



Research Brief

Role of N-terminal pro-B-type natriuretic peptide in the prediction of outcomes in ST-elevation myocardial infarction complicated by cardiogenic shock



Yash Paul Sharma^a, Kewal Kanabar^{b,*}, Krishna Santosh^a, Ganesh Kasinadhuni^a, Darshan Krishnappa^c

^a Department of Cardiology, Postgraduate Institute of Medical Education and Research, Chandigarh, India

^b Department of Cardiology, U.N. Mehta Institute of Cardiology and Research Centre, Ahmedabad, India

^c Cardiovascular Division, University of Minnesota, Minneapolis, MN, USA

ARTICLE INFO

Article history:

Received 15 June 2020

Accepted 5 July 2020

Available online 12 July 2020

Keywords:

Cardiogenic shock

ST-elevation myocardial infarction

NT-proBNP

Mortality

ABSTRACT

Although measurements of natriuretic peptides have a role in chronic heart failure and acute coronary syndrome, their role has not been studied in ST-elevation myocardial infarction complicated by cardiogenic shock (CS-STEMI). Sixty-four patients with CS-STEMI were prospectively recruited to assess the prognostic value of N-terminal pro-B-type natriuretic peptide (NT-proBNP) measurement after 24 h of the onset of angina or anginal equivalent. Patients who died within 24 h were excluded. The mean age was 56.9 ± 10.6 years and the median time to presentation was 22 h (Interquartile range 7–48 h). Thrombolysis was done in 51% and PCI in 31% of cases. The in-hospital mortality was 26.5%. The ROC analysis showed a strong relationship between elevated NT-proBNP and in-hospital mortality (AUC = 0.748; $p = 0.003$). An NT-proBNP value > 8582 pg/mL showed 76.5% sensitivity, 68% specificity, 46.4% positive predictive value, and 89% negative predictive value for in-hospital mortality. Acute kidney injury [Odds ratio (OR) 7.30; 95% confidence interval (CI) 1.42–37.37] and NT-proBNP (OR 1.12 per 1000 pg/mL; CI 1.012–1.25) were independent predictors of mortality in multivariate regression analysis. Although we found plasma NT-proBNP at 24 h to be an independent predictor of in-hospital mortality in CS-STEMI, additional studies with a larger sample are required to ascertain these findings and validate the appropriate cut-off values.

© 2020 Cardiological Society of India. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

The outcomes of cardiogenic shock complicating ST-elevation myocardial infarction (CS-STEMI) remain sub-optimal despite early revascularization and the use of mechanical circulatory support.¹ None of the studied biomarkers, except interleukin-6 and adrenomedullin, have sufficient predictive value to be useful in CS-STEMI.^{2–4} N-terminal pro- (NT-pro) B-type natriuretic peptide (NT-proBNP), a strong surrogate marker of ventricular wall stress and congestion, is an indicator of the severity of ventricular dysfunction and the attendant impairment of renal and hepatic functions.⁵ Although natriuretic peptides BNP and NT-proBNP have

established predictive value in acute MI,⁶ especially in diabetic patients,⁷ limited data is available in CS-STEMI. In the present study, we analyzed the relationship between NT-proBNP measurement at 24 h of the onset of angina/anginal equivalent with in-hospital mortality in CS-STEMI.

2. Methods

2.1. Study design and patient selection

This was a prospective, single-center, observational review of patients with CS-STEMI presenting to a tertiary hospital in North India between January 2017 to June 2018. The study protocol conforms to the ethical guidelines of the Declaration of Helsinki and was reviewed and approved by the institutional ethics committee. Informed written consent was obtained from all patients or appropriate legally authorized representatives.

* Corresponding author. Department of Cardiology, U.N. Mehta Institute of Cardiology and Research Centre, Ahmedabad-380016, India.

E-mail address: kewal.kanabar14@gmail.com (K. Kanabar).

STEMI was defined as per the ESC/ACCF/AHA/WHF third universal definition.⁸ Cardiogenic shock was defined as a systolic blood pressure <90 mm Hg for at least 30 min or the need of supportive measures to maintain a systolic blood pressure >90 mm Hg despite adequate filling pressures, and signs of end-organ hypoperfusion. Two-dimensional echocardiogram (Vivid Q, GE Healthcare, New York, USA) was performed to assess the left ventricular (LV) ejection fraction. Acute kidney injury was defined as per the KDIGO 2012 practice guideline.⁹

2.2. Laboratory methods

Complete blood count, renal and liver function tests, high-sensitivity troponin-I, and creatine kinase-MB (CK-MB) were performed immediately upon hospital admission. Since cardiovascular natriuretic peptides peak and have the best prognostic value at approximately 24 h of onset,⁵ samples for NT-proBNP were obtained at approximately 24–36 h of the onset of angina/anginal equivalent or at hospital admission in patients who presented later. Patients who died within 24 h/before collection of blood samples were excluded. NT-proBNP levels were measured using Elecsys ProBNP II immunoassay (Roche Diagnostics, Mannheim, Germany) using Cobas 6000 analyzer.

