RESEARCH ARTICLE

NT-proBNP Level Predicts Extent of Myonecrosis and Clinical Adverse Outcomes in Patients with ST-Elevation Myocardial Infarction: A Pilot Study

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Abstract

Background and Hypothesis: The initial assessment of late gadolinium enhancement (LGE) on cardiac magnetic resonance imaging (CMR) reflects cardiac damage and is an important prognostic factor in patients with acute ST-elevation myocardial infarction (STEMI). N-Terminal prohormone of brain natriuretic peptide (NT-proBNP) is released following cardiomyocytes injury. However, the relationship between NT-proBNP levels, myocardial damage and clinical outcomes after STEMI has not been well defined.

Methods: Plasma levels of NT-proBNP, troponin I and creatinine kinase (CK) were assessed in 75 patients with STEMI. Echocardiography and CMR were performed prior to hospital discharge. Cardiac damage was quantified using peak biomarker levels and LGE. Patients were followed for a median of 975 days (IQR 823-1098 days) for major adverse cardiac events (MACE) (all-cause mortality, recurrent myocardial infraction, unplanned recurrent revascularization and recurrent hospitalization for heart failure).

Results: Plasma levels of NT-proBNP increased following STEMI to peak at 24 hours. The dynamic changes in plasma NT-proBNP were similar to those noted with troponin I and its delayed peak but not those observed with plasma CK levels. Peak NT-proBNP levels correlated positively with indices of myocardial damage such as peak troponin I (R^2=0.38, P <0.001), peak CK (R^2=0.22, P = 0.01) and LGE examination (R^2 = 0.46, P <0.001). Peak plasma level of NT- proBNP was strongly predictive of MACE during the follow-up period.

Conclusions: Peak levels of NT-proBNP following STEMI are predictive of the extent of myocardial damage and clinical outcomes. These results suggest an important prognostic role for NT-proBNP assessment in STEMI patients.

Keywords: ST-elevation myocardial infarction; NT-proBNP; cardiac biomarkers; cardiac magnetic resonance imaging; cardiac outcome

INTRODUCTION

Patients with ST-elevation myocardial infarction (STEMI) are at high risk for mortality and recurrent ischemic events. Typical risk stratification models such as the TIMI risk score includes age, weight, time to treatment, hemodynamic status, location of STEMI and clinical presence of heart failure. While these clinical risk scores have excellent predictive value for major adverse cardiovascular events (MACE) during short-term follow-up with a C statistic of 0.779 for the TIMI score (1), they do not incorporate some of the well-defined markers that reflect the degree of cardiac damage such as microvascular obstruction (MVO) and late gadolinium enhancement (LGE) on cardiac MRI (CMR) which have been shown to accurately predict clinical outcomes in STEMI patients (2).

N-Terminal prohormone of brain natriuretic peptide (NT-proBNP) is the biological inert byproduct of the degradation of pre-proBNP. NT-proBNP has been established as a biological marker in the diagnosis and staging of heart failure and has been recommended as a diagnostic tool by the American College of Cardiology/American Heart Association guidelines (3). Additionally, BNP and NT-proBNP are important prognostic markers in patients with chronic heart failure (4) as well as stable coronary artery disease (5-7). Recently, NT-proBNP has been used as a prognostic marker for patients with acute coronary syndrome (ACS) (8-10). However, the correlation between serial NT-proBNP measurements and cardiac MRI assessments of myocardial damage as well as long term clinical outcomes in patients with STEMI are poorly understood.

The addition of biomarkers to traditional risk assessment prognostic tools in patients with STEMI has multiple advantages and can further risk stratify patients (11,12). Sabatine et al reported that the addition of cardiac troponin T, C-reactive protein and NT-proBNP added significant prognostic value to traditional risk factors in patients admitted with Non-STEMI (13). Accordingly, we hypothesized that NT-proBNP is a sensitive marker of early myocardial damage in patients admitted with STEMI. We investigated the dynamic changes in NT-proBNP in relation to markers of cardiac damage such as cardiac enzyme levels and cardiac MRI as well as clinical outcomes at long-term clinical follow up.

