Prognostic Value of Plasma Intermedin Level in Patients With Non-ST-Segment Elevation Acute Coronary Syndrome

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Abstract: Intermedin (IMD), an autocrine/paracrine biologically active peptide, plays a critical role in maintaining vascular homeostasis. Recent research has shown that high plasma levels of IMD are associated with poor outcomes for patients with ST-segment elevation acute myocardial infarction. However, the prognostic utility of IMD levels in non-ST-segment elevation acute coronary syndrome (NSTE-ACS) has not yet been investigated. We hypothesized that the level of plasma IMD would have prognostic value in patients with NSTE-ACS.

Plasma IMD was determined by radioimmunoassay in 132 NSTE-ACS patients on admission to hospital and 132 sex- and age-matched healthy-control subjects. Major adverse cardiovascular events (MACEs), including death, heart failure, hospitalization, and acute myocardial infarction, were noted during follow-up. In total, 23 patients suffered MACEs during the follow-up period (mean 227 ± 118 days, range 2–421 days). Median IMD levels were higher in NSTE-ACS patients than control [320.0 (250.9/384.6) vs. 227.2 (179.7/286.9) pg/mL, P < 0.001]. The area under the receiver-operating characteristic curve for IMD and N-terminal pro-B-type brain natriuretic peptide (NT-proBNP) did not significantly differ (0.73 and 0.79, both P < 0.001). ROC curve analysis revealed a cut-off value for IMD at 340.7 pg/mL. Cox regression analysis with cardiovascular risk variables and NT-proBNP showed that the risk of MACEs increased by a factor of 12.96 (95% CI, 3.26–49.42; P < 0.001) with high IMD levels (at the cut-off value).

IMD has potential as a prognostic biomarker for predicting MACEs in patients with NSTE-ACS.

INTRODUCTION

Non-ST-segment elevation acute coronary syndrome (NSTE-ACS) refers to a spectrum of clinical presentations ranging from non-ST-segment elevation myocardial infarction (NSTEMI) to unstable angina. Each year, NSTE-ACS is responsible for approximately 2.5 million hospital admissions worldwide with an in-hospital mortality rate of approximately 5%. Early risk stratification can help identify high-risk patients who may benefit from early treatment with aggressive antithrombotic treatment, angiography, and coronary revascularization. Intermedin, also called adrenomedullin 2 (ADM2), is a recently defined member of the calcitonin gene-related peptide (CGRP) family which may have a range of biological effects because of its wide tissue distribution and nonselectivity for CGRP family receptors. Animal studies have indicated that intermedin (IMD) plays a critical role in the regulation of blood pressure and cardiac function, acceleration of angiogenesis, and has antiapoptotic functions. Moreover, IMD is involved in the pathogenesis of cardiovascular diseases such as hypertension, atherosclerosis, and vascular calcification. In humans, the plasma concentration of IMD is elevated in various cardiovascular diseases, including acute myocardial infarction (AMI) and ACS. A high transcription level of IMD has also been observed in the leukocytes of patients with chronic heart failure, correlating with clinical severity. A recent clinical trial showed that elevated plasma IMD level is associated with poor outcomes in patients with ST-segment elevation acute myocardial infarction (STEMI), and it has been added as a prognostic indicator to the Global Registry of Acute Coronary Events (GRACE) scoring system.
Biomarkers such as N-terminal pro-B-type brain natriuretic peptide (NT-proBNP) have helped identify patients at risk of poor outcomes and are used to guide therapy. For better stratification, a multimarker strategy has become popular and may be more effective for risk assessment in NSTE-ACS. Thus, new peptides that provide prognostic information, particularly those independent of the abovementioned biomarkers, may be useful additions to a multimarker strategy for identifying patients at the highest risk and who have the most to gain from effective therapies.

The prognostic utility of IMD levels in NSTE-ACS has not yet been assessed, so we analyzed its prognostic performance relative to major adverse cardiovascular events (MACEs) in a cohort of patients with NSTE-ACS and compared its sensitivity to that of NT-proBNP, a peptide of established prognostic value in these patients.

