The Prognostic Value of Cardiovascular Risk Factors and Laboratory Biomarkers in Predicting 6-Month Outcomes in High-risk Patients with Non-ST Segment Elevation Myocardial Infarction

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ABSTRACT **Background:** Acute coronary syndrome (ACS) represents a spectrum of ischemic myocardial disease including unstable angina (UA), non-ST-segment elevation myocardial infarction (NSTEMI), and ST-elevation myocardial infarction (STEMI). Various prognostic scores were developed for patients presenting with NSTEMI-ACS. Among these scores, the GRACE risk score offers the best discriminative performance for prediction of in-hospital and 6-month mortality. However, the GRACE score is limited and cannot be used in several ethnic populations. Moreover, it is not predictive of clinical outcomes other than mortality.

Objective: To assess the prognostic value of traditional cardiovascular risk factors and laboratory biomarkers in predicting 6-month major adverse cardiac and cerebrovascular events (MACCE), including hospitalization, recurrent percutaneous coronary intervention (PCI), stroke, and cardiovascular mortality in patients with NSTEMI treated with PCI.

Methods: This retrospective study included consecutive patients admitted with an initial diagnosis of NSTEMI to the cardiac intensive care unit (CICU) at the Tzafon Medical Center, Israel, between April 2015 and August 2018 and treated by PCI within 48 hours of admission.

Results: A total of 223 consecutive patients with NSTEMI treated by PCI were included in the study. Logarithm$_e$brain natriuretic peptide (Log$_e$BNP), prior MI, and Hb levels were found to be significant predictors of any first MACCE. Only log$_e$BNP was found to be an independent predictor of a first MACCE event by multivariate logistic regression analysis.

Conclusions: Log$_e$BNP is an independent predictor of worse prognosis in patients with NSTEMI. Routine evaluation of BNP levels should be considered in patients admitted with NSTEMI.

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KEY WORDS: acute coronary syndrome (ACS), Logarithm$_e$brain natriuretic peptide (Log$_e$BNP), major adverse cardiac and cerebrovascular events (MACCE), non-ST-segment elevation myocardial infarction (NSTEMI)

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Acute coronary syndrome (ACS) represents a spectrum of ischemic myocardial disease and diagnoses encompassing non-ST-elevation ACS, unstable angina (UA), non-ST-segment elevation myocardial infarction (NSTEMI), and ST-elevation myocardial infarction (STEMI). About three-fourths of ACS patients present with non-ST-segment elevation ACS (NSTE-ACS), with annual prevalence of 750,000 in the United States [1,2]. Various prognostic models were developed to estimate the risk of mortality in patients presented with NSTE-ACS [3-6]. These models were formulated into clinical risk scores. Among these scores, the GRACE risk score offers the best discriminative performance for predicting in-hospital and 6-month mortality. However, the GRACE score is limited and cannot be used in several ethnic populations. Moreover, it is not predictive of clinical outcomes other than mortality [7-9].

The objective of this study was to assess the prognostic value of traditional cardiovascular risk factors and laboratory biomarkers in predicting 6-month major adverse cardiac and cerebrovascular events (MACCE), including hospitalization, recurrent percutaneous coronary intervention (PCI), stroke, and cardiovascular mortality in patients with NSTEMI treated with PCI.

PATIENTS AND METHODS

STUDY DESIGN

This retrospective study included consecutive patients admitted with an initial diagnosis of NSTEMI to the cardiac intensive care unit (CICU) at the Tzafon Medical Center, Israel, between April 2015 and August 2018. All patients underwent PCI within 48 hours of admission. The study was approved by the institutional review board, and it complies with the Declaration of Helsinki in accordance with the International Conference on Harmonisation for Good Clinical Practice guidelines.

Laboratory and clinical data were extracted from electronic medical records. Direct phone calls to the patients were used to collect 6-month MACCE data; and 6-month mortality data were recorded from the database of the Israel Ministry of Internal Affairs.