MATERIALS AND METHODS

The study population consists of 75 patients with acute ST-elevation myocardial infarction (STEMI) enrolled at the University of Kentucky hospitals between January 2014 and July 2015. Patients with STEMI were referred within 12 h of symptom onset for primary percutaneous coronary intervention (PPCI). Patients underwent cardiac imaging using cardiac MRI (CMR) and/or echocardiography within 72 hours of PPCI. Peripheral blood (PB) samples were obtained at presentation in all patients (BSL) followed by samples at 6, 12, 24, and 48 after PPCI (**Figure 1A**). Patients were excluded if they had chronic kidney disease, systemic inflammatory process, cancer, recent motor vehicle accident, recent surgery, active infection, history of MI or revascularization (coronary artery bypass graft, PCI), unsuccessful revascularization, or onset of the symptoms >12 h. The study protocol complies with the Declaration of Helsinki and was approved by the institutional Ethics Committee. All patients provided written informed consent.

Figure 1.

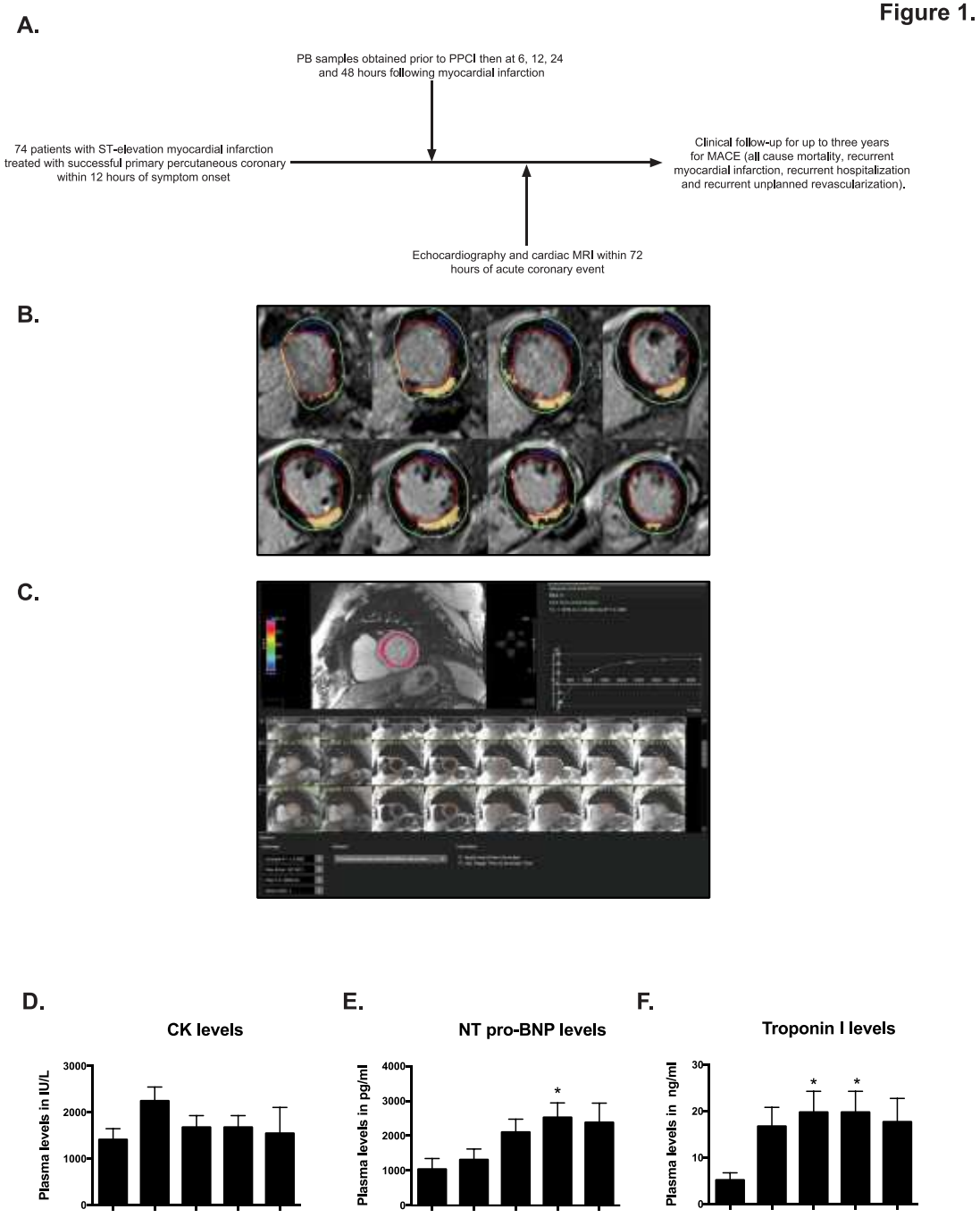

Figure 1. A diagram summarizing the study design (**Panel A**). **Panel B** shows automated quantification of scar by automated signal thresholding. Endocardial and epicardial border tracing was done first (red and green lines) followed by drawing a reference region in the remote healthy myocardium (blue lines). The machine automatically delineates the area of late gadolinium enhancement (yellow color). **Panel C** shows native myocardial T1-relaxation times calculated using a modified Look-Locker imaging (MOLLI) sequence. Bar graphs depicting the temporal changes in plasma creatinine kinase (CK), NT-proBNP and troponin I following STEMI. This figures shows an early peak for CK (**Panel D**) while there is delayed peak of NT-proBNP (**Panel E**) similar to changes in troponin I (**Panel F**).

Assessment of cardiac function by echocardiography

Echocardiograms were recorded using a standard echocardiography machine (Phillips Ultrasound, Netherlands). Standard short axis and long axis views will be obtained from parasternal, apical and subcostal windows. Images were digitally stored, blinded and analyzed on a separate work station by a single certified reader. Left ventricular volumes were computed using the modified Simpson`s rule by manually tracing the endocardial border on end-diastole and end-systole images. All analyses were performed by a blinded physician unaware of the laboratory values or clinical scenario.

