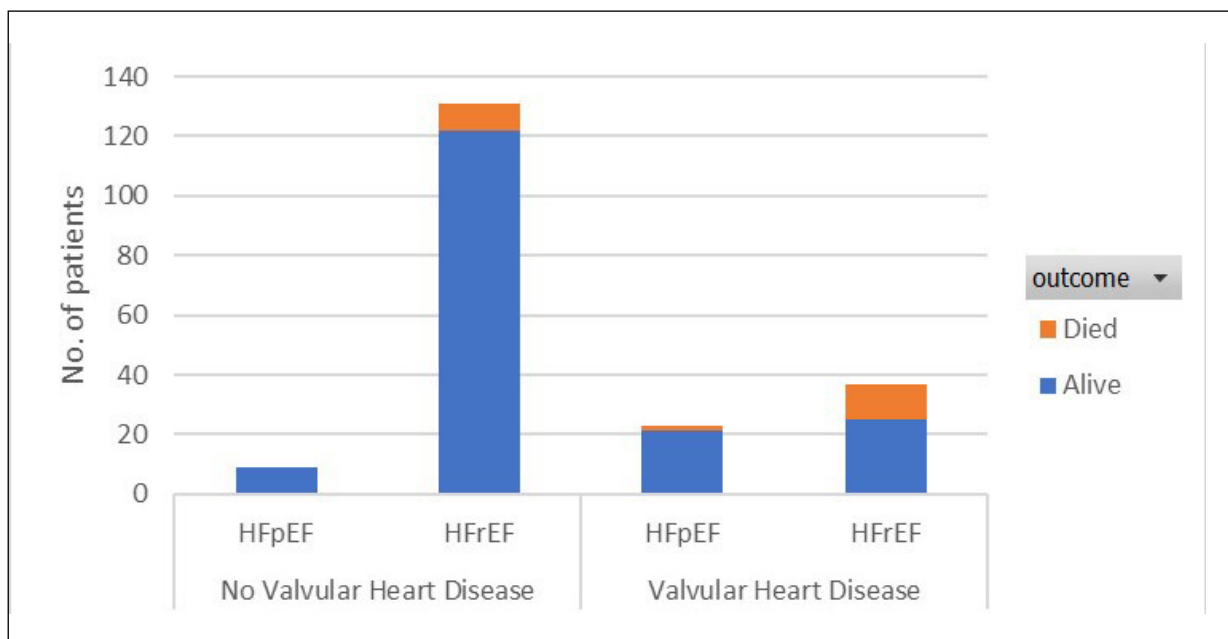


**Figure 1.** Age group and sex of the patients with AHF in relation to patient outcomes on day 5 of hospitalization.

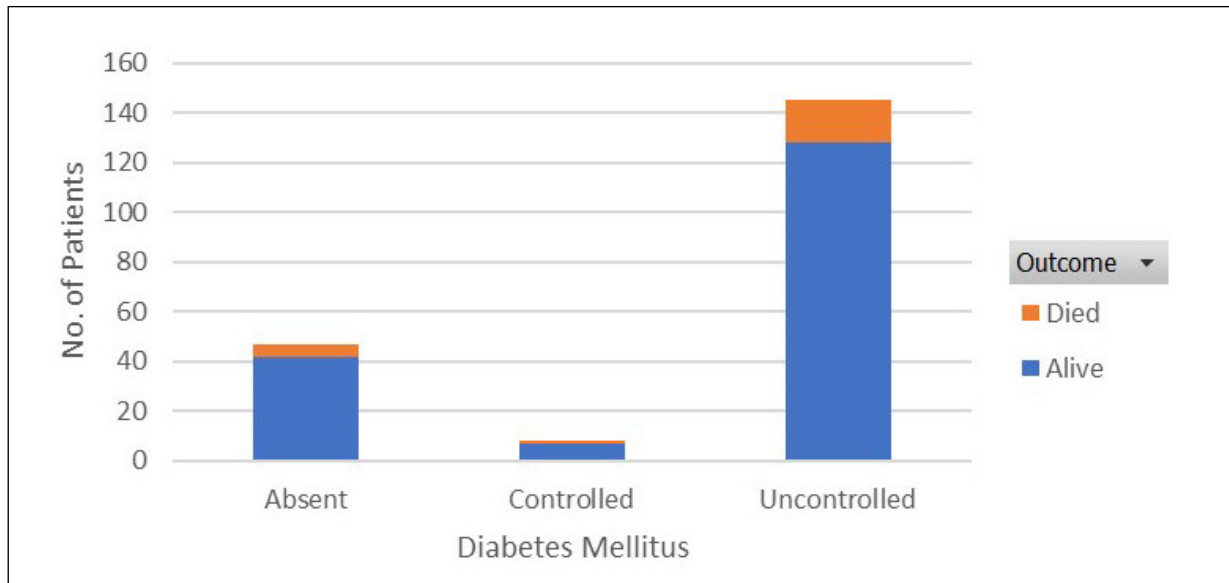
of the 72.5% (145) had poorly controlled glycaemic status. Diabetes was absent in 23% (47) of patients only. The mortality was significantly higher in patients with diabetes 8.5% (n=17) as compared to non-diabetic patients where mortality was 2.5% (n=5).