We recorded baseline demographic (age, sex), clinical (cardiovascular risk factors including hypertension, hyperlipidemia, diabetes mellitus, smoking history), echocardiographic (left ventricular ejection fraction [LVEF]) characteristics, laboratory parameters (white blood cell count and Hb levels on admission, peak brain natriuretic peptide [BNP] and troponin-I levels), and 6-month MACCE (defined as combined outcome of stroke and re-hospitalization for a cardiovascular cause, recurrent PCI and, cardiovascular mortality). Patients were divided into two subgroups based on 6-month MACCE: patients with occurrence of MACCE and patients without MACCE. Subgroups were compared for differences in baseline demographic, clinical, echocardiographic (LVEF), or laboratory characteristic. In addition, we performed logistic regression analysis of several clinical parameters, laboratory parameters, and LV function on echocardiogram to identify relevant predictors of a first MACCE.

STATISTICAL METHODS

Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 22 (SPSS, IBM Corp, Armonk, NY, USA). Baseline characteristics are presented as mean ± standard deviation (SD) or percentages in Table 1. The differences between continuous variables between patients with and without MACCE were examined using an independent-samples *t*-test. Dichotomous variables were analyzed using the chi-square test.

The distribution of peak BNP levels in the cohort was found to be right-skewed. All the BNP values were $\log_e$-transformed

Table 1. Baseline clinical characteristics

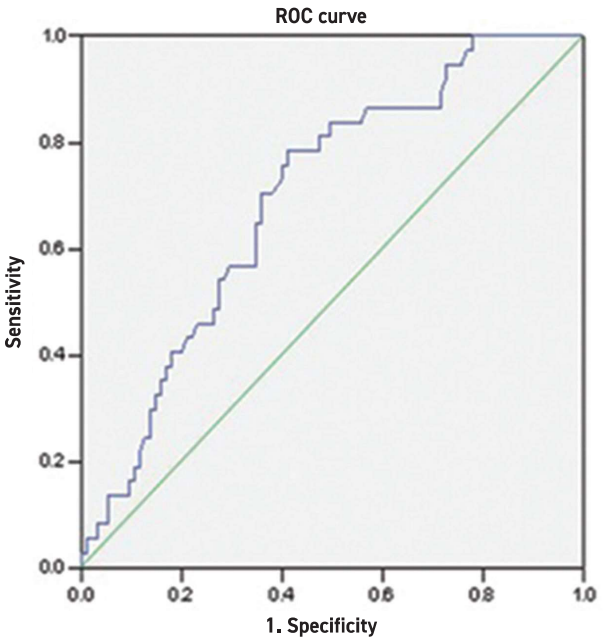
Characteristics	Values
N	223
Age, mean ± SD	63.5 ± 12.1
Male sex, %	72.9
BMI, mean ± SD	29 ± 5
Hypertension, %	66
Diabetes mellitus, %	49.5
Hyperlipidemia, %	66.8
Smoking history, %	76.5
Prior myocardial infarction, %	45.8
GRACE score, mean ± SD	168 ± 45
MACCE, %	29

BMI = body mass index, MACCE = major adverse cardiac and cerebrovascular events, SD = standard deviation

Figure 1. ROC curve for $\log_e$BNP values and Kaplan-Meier curve for 6 months of event-free survival in patients

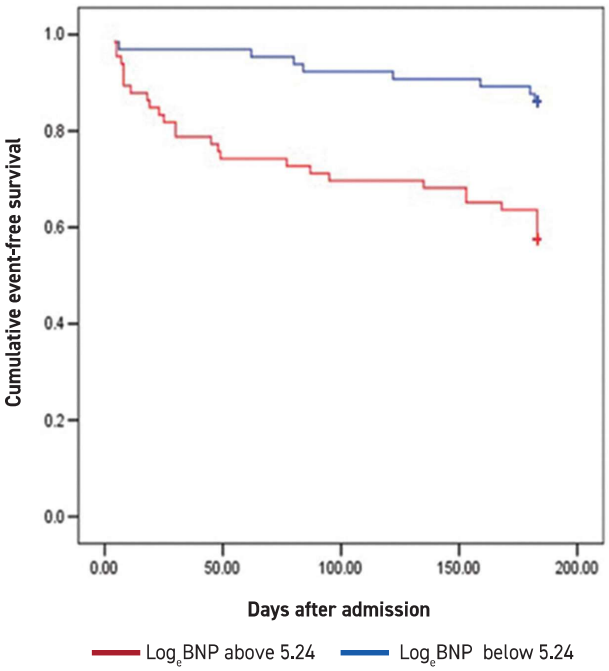
BNP = brain natriuretic peptide, ROC = receiver operating characteristic