METHODS

Study Population
We recruited 132 NSTE-ACS patients admitted to Aerospace Central Hospital (a training hospital of Peking University, Haidian district, Beijing, China), between March and September 2014 who presented with at least 10 minutes of ischemic symptoms of unstable coronary artery disease and clear signs of myocardial ischemia, such as electrocardiographic changes (ST-segment decrease ≥ 0.1 mV or T-wave inversion ≥ 0.1 mV) or elevated levels of biochemical markers of myocardial necrosis. The exclusion criteria were known malignancy, surgery, or renal replacement therapy in the previous month. All patients received standard medical treatment, and revascularization was at the discretion of the attending physician. Plasma IMD levels were also measured in 132 healthy sex- and age-matched controls, who were given physical examinations at our hospital during the same period. Those with diabetes, hyperlipidemia, liver or kidney diseases, hypertension, and other cardiovascular diseases were excluded. The study complied with the Declaration of Helsinki and was approved by the ethics committees of the hospital and the Peking University Health Science Center; written informed consent was obtained from all patients.

Laboratory Methods
Routine laboratory variables including NT-proBNP, high-density lipoprotein cholesterol (HDLC), low-density lipoprotein cholesterol (LDLC), myoglobin (MYO), creatine kinase MB (CK-MB), and troponin I were measured immediately after taking blood samples by standardized methods. The estimated glomerular filtration rate (eGFR) was calculated using the abbreviated equation for modification of diet in renal disease. Glomerular filtration rate (eGFR) was calculated using the abbreviated equation for modification of diet in renal disease. Glomerular filtration rate (eGFR) was calculated using the abbreviated equation for modification of diet in renal disease.

Radioimmunoassay Determination of IMD Level
Plasma samples were extracted using a SepPak C18 cartridge as described, and were assayed with an IMD radioimmunoassay kit (Phoenix Pharmaceuticals, Belmont, CA). The IC50 of human IMD was 100.10 pg per tube, and the cross-reactivity with human IMD was 100%, with no cross-reactivity between human CGRP and AMD (adrenomedullin).

All biomarker testing was performed by staff who were blinded to the clinical outcomes.

ENDPOINT
The composite endpoint was MACEs, including death, hospitalization for heart failure, and AMI. Patients were individually contacted by telephone, and events were characterized using hospital charts and available outpatient information.

Statistical Analysis
Normally distributed variables are described using mean ± SD and abnormally distributed variables with median (25th and 75th quartiles). Categorical variables are expressed as percentages. Differences between categorical variables were analyzed by \( \chi^2 \) test, and continuous variables by ANOVA. Nonparametric tests were used for abnormally distributed data (Mann–Whitney \( U \) or Kruskal–Wallis test, Wilcoxon signed-rank test and Spearman \( \rho \) correlations). Plasma level of IMD was categorized in tertiles. To evaluate effects over time, we performed Kaplan–Meier analysis according to IMD levels on admission (in tertiles). To compare the prognostic utility of levels of IMD and NT-proBNP, receiver-operating characteristic (ROC) curves were generated and the area under the ROC curve (AUC) was calculated. The cut-off value for IMD level was determined by the maximum value on the Youden index. To assess the relative prognostic accuracy of IMD, a Cox regression model introducing IMD levels as a categorical variable (using the cut-off value) adjusted for normative risk factors (age, sex, body mass index, hypertension, diabetes, hyperlipidemia, family history, current cigarette smoking, and eGFR) and NT-proBNP level (NT-proBNP was log10-transformed; thus, the hazard ratio refers to a 10-fold increase in the level of NT-proBNP). In all tests, \( P < 0.05 \) was considered statistically significant. SPSS 22.0 (IBM, Armonk, NY) was used for analysis.

RESULTS

Patient Characteristics
Patients’ demographic data are set out in Table 1. The study population was 100% ethnic Han Chinese. No patient was omitted from follow-up, whose mean duration was 227 ± 118 days (ranging from 2 to 421 days). During follow-up, 4 (3.0%) patients died, 6 (4.5%) had AMI, and 13 (9.8%) were readmitted to hospital.