Assessment of cardiac parameters using cardiac magnetic resonance imaging (CMR)

Size of myocardial injury was determined by delayed gadolinium enhancement technique using the inversion recovery sequence using an automated border tracking software. Gadolinium DTPA (0.2 mmol/kg) was administered intravenously as a bolus (rates ranged from 2 ml/s to 5 ml/s) and after 15 min, LGE images were obtained using segmented gradient recalled echo inversion recovery (slice thickness: 8mm, gap: 2mm, TE: 3.2 ms, TR: 8.3 ms, flip angle: 25°, Bandwidth:140Hz) in a short axis stack from base to apex with inversion time set to optimally null the myocardium. For each slice, LGE was measured by automated segmentation methods with a threshold of 5 standard deviations (SD) above the signal intensity in the remote myocardium (**Figure 1B**). The total area of the left ventricular wall were manually drawn. The areas were summed for calculation of total left ventricular LGE and left ventricular mass. Size of myocardial damage was defined as total LGE mass and as a percentage of total left ventricular mass (total delayed enhancement mass/total left ventricular wall mass x 100%). Analyses were performed by a physician blinded to patient characteristics. Native myocardial T1-relaxation times was assessed using a modified Look-Locker imaging (MOLLI) sequence (5(3)3, TE: 1.1 ms, TR: 2.7 ms, flip angle: 35°, bandwidth: 1085Hz, field of view: 272x 272 mm, slice thickness:
8 mm, gap: 2mm, 256 matrix with 66 % phase resolution, partial Fourier transform 7/8, GRAPPA 2) in the short-axis stack from base to apex (**Figure 1C**). Global average native myocardial T1 time was assessed as the average T1 time per slice x LV myocardial slice mass / total LV myocardial mass. All analyses were performed by a blinded physician unaware of the laboratory values or clinical scenario.

Assessment of Clinical Outcomes

Patients were followed up for at least 12 months and up to 4 years using outpatient and inpatient records, phone contact and clinic attendance. We defined the combined major adverse cardiovascular events (MACE) as the occurrence of any of the following events during the follow up period: death from any cause, recurrent myocardial infraction, unplanned recurrent revascularization and hospitalization for heart failure.