[A] ROC curve for $\log_e$BNP values



Diagonal segments are produced by ties

[B] Kaplan-Meier curve for 6 months of event-free survival in patients with $\log_e$BNP above 5.24 vs. in patients with $\log_e$BNP less than 5.24



before statistical analysis.

Cox regression analysis was performed to examine whether cardiovascular risk factors and laboratory biomarkers could predict a first MACCE within 6 months of follow-up. All covariates with univariable statistical significance < 0.175 were included into a multivariable Cox regression model. Backward variable elimination was used to develop the regression model. Variables with adjusted statistical significance < 0.1 were retained in the final model. *P*-value < 0.05 was considered statistically significant. Multivariate Logistic regression analysis was performed to determine independent predictors of first MACCE event.

A receiver-operating characteristic (ROC) curve was calculated for prediction of 6-month MACCE by log_eBNP levels and sensitivity and specificity were computed [Figure 1].

The risk of MACCE at 6 months follow up was estimated using the Kaplan–Meier method, with 95% confidence interval (95%CI). Incidence rates were calculated from life tables. The log-rank test was used to examine differences in MACCE risk between patients with log_eBNP levels below or equal to the cut off value (log_eBNP ≤ 5.24) and above the cut off value (log_eBNP > 5.24) at the 6-month follow-up. Two-sided *P*-value < 0.05 was considered statistically significant.

RESULTS

PATIENT POPULATION

A total of 223 consecutive patients with NSTEMI treated by PCI were included in the study. Basic clinical, laboratory, and echocardiographic characteristics of the cohort are presented in Table 1. The mean age of the patients was 63.5 ± 12.1 years. Most of the patients were male. Most of the patients (76.5%) were current smokers. Two-thirds of the patients presented with hypertension, and two-thirds of the patients were diagnosed with hyperlipidemia. Almost half of the patients had diabetes mellitus and previous history of myocardial infarction (MI).

COHORT OUTCOME

The 6-month mortality and MACCE rate of the cohort were 1.8% and 29%, respectively. The results of comparative analysis of the patients with MACCE and patients without MACCE are presented in Table 2. Patients with MACCE had higher frequency of hypertension and prior MI compared to patients without MACCE (75.8% vs. 61.6%, *P* = 0.045 and 57.4% vs. 40.4%, *P* = 0.025 respectively). In addition, patients with MACCE had higher log_eBNP value (5.9 ± 1.2 vs. 4.9 ± 1.5, *P* > 0.0001). Interestingly, GRACE score was not predictive of 6-month MACCE in our cohort.

The results of Cox regression analysis for possible predictors of the first MACCE are presented in Table 3. Log_eBNP, prior MI, and Hb levels were found to be significant predictors of any first MACCE. However, only Log_eBNP was found to be an independent predictor of first MACCE event by multivariate logistic regression analysis (OR 1.47, *P* = 0.004).

The ROC curve for Log_eBNP values is presented in Figure 1A. The AUC was 0.70 (95%CI 0.60–0.80) when stratified by Log_eBNP. A cutoff of Log_eBNP ≤ 5.24 had a sensitivity of 76% and specificity of 60%.