2.3. Management strategy

Patients were treated with dual antiplatelets, statin, and low-molecular-weight heparin. As reported previously,¹⁰ due to the significantly late presentation to our center, the decision of revascularization was based on delay from symptom onset, presence of anginal pain/electrical instability, hemodynamic parameters, end-organ failure, myocardial viability, mechanical complications, coronary anatomy, and patient consent and willingness for revascularization. The primary end-point of the study was in-hospital mortality.

2.4. Statistical analyses

Statistical analysis was done using the Statistical Package for social sciences (SPSS Inc. Version 23.0, IBM Corporation, Chicago, USA). Parametric continuous variables were described as mean \pm SD, non-parametric as median [interquartile range (IQ)], and categorical variables as number and percent. The comparison between groups was done using *t*-test for continuous variables (parametric), Mann–Whitney test (non-parametric), and chi-square test (categorical). The area under the curve was calculated using receiver operating characteristic (ROC) for NT-proBNP against in-hospital mortality. A binomial logistic regression model for predicting mortality was devised and variables with $p \leq 0.10$ on univariate analysis were included. All other *p* values are two-tailed and set at a statistical significance of 0.05.

3. Results

3.1. Baseline characteristics

A total of 64 patients were included (Fig. 1). The mean age was 56.9 ± 10.6 years and the median time to presentation was 22 h (IQ 7–48). Thrombolysis was done in 51% of cases and streptokinase was the most commonly used agent (78%). Coronary angiogram was done in 61% and percutaneous coronary intervention (PCI) in 31% of cases (Table 1). The in-hospital mortality was 26.5%.

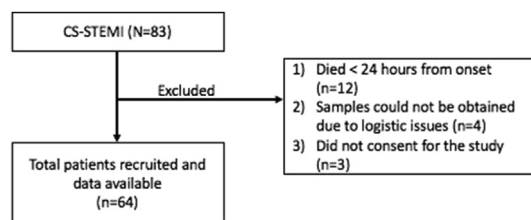


Fig. 1. STROBE diagram of the patients in the study. CS-STEMI= ST-elevation myocardial infarction complicated by cardiogenic shock.

3.2. Comparison between survivors and non-survivors

The non-survivors were older, had lower LV ejection fraction, less likely received fibrinolysis, and were more likely to develop acute kidney injury and mechanical complications compared to the survivors. There were no significant differences in the angiographic patterns of survivors and non-survivors (Table 1).

3.3. Prognostic value of NT-proBNP

The median NT-proBNP was 7669 pg/mL (IQ 3571–12801 pg/mL) and was higher in non-survivors compared to the survivors (15,187 pg/mL vs 6213 pg/mL; $p = 0.003$) (Table 1). The ROC analysis revealed a strong relationship between NT-proBNP and in-hospital mortality (Area under the curve = 0.748; $p = 0.003$) (Fig. 2). An NT-proBNP value > 8582 pg/mL showed 76.5% sensitivity, 68% specificity, 46.4% positive predictive value, 89% negative predictive value, positive likelihood ratio of 2.4, negative likelihood ratio of 0.34, and a diagnostic accuracy of 70.3% for in-hospital mortality.

A binary logistic regression was performed to determine the effects of age, fibrinolysis, LV ejection fraction, acute kidney injury, type of MI, and NT-proBNP on in-hospital mortality. Acute kidney injury [Odds ratio (OR) 7.30; 95% confidence interval (CI) 1.42–37.37; $p = 0.01$] and NT-proBNP (OR 1.12 per 1000 pg/mL; CI 1.012–1.25; $p = 0.029$) were independent predictors of mortality in multivariate regression analysis (Supplementary Table S1). In linear regression analysis, serum creatinine accounted for only 13.4% of the variation in NT-proBNP ($p = 0.003$).

