C-reactive protein as a predictor of malignant ventricular arrhythmias in non-ST elevation myocardial infarction

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Abstract

Objective To investigate whether C-reactive protein (CRP) is a biomarker of malignant ventricular arrhythmias (MVA) occurring in non-ST elevation myocardial infarction (NSTEMI) patients with Global Registry of Acute Coronary events (GRACE) scores < 140.

Methods A total of 1450 NSTEMI patients were included in this study. Hs-CRP blood levels were measured via a turbidimetric immunoassay after confirming the diagnosis of NSTEMI with GRACE scores < 140.

Results Consistent with prior studies, the MVA occurrence rate in our cohort was 6.7%, and patients with MVA exhibited a reduced left ventricular ejection fraction (46.1% ± 6.9% vs. 61.5% ± 8.7%, P = 0.032), a higher incidence of Killip classification > 1 (34.1% vs. 24.2%, P < 0.001), an increased surgical revascularization rate (34.1% vs. 9.7%, P < 0.001), and increased mortality (16.5% vs. 5.8%, P < 0.001). Serum hs-CRP levels were higher (P = 0.003) in NSTEMI patients with MVA, and this increase appeared unrelated to other clinical parameters. The C-statistic to discriminate MVA was 0.82 (95% CI: 0.74–0.89). Using receiver operating characteristics analysis, we optimized a cutoff point of 16 mL/L, and the sensitivity and specificity were 95% and 61%, respectively; the positive predictive value was 20% and the negative predictive value was 99%.

Conclusions An hs-CRP assay is a potential MVA biomarker in low-risk NSTEMI patients with GRACE scores < 140. If validated in prospective studies, hs-CRP may offer a low-cost supplementary strategy for risk stratification for NSTEMI patients.

Keywords: Biomarker; C-reactive protein; Myocardial infarction; Ventricular arrhythmias

1 Introduction

Acute myocardial infarction (AMI) is frequently complicated by life-threatening malignant ventricular arrhythmias (MVAS) caused by severe metabolic and electrophysiological changes at the time of coronary obstruction.[1] All AMIs are subdivided into ST elevation myocardial infarctions (STEMI) and non-ST elevation myocardial infarctions (NSTEMI). The incidence of MVAs in AMIs is reported to be between 2% and 20%, with much higher frequency in patients with STEMI compared with those with NSTEMI.[2,3]

STEMI patients are a particularly high-risk cohort that demonstrate clear benefit from immediate revascularization with primary percutaneous coronary intervention (PCI) to reduce the complications of AMI. In contrast with STEMI patients, NSTEMI patients represent a heterogenous population with difficult risk stratification at presentation. Current guidelines recommend early intervention (< 24 h) for high-risk NSTEMI patients [as defined by a Global Registry of Acute Coronary Events (GRACE) score > 140];[4] a delayed interventional strategy (24–72 h) is considered reasonable for low-risk NSTEMI patients (GRACE score < 140).[5] However, the current scoring system (GRACE score) for risk stratification of NSTEMI patients leaves uncertainty about the risk of MVAs. Several studies found the rate of MVAs in large NSTEMI cohorts to be as high as 2.1%–7.6%. There is no agreed-upon method to assess the risk of MVAs in low-risk NSTEMI patients. Therefore, many hospitals admit all patients with low-risk NSTEMI to hospital units with continuous electrocardiographic and hemodynamic monitoring at a substantial cost. A method to further risk stratify for MVA occurrence in low-risk NSTEMI patients could lead to substantial cost savings and improved patient care.

Many studies have found a mechanistic link between inflammatory processes and the development of atherosclerosis.[6] One study demonstrated that C-reactive protein (CRP), a marker of inflammatory activity, is related to atherosclerotic progression and cardiovascular events.[7]
Other studies have shown that CRP levels positively correlated with the incidence of adverse outcomes in NSTEMI patients, even after PCI. Furthermore, it has been reported that systemic inflammation is associated with arrhythmia occurrence. Although levels of CRP correlate with the incidence of ventricular arrhythmias in patients with structural heart disease, there are few reports about the relationship between CRP levels and MVA incidence in NSTEMI patients, despite its rate of occurrence in “low-risk” NSTEMI patients.