Table 2. Results of the comparative analysis of clinical characteristics, biomarkers, and left ventricular function between the two study groups

	Patients with MACCE (n=65)	Patients without MACCE (n=158)	*P*-value
Age, mean ± SD	64.8 ± 12.1	62.9 ± 12.2	0.31
Male sex, %	72.3	73.5	0.91
BMI, mean ± SD	29 ± 5	29 ± 5	0.70
Diabetes mellitus, %	57.6	45.9	0.116
Hypertension, %	75.8	61.6	0.045
Hyperlipidemia, %	69.7	65.3	0.47
Smoking history, %	76.4	76.6	0.976
Prior myocardial infarction	57.4	40.4	0.025
GRACE score, mean ± SD	174 ± 49	166 ± 44	0.30
Troponin (mean), ng/L	4044 ± 1154	6998 ± 1194	0.08
Leukocytes, µL/1000	11.12 ± 5.05	11.10 ± 8.66	0.99
LVEF, %	49 ± 11	50 ± 11	0.49
LVEF ≤ 45, %	50	42	0.26
Hemoglobin, g/dl	13.03 ± 2.11	13.61 ± 1.95	0.06
Log_eBNP, mean ± SD	5.9 ± 1.2	4.9 ± 1.5	< 0.0001

BMI = body mass index, BNP = brain natriuretic peptide, LVEF = left ventricular ejection fraction, MACCE = major adverse cardiac and cerebrovascular events, SD = standard deviation

Table 3. Results of Cox regression analysis of possible predictors of the first MACCE

Variable	B	Odds ratio	95% confidence interval	*P*-value
Mean LVEF	-0.08	0.99	0.97–1.01	0.452
LVEF ≤ 45, %	0.320	1.38	0.84–2.25	0.200
Troponin	0.000	1.0	1.00–1.00	0.164
Leukocytes	-0.01	0.1	0.97–1.03	0.971
Hemoglobin	-0.121	0.89	0.79–0.1	0.042
Log_eBNP	0.398	1.49	1.18–1.89	0.001
Hypertension	0.551	1.74	0.1–3.05	0.055
Prior myocardial infarction	0.555	1.72	1.05–2.89	0.032
GRACE score, mean ± SD	0.003	1.00	0.1–1.01	0.263

BNP = brain natriuretic peptide, LVEF = left ventricle ejection fraction, MACCE = major adverse cardiac and cerebrovascular events, SD = standard deviation

The Kaplan–Meier survival analysis [Figure 1B] and log-rank test revealed that Log_eBNP above 5.24 was associated with reduced event-free 6-month survival (58% vs. 86%, chi-square 13.49, $P < 0.001$).

DISCUSSION

In this study of high risk NSTEMI patients, we found that patients with 6-month MACCE had higher frequency of prior MI and hypertension and higher Log_eBNP levels. Moreover, prior MI, Log_eBNP, and hypertension were univariate predictors of any first MACCE. However, only Log_eBNP was found to be and independent predictor of any first MACCE within 6 months.

The correlation of prior MI and higher BNP levels with worse prognosis in patients with NSTEMI was demonstrated by previous studies [10-12]. Previous small studies that investigated the prognostic significance of silent MI in non-acute MI territory was found in cardiovascular magnetic resonance in patients admitted for acute MI. The researchers demonstrated that prior silent MI was independently associated with poorer long-term clinical outcome, including more than 3-fold risk of mortality and MACCE [11]. A large-scale analysis of 2525 patients with ACS recruited to the Orbofiban in Patients with Unstable Coronary Syndromes–Thrombolysis in Myocardial Infarction 16 study, also demonstrated that baseline BNP levels correlated with worse short- and long-term clinical outcomes including mortality and heart failure [12].

The mean BNP level in our patient cohort was at the normal limits (mean Log_eBNP value was 5.2, which corresponds to 181 pg/ml). However, even levels in the normal range were associated with worse 6-month clinical outcomes, so patients with Log_eBNP above 5.24 had almost 30% reduction in 6-month event-free survival.

