Predictive value of myeloperoxidase to identify high risk patients admitted to the hospital with acute chest pain

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Summary

Background: Myeloperoxidase (MPO) is a highly expressed enzyme due to leukocyte activation, with multiple atherogenic actions, including LDL cholesterol oxidation, and is related to the instability of atherosclerotic plaque. It is a predictor of adverse events in healthy individuals, patients with heart disease or those undergoing chest pain investigations.

Objective: To analyze the contribution of MPO to identify patients with acute chest pain, non-ST elevation ECG and at high risk for in-hospital adverse events.

Methods: Patients presenting acute chest pain and a non-ST elevation ECG, were admitted to the hospital and submitted to serum MPO level measurements and a structured examination protocol.

Results: From a cohort of 140 patients, 49 (35%) were diagnosed with acute coronary syndrome, of which 13 patients (9.3%) were diagnosed with non-ST elevation acute myocardial infarction (AMI) (troponin I >1.0 ng/mL). The best MPO cut-off point for AMI was identified as ≥100 pM using the ROC curve (AUC=0.662; CI 95%=0.532-0.793) revealing elevated sensitivity (92.3%) and negative predictive value (98.1%), however with low specificity (40.2%). In the multivariate analysis, MPO proved to be the only independent variable to diagnose AMI in evolution, with an odds ratio of 8.04 (p=0.048).

Conclusion: In patients with acute chest pain and no ST elevation, high MPO levels upon admission to the hospital are an important tool to predict in-hospital adverse events, with an odds ratio of eight for the diagnosis of AMI. (Arq Bras Cardiol 2007;89(6):341-347)

Key words: Peroxidases/diagnostic use, inflammation mediators, coronary disease/blood, chest pain/diagnosis.

Introduction

Acute myocardial ischemia is one of the main causes of chest pain and accurate identification through the use of structured protocols is of utmost importance to avoid unnecessary hospital admissions and inadequate hospital releases[1-4]. The correct final diagnosis is supported by the type of pain, electrocardiogram (ECG) and release pattern of myocardial necrosis markers (MNM); however, sometimes the use of methods to induce ischemia is required. When initially normal, MNMs should be reanalyzed during subsequent hours for a definite diagnosis. In addition to diagnostic criterium for acute myocardial infarction (AMI), the elevation of these markers is directly related to the incidence of main adverse cardiovascular events, over both the short and long term.

In the atherosclerotic plaque process of onset, progression and vulnerability, several steps are related to the actions of various cells and inflammatory mediators[5,6] which have demonstrated significant diagnostic and prognostic accuracy in various clinical trials related to ischemic heart disease.

Myeloperoxidase (MPO) is an enzyme released by the activation and degranulation of polymorphonuclears in the coronary microcirculation in acute coronary syndromes[7]. In atherosclerosis, MPO is involved in the oxidation of LDL cholesterol[8,9] and the activation of metalloproteinases, participating in the instability and rupture of plaque,[10] interfering in the bioavailability of nitric oxide derived from the endothelium[11], therefore altering vasomotor tonus and certain anti-inflammatory properties. The elevation of MPO has been studied in various clinical trials involving healthy individuals[12], as well as patients with chronic heart disease[13], acute heart disease[14], undergoing investigations for chest pain[15], and heart failure[16], revealing elevated sensitivity and specificity, good accuracy for myocardial necrosis diagnosis and significant prognostic value for main adverse cardiovascular events.

The present study tested the hypothesis that MPO is a significant value-added factor for the diagnosis of acute coronary syndromes and to identify high risk subgroups among patients treated for acute chest pain with non-ST elevation

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electrocardiograms.

Methods

Between July 1 and December 31, 2004, one hundred and forty consecutive patients admitted to the emergency ward presenting chest pain were included in the protocol. Patient inclusion criteria comprised: complaint of acute chest pain (up to 24 hours of evolution), age over 21 years and signature of the free and informed consent form that had been previously approved by the Scientific Commission and the institution's Ethics Committee, in accordance with the Helsinki Declaration. Exclusion criteria included ST elevation on the ECG performed at admission, presence or suspicion of inflammatory or infectious syndrome, presence of neoplasia or the use of drugs known to have relevant action on the immune system.