In this study, we assessed the association between the incidence of MVA and the serum levels of hs-CRP in low-risk NSTEMI patients. Our goal was to determine if the hs-CRP level could predict the incidence of MVA occurrence in this heterogeneous group, enabling additional risk stratification. For instance, hs-CRP levels may assist the clinician in determining which NSTEMI patients may be admitted to a less monitored setting and which should receive angiography as soon as possible.

2 Methods

2.1 Study population

From June 2006 to March 2016, we prospectively evaluated 1450 patients (762 women and 688 men, aged: 51.8 ± 10.6 years) admitted to Anzhen Hospital, Beijing, China with a diagnosis of low-risk NSTEMI (as defined by the 2007 European Society of Cardiology guidelines). The inclusion criteria were: (1) patients received full-dose anticoagulant and antiplatelet therapy on admission; (2) patients did not undergo PCI within 72 h of admission; and (3) Global Registry of Acute Coronary events (GRACE) score < 140. The exclusion criteria included concomitant systemic diseases (cancer/chronic liver disease, sepsis, and other infectious diseases). All patients were monitored with continuous telemetry during hospitalization. The decision as to whether to perform PCI or coronary artery bypass grafting (CABG) was based on the SYNTAX score. MVAs were defined as sustained ventricular tachycardia (VT, defined by the presence of a series of consecutive ectopic ventricular beats at a rate of > 100 beats/min lasting > 30 s or lasting < 30 s but producing hemodynamic compromise); and ventricular fibrillation (VF). Concomitant VT and VF were also considered to be MVAs. Although non-sustained ventricular tachycardia (NSVA) is common after AMI, it was not classified as an MVA. The diagnosis of arrhythmias was confirmed by two experienced senior cardiologists.

This study protocol was approved by the Ethics Committee of Anzhen Hospital and was conducted in accordance with the Declaration of Helsinki. The authors certify that they obtained all appropriate patient consent forms. In the form, the patient(s) gave his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understood that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

2.2 Hs-CRP measurement

We measured hs-CRP within 6 h of the onset of chest pain (pre-MVA) by the turbidimetric immunoassay method. For those patients with confirmed MVA, additional specimens were obtained 4–8 h post-MVA and the third day after diagnosis.

2.3 Statistical analysis

Continuous data are described as the mean ± SD. Differences in those groups with normal distribution were measured by an unpaired t-test with continuous variables and Fisher’s exact test for categorical variables. Multivariate logistical regression analysis was performed to determine the associations between baseline parameters and the incidence of MVA in the low-risk NSTEMI patients. The performance metrics of hs-CRP in the diagnosis of rejection were assessed. Receiver operator curves were generated for each measure, with area under curve estimates interpreted as a measure of the potential utility of each test, and test performance explored for optimal predictive values. Optimal “cut point” were determined as those providing the best balance of sensitivity and specificity to balance false positive and negative findings. Significance was defined as $P < 0.05$. Statistical analyses were performed using SPSS software V 10.0 (SPSS, Inc, Chicago, IL, USA).

3 Results

MVAs were detected in 97 of 1450 low-risk NSTEMI patients (6.7%). There were 52 cases of sustained VT lasting > 30 s in 44 patients and producing hemodynamic compromise in 8 patients, and 45 (46.4% of MVA patients) VF patients. 89 MVA events (91.8%) were recorded within the first 72 h, 8 MVA events (8.2%) were found over 72 h and less than one week after NSTEMI diagnosis. All MVA episodes converted to sinus rhythm, some spontaneously (24 VT patients) or by electrical (All VF and 15 VT patients) or chemical (13 VT patients) cardioversion.

