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Diagnostic evaluation of the MRP-8/14 for the emergency assessment of chest pain

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Abstract

Elevated levels of myeloid-related protein (MRP)-8/14 (S100A8/A9) are associated with first cardiovascular events in healthy individuals and worse prognosis in patients with acute coronary syndrome (ACS). The diagnostic utility of MRP-8/14 in patients presenting to the emergency room with symptoms concerning for ACS is uncertain. MRP-8/14 was measured in serial serum and plasma samples in a single center prospective cohort-study of patients presenting to the emergency room with non-traumatic chest pain concerning for ACS. Final diagnosis was adjudicated by an endpoint committee. Of patients with baseline MRP-8/14 results ($n = 411$), the median concentration in serum was 1.57 $\mu\text{g/ml}$ (25th, 75th: 0.87, 2.68) and in plasma was 0.41 $\mu\text{g/ml}$ (<0.4 , 1.15) with only moderate correlation between serum and plasma ($\rho = 0.40$). A final diagnosis of MI was made in 106 (26%). Peak serum MRP-8/14 was higher in patients presenting with MI ($p < 0.001$). However, the overall diagnostic performance of MRP-8/14 was poor: sensitivity 28% (95% CI 20–38), specificity 82% (78–86), positive predictive value 36% (26–47), and negative predictive value 77% (72–81). The area under the ROC curve for diagnosis of MI with MRP-8/14 was 0.55 (95% CI 0.51–0.60) compared with 0.95 for cTnI. The diagnostic performance was not improved in early-presenters, patients with negative initial cTnI, or using later MRP-8/14 samples. Patients presenting with MI had elevated levels of serum MRP-8/14 compared to patients with non-cardiac chest pain. However, overall diagnostic performance of MRP-8/14 was poor and neither plasma nor serum MRP-8/14 offered diagnostic utility comparable to cardiac troponin.

Keywords

Biomarkers; Unstable angina; Myocardial infarction; Platelets

For patients who present to the emergency department with non-traumatic chest pain, rapid, accurate diagnosis is a clinical priority [1, 2]. Sensitive biomarkers of myocardial necrosis have improved early diagnostic sensitivity and overall accuracy [3]. However, the development of tools to detect processes inherent to plaque destabilization and thrombosis has the potential to complement biomarkers of necrosis and has remained a major objective of biomarker research.

Platelet activation and aggregation are critical steps in coronary thrombosis [4, 5]. Generated from megakaryocytes, platelets lack a nucleus for transcription of new mRNA and rely on already existing mRNA transcripts (the transcriptome) for the life-time of the circulating platelet, generally 7 to 10 days [6, 7]. As a result, platelets cannot activate additional gene transcription in response to a new ischemic event and present a unique opportunity to study gene expression in the days prior to a thrombotic event [8]. Using the platelet transcriptome, Healy and colleagues previously identified the protein MRP-14 (S100A9) as significantly

upregulated in patients presenting with acute myocardial infarction compared with controls with stable atherosclerosis.

In humans, the most abundant form of MRP-14 is the MRP-8/14 (S100A8/A9) heterodimer, also known as calgranulin B, a member of the S100 family of calcium modulated proteins that have significant roles in intra- and extracellular signaling, arachadonic acid metabolism, neutrophil trafficking, and cytoskeletal reorganization [9, 10]. In animal models, MRP-8/14 plays a role in the response to vascular injury, with a significant reduction in leukocyte recruitment in MRP-14-deficient mice [11]. In humans, MRP-8/14 concentration is associated with the risk of first cardiovascular events in apparently healthy women [12] and recurrent events in patients with acute coronary syndrome (ACS) [8]. While an association of MRP-8/14 with cardiovascular prognosis is now reasonably supported, the performance of MRP-8/14 for the diagnosis of ACS has had very limited evaluation. Therefore, we prospectively assessed the diagnostic performance of MRP 8/14 in a cohort of patients presenting to the emergency department with acute non-traumatic chest pain.