Laboratory Data

Blood samples were collected in the first 48 hours after admission: at baseline (prior to PPCI) then at 6, 12, 24 and 48 hours after the acute event. All samples were collected into tri- sodium-citrated tubes without stasis and were centrifuged at 2,000 g for 10 min within 30 min of sample collection. Plasma samples were collected into aliquots and stored at -80 °C until batch analysis. Cardiac troponin I levels were determined in plasma samples taken at the

predefined time points using one-step enzyme immunoassay based on electrochemoluminiscence technology in the clinical laboratory using standard techniques (Elecsys; Roche Diagnostics, Basel, Switzerland). Serum samples were used for measurement of NT-proBNP, using a Roche Diagnostic proBNP assay on a Elecsys 2010 analyser (Roche Diagnostics, Mannheim, Germany).

Statistical Analysis

Numerical data are presented as mean ± standard error and compared between two groups using a T test or ANOVA (one way or multiple comparisons) as appropriate. Post hoc multiple comparison procedures (MCP) were performed using 2 sided Dunnett or Dunn tests as appropriate with baseline data as the control category. We used linear regression analysis to compare the levels of NT-proBNP, troponin and cardiac CK, cardiac imaging assessment of LV function and CMR assessment of injury size. Categorical data are presented as number (percent) or as percent ± standard error and compared between two groups using a chi-square test or Fisher's exact test. Kaplan-Meier analyses were performed to explore the associations between NT-proBNP, cardiac troponin I, CK, baseline cardiac function and parameters of cardiac injury by CMR; and major adverse cardiovascular clinical events (recurrent myocardial infraction, unplanned recurrent revascularization and recurrent hospitalization for heart failure) regarded as time-to-event endpoints. A *P* value $\leq$ 0.05 was used as a cutoff for statistical significance throughout the analyses. All statistical analyses were performed using the Graphpad Prism (version 7) statistical software (Graphpad Software Inc., La Jolla, CA).

RESULTS

Patient Population

From January 2014 to June 2016, seventy-five patients with ST-elevation myocardial infarction undergoing PPCI were enrolled in the study. The baseline patient-specific and clinical characteristics-including imaging details, cardiac enzyme levels, measured NT-proBNP and median follow up days- of the study population are reported in ***Table 1***. Study population was relatively young in age with median age of 58 years but had higher percentage of comorbidities such as diabetes (60%), hypertension (34%), hyperlipidemia (47%) and smoking (49%). Of note, patients with renal dysfunction were excluded from the study. Patients were followed up for clinical events for a median of 975 days (IQR 823-1098 days). Due to the long-follow up duration, the study publication was delayed. Our patient population were relatively high-risk with larger MI (peak CK of 2191 ± 275 IU/L and peak troponin 18.6 ± 3.7 ng/ml), with the left anterior descending (LAD) being the culprit artery in 42% of patients.

Table 1: Patient characteristics

	patients
Age (median an IQR)	58 (51-65)
Diabetes (%)	60 ± 0.06
Hypertension (%)	34 ± 0.06
Hyperlipidemia (%)	47 ± 0.06
Smoking (%)	49 ± 0.06
LAD Culprit (%)	42 ± 0.06
Peak CK	2191 ± 275
Peak CK-MB	185 ± 17
Peak troponin 1	18.6 ± 3.7ng/ml
Baseline LVEF	44 ± 1.4
Scar Mass (g)	32.8 ± 4
Scar Size (Percentage of LV mass)	22 ± 0.02
Follow-up (Median and IQR)	975 (823-1098)

All values are presented as mean SEM unless otherwise specified. CK, creatinine kinase; CK-MB, MB fraction of creatinine kinase; LAD, left anterior descending artery; LVEF, left ventricular ejection fraction; STEMI, ST elevation myocardial infarction.