Clinical characteristics of our cohort are shown in Table 1. Patients with and without MVAs exhibited no significant differences in age, gender, diabetes mellitus, coronary artery disease, myocardial infarction, prior history of arrhythmias,
Table 1. Clinical characteristics of the two low-risk NSTEMI groups.

| Patients characteristic | With MVA (n = 97) | Without MVA (n = 1353) | P-value |
|-------------------------|------------------|------------------------|---------|
| Age, yrs                | 52.7 ± 6.8       | 51.8 ± 10.6            | 0.767   |
| Gender                  |                  |                        |         |
| Male                    | 43 (44.3%)       | 645 (47.7%)            | 0.524   |
| Female                  | 54 (55.7%)       | 708 (52.3%)            |         |
| Medical history         |                  |                        |         |
| Hypertension            | 44 (45.3%)       | 485 (35.8%)            | 0.06    |
| Diabetes mellitus       | 29 (29.9%)       | 338 (24.9%)            | 0.28    |
| Coronary artery disease | 27 (27.8%)       | 303 (22.4%)            | 0.217   |
| Myocardial infarction   | 18 (18.6%)       | 245 (18.1%)            | 0.911   |
| Arrhythmias             | 8 (8.2%)         | 98 (7.2%)              | 0.713   |
| Chronic kidney disease  | 17 (17.4%)       | 227 (16.7%)            | 0.849   |
| Prior angioplasty       | 9 (9.3%)         | 198 (14.6%)            | 0.145   |
| Prior CABG              | 6 (6.2%)         | 97 (7.2%)              | 0.716   |
| Killip class on admission |                |                        |         |
| I                       | 64 (65.9%)       | 1028 (75.8%)           | 0.027   |
| II                      | 9 (9.4%)         | 251 (18.8%)            |         |
| III                     | 13 (13.4%)       | 47 (3.4%)              |         |
| IV                      | 11 (11.3%)       | 27 (2.0%)              |         |
| Echocardiography        |                  |                        |         |
| Left ventricular ejection | 46.1% ± 6.9%    | 61.5% ± 8.7%           | 0.032   |
| Left ventricular end-diastolic dimension, mm | 59.5 ± 6.6 | 47.2 ± 7.52 | 0.06 |
| Cardiac catheterization |                  |                        |         |
| Normal angiogram        | 0 (0%)           | 216 (15.9%)            | -       |
| One-vessel disease      | 22 (22.7%)       | 744 (54.9%)            | 0.001   |
| Two-vessel disease      | 55 (56.8%)       | 309 (22.8%)            |         |
| Three-vessel disease    | 20 (20.5%)       | 84 (6.3%)              |         |
| Intervention            |                  |                        |         |
| Percutaneous coronary intervention | 64 (65.9%) | 957 (70.7%) | 0.252 |
| CABG                    | 33 (34.1%)       | 131 (9.7%)             | 0.001   |
| Acute medications       |                  |                        |         |
| Aspirin                 | 97 (100%)        | 1353 (100%)            | -       |
| Clopidogrel/Ticagrelor  | 95 (97.9%)       | 1332 (98.4%)           | 0.697   |
| GpIIb/IIIa antagonist   | 32 (33.0%)       | 465 (34.4%)            | 0.782   |
| Heparin                 | 93 (95.9%)       | 1312 (97.1%)           | 0.548   |
| Beta-blocker            | 87 (90.1%)       | 1271 (93.9%)           | 0.097   |
| Lidocaine               | 2 (3.2%)         | 0 (0%)                 | -       |
| Laboratory values       |                  |                        |         |
| cTnl, ng/mL             | 13.41 ± 5.82     | 11.09 ± 6.31           | 0.061   |
| CRP, mg/dL              | 14.56 ± 4.11     | 8.89 ± 3.41            | 0.003   |
| Leukocyte, ×10⁹·L⁻¹     | 11.61 ± 4.74     | 11.21 ± 4.12           | 0.245   |
| Neutrophil, ×10⁹·L⁻¹    | 9.81 ± 4.91      | 8.32 ± 4.11            | 0.079   |
| Lymphocyte,×10⁹·L⁻¹     | 1.49 ± 0.79      | 1.81 ± 0.91            | 0.043   |
| NLR                     | 8.45 ± 6.56      | 6.11 ± 4.21            | 0.023   |
| K⁺ , mmol/L             | 3.71 ± 0.32      | 3.73 ± 0.29            | 0.245   |
| Na⁺ , mmol/L            | 134.2 ± 1.29     | 135.1 ± 1.19           | 0.324   |
| Cl⁻ , mmol/L            | 103.3 ± 4.13     | 106.2 ± 4.11           | 0.312   |
| Mortality at one month  | 16 (16.5%)       | 79 (5.8%)              | 0.001   |