**Precipitating Factors**

Anaemia was noted as one of the precipitating factors for acute heart failure in the study. It was present in 7.5% (n=15) patients only. There was no difference in mortality in patients who had anemia (1 death out of 15) as compared to those who did



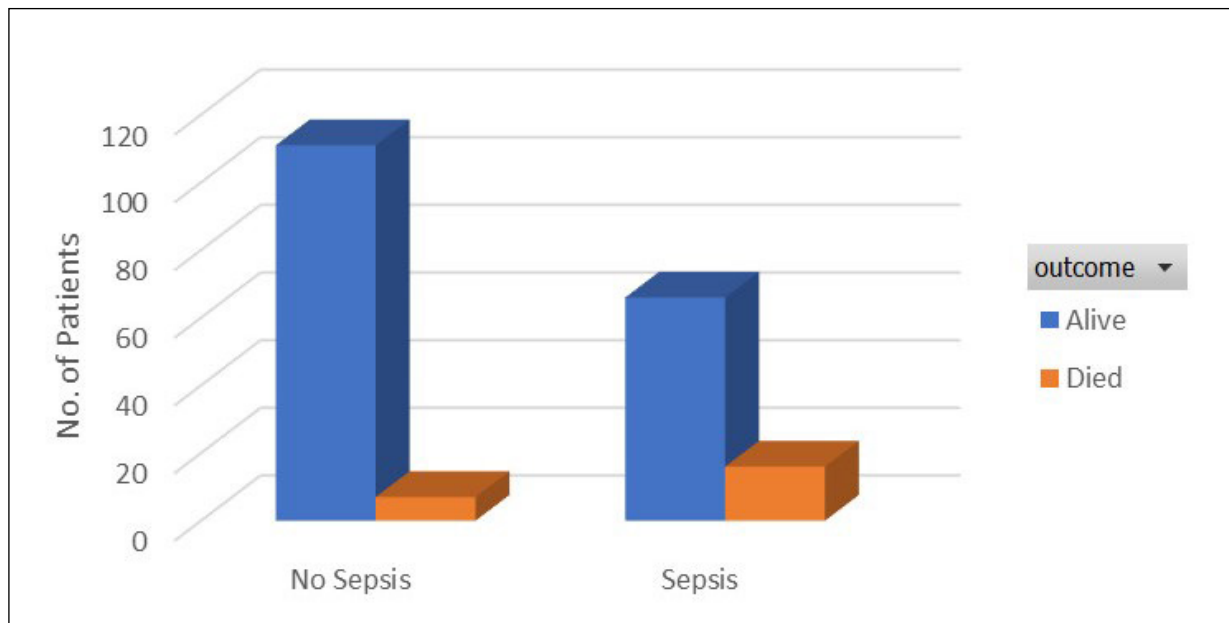
**Figure 2.** The relationship between left ventricular ejection fraction and valvular abnormalities with mortality in patients with AHF.