The patients were submitted to a systematic examination protocol for chest pain investigations. Briefly, this protocol proposed an ECG and MNM measurements upon admission and every 3-6 hours thereafter, two-dimensional echocardiogram, and provocative tests for patients where the presence of necrosis or resting myocardial ischemia were eliminated (treadmill test or myocardial scintigraphy). A coronary angiography (strategy no. 1) was performed within 12 hours of hospital admission on patients who the assistant physician considered to be at greater risk for adverse events, based on analysis of clinical and laboratory data . The number of ECGs as well as MNM measurements varied depending on the pain characteristics, using the following recommendations: at least 3 measurements for presentations of probable angina (strategy no. 2) and at least 2 measurements for patients with improbable angina (strategy no. 3) or definitely not anginous (strategy no. 4). The biochemical analyses of the examination protocol were processed immediately and the results were used to make the clinical decision. Troponin serum level was evaluated using the immunofluorescence assay sold by Dade-Behring, with an analytic sensitivity of 0.1 ng/mL and upper normal limit for the diagnosis of acute myocardial infarction of 1.0 ng/mL. MPO was collected on admission and the samples were frozen and processed at the end of the inclusion period by a single independent biologist who was unaware of the clinical course of the patients. MPO was quantified using the ELISA assay, imported from Oxis Research International, Inc. (Portland, Oregon, USA) after authorization from the *Agência Nacional de Vigilância Sanitária(Brazilian Agency for Sanitation Vigilance)*. The sensitivity of the assay (lowest detection level) is between 0.7 ng/mL and 1.5 ng/mL and the normal values for humans range from 40 ng/mL to 80 ng/mL.

Final Diagnosis - The patients were grouped according to the following diagnoses upon release from the hospital:

- Group 1 – Non-ST elevation acute myocardial infarction (AMI): troponin I elevation (>1.0 ng/mL) at any time during the first 12 hours, with or without a typical CK-MB curve, with or without ST/T modifications, and lack of any other apparent cause of chest pain;

- Group 2 - Unstable Angina: typical chest pain lasting longer than 20 minutes, without elevation of troponin I or CK-MB associated with ST segment depression (>0.1 mV) or inversion of the T wave on the ECG, or positive provocative test for myocardial ischemia or significant coronary artery disease on the coronary angiography performed during hospital admission.

- Group 3 - Not acute coronary syndrome (ACS): chest pain without elevation of troponin I or CK-MB, no ST segment depression (>0.1 mV) or T-wave inversion on the ECG, and no positive provocative test for myocardial ischemia or significant coronary artery disease on the coronary angiography performed during hospital stay.

- Group 4 - Undetermined not AMI: chest pain without elevation of troponin I or CK-MB, no ST segment depression (>0.1 mV) or T-wave inversion on the electrocardiogram, but with no provocative test for myocardial ischemia or coronary angiography performed during hospital stay.

- Group 5 - Undetermined: chest pain with release from the hospital without completing the diagnostic investigation route of MNM measurements, ECG, provocative test for ischemia or coronary angiography.

Material and follow-up costs not covered by the health care plan were paid for by the institution.

Statistical analysis - The Kolmogorov Smirnov test was used to test the sample distribution. Univariate analysis was used to define the study variables, based on simple frequency tables, discrete variable percentages, mean and standard deviation values of the continuous variables. Bivariate analysis was used for the discrete variables using contingency tables, and when indicated, the chi-square and Fisher exact tests. The paired and unpaired Student's t-tests and Mann-Whitney tests were used for the continuous variables. The ROC (Receiver Operating Characteristic) curve was used to determine the best cut-off point for MPO and the parameters of this statistical test were calculated. Logistic regression was used to determine the predictive value of MPO for the diagnosis of in-hospital acute myocardial infarction.

Results

Table 1 describes the demographic data, risk factors for coronary artery disease (CAD) and vital signs upon admission, and table 2 describes the investigations performed and the final diagnoses of the cohort. A little more than half of the patients were male, with elevated prevalence of risk factors such as hypertension (62.8%), diabetes mellitus (27.8%), prior myocardial infarction (27.1%), hypercholesterolemia (54.2%) and report of prior coronary angiography (38.5%). A small number of patients were submitted to coronary angiographies within the first 12 hours (strategy no. 1 = 7.1%) or considered to have a low possibility of ACS (strategy no. 4 = 4.2%). For most of the patients a more thorough chest pain investigation was proposed, with multiple ECGs and MNM measurements (strategy no. 2 =72.1%).