CABG: coronary artery bypass grafting; CRP: C-reactive protein; NSTEMI: non-ST elevation myocardial infarctions.

chronic kidney disease, prior angioplasty, prior CABG, or blood electrolyte values.

Patients with MVAs exhibited reduced left ventricular ejection fractions (46.1% ± 6.9% vs. 61.5% ± 8.7%, P =
creased, while the mean left ventricular end-diastolic dimension was elevated (59.5 ± 6.6 vs. 47.2 ± 7.52, P = 0.06), though not to a statistically significant degree. Insignificantly increased levels of neutrophil-to-lymphocyte ratios (8.45 ± 6.56 vs. 6.11 ± 4.21, P = 0.023), and more hypertension (45.3% vs. 35.8%, P = 0.06) were also found in low-risk NSTEMI patients with MVAs compared to those without MVAs. Serum hs-CRP levels were significantly increased (P = 0.003) in low-risk NSTEMI patients with MVAs and this increase appeared unrelated to other clinical parameters. Patients with MVAs demonstrated a significantly higher Killip classification than patients without MVA (34.1% vs. 24.2%, Killip class > 1, P < 0.001), and more two- or three-vessel disease (77.3% and 29.1%).

There was no significant differences in the proportion of the probability of cardiac interventional therapy during this admission between groups. However, the number of patients undergoing CABG was significantly higher in the admission between groups. However, the number of patients undergoing CABG was significantly higher in the low-risk NSTEMI cohort, the incidence of life-threatening NSVA, atrial fibrillation (AF) and MVAs (Figure 2). Exploratory analyses were performed in the 97 low-risk NSTEMI patients with MVAs. The admission hs-CRP values of the 97 patients developing MVAs were compared with the values measured 4–8 h after MVA and with non-MVA samples drawn 4–6 h after MVA, and the 72 h post-diagnosis hs-CRP levels of the 97 MVA patients were compared with the 72 h samples of the 97 low-risk NSTEMI patients without MVAs. Hs-CRP levels were increased 4–8 h after MVA when compared with admission values (P < 0.05). The hs-CRP level decreased at 72 h after diagnosis, however it was still significantly higher than the control group (P < 0.05, Figure 3).

The C-statistic for admission hs-CRP to predict MVA was 0.82 (95% CI: 0.74–0.89). Using receiver operating characteristics analysis, we optimized a cutoff point of 16 mL/L, and the sensitivity and specificity were 95% and 61%, respectively; the positive predictive value was 20% and the negative predictive value was 99%. The negative predictive value was high in each subgroup, and sensitivity was higher in Killip I-II and PCI groups when compared with Killip III-IV patients and CABG patients (94% and 100 % vs. 92% and 96%).

### 4 Discussion

The patients in our study with delayed intervention (> 72 h) were low-risk NSTEMI patients (GRACE < 140), this is the first study have paid so much attention to this cohort. Because of this, the incidence of MVA was lower in our study (6.7%) than previously reported (10.5%) in NSTEMI patients of all risk categories.[12] However, even in our low-risk NSTEMI cohort, the incidence of life-threatening MVAs was considerable.