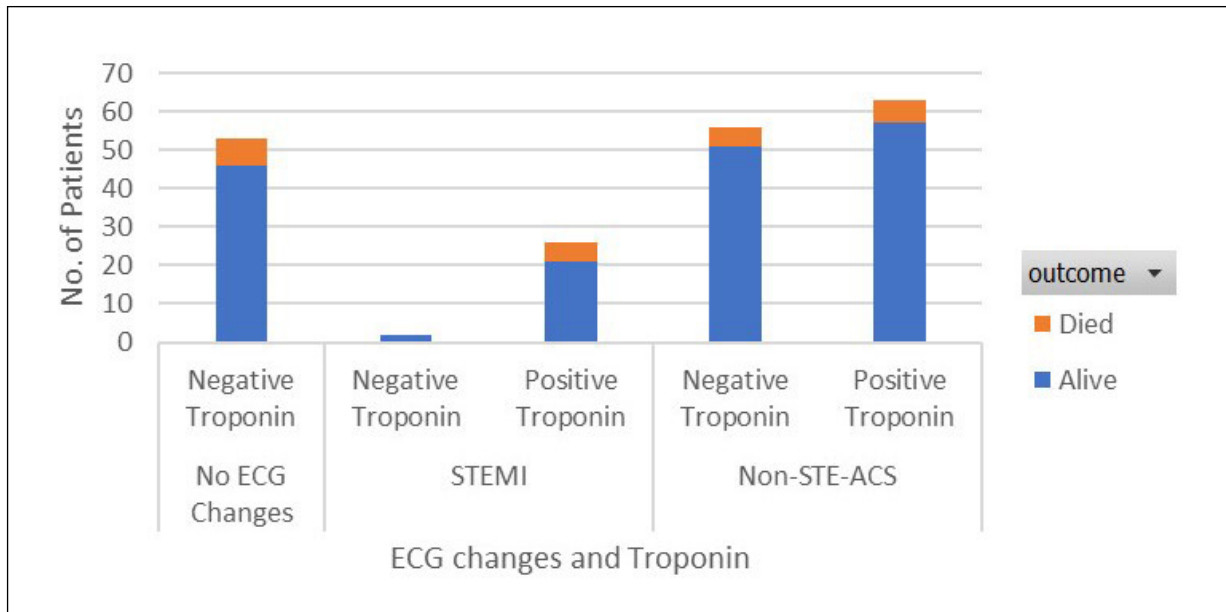
**Figure 3.** The relationship between diabetes and mortality in patients hospitalized with acute heart failure.

not have anemia (22 deaths out of 185) fishers exact test odds ratio was 1.885, 95% CI (0.261 to 83.457),  $p=1.00$  which was not significant. Sepsis in the study was defined as the combination of 3 parameters i.e. presence of fever, TLC count more than 11,000, and procalcitonin value more than 0.5 ng/ml. Sepsis was one of the most common precipitating factors for acute heart failure in the study as depicted in Figure

4, and it was present in 41% (n=81) patients. The mortality was higher in patients with acute heart failure who had sepsis as precipitating factor (16 deaths out of 82) as compared to those who did not have sepsis as precipitating factor (7 deaths out of 118 patients),  $X^2=8.766$ ,  $df=1$ ,  $p=0.003$  which was significant. Poor medical compliance to treatment was the most frequent precipitating factor for acute



**Figure 4.** The relationship between sepsis and mortality in patients hospitalized with acute heart failure.



**Figure 5.** The relationship between acute coronary syndrome and mortality in patients hospitalized with acute heart failure.

heart failure which was encountered in our study. It was present in 75.5% (n=151) of patients. Poor medical compliance did not affect the mortality of patients with acute heart failure (20 deaths out of 150) as compared to patients who had good compliance to treatment (3 deaths out of 48),  $X^2=1.844$ ,  $df=1$ ,  $p=0.174$  which was statistically not significant. Arrhythmias as precipitant were present in 36% (n=72). Atrial fibrillation was the most common tachyarrhythmia noted in the study it was present in 32.5% (n=65) patients. A small number of patients 3.5% (n=7) had bradyarrhythmia. Acute coronary syndrome as the precipitating factor for acute heart failure was defined based on ECG changes and cardiac troponin values. As depicted in Figure 5, T wave depression along with ST changes were present in 59.5% (n=119) and ST-elevation was present in 14% (n=28) patients, 26.5% (n=53) patients have no ischemic changes on ECG. Troponin T was positive in 44.5% (n=89) patients. ST-elevation MI was present in 13% (n=26) patients whereas NSTEMI was present in 31.5% (n=63) patients. There was no difference in mortality among patients who had ACS (11 deaths out of 89) as compared to those who did not have ACS as precipitating factor (12 deaths out of 111),  $X^2=0.116$ ,  $df=1$ ,  $p=0.733$  which was not significant statistically.