4. Discussion

To the best of our knowledge, this is the second largest study assessing the prognostic value of NT-proBNP in CS-STEMI. We found a significant delay in seeking medical care after the onset of angina/anginal equivalent. Around half of the patients received fibrinolysis (most commonly with streptokinase), two-thirds underwent an angiogram, and less than one-third underwent PCI. Acute kidney injury and NT-proBNP were found to be the only independent predictors of mortality in multivariate analysis.

In patients with acute MI, NT-proBNP has been shown an independent predictor of cardiovascular mortality beyond LV ejection fraction.^{6,11} Studies have demonstrated that NT-proBNP levels within 24 h of symptom onset are much higher in patients with CS and severe heart failure than in patients without them and tend to correlate with LV ejection fraction.¹² However, limited data is available regarding the prognostic role of NT-proBNP in CS-STEMI.³

Except for the younger age and delay in presentation, our cohort is similar to other studies of CS-STEMI.¹ The lower mortality is due to the exclusion of patients who succumbed within 24 h/before samples were obtained. The comparison of the current study with the studies assessing the prognostic role of NT-proBNP in CS-STEMI is depicted in Table 2. The patients in our study were younger

Table 1
Characteristics of the study population.

Characteristic	Overall cohort n = 64	Survivors n = 47	Non-survivors n = 17	p value
Age, years, mean ± SD	56.9 ± 10.6	55.2 ± 10.33	61.52 ± 10.27	0.03
Sex, n (%)				
Male	50 (78.1)	37 (78.7)	13 (76.5)	1.00
Female	14 (21.9)	10 (21.3)	4 (23.5)	
Risk factors, n (%)				
Diabetes Mellitus	25 (39.1)	17 (36.2)	8 (47.1)	0.43
Hypertension	30 (46.9)	22 (46.8)	8 (47.1)	0.98
Smoking	27 (42.2)	19 (40.4)	8 (47.1)	0.63
Family History	3 (4.7)	3 (6.4)	0	0.55
Prior MI	8 (12.5)	6 (12.8)	2 (11.8)	1.00
Time to presentation, hours, median (IQ)	22 (7–48)	16 (6–48)	24 (12–60)	0.21
Anterior MI, n (%)	41 (61.1)	27 (57.4)	14 (82.4)	0.06
LV ejection fraction, %, mean ± SD	30.3 ± 9.3	31.70 ± 9.04	26.47 ± 9.14	0.04
Acute kidney injury, n (%)	31 (48.4)	17 (36.2)	14 (82.4)	0.001
IABP use, n (%)	5 (7.8)	3 (6.4)	2 (11.4)	0.60
Fibrinolysis, n (%)	33 (51.6)	28 (59.6)	5 (29.4)	0.03
Major complications, n (%)				
VT/VF	9 (14.1)	5 (10.6)	4 (23.5)	
Ventricular septal rupture	3 (4.8)	0	3 (17.6)	0.23
Cardiac rupture	0	–	–	0.01
Culprit lesion, n (%) ^a				
LAD	21 (53.8)	17 (51.5)	4 (66.7)	0.75
LCX	1 (2.6)	1 (3)	0	
RCA	17 (43.6)	15 (45.5)	2 (33.3)	
Type of vessel involvement, n (%) ^a				
Single-vessel disease	19 (48.7)	15 (45.5)	4 (66.7)	0.40
Double-vessel disease	11 (28.2)	11 (33.3)	0	0.15
Triple-vessel disease	9 (23.1)	7 (21.2)	2 (33.3)	0.60
PCI, n (%)	20 (31.2)	17 (36.2)	3 (17.6)	0.15
Laboratory parameters				
NT-proBNP, pg/mL, median (IQ)	7669 (3571–12801)	6213 (3447–10353)	15,187 (7433–29170)	0.003
Creatinine, mg/dl, mean ± SD	1.43 ± 0.7	1.24 ± 0.59	1.97 ± 0.89	0.001
Albumin, gm/dl, mean ± SD	3.40 ± 0.41	3.47 ± 0.39	3.28 ± 0.47	0.12
Total leucocyte count, cells/mm ³ , mean ± SD	13,075 ± 5156	12,627 ± 4406	14,311 ± 6832	0.25

IABP = intra-aortic balloon pump; IQ = interquartile range; LAD = left anterior descending artery; LCX = left circumflex artery; LV = left ventricular; MI = myocardial infarction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PCI = percutaneous coronary intervention; RCA = right coronary artery; VT/VF = ventricular tachycardia/ventricular fibrillation.

^a Values are based on 39 patients (33 survivors and 6 non-survivors) who underwent an angiogram. More than 70% stenosis of the left anterior descending artery, right coronary artery, and left circumflex artery was considered significant.