Dynamic Changes in NT-proBNP Levels and Correlation with parameters of Cardiac Damage

Changes in the levels of NT-proBNP are presented in **Figure 1E**. NT-proBNP levels increased after the acute injury, peaking at 24-hours before plateau (P <0.05). This change in NT-proBNP was temporally correlated with the plasma levels of cardiac enzymes (CK and troponin I) but the pattern resembled the troponin I more closely. As expected, CK levels peaked earlier than troponin I following STEMI. Levels of NT-proBNP directly correlated with the degree of cardiac damage assessed through cardiac enzyme measurement and size of myocardial injury on CMR imaging. This correlation holds valid when examining the levels of either creatinine kinase (CK) (R^2 = 0.22, P = 0.01), the levels of troponin I (R^2 = 0.38, P <0.001) and cardiac injury based on LGE on CMR assessment (R^2 = 0.46, P <0.001). We also noted strong correlation between the peak level of NT-proBNP and the global average T1 assessment by CMR (R^2 = 0.14, P = 0.04) (**Figure 2**).

Figure 2.

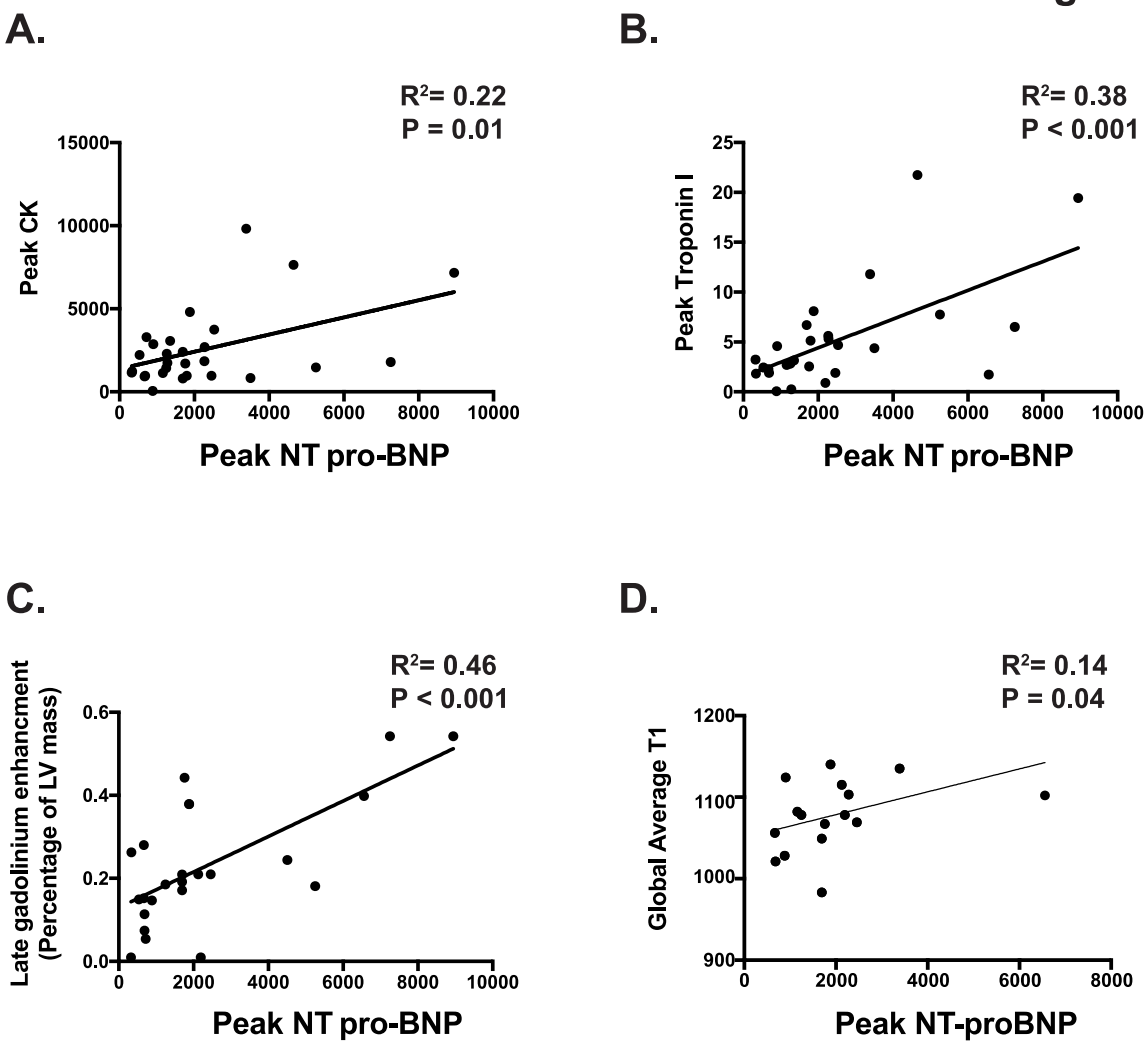

Figure 2 outlines the correlation between peak NT-proBNP levels and various parameters of cardiac damage such as peak CK (**Panel A**), peak Troponin I (**Panel B**), late gadolinium enhancement (defined as percentage of late gadolinium enhancement to myocardial mass) (**Panel C**) and global average T1 mapping (**Panel D**) by CMR.

Peak NT-proBNP Levels Predict Subsequent Adverse Cardiac Events