Subject IMD Levels
The median plasma level of IMD in patients with NSTE-ACS was 320.0 (range, 73.0–2121.9) pg/mL. Plasma IMD concentration was higher in NSTE-ACS patients than in the control group [320.0 (250.9/354.6) vs. 227.2 (179.7/286.9) pg/mL, \( P < 0.001 \)]. IMD was higher in patients with subsequent MACEs than in MACE-free survivors [380.9 (345.2/470.8) vs. 309.0 (241.2/371.6) pg/mL, \( P < 0.001 \)]. IMD concentrations were lower in patients with hyperlipidemia than in those without (\( P = 0.019 \)), with no difference noted between other subgroups of patients (Table 2). Of the biomarkers NT-proBNP, Troponin I, MYO, and CK-MB, none correlated with IMD (Table 3).

IMD Has Utility as a Predictor of MACEs in NSTE-ACS Patients
Kaplan–Meier analysis of plasma IMD level on admission, with the cohort separated into 3 groups by tertiles (<717.2;
### TABLE 1. Characteristics of the 132 NSTE-ACS Patients According to IMD Levels on Admission

| Demographics | All Patients (n = 132) | IMD Tertiles, pg/mL | P Value |
|--------------|------------------------|---------------------|---------|
| **IMD Tertiles, pg/mL** | 1 (n = 44) | 2 (n = 44) | 3 (n = 44) |
| **Demographics** | 271.2 | 271.2–362.4 | >362.4 |
| Age, yr | 66.67 ± 12.26 | 67.09 ± 11.05 | 65.39 ± 13.45 | 67.55 ± 12.33 | 0.752 |
| Male sex, n (%) | 79 (59.8) | 25 (56.8) | 26 (59.1) | 28 (63.6) | 0.802 |
| Classic cardiovascular risk factors | | | | | |
| Body mass index, kg/m² | 24.86 ± 3.37 | 25.00 ± 2.95 | 24.84 ± 3.57 | 24.75 ± 3.61 | 0.825 |
| Hypertension, n (%) | 77 (58.3) | 27 (61.4) | 26 (59.1) | 24 (54.5) | 0.804 |
| Diabetes, n (%) | 54 (40.9) | 19 (43.2) | 17 (38.6) | 18 (40.9) | 0.910 |
| Hyperlipidemia, n (%) | 59 (44.7) | 27 (61.4) | 17 (38.6) | 15 (34.1) | 0.022 |
| Family history | 18 (13.6) | 6 (13.6) | 7 (15.9) | 5 (11.4) | 0.824 |
| Smoking status | | | | | 0.158 |
| Never smoked, n (%) | 68 (51.5) | 22 (50.0) | 18 (40.9) | 28 (63.6) | 0.802 |
| Ex-smoker, n (%) | 28 (21.2) | 8 (18.2) | 14 (31.8) | 6 (13.6) | 0.802 |
| Current smoker, n (%) | 36 (27.3) | 14 (31.8) | 12 (27.3) | 10 (22.7) | 0.802 |
| Lipid status | | | | | |
| Total cholesterol, mmol/L | 4.07 ± 0.97 | 4.12 ± 0.90 | 4.12 ± 0.99 | 3.97 ± 1.03 | 0.724 |
| LDL cholesterol, mmol/L | 2.22 ± 0.75 | 2.25 ± 0.74 | 2.25 ± 0.79 | 2.15 ± 0.73 | 0.775 |
| HDL cholesterol, mmol/L | 0.76 (0.65/0.88) | 0.76 (0.68/0.86) | 0.76 (0.65/0.90) | 0.76 (0.62/0.89) | 0.850 |
| Triglycerides, mmol/L | 1.34 (1.01/1.94) | 1.40 (1.06/2.07) | 1.35 (0.96/1.97) | 1.32 (1.10/1.72) | 0.906 |
| Blood glucose, mmol/L | 6.37 (5.29/9.19) | 6.94 (5.20/10.64) | 6.02 (5.25/7.21) | 7.23 (5.31/9.92) | 0.211 |
| Cardiac status | | | | | |
| Diastolic dysfunction, n (%) | 67 (50.8) | 24 (54.5) | 24 (54.5) | 19 (43.2) | 0.469 |
| Left-ventricular EF <50%, n (%) | 21 (15.9) | 5 (11.4) | 6 (13.6) | 10 (22.7) | 0.304 |
| Medication | | | | | |
| Beta-blocker, n (%) | 14 (10.6) | 5 (11.4) | 5 (11.4) | 4 (9.1) | 1.000 |
| Statin, n (%) | 30 (22.7) | 8 (18.2) | 12 (27.3) | 10 (22.7) | 0.596 |
| ACE inhibitor or ARB, n (%) | 34 (25.8) | 8 (18.2) | 15 (34.1) | 11 (25.0) | 0.231 |
| Calcium antagonists, n (%) | 26 (19.7) | 10 (22.7) | 10 (22.7) | 6 (13.6) | 0.465 |
| Aspirin, n (%) | 15 (11.4) | 4 (9.1) | 4 (9.1) | 7 (15.9) | 0.508 |
| Biomarkers | | | | | |
| NT-proBNP, ng/L | 74.50 (13.25/521.50) | 139.00 (24.65/366.75) | 32.00 (6.75/327.75) | 79.00 (13.25/1044.75) | 0.367 |
| Troponin I, ng/mL | 0.030 (0.004/0.150) | 0.035 (0.004/0.160) | 0.010 (0.004/0.090) | 0.060 (0.005/0.168) | 0.362 |
| MYO, ng/mL | 98.50 (61.43/148.45) | 91.35 (51.28/193.20) | 99.40 (65.75/148.45) | 96.50 (57.80/137.93) | 0.868 |
| CK-MB, IU/L | 12.45 (9.73/16.73) | 11.80 (9.75/16.73) | 11.80 (8.48/14.78) | 14.00 (10.80/20.70) | 0.062 |
| Creatinine, umol/L | 73.95 (63.13/91.05) | 73.40 (58.53/99.10) | 74.45 (66.70/87.63) | 73.95 (63.18/86.52) | 0.797 |
| Clinical data at admission | | | | | |
| Systolic blood pressure, mm Hg | 128.87 ± 15.27 | 127.89 ± 17.07 | 130.07 ± 14.07 | 128.66 ± 14.76 | 0.796 |
| Diastolic blood pressure, mm Hg | 76.49 ± 12.10 | 75.73 ± 11.09 | 78.82 ± 12.65 | 74.93 ± 12.42 | 0.284 |
| MACEs | 23 (17.4) | 4 (9.1) | 5 (11.4) | 14 (31.8) | 0.008 |