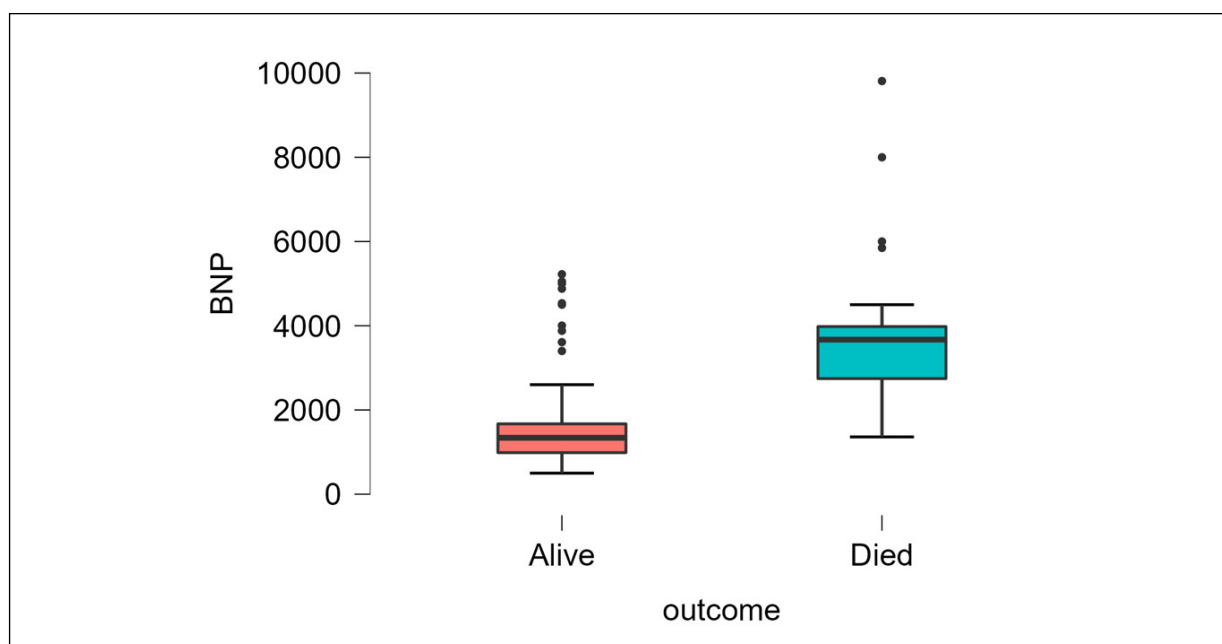
#### Pro-BNP Values

As depicted in Figure 6 the mortality in the group of patients with very high Pro-BNP levels  $\geq$

2000 pg/ml (21 deaths out of 48) was significantly higher than the group of patients who had moderately elevated Pro-BNP  $<2000$  pg/ml (2 deaths out of 152),  $X^2=64.543$ ,  $df=1$ ,  $p<0.001$  which is statistically significant. The median value of Pro-BNP was significantly higher in patients who had fatal outcomes 3670 (IQR- 2745 to 3980) as compared to patients who survived after 5 days of hospitalization. Their median value was 1340 (IQR- 987 to 1670). Mann Whitney  $U=272.5$ ,  $p<0.001$  which was statistically significant.

## Discussion

This study highlights the importance of Pro-BNP values and various precipitating factors of acute heart failure in patients presenting to a medical emergency and their relationship with mortality. The mean age of patients in our study was 57.745 (SD-14.104) whereas a similar study carried out in Israel had a mean age of  $70 \pm 10$  suggesting that Indian patients may develop acute failure at least one decade earlier compared to the western population<sup>17</sup>. The majority of the patients in our study had 84% HFrEF and 16% had HFpEF. An earlier study estimated that as many as 40 to 60% of patients with HF have HFpEF as defined by a normal LVEF<sup>18</sup>. In contrast, our study had a higher prevalence of HFrEF as compared to HFpEF. The reason we



**Figure 6.** Boxplot of serum Pro-BNP concentrations in pg/ml in relation to patient outcomes at 5 days of hospitalization.

found higher patients in HFrEF in our study was due to the fact that the HFrEF is more commonly present as AHF in comparison to HFpEF which has more or less subacute presentations. In our study mortality of patients with HFrEF was similar to patients who had HFpEF. Our results did not match with previous studies where the risk of death from any cause was lower than in HFpEF as compared to HFrEF<sup>19</sup>. Valvular heart disease and heart failure frequently coexist. In our study valvular heart disease was present in 30% of patients which was significantly higher compared to the western population; according to the study it was 14%. The high incidence of valvular heart disease in the Indian subcontinent might be due to the high burden of rheumatic heart disease. Mortality in patients with acute failure with valvular heart disease was significantly high as compared to those who didn't have valvular heart disease. This is probably because a very little number patients opt for valve replacement due to the high cost involved and lack of availability of surgical centres that are doing valve replacement. Diabetes and heart failure often occur concomitantly, and each disease independently increases the risk for the other. In HF cohorts, including both HFrEF and HFpEF, the prevalence of DM ranges from 10% to 47%<sup>20-22</sup>. In our study diabetes was present in 76% of patients. These high numbers of diabe-