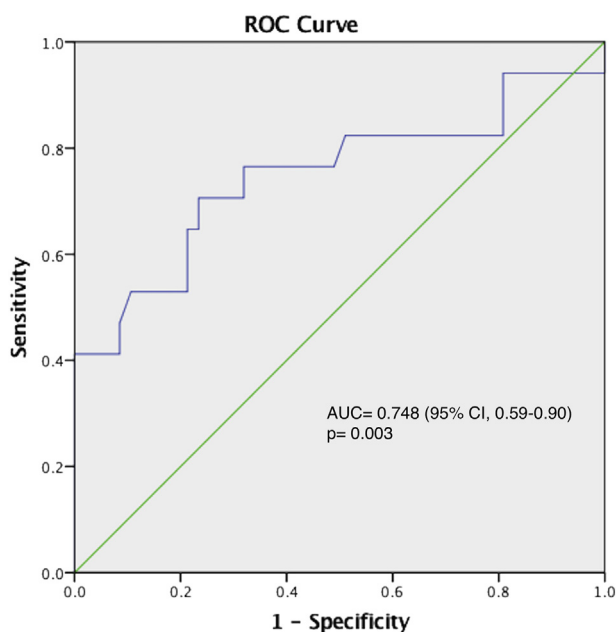


Fig. 2. Receiver operating characteristic (ROC) curve of serum NT-proBNP for the prediction of in-hospital mortality. AUC = area under the curve.

compared to the other studies. Similar to some of the outlined studies, we found NT-proBNP to be an independent mortality predictor in the multivariate regression analysis. Acute kidney injury and NT-proBNP were independently associated with mortality in multivariate analysis, which is consistent with the already established data.^{1,13} We demonstrated highly elevated NT-proBNP in patients with CS-STEMI. The high median NT-proBNP may be attributed to several factors such as ventricular dysfunction (mean LV ejection fraction 30%), high prevalence of renal dysfunction (48%), high levels of systemic inflammation, late presentation, and low rates of revascularization. Unlike Jarai et al,³ we found a complementary role of NT-proBNP and serum creatinine in the prediction of mortality, which can be partly attributed to the larger sample size. Although renal functions have a significant impact on the levels of natriuretic peptides, serum creatinine accounted for a small variation in NT-proBNP in the study.

To the best of our knowledge, this is one of the largest studies assessing the role of NT-proBNP in CS-STEMI. However, there are several limitations to this study. The small sample at a single center means that these results need to be confirmed in a large trial. Given the study design, all the limitations of a nonrandomized, observational sample apply to our study. Since we excluded patients who died within 24 h/before obtaining samples, the predictive value of NT-proBNP in the overall cohort remains uncertain. The low rates of PCI due to late presentation and high prevalence of multi-organ dysfunction including acute kidney injury (48%) which made

Table 2
Comparison of studies assessing the role of NT-proBNP in CS-STEMI.

Study	No. of patients	Mean age (years)	Mortality (%)	NT-proBNP cut-off (pg/mL)	Remarks
Katayama et al ¹²	28	72	–	769 for BNP	BNP is not a predictor of mortality in CS.
Katayama et al ⁴	42	72	36%	–	BNP a predictor of mortality in multivariate analysis.
Tolppanen et al ⁵	122	68	42%	4500	NT-proBNP and sST-2 independent predictors of mortality. AUC for NT-proBNP = 0.78 at 24 h.
Jarai et al ³	47	65	62.5%	12,783	NT-ProBNP and IL-6 independent predictor of mortality. AUC for NT-ProBNP = 0.72
Pöss et al ¹⁴	51	68	37.2	12,782	NT-proBNP not a predictor of mortality.
Prondzinsky et al ¹⁵	40	64	32.5	–	BNP a weak predictor of mortality.
Current study	64	57	26.5%	8582	NT-ProBNP and AKI independent mortality predictors in multivariate analysis. AUC for NT-ProBNP = 0.74.

AKI = acute kidney injury; AUC = area under the curve; BNP= B-type natriuretic peptide; CS = cardiogenic shock; CS-STEMI= ST-segment elevation myocardial infarction complicated by cardiogenic shock; IL-6 = interleukin-6; NT-proBNP = N-terminal pro-B-type natriuretic peptide; sST-2 = soluble ST-2.

them unsuitable for PCI, may have affected our results and the NT-proBNP measurements and the cut-off values. Also, since NT-proBNP was measured only once after hospitalization, the prognostic value of serial trends of NT-proBNP remains unknown. Measurements of additional markers such as IL-6, adrenomedullin, soluble ST2, and BNP would have been highly desirable. Also, since only in-hospital outcomes were recorded, the role of NT-proBNP in intermediate and long-term outcomes remains unknown.