Data presented are number (%) of patients, mean ± SD for symmetric variables, or median (25th/75th centiles) for skewed variables. The tests performed were one-way ANOVA analysis of variance for symmetric variables, Kruskal–Wallis for skewed variables, and χ² test or Fisher exact test for categorical variables.

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; CK-MB = creatine kinase MB; EF = ejection fraction; eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; IMD = intermedin; LDL = low-density lipoprotein; MACEs = major adverse cardiovascular events; MYO = myoglobin.
271.2–362.4; >362.4 pg/mL), identified patients at low, medium, and high risk of MACEs (log-rank test: 10.10, \( P = 0.006 \)), with early separation of the survival plot (Figure 1). A threshold effect was apparent, because the risk of MACEs was broadly similar in patients of the 2 lower 2 tertiles of IMD level, while a significantly increased risk was noted in subjects belonging to the upper tertile. The AUCs for the IMD and NT-proBNP levels were 0.73 (95% CI, 0.62–0.85, \( P < 0.001 \)) and 0.79 (95% CI 0.68–0.91, \( P < 0.001 \)) respectively, with no significant difference between the AUCs (\( P = 0.946 \)) (Figure 2). ROC curve analysis with determination of the Youden index for the follow-up time revealed a cut-off value of 340.7 pg/mL, with a sensitivity of 82.6% and specificity of 64.2%, a negative likelihood ratio of (LR–) of 0.27 and a positive likelihood ratio (LR+) of 2.31.

High IMD (>340.7 pg/mL) NSTE-ACS subjects had an adjusted hazard ratio for MACEs of 12.96 (95% CI, 3.26–49.42; \( P < 0.001 \)) (Table 4). The correlation between IMD level and risk of MACEs was independent in the overall sample (Table 4).