Methods

Study design and patient population

We performed a single-center prospective observational study coordinated by the TIMI Study Group among patients presenting to the Brigham and Women's Hospital with non-traumatic chest symptoms suspicious for ACS. A total of 442 patients were enrolled between July 2005 and June 2007. Pertinent inclusion criteria were age $\geq$ 18 years and onset of symptoms within the previous 24 h. Symptoms were defined as either chest symptoms consistent with angina occurring at rest and lasting at least 10 min, or in a clear crescendo pattern culminating in symptoms occurring with minimal exertion. Exclusion criteria were recent hospitalization for ACS within the previous 28 days, known chronic or acute inflammatory disease or infection, or severe renal insufficiency. All subjects provided informed written consent, and the study was approved by the Brigham and Women's Hospital Institutional Review Board.

Blood sampling

Blood samples were collected in serum-separator and EDTA-anticoagulated tubes at enrollment, and serially (if not already discharged) at 4–6, 12–24, and 36–48 h. Serum and plasma were separated within 1 h of sample acquisition and stored at -70°C . Plasma samples were centrifuged at $3000\times g$ for 20 min to obtain platelet poor plasma.

MRP-8/14 testing

MRP-8/14 was measured in both serum and EDTA plasma samples using a commercially available ELISA kit (Buhlmann Laboratories AG, Switzerland) adapted to a Dynex DSX platform (Dynex Technologies GmbH, Denkendorf, Germany). This assay has a dynamic range of 0.4–24 $\mu\text{g/l}$ and performance characteristics showed intra-assay imprecision of 2.0–4.7% at 3.0–6.4 $\mu\text{g/l}$, inter-assay imprecision of 2.5–6.4% at 1.8–9.0 mg/l , and total imprecision $<10\%$ over the entire standard range from 0.4–24 $\mu\text{g/ml}$. In a previously studied

normal population, the median MRP-8/14 and 95th percentile were 0.79 and 2.7 µg/ml for EDTA plasma and 1.14 and 2.9 µg/ml for serum samples, respectively [13].

Adjudication of final diagnosis

Final diagnosis was adjudicated for each patient by a clinical endpoints committee consisting of two independent adjudicators using all available data during the patient's hospitalization, blinded to MRP-8/14 results. If there was disagreement, a third reviewer was consulted. All patients were adjudicated into the following diagnostic categories: acute coronary ischemic events (myocardial infarction, unstable angina); non-coronary acute cardiopulmonary processes; and non-cardiac chest pain.

Statistical analysis

Continuous variables are presented as median (interquartile range) and categorical variables as proportions. *p* values for baseline characteristics were calculated using a Chi-squared test for categorical variables and a Wilcoxon rank-sum test for continuous variables. MRP-8/14 was dichotomized at an a priori cut-point of 3 µg/ml based on the 95th percentile of a normal population. Sensitivity, specificity, and positive/negative predictive values were calculated at each timepoint as well as for peak values. Diagnostic accuracy of the assay was characterized using a receiver operating characteristic (ROC) curve. All analyses were performed using STATA version 9.2 (StataCorp LP, College Station, Texas).

Results

Baseline characteristics

MRP-8/14 was measured in all available samples. Among subjects with baseline MRP-8/14 samples (*n* = 411), 36% were age 65 or older, 62% were male, 17% were smokers, 29% were diabetic, 66% had a history of hypertension, and 65% had a history of hypercholesterolemia. Less than 30% of the cohort had a prior history of MI, and about one third of patient had a history of prior PCI. After final adjudication, 106 patients (26%) were diagnosed with MI, of which 13 (12%) were ST-elevation MI. Patients with elevated MRP-8/14 levels were more likely to be smokers (*p* = 0.002) and had worse renal function (*p* = 0.03). Serum levels of MRP-8/14 were not correlated with renal function (*r* = −0.04). Other clinical characteristics, including age, sex, weight, and cardiovascular risk factors were similar between patients with and without elevated MRP-8/14 at baseline (Table 1).