In this study, we found that low-risk NSTEMI patients exhibiting higher levels of hs-CRP and lower left ventricular

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**Table 2. Multivariable regression analysis for malignant arrhythmias.**

| Parameter                        | Odds ratio (95% CI) | P-value |
|----------------------------------|---------------------|---------|
| Killip class on admission        | 1.11 (0.97–1.77)    | 0.039   |
| Left ventricular ejection        | 1.23 (1.01–1.09)    | 0.021   |
| Left ventricular end-diastolic dimension | 1.53 (0.19–12.17) | 0.721   |
| Coronary artery bypass grafting  | 3.61 (1.31–9.71)    | 0.023   |
| TnI                              | 0.97 (0.89–1.09)    | 0.059   |
| Hs-C reactive protein            | 3.98 (1.65–11.23)   | 0.011   |

**Table 3. Performance metrics of the hs-C reactive protein assay for the assessment of MVA in the entire cohort and selected subgroups.**

|                      | Entire cohort | One vessel disease | ≥ One vessel disease | Killip class (I, II) | Killip class (III, IV) | CABG | PCI |
|----------------------|--------------|-------------------|---------------------|---------------------|-----------------------|------|-----|
| N                    | 1450         | 766               | 468                 | 1352                | 98                    | 164  | 1021|
| MVA, n               | 97           | 22                | 75                  | 73                  | 24                    | 33   | 64  |
| C-statistic          | 0.82 (0.74–0.89) | 0.76 (0.66–0.86) | 0.81 (0.72–0.90)    | 0.79 (0.64–0.86)    | 0.88 (0.78–0.95)      | 0.80 (0.72–0.87) | 0.91 (0.86–0.97) |
| Sensitivity          | 95%          | 93%               | 93%                 | 94%                 | 92%                   | 96%  | 100% |
| Specificity          | 61%          | 56%               | 62%                 | 57%                 | 63%                   | 61%  | 64%  |
| Positive predictive value | 20%          | 19%               | 17%                 | 14%                 | 8%                    | 14%  | 17%  |
| Negative predictive value | 99%          | 98%               | 99%                 | 99%                 | 100%                  | 100% | 100% |

CABG: coronary artery bypass grafting; MVA: malignant ventricular arrhythmias; PCI: percutaneous coronary intervention.

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Figure 1. Hs-CRP protein concentrations in no arrhythmias and MVA group. The line represents the median value, the boxes the 25th and 75th percentile, and the error bars represent the 5th and 95th percentiles. Hs-CRP: Hs-C reactive protein; MVA: malignant ventricular arrhythmias.

Figure 2. Hs-CRP concentrations stratified by different arrhythmia types: no arrhythmias, AF, NSVT and MVA. The line represents the median value, the boxes the 25th and 75th percentile, and the error bars represent the 5th and 95th percentiles. AF: atrial fibrillation; Hs-CRP: Hs-C reactive protein; MVA: malignant ventricular arrhythmias; NSVT: non-sustained ventricular tachycardia.

function (higher Killip class or lower left ventricular ejection fraction) were more likely to have MVAs. Others have reported different factors associated with increased risk of MVA in NSTEMI patients, such as coronary artery disease, previous myocardial infarction, chronic kidney disease, etc.\(^{(13,14)}\) None of these factors was consistently observed by us previously or in the current study. NSTEMI patients result in CABG tend to have a higher risk of MVA; in addition, two- or three-vessel disease patients had a higher risk of MVA. This means that the more severe the coronary condition, the higher the risk of MVA.