To conclude, NT-proBNP measurement at 24 h along with acute kidney injury were found to be independent predictors of mortality in patients with CS-STEMI. Notwithstanding the various limitations, it seems that NT-proBNP provides additional prognostic information in CS following an acute MI with a high negative predictive value. However, additional studies with a larger sample and serial measurements during hospital stay may provide more information regarding the prognostic utility of NT-proBNP in CS-STEMI.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

The authors declare that there is no conflict of interest.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.ihj.2020.07.002>.

References

- Hochman JS, Sleeper LA, Webb JG, et al. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. SHOCK investigators. Should we emergently revascularize occluded coronaries for cardiogenic shock. *New England Journal of Medicine*. 1999;341:625–634.
- Andrié RP, Becher UM, Frommold R, et al. Interleukin-6 is the strongest predictor of 30-day mortality in patients with cardiogenic shock due to myocardial infarction. *Journal of critical care*. 2012;16(4):R152.
- Jarai R, Fellner B, Haoula D, et al. Early assessment of outcome in cardiogenic shock: relevance of plasma N-terminal pro-B-type natriuretic peptide and interleukin-6 levels. *Critical Care Medicine*. 2009 Jun;37(6):1837–1844.
- Katayama T, Nakashima H, Takagi C, Honda Y, Suzuki S, Yano K. Predictors of mortality in patients with acute myocardial infarction and cardiogenic shock. *Journal is the official journal of the Japanese Circulation Society*. 2005 Jan;69(1):83–88.
- Tolppanen H, Rivas-Lasarte M, Lassus J, et al. Combined measurement of soluble ST2 and amino-terminal pro-B-type natriuretic peptide provides early assessment of severity in cardiogenic shock complicating acute coronary syndrome. *Critical Care Medicine*. 2017 Jul;45(7):e666–e673.
- Scirica BM, Kadakia MB, de Lemos JA, et al. Association between natriuretic peptides and mortality among patients admitted with myocardial infarction: a report from the ACTION Registry(R)-GWTG™. *Clinical Chemistry*. 2013 Aug;59(8):1205–1214.
- Vergès B, Zeller M, Desgrès J, et al. High plasma N-terminal pro-brain natriuretic peptide level found in diabetic patients after myocardial infarction is associated with an increased risk of in-hospital mortality and cardiogenic shock. *European Heart Journal*. 2005 Sep;26(17):1734–1741.
- Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. *Circulation*. 2012 Oct 16;126(16):2020–2035.
- Khawaja A. KDIGO clinical practice guidelines for acute kidney injury. *Nephron Clinical Practice*. 2012;120(4):c179–c184.
- Sharma YP, Krishnappa D, Kanabar K, et al. Clinical characteristics and outcome in patients with a delayed presentation after ST-elevation myocardial infarction and complicated by cardiogenic shock. *Indian Heart Journal*. 2019 Oct;71(5):387–393.
- Omland T, Aakvaag A, Bonarjee VV, et al. Plasma brain natriuretic peptide as an indicator of left ventricular systolic function and long-term survival after acute myocardial infarction. Comparison with plasma atrial natriuretic peptide and N-terminal proatrial natriuretic peptide. *Circulation*. 1996 Jun 1;93(11):1963–1969.
- Katayama T, Nakashima H, Furudono S, Honda Y, Suzuki S, Yano K. Evaluation of neurohumoral activation (adrenomedullin, BNP, catecholamines, etc.) in patients with acute myocardial infarction. *International Medicine Tokyo Japan*. 2004 Nov;43(11):1015–1022.
- Acharya D. Predictors of outcomes in myocardial infarction and cardiogenic shock. *Cardiol Review*. 2018 Oct;26(5):255.
- Pöss J, Mahfoud F, Seiler S, et al. FGF-23 is associated with increased disease severity and early mortality in cardiogenic shock. *European Heart Journal Acute Cardiovascular Care*. 2013 Sep;2(3):211–218.
- Prondzinsky R, Lemm H, Swyter M, et al. Intra-aortic balloon counterpulsation in patients with acute myocardial infarction complicated by cardiogenic shock: the prospective, randomized IABP SHOCK Trial for attenuation of multiorgan dysfunction syndrome. *Critical Care Medicine*. 2010 Jan;38(1):152–160.