There were no deaths during the hospital phase. At the end of the investigation, thirteen (9.3%) of the one hundred and forty patients evaluated were diagnosed with AMI, in accordance with the criterium of elevated serum tropinin ≥1.0 ng/mL; and

Table 1 - Demographic data, risk factors and vital signs

Characteristics	Total Cohort (n = 140)
Age ± SD (minimum – maximum), years	63.05 ± 13.9 (34 – 90)
Male gender, n (%)	76 (54.2)
Systemic hypertension, n (%)	88 (62.8)
Diabetes mellitus, n (%)	39 (27.8)
Smoking, n (%)	23(16.4)
Prior AMI, n (%)	38 (27.1)
Prior coronary angiography, n (%)	54 (38.5)
Hypercholesterolemia, n (%)	76 (54.2)
Use of statins, n (%)	38(27.1)
Family history of CAD, n (%)	63 (45.0)
Body mass index ≥30 kg/m², n (%)	24 (17.1)
Systolic BP (mean ± SD) [min – max], mmHg	142.11± 23.29 [100-210]
HR (mean ± SD) [min – max], bpm	73.65 ± 13.84 [48-130]

AMI - acute myocardial infarction; BP - blood pressure; CAD - coronary artery disease; HR - heart rate; n - number of patients; SD - standard deviation.

Table 2 - Investigation strategies and diagnoses upon release

Investigation Strategies	n (%)
Strategy 1	10 (7.1)
Strategy 2	101 (72.1)
Strategy 3	23 (16.4)
Strategy 4	6 (4.2)
Diagnoses upon Release	
Group 1 - Non-ST elevation AMI	13 (9.3)
Group 2 - Unstable angina	36 (25.7)
Group 3 - Not ACS	45 (32.1)
Group 4 - Undetermined not AMI	15 (10.7)
Group 5 - Undetermined	31 (22.1)

ACS - acute coronary syndrome; AMI - acute myocardial infarction; n - number of patients.

36 (25.7%) were diagnosed with unstable angina. For most of the cohort it was possible to eliminate the diagnosis of acute coronary syndrome, even though the diagnosis for close to one quarter of the patients was classified as undetermined.

In this small cohort, it was not possible to establish significant differences in the mean, median or percentile values of the various subgroups, or even in the comparative analysis between the ACS (groups 1 + 2) and the other groups, possibly due to some very elevated maximum values (Table 3).

The MPO cut-off point that generated the best area under the ROC curve (statistic C) (Figure 1) for the diagnosis of AMI was the value of 100pM; an area of 0.662 (CI 95% = 0.532-0.793) was identified.

Analyzing the subgroup diagnosed with AMI, it is observed that twelve of the thirteen patients presented MPO ≥100 pM on admission (Table 4), resulting in sensitivity of 92.3% (CI 95% 66.7% - 99.6%), specificity of 40.2% (CI 95% 32.0% - 48.9%), positive predictive value of 13.6% (CI 95% 8.0% - 22.3%), negative predictive value of 98.1% (CI 95% 89.9% - 99.9%), positive verisimilitude ratio of 1.543 (CI 95% 1.248 – 1.907) and negative verisimilitude ratio of 0.192 (CI 95% 0.029 – 1.274) for this parameter. From the thirteen patients, only six presented positive troponin upon admission, and the other seven presented elevation during the subsequent analyses.

Logistic regression was used to analyze the predictive value of MPO and the main risk factors for coronary disease, so as to determine the final diagnosis of AMI. In the multivariate analysis, only the MPO serum level ≥100 pM upon hospital admission proved to be an independent predictor, with an odds ratio of 8.04 (p=0.048). The other variables, including systemic hypertension, diabetes mellitus, dyslipidemia, smoking, prior history of acute myocardial infarction, obesity, and family history of coronary artery disease, were not identified as independent variables.

No difference was found between the MPO subgroups in relation to the various clinical variables. (Table 4).

Discussion

Depending on the study population, up to 50% of patients presenting chest pain can be admitted to the hospital; however, no more than 20% receive a final diagnosis compatible with some type of coronary disease[1-4]. On the other hand, roughly 4% to 5% of the patients are released without a correct diagnosis, and the presence of acute coronary syndrome is discovered later.