**TABLE 2.** Comparison of IMD Levels in Different Patient Subgroups

| Subgroup                        | Median IMD (pg/mL) | \( P \) Value |
|---------------------------------|-------------------|---------------|
| MACEs vs. MACEs free            | 380.9 vs. 309.0    | <0.001        |
| Male vs. female                 | 324.0 vs. 314.9    | 0.317         |
| Hypertension vs. no hypertension| 316.2 vs. 324.0    | 0.868         |
| Diabetes vs. no diabetes        | 322.1 vs. 319.7    | 0.886         |
| Hyperlipidemia vs. no hyperlipidemia | 292.1 vs. 342.9 | 0.019         |

IMD = intermedin; MACEs = major adverse cardiovascular events.

**DISCUSSION**

IMD is an autocrine/paracrine biologically active peptide, identified independently in 2004 by 2 groups of researchers.\(^{21,22}\) It is expressed in a wide range of tissues including the gastrointestinal tract, submaxillary gland, lungs, skin, cardiovascular and renal systems, hypothalamus, pituitary gland, placenta, pancreas, spleen, thymus, uterus, and ovaries.\(^{21–24}\) Notably, it is present in endothelial cells and is up-regulated in stressed myocardial cells.\(^{9,24–26}\) Since its discovery, IMD has attracted interest in cardiovascular research because of its multiple cardiovascular biological functions, which include induction of vasodilation and hypotension,\(^{21,24,27}\) increasing cardiac perfusion,\(^{28}\) and stabilizing endothelial barriers,\(^{29}\) attenuating myocardial infarction through activation of autophagy,\(^{30}\) as well as lowering serum LDL-C and total cholesterol levels.\(^{31}\)

This study assesses the prognostic utility of IMD levels in a prospective observational cohort of NSTE-ACS patients at a single center. The plasma level of IMD was higher in NSTE-ACS patients than in healthy controls. Plasma IMD levels were higher in patients with subsequent MACEs than without and were lower in patients with hyperlipidemia than in those without. Moreover, survival analysis showed that IMD level was an independent predictor of MACEs with a prognostic accuracy comparable to that of NT-proBNP level. The risk of MACEs in NSTE-ACS patients with high levels of plasma IMD increased 12.69-fold (with a cut-off value set at 340.7 pg/mL).

Several clinical studies have focused on the role of IMD in human cardiovascular diseases. Plasma IMD level has been found to be markedly elevated in ACS patients and correlative to BNP and CK-MB levels and Gensini scores, which reflect the severity of coronary stenosis.\(^{11}\) Plasma IMD levels were elevated in patients with stable coronary heart disease and AMI, and were higher in AMI patients with stenotic lesions \(\geq 75\% \) in all 3 coronary branches than in those patients with this level of lesions in just 1 or 2 coronary branches.\(^{10}\) Another prospective

**TABLE 3.** Correlation Between IMD Concentrations and Other Biomarkers

| Correlations | \( r_s \) | \( P \) Value |
|--------------|---------|-------------|
| NT-proBNP    | 0.032   | 0.719       |
| Troponin I   | 0.053   | 0.545       |
| MYO          | 0.027   | 0.757       |
| CK-MB        | 0.157   | 0.072       |

Data are Spearman correlation coefficients.

CK-MB = creatine kinase MB; MYO = myoglobin.

**FIGURE 1.** Kaplan–Meier plot of cumulative MACEs rates associated with IMD levels. IMD = intermedin; MACEs = major adverse cardiovascular events.
study of 128 STEMI patients showed that elevated plasma IMD level is an independent predictor of 6-month MACEs, with a predictive value similar to GRACE scores. In the present study, plasma IMD level was significantly elevated in NSTE-ACS patients. Higher levels of IMD were observed in patients who went on to present with MACEs than in those who were MACE-free throughout the follow-up period. Plasma IMD level retains its independent prognostic accuracy even after adjustment for NT-proBNP level and other normative risk factors in NSTE-ACS. IMD appears to play an important role in the progression of coronary heart disease and the plasma level may reflect its pathophysiologic roles in the natural course of coronary heart disease as well as correlating to the severity of the disease.