BNP is secreted from ventricular myocytes in response to increased left ventricular end diastolic pressure or volume. BNP is an established diagnostic and prognostic marker in systolic heart failure. However, the levels of BNP have been shown to be much lower in patients with diastolic heart failure than in patients with systolic heart failure and there was a positive correlation between Left ventricular end-diastolic pressure (LVEDP) measured by left heart catheterization and BNP levels [13].

One plausible biological explanation for higher BNP levels, even in the normal range being associated with worse prognosis in our high risk NSTEMI cohort, is that these higher levels represent increased LVEDP and higher ischemic load. In contrast to previous reports demonstrating adverse outcomes associated with increased troponin and WBC levels, we found no correlation between these laboratory parameters and MACCE [14,15].

Surprisingly there was no correlation between presence of diabetes mellitus and MACCE in our cohort. This finding is contradictory to several previous studies that demonstrated worse prognosis in diabetic patients with NSTEMI [15,16]. One plausible explanation for these finding could be that our cohort included very high-risk patients with mean GRACE score of 168 and very high 6-month MACCE (29 % MACCE) rates, which are much higher than the rate reported in previous studies. [16,17].

Interestingly, low LVEF was not a significant prognostic factor in our cohort of NSTEMI patients. This finding contrasts with findings of two previous contemporary studies demonstrating that reduced LVEF correlated with increased mortality in patients with NSTEMI [18,19]. In the MADDEC study, a large-scale single center retrospective analysis of over 1500 patients admitted with NSTEMI, low LVEF was associated with increased 6-month mortality and had an added value over the GRACE scoring [18]. Previous retrospective analysis of almost 9000 patients with NSTEMI and STEMI in the ACSIS registry demonstrated that low LVEF was an independent risk factor for increased mortality in patients with NSTEMI [19]. One plausible explanation for why we did not find any correlation between LVEF and prognosis could be the high-risk patient profile in our cohort as defined by high GRACE score.

This study has several limitations related to the relatively small cohort size. However, it consists of real-life experience of an academic center, including only high-risk patients admitted to CICU with NSTEMI.

CONCLUSIONS

High BNP level is an independent predictor of any first MACCE and event-free survival within 6 months of hospital discharge in patients with high risk NSTEMI. It may be a marker of increased LVEDP and increased ischemic load, thus dictating more aggressive therapeutic approach. Routine evaluation of BNP levels should be considered in patients admitted with NSTEMI.

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The world is changed not by the self-regarding, but by men and women prepared to make fools of themselves.

Phyllis Dorothy James, Baroness James of Holland Park, OBE, FRSA, FRSL, known professionally as P. D. James (1920–2014), was an English novelist and politician. Her rise to fame came with her series of detective novels featuring Adam Dalgliesh, the police commander and poet.

**People are like stained glass windows: they sparkle and shine when the sun is out,
but when the darkness sets in, their true beauty is revealed only if there is a light within.**

Elisabeth Kubler-Ross (1926–2004), psychiatrist and author

Capsule

Influenza-trained mucosal-resident alveolar macrophages confer long-term antitumor immunity in the lungs

Respiratory viral infections reprogram pulmonary macrophages with altered anti-infectious functions. However, the potential function of virus-trained macrophages in antitumor immunity in the lung, a preferential target of both primary and metastatic malignancies, is not well understood. Using mouse models of influenza and lung metastatic tumors, **Wang** et al. showed that influenza trains respiratory mucosal-resident alveolar macrophages (AMs) to exert long-lasting and tissue-specific antitumor immunity. Trained AMs infiltrate tumor lesions and have enhanced phagocytic and tumor cell cytotoxic functions, which are associated with epigenetic, transcriptional, and metabolic resistance to tumor-induced immune suppression. Generation of antitumor trained immunity in AMs is dependent on interferon-γ and natural killer cells. Notably, human AMs with trained immunity traits in non-small cell lung cancer tissue are associated with a favorable immune microenvironment. These data revealed a function for trained resident macrophages in pulmonary mucosal antitumor immune surveillance. Induction of trained immunity in tissue-resident macrophages might thereby be a potential antitumor strategy.

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