tes are explained by the simple fact that India has a very high prevalence (8.9%) of diabetes and an estimated 77 million patients with diabetes live in India. The prevalence of anemia in patients with HF is  $\approx 30\%$  in stable and  $\approx 50\%$  in hospitalized patients, regardless of whether patients have HFrEF or HFpEF<sup>23</sup>. Anaemia is independently associated with increased mortality and hospitalizations in patients with both HFrEF and HFpEF<sup>24,25</sup>. Paradoxically, anemia was present in only 7.5% of patients with AHF in our study and was not associated with increased mortality. The probable reason for this is that anemia is a correctable precipitating factor. Sepsis was one of the most common precipitating factors for acute heart failure and was present in 41% of patients. The mortality was higher in patients with acute heart failure who had sepsis as precipitating factor. Our results are similar to another study which has shown sepsis is a common driver of hospitalization in HFrEF and often presents without classical signs. It is associated with high mortality rates, comparable to decompensated HF, and a major burden of rehospitalization caused by recurrent episodes of infection<sup>26</sup>. Poor medical compliance to treatment was the most frequent precipitating factor for acute heart failure which was encountered in our study. It was present in 75.5% of patients. Our results were different from a study done

in Israel where non-compliance to treatment was present in only 17% of patients. Our study highlights that non-compliance to treatment is much more prevalent in India as compared to the western population. Fortunately, poor medical compliance did not affect the mortality of patients with acute heart failure as compared to patients who had good compliance to treatment. Atrial fibrillation was the most common tachyarrhythmia noted in our study (32.5% of patients). Atrial fibrillation (AF) and heart failure have emerged as new cardiovascular epidemics over the last decade. The reported prevalence of AF in modern heart failure series ranges from 13% to 27%<sup>27-29</sup>. Acute coronary syndrome as precipitating factor was present in 44.5% of patients. ST-elevation MI was present in 13% of patients whereas NSTEMI was present in 31.5% of patients. There was no difference in mortality among patients who had ACS as compared to those who did not have ACS as precipitating factor. Our results were similar to another study done in Israel in which an acute ischemic precipitant was identified in (46%) of individuals. The majority of patients with an ischemic precipitant had a non-ST elevation MI, only (15%) had a STEMI<sup>17</sup>. Previous studies have shown that Pro-BNP is an independent predictor of mortality and other cardiac outcomes in patients with heart failure (HF)<sup>30-33</sup>. In our study, the mortality in the group of patients with very high Pro-BNP levels >2000 pg/ml was significantly higher than in the group of patients who had moderately elevated Pro-BNP <2000 pg/ml. The median value of Pro-BNP was significantly higher in patients who had fatal outcomes 3670 (IQR- 2745 to 3980) as compared to patients who survived after 5 days of hospitalization; their median value was 1340 (IQR- 987 to 1670) suggesting that values of Pro-BNP above 2000 pg/ml are associated with poor prognosis.

### **Strengths of the Study**

This study was done in the Emergency Department of an academic tertiary care hospital in north India in which patients of different age groups were enrolled.

### **Limitations of the Study**

This was a single-centre study and all the patients were enrolled from emergency only and no patient was enrolled from Out-Patient Department (OPD), where relatively stable patients receive treatment and follow-up.

## **Conclusions**

Poor compliance with medications and sepsis are the most common precipitating factors for acute heart failure in north Indian patients. Sepsis as a precipitating factor is a significant risk factor for in-hospital mortality in acute heart failure patients presenting to the Emergency Department. Pro-BNP values above 2000 pg/ml in patients with acute heart failure requiring emergency admission are associated with a poor prognosis.

### **Conflict of Interest**

The Authors declare that they have no conflict of interests.

### **Acknowledgments**

We acknowledge Professor Sanjay Jain and Professor Navneet Sharma for their guidance and support.

### **Informed Consent**

Patients gave written informed consent for participation in the study.

### **Authors' Contribution**

MSB proposed the idea of the study. MSB and ND collected the data. SCS did the statistical analysis. MSB and RA drafted the manuscript; SCS and AKP contributed substantially to its revision. All authors have read and approved the manuscript.

### **Funding**

None.

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### **Ethics Approval**

Study was approved by the Institute Ethics Committee, Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh (Ref. No.- NK/7678/Study/588).

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