We found lower IMD levels in patients with than without hyperlipidemia. This finding agrees with earlier studies showing that IMD treatment can modify serum lipid profiles, decreasing serum total cholesterol and LDL-C levels and increasing the level of HDL-C, as well as it can reduce LDL uptake and intracellular cholesterol content in macrophages. The lower IMD levels in hyperlipidemic patients could be an indication of the beneficial effects of IMD on the lipid metabolism. However, plasma IMD and its receptor components are found elevated in hypercholesterolemia rats. This contradiction may be due to the course of hypercholesterolemia. In the early stage, up-regulated IMD may protect against hypercholesterolemia; with the progression of the disease, the secretion of IMD may somehow be impaired. Further studies are needed to better understand the role of IMD in hypercholesterolemia.

Unlike BNP, the primary source of plasma IMD remains unclear. Although there are studies demonstrating that IMD is involved in the gene expression of BNP in cardiac tissue, how IMD affects plasma BNP is not addressed yet. Study of Yuan et al found up-regulated gene expression of BNP in spontaneously hypertensive rats when given exogenous IMD. That may be a secondary response to the antidiuretic effect of IMD and synergize the cardioprotective effect of IMD. While another study showed that IMD significantly decreased BNP expression in heart of hypertrophic mouse and improved cardiac functions. In this study, we did not find any correlation between IMD and biomarkers of myocardial necrosis (troponin I, MYO, or CK-MB) or hemodynamic stress (NT-proBNP). This finding is consistent with that of Lv et al for AMI but contradicts that of Qin et al for ACS. However, these studies were conducted in a variety of clinical settings and with different criteria for inclusion and exclusion. It should also be noted that other mechanisms, beyond cell injury and hemodynamic stress, may be causative in the elevated levels of IMD in NSTE-ACS.

Our study has some limitations. First, this was a single-center study with very small cohort. Second, the incidence of MACEs was low in our NSTE-ACS population, and the follow-up period relatively short, thus our data may not fully reflect the prognostic utility of IMD levels over the longer term. Third, in this study the biochemical indicators of healthy controls were in the normal range, and subjects presenting with hypertension, diabetes, hyperlipidemia, liver or kidney diseases, and cardiovascular diseases were excluded, with the result that detailed parameters were not established. One further limitation is that some polymorphisms linked to endothelial dysfunction and

| TABLE 4. Multivariate Cox Proportional Hazards Regression Model of MACEs |
|---------------------------------|-----------------|-----------------|-----------------|
| **Risk Factors**               | **Hazard Ratio** | **95% Confidence Interval** | **P Value** |
| Age                            | 0.99            | 0.94–1.04       | 0.709          |
| Male                           | 1.39            | 0.53–3.61       | 0.502          |
| BMI                            | 1.00            | 0.84–1.20       | 0.968          |
| Hypertension                   | 0.62            | 0.23–1.66       | 0.338          |
| Diabetes                       | 1.50            | 0.59–3.81       | 0.400          |
| Hyperlipidemia                 | 0.85            | 0.27–2.70       | 0.778          |
| eGFR                           | 1.00            | 0.98–1.01       | 0.734          |
| Current cigarette smoking      | 3.13            | 1.19–8.19       | 0.020          |
| Log_{10} NT-proBNP             | 3.50            | 1.91–6.39       | <0.001         |
| IMD levels >340.7 pg/ml        | 12.69           | 3.26–49.42      | <0.001         |
| Family history                 | 2.45            | 0.58–10.35      | 0.224          |

The model was adjusted for age; sex; BMI = body mass index; hypertension; diabetes; hyperlipidemia; current cigarette smoking; eGFR = estimated glomerular filtration rate and log_{10} NT-proBNP.
CAD, such as CaMK4 (calmodulin-dependent protein kinase 4), PIA2 (phospholipase A2), and GRKs (G protein-coupled receptor kinases) are not discussed.

CONCLUSION

In summary, we found elevated plasma IMD levels in NSTE-ACS patients. NSTE-ACS patients with subsequent MACEs were found to have higher IMD plasma concentrations than those whose follow-up periods were MACE-free, while the risk of MACEs increased 12.96-fold in NSTE-ACS patients presenting with high IMD plasma levels (at the cut-off value of 340.7 pg/mL). IMD level could thus be a useful additional prognostic tool in cases of NSTE-ACS.

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