It has been reported that inflammation plays a significant role in the pathogenesis of AMI.\(^{(15)}\) Previous studies demonstrated that CRP is increased in acute coronary syndromes (angina, NSTEMI, STEMI) and is associated with a worse prognosis.\(^{(16)}\) Elevated CRP levels are associated with greater risk of AF recurrence after electrical cardioversion\(^{(17)}\) and MVA occurrence in implantable cardioverter-defibrillator patients.\(^{(10)}\) In addition, patients with MVAs are more likely to experience higher systemic inflammation.\(^{(18)}\) However, there have been no previous studies investigating the relationship between the prevalence or outcome of low-risk NSTEMI and CRP levels.

Our finding of an association between MVA and low left ventricular ejection fraction is consistent with previous reports,\(^{(19,20)}\) and suggests that patients with larger myocardial infarctions and more severe myocardial damage are at greater risk of MVA occurrence; unfortunately, we could not precisely estimate infarct size by radionuclide myocardial perfusion imaging or magnetic resonance imaging for financial reasons.

The serum level of cTnI has been found to be an excellent indicator of myocardial necrosis, and provides quantitative information with respect to infarct size and prognosis in STEMI patients.\(^{(18)}\) In our study, the mean cTnI did not differ between the patients with and without MVAs. This is not surprising given findings by Giannitsis, et al.\(^{(21)}\) who suggest that correlations between cTnI levels and infarct size are significantly weaker in NSTEMI populations compared to STEMI cohorts.

The association of hs-CRP and arrhythmias in low-risk NSTEMI patients is further strengthened by comparisons of patients with different arrhythmias. The mean hs-CRP was higher in patients with MVAs than in patients with AF or NSVA, and hs-CRP was also higher in AF patients than NSVA patients. These results indicate, that higher stepwise hs-CRP levels were observed in patients with increasingly
aggressive arrhythmias. These results support several previous studies’ findings, the largest of which showed that CRP was higher in patients with persistent AF compared with those with paroxysmal AF. Furthermore, hs-CRP was also elevated 4–8 h after MVA activity when compared with samples obtained at admission, then decreased at 72 h after MVA, though they still were higher than the levels at 72 h in the control group. Interestingly, in patients with AMI, C-reactive protein increases within 4–6 h of symptoms and peaks 2–4 days later. Therefore, whether inflammation is a consequence rather than a cause of MVA cannot be determined by these results.

To our knowledge, there are no previous studies evaluating the performance metrics of hs-CRP for the assessment of MVA in AMI patients. In our study, although the positive predictive value was notably low (about 19%), the negative predictive value was high (about 99%) in the entire cohort and all subgroups. It is likely that the use of a hs-CRP cut point-based screening strategy would be able to rule out the possibility MVA occurrence in NSTEMI patients. However, the samples size is still not large enough to draw a solid conclusion. We will try to recruit more medical centers and collect more samples in this project.

This study is the first to demonstrate that the elevated serum levels of hs-CRP are associated with MVA occurrence in low-risk NSTEMI patients. Hs-CRP may be a potential supplementary biomarker to evaluate the risk of MVA in NSTEMI patients. Furthermore, hs-CRP could be helpful for physicians determining the level of care, monitoring, or even timing intervention during admission for low-risk NSTEMI. This has the potential to reduce healthcare costs and improve resource utilization for this common disease.

4.1 Limitations

In this study, the sample size, while larger than any previous study of hs-CRP for NSTEMI screening, is still modest, especially as there were only 97 patients with MVA in this cohort. In addition, we were unable to regularly collect blood samples, which resulted in some deficiencies in rigorous establishment of timing between CRP concentration and the occurrence of arrhythmic events. Moreover, we failed to monitor patients’ electrocardiogram after discharged from hospital, so we could not follow these patients’ cardiac electrical activity, Even if some of them finally died of sudden death.

4.2 Conclusions

An hs-CRP assay is a potential MVA biomarker in low-risk NSTEMI patients with GRACE scores < 140. If validated in prospective studies, hs-CRP may offer a low-cost supplementary strategy for risk stratification for NSTEMI patients.

Acknowledgments

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