The main MNMs are creatine kinase-MB fraction and troponins, and they add important diagnostic and prognostic information in the evaluation of chest pain and ACS. Nevertheless, many patients with normal ECG and MNM, are later identified as high risk patients for myocardial infarction or coronary syndrome. Allocation in investigation routes, with a higher or lower number of ECGs or MNM measurements, as well as the performance of provocative tests for myocardial ischemia depend on whether or not the examiner believes that an ACS diagnosis is probable, which is consistent with clinical practice and recommendations in medical literature[3,4].

The involvement of mediators and inflammatory reactions is demonstrated in all evolution stages of atherosclerotic plaque, from the initial phases of endothelial dysfunction, to the formation of the atheroma and its rupture[5,6]. MPO could introduce a new significance in the tracking of ACS, since it can express not only the presence of necrosis or ischemia,

Table 3 - Diagnoses upon release and myeloperoxidase values (mean ± SD, median, minimum, maximum and percentiles)

	Mean ± SD	Median	Minimum	Maximum	Percentile		
					25	50	75
Group 1 - Non-ST elevation AMI (n = 13)	233.8 ± 126.3	186.0	98.8	521.4	146.4	186.0	297.8
Group 2 - Unstable angina (n = 36)	220.2 ± 279.0	145.3	39.5	1674.9	74.9	145.3	264.8
Group 3 - Not ACS (n = 45)	273.6 ± 514.5	181.4	0.0	3485.5	70.1	181.4	295.3
Group 4 - Undetermined not AMI (n = 15)	167.9 ± 188.5	88.0	53.5	703.9	59.5	88.0	186.0
Group 5 - Undetermined (n = 31)	159.9 ± 122.8	145.3	0.0	548.4	64.9	145.3	210.6
Groups 1 + 2 (n = 49)	223.8 ± 246.5	173.1	39.5	1674.9	98.2	173.1	277.1
Groups 3 + 4 + 5 (n = 91)	217.5 ± 378.2	145.3	0.0	3485.5	64.9	145.3	233.8

ACS - acute coronary syndrome; AMI - acute myocardial infarction; n - number of patients; SD - standard deviation.

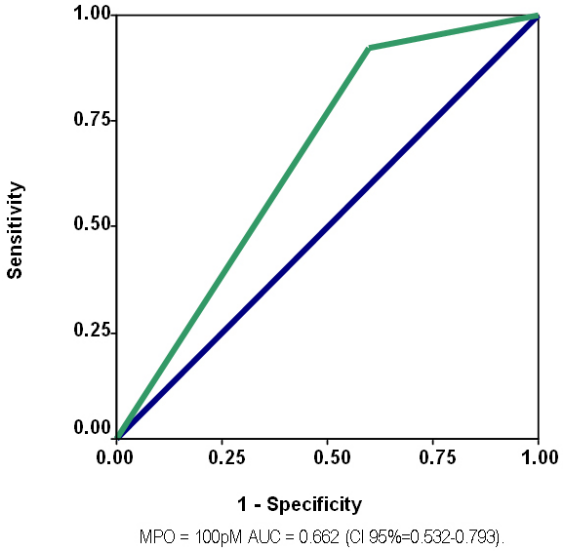

Fig. 1 - *Myeloperoxidase ROC Curve (Receiver Operating Characteristic) for the diagnosis of acute myocardial infarction.*

but also the presence of vulnerable plaque, which enables the identification of patients in the initial stages of the ACS clinical instability process. The involvement of reactions catalyzed by MPO in the early stages of atherosclerosis in vivo has been suggested, based on the detection of MPO[17] and specific markers of the oxidation catalyzed by MPO[18,19] in human atherosclerotic lesions, where it co-localizes[20] itself in the lipid rich macrophages.

The co-localization of MPO and HOCl (hypochlorous acid) modified proteins has also been reported in the subendothelial of culprit plaque in sites of fissure or rupture or even superficial erosion[10,21]. Reduced levels of MPO-generated HOCl released by macrophages in the atherosclerotic plaque activate endothelial cells, leading to the expression and activation of the tissue factor. Higher levels of MPO-generated oxidants promote apoptosis of the endothelial cell. MPO also appears to be involved in the activation of latent metalloproteinases in their active forms[10,22].