Myocardial damage as assessed by CMR provides valuable prognostic information in STEMI patients(2). We demonstrated strong correlation between NT-proBNP level and area of LGE and global average T1 mapping on CMR. Therefore, we examined the clinical predictive utility of NT-proBNP in patients with STEMI. Patients with higher level of NT-proBNP had significantly higher rates of MACE during the follow up period (**Figure 3A**). We also noted similar strong predictive value for peak troponin I (**Figure 3B**). Other variables associated with higher MACE were lower baseline LVEF and higher peak troponin levels (**Figure 3C**). Not surprisingly, and in agreement with the available literature, CMR measures of increased myocardial damage such as LGE mass (**Figure 3D**), LGE as percentage of left ventricular area (**Figure 3E**) and

average global T1-relaxation time (**Figure 3F**); were associated with significant increase in the rate of MACE.

DISCUSSION

Patients with STEMI represent a heterogeneous population and methods to identify vulnerable individuals with elevated risk for recurrent clinical events are lacking. In this pilot study, we demonstrate that NT-proBNP levels undergo dynamic changes following ST-elevation myocardial infarction, with a peak serum level observed approximately 24 hours after the acute event. The peak level not only correlated with the severity of cardiac injury but could also serve as a prognostic indicator for major adverse cardiac events. This is the longest follow-up data available on the prognostic value of NT-proBNP levels in patients with STEMI. These findings suggest that monitoring NT-proBNP levels has the potential to identify the highest risk patient population who would benefit from closer follow-up and more aggressive secondary preventive therapies.

Figure 3.

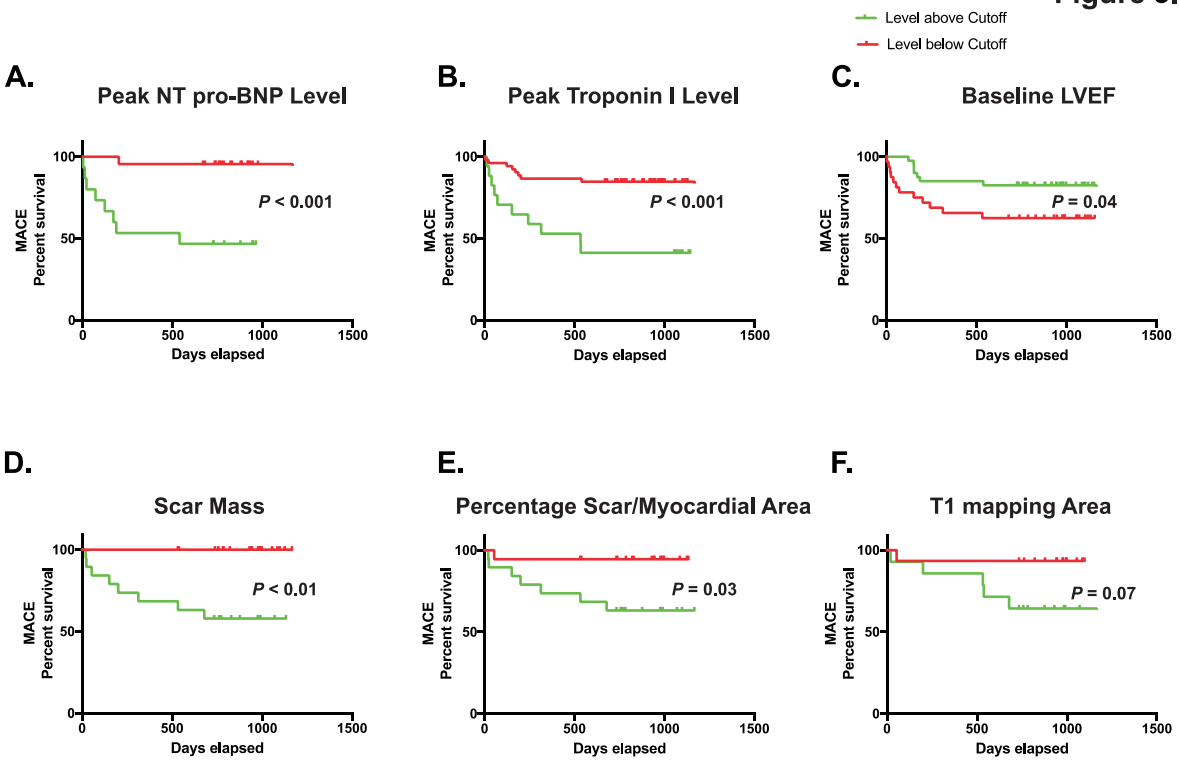

Figure 3 shows the clinical prognostic value of plasma cardiac enzyme level for major adverse cardiac events (MACE). Patients with high NT-proBNP, above the median value of 1882, showed worse event free survival form the primary endpoint compared to those with low peak NT-proBNP (**Panel A**). Similarly, patients with high peak troponin (above the median of 6) showed worse survival compared to those who had lower troponin levels (**Panel B**). On the other hand, patients with lower baseline left ventricular ejection fraction (LVEF) after myocardial infarction demonstrated worse survival compared to those with higher baseline cardiac function (**Panel C**). Patients with higher scar mass (grams), above the mean value of 32.8 grams, showed worse event free survival form the primary endpoint compared to those with lower sc mass (**Panel D**). Similarly, patients with higher scar percentage (above the mean of 22%) showed worse survival compared to those who had lower troponin levels (**Panel E**). Finally, patients with larger T1 average global mapping (above the mean of 1061) showed worse survival compared to those who had smaller T1 average global mapping (**Panel F**).

Traditionally, elevation in NT-proBNP levels has been associated with congestive heart failure (14,15). However, a rise in NT-proBNP is seen in a variety of conditions including acute coronary syndrome, pulmonary thromboembolism, valvular heart disease, atrial fibrillation, sepsis, and renal insufficiency (16,17). This hormone acts to promote natriuresis, diuresis and induce vasodilation (18). The clearance of NT-proBNP occurs primarily in the kidneys and the plasma levels are therefore affected by renal dysfunction. We have excluded patients with chronic kidney disease or renal failure from our study to avoid the variability induced on NT-proBNP levels. Previously, it has been suggested that higher baseline level of NT-proBNP and lack of a rapid decline in hormone levels following PCI were associated with worse short-term prognosis in patients with ACS (19,20). Whereas these studies examined short term outcomes, our study establishes follow-up for a 3-year period following the initial event. Our data suggest that higher NT-proBNP level is linked to worse long-term clinical outcomes with significant increase in MACE as demonstrated by the Kaplan-Meier curves.

Beyond the peak level, our results strongly suggest that NT-ProBNP levels dynamically change following the ischemic injury peaking at 24 hours. Interestingly, the observed change in NT-proBNP over the initial 6 hours is not statistically significant as shown in **Figure 1**. This comes in accordance with previously published data, showing NT-proBNP measurements on admission and at 6 hours to be nearly identical (20,21). Beyond the 6-hour point, the levels of NT-proBNP reflect a statistically, and likely clinically, significant change (**Figure 1**). As demonstrated above, patients with higher peak NT-Pro BNP and statistically significant temporal rise were more likely to experience adverse outcomes over the 3-year follow up period.