In our cohort of consecutive patients admitted for chest pain with no ST segment elevation, MPO was the only independent variable for the final diagnosis of AMI. Patients with serum MPO levels ≥100 pM upon admission, presented a high probability of elevated troponin during the investigation (odds ratio = 8.04; p = 0.048).

The myeloperoxidase cut-off point that generated the best area under the ROC curve for the final diagnosis of AMI was the value of 100 pM, with an area under the curve equal to 0.662 (CI 95% = 0.532-0.793). No difference was found in regard to the main demographic data and coronary disease risk factors among the patients with MPO ≥100 pM or <100 pM, similar to that observed in other studies[14].

Thirteen of the one hundred and forty patients (9.3%) with chest pain and non-ST elevation ECG presented elevation of this marker (troponin >1.0 ng/mL) upon admission (six patients) or in at least one of the subsequent measurements, thus identifying the AMI diagnosis. From these, twelve patients (92.3%) presented MPO ≥100 pM (mean = 233.8 ± 126.3 pM). The sensitivity, specificity, positive predictive value and negative predictive value results should be analyzed carefully due to the size of the cohort. Nevertheless, the high sensitivity (92.3%) of MPO for troponin elevation should be emphasized, since it demonstrates its potential as a new AMI diagnosis marker, assisting particularly in the judicious clinical practice and minimizing the risk of inadequate hospital releases. The high negative predictive value (98.1%) indicates that few patients with negative MPO will present positive troponin.

The results found are in agreement with the main conclusions

Table 4 - Demographic data, vital signs, investigation strategies and final diagnosis according to serum myeloperoxidase level

Variable	MPO <100 pM (n = 52)	MPO ≥100 pM (n = 88)	p Value
Age ± SD, years	64.34 ± 15.27	62.53 ± 13.15	0.48
Male gender, n (%)	24 (46.1)	52 (59.0)	0.095
Systemic hypertension, n (%)	30 (57.6)	58 (65.9)	0.21
Prior myocardial infarction, n (%)	15 (28.8)	23 (26.1)	0.43
Prior coronary angiography, n (%)	21 (40.3)	33 (37.5)	0.43
Diabetes mellitus, n (%)	11 (21.1)	28 (31.8)	0.12
Hypercholesterolemia, n (%)	27 (51.9)	49 (55.6)	0.39
Use of statins, n (%)	15 (28.8)	23 (26.1)	0.43
Family history of CAD, n (%)	26 (50.0)	37 (42.0)	0.23
Smoking, n (%)	8 (15.3)	15 (17.0)	0.49
Body mass index ≥30 kg/m², n (%)	10 (19.2)	14 (15.9)	0.39
Systolic BP (mean ± SD), mmHg	140.65 ± 22.97	142.97 ± 23.57	0.57
HR (mean ± SD), bpm	74.33 ± 15.78	73.25 ± 12	0.67
MPO (mean ± SD), pM	64.62 ± 25.24	312.56 ± 397.18	<0.0001
Investigation Strategies			
Strategy 1, n (%)	4 (7.6)	6 (6.8)	0.54
Strategy 2, n (%)	39 (75.0)	62 (70.4)	0.35
Strategy 3, n (%)	8 (15.3)	15 (17.0)	0.49
Strategy 4, n (%)	1 (1.9)	5 (5.6)	0.38
Diagnosis upon Release			
Group 1 - Non-ST elevation AMI, n (%)	1 (1.9)	12 (13.6)	0.028
Group 2 - Unstable Angina, n (%)	12 (23.0)	24 (27.2)	
Group 3 - Not ACS, n (%)	18 (34.6)	27 (30.6)	
Group 4 - Undetermined not AMI, n (%)	10 (19.2)	5 (5.6)	
Group 5 - Undetermined , n (%)	11 (21.1)	20 (22.7)	

ACS - acute coronary syndrome; AMI - acute myocardial infarction; BP - blood pressure; CAD - coronary artery disease; HR - heart rate; MPO - myeloperoxidase; n - number of patients; SD - standard deviation.

of various authors. The MPO levels in our cohort vary from 0 to 3,485 pM (mean = 219.73 ± 337.14 pM) similar to other series (mean - 198 pM; range between 0 and 4,666 pM)[15].

Subanalysis of the CAPTURE study that tested the use of abciximab, a glycoprotein IIb/IIIa inhibitor, in patients with ACS, revealed that MPO was detected in all patients, with a median value of 1,980.3 pM (range between 10.3 pM and 7,672.8 pM)[14].

In another important series with 604 patients, Brennan et al[15] demonstrated a direct relation between MPO values on admission and the AMI diagnosis, with an odds ratio of 3.7 (CI 95% = 1.6 – 8.5) when comparing the first and fourth population quartiles[15]. These authors also demonstrated that the MPO level on admission is directly proportional to the prognostic value and degree of risk for adverse events within 30 days and 6 months.

The use of new and multiple markers has proven to be reliable in various series and, generally speaking, the higher the number of positive markers the higher the probability of the presence of ACS and a worse prognosis[23-27]. In the prospective trial, Multicentre Biomarker Study, Blankenberg et al[28] analyzed the behavior of various markers in the tracking of chest pain including MPO, myoglobin, troponin I, creatine kinase-MB and B-type natriuretic peptide (BNP)[28]. MPO was the marker that had the earliest elevation and, in patients with presentation between 0 and 3 hours, it demonstrated the best area under the curve when compared with any other isolated marker to identify unstable angina (AUC of 0.92 compared to healthy controls; 0.77 compared with noncardiac pain), or unstable angina and ST-elevation AMI (AUC of 0.88 for controls; 0.71 for noncardiac pain). For the diagnosis of ACS, this MPO performance was only lower than that

exhibited by the multiple marker index, with AUC of 0.94 (in comparison with the controls) and 0.81 (compared with noncardiac pain). In prospective analysis, BNP was the best risk predictor of late mortality. For clinical decision making, these values under the curve are much more significant than the values observed in the present study. In addition, it was not possible to demonstrate a temporal relation of MPO due to the reduced size of the cohort.

Mocatta et al[29] followed 512 patients with AMI (81% with ST elevation) for a period of five years and observed an adjusted death risk 1.8 times higher in patients with elevated MPO (>380 pM)[29].

The analysis of MPO in patients with stable coronary artery disease revealed controversial results. Zhang et al[13] were the first to describe the correlation between serum MPO levels, leukocyte MPO levels and the presence of coronary artery disease[13]. In another series of patients submitted to coronary angiography, the serum MPO levels did not differ between the groups with and without coronary artery disease, suggesting its restricted use for patients with acute symptoms[30]. Other authors considered that MOP is related to the late prognosis of patients with stable angina[28]. More recently, in healthy individuals followed for close to eight years, it was reported that elevated levels of MPO indicate greater future risk of coronary artery disease, even in low risk individuals (LDL cholesterol <130 mg/dL, HDL cholesterol >50 mg/dL or C-reactive protein <2 mg/dL), suggesting that inflammatory activation begins many years before the onset of artery disease[12].

The intensity of the MPO expression influences and alters both the diagnostic accuracy and prognostic value of MPO. The genotype GG for MPO is present in 60% to 66% of the western population and is associated with higher levels of myeloperoxidase than the genotypes AG or AA[31]. Genetic polymorphism studies have identified different individual abilities of expression, observing that patients with low expression present fewer cardiovascular events and higher susceptibility for severe infections[32]. On the other hand, GG homozygotic individuals for MPO submitted to elective coronary angiographies present strong expression and lower survival rates[33].

Our study and results present various limitations. The cohort was obtained in an emergency ward with specific characteristics as it is a private hospital directed mainly at treating clinical and cardiovascular diseases, and treatment therapies are frequently determined by the assistant physician, regardless of the institutional protocol. Additional study limitations include the reduced number of patients, long interval (up to 24 hours) between the onset of symptoms and admission, the low incidence of in-hospital adverse events and the lack of definite diagnosis for part of the sample (groups "undetermined not AMI" and "undetermined") since the investigation was not completed, particularly provocative tests for ischemia.

In conclusion, myeloperoxidase should be regarded as a new marker to evaluate patients with chest pain without ST segment elevation and negative troponin. It has proven to have significant predictive value for adverse events, with elevated sensitivity. When MPO is ≥100 pM on admission, it presents a risk eight times higher for a final diagnosis of acute myocardial infarction. Further trials with patients undergoing chest pain investigations and/or with acute coronary syndromes are required to evaluate the isolated use of MPO as well as its use in association with other markers.

Potencial Conflito de Interesses

Declaro não haver conflito de interesses pertinentes.

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Study Association

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