Our data suggest that ischemic injury plays a role in NT-proBNP release, although the exact mechanism is not yet defined. This could be explained by NT-proBNP release from necrotic cardiomyocytes and/or obstruction of microvasculature caused by myocardial edema/ischemia. Indeed, our data demonstrate strong correlation between plasma NT-proBNP level and LGE on CMR performed within 48 hours of STEMI. In agreement with our data, previous studies show strong positive correlation between NT-proBNP levels and myocardial damage but negative correlation with myocardial salvage index, assessed by single-photon emission computed tomography, in STEMI patients (22). Additionally, the subsequent development of left ventricular dysfunction could result in the subsequent elevation in plasma NT-proBNP levels. Hence, we can postulate that this dynamic change in NT-proBNP could be caused, at least in part, by infarct expansion and subsequent left ventricular remodeling seen in the recovery phase of ischemia-reperfusion injury.

Post-STEMI adverse cardiac remodeling leads to altered chamber geometry and increased volume in conjunction with compromised ventricular function, eventually leading to heart failure with reduced systolic function and clinical decompensation (23-26). Assessment of myocardial damage predicts future adverse remodeling (27,28), however, clinical assessment in STEMI patients is cumbersome. There are no echocardiographic parameters to predict myocardial salvage after STEMI. Nuclear imaging can provide an estimate of area at risk but it carries multiple logistical and technical difficulties that limit its clinical use in the acute setting.(28) On the other

hand, new CMR techniques such as T1- and T2-weighted imaging mapping could provide valuable direct clinical assessment (29-31) but are technically demanding and difficult to generalize. Conversely, our data suggest that NT-proBNP correlates directly with biochemical and imaging parameters of myocardial damage and edema. Hence, NT-proBNP measurements could represent a practical method of assessing initial myocardial damage and serve as a surrogate for LGE on CMR. Our data is in agreement with prior studies showing NT-proBNP to be an independent predictor of post-infarction LV remodeling, heart failure and/or death (26,32-34) .

This is the longest published follow-up period examining the prognostic implications of NT-proBNP level after STEMI. Visual inspection of the K-M curves suggests that the curves continue to diverge for up to 2 years after the acute event. Higher peak NT-proBNP may reflect an increased likelihood of future LV remodeling and subsequent heart failure and mortality (20,26). This association had been proposed is multiple previous studies, where data show plasma levels of NT-proBNP to correlate with left ventricular end-diastolic volume index (LVEDVI) and left ventricular end-systolic volume index (LVESVI) after cardiac ischemic injury (26,35,36).

Limitations.

While our study is prospective in nature, our center is a tertiary center that receives referrals from a large catchment area. The small number of patients from a single center may affect the generalizability of the results. Our study focused on the initial late gadolinium enhancement on CMR within the first 72 hours after STEMI. Hence, our assessment does not include the final scar size which is typically assessed at 3-6 months after STEMI. Therefore, our CMR parameters included both cardiac infarction and myocardial edema/micro-vascular obstruction.

Conclusions.

We present, for the first time, evidence supporting the dynamic changes in NT-proBNP in patients with ST-elevation myocardial infarction. Accordingly, elevated levels of NT-proBNP after STEMI was highly predictive of the occurrence of major adverse cardiac events after infarction in long-term follow-up. Future studies examining the utility of incorporating NT-proBNP in risk assessment models and therapeutic strategies for patients with myocardial infarction are warranted.

ACKNOWLEDGMENTS

Funding Sources:

Dr. Abdel-Latif is supported by the University of Kentucky Clinical and Translational Science Pilot Award (UL1TR000117) and the NIH Grant R56 HL124266.

The study was partially funded by a research grant from Roche Diagnostics, Mannheim, Germany, which provided the NT-proBNP measurement kits.

Conflict of interest: None. The authors had full access to the data and performed the analysis and written the manuscript independently.

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