Distribution of MRP-8/14 concentration

At presentation, the median MRP-8/14 value in serum was 1.57 µg/ml (25th, 75th percentiles: 0.87, 2.68, range <0.4–33) and in plasma was 0.41 µg/ml (25th, 75th percentiles: <0.4, 1.15, range <0.4–29.0). Overall, there was only moderate correlation between serum and plasma levels of MRP 8/14 (*ρ* = 0.40, *p* <0.001). Serum values were consistently higher than plasma results (slope = 0.89 from linear regression). The peak concentration of MRP-8/14 was 2.59 µg/ml (25th, 75th percentiles: 1.53, 3.89, range <0.4–33) in serum and 0.61 µg/ml (25th, 75th percentiles: 0, 1.34, range <0.4–29.0) in plasma. The temporal course of serum MRP-8/14 concentration in patients with three serial measurements is shown in Fig. 1. There was no significant difference in median serum concentration in the baseline

sample of MRP-8/14 when stratifying by time to symptom onset, neither for the serum ($p = 0.20$) nor plasma ($p = 0.27$) samples.

In patients for whom the baseline troponin was negative ($n = 303$ patients at baseline), serum MRP-8/14 at baseline was 1.48 $\mu\text{g/ml}$ (25th, 75th percentiles: 0.80, 2.48, range <0.4–33). Among patients presenting within 6 h of symptoms onset ($n = 115$), serum MRP-8/14 at baseline was 1.60 $\mu\text{g/ml}$ (25th, 75th percentiles: 0.93, 2.75, range <0.4–8.82).

Diagnostic performance (Serum)

Patients who presented with an MI had a significantly higher peak serum concentration of MRP-8/14 (3.44 $\mu\text{g/ml}$ vs. 2.00 $\mu\text{g/ml}$ for non-cardiac, $p < 0.001$). However, baseline concentrations of MRP-8/14 did not differ significantly (1.78 $\mu\text{g/ml}$ vs. 1.37 $\mu\text{g/ml}$, $p = 0.08$), and the overall diagnostic performance of MRP-8/14 for MI alone was poor (Table 2). At presentation, serum MRP-8/14 dichotomized at 3 $\mu\text{g/ml}$ had a sensitivity of 28% (95% CI 20–38), specificity of 82% (95% CI 78–86), a positive predictive value of 36% (95% CI 26–47), and a negative predictive value of 77% (95% CI 72–81). The area under the ROC curve for diagnosis of MI was 0.55 (95% CI 0.51–0.60), compared with 0.95 for cTnI. Use of later timepoints or the peak value only modestly improved diagnostic performance (Table 2). Moreover, when the performance of MRP-8/14 was assessed for the diagnosis of ACS (inclusive of unstable angina), the area under the ROC curve remained poor (0.57, 95% CI 0.51–0.63).

Troponin negative and early presenters

Among the cTnI negative cohort, the sensitivity and specificity of the baseline samples were similar to the overall cohort (Table 3). The negative predictive value was improved (93% vs. 77%). The AUC for diagnosis of MI ranged from 0.53 to 0.61 among the timepoints, indicating poor overall accuracy for diagnosis of MI.

Among early presenters, sensitivity and specificity of MRP-8/14 were 50% (95% CI 26–74) and 84% (95% CI 75–90), respectively, with a negative predictive value of 90% (95% CI 82–95). Overall diagnostic accuracy was slightly improved when compared to the other cohorts, with an AUC of 0.67–0.83.

Use in conjunction with cardiac troponin

We also assessed whether the application of MRP-8/14 in conjunction with cTnI improved the clinical specificity of cTnI for the diagnosis of MI. However, use of MRP-8/14 together with a positive troponin did not meaningfully improve specificity for the diagnosis of MI (67%, 95% CI 29.9–92.5) compared to the overall cohort. Moreover, the addition of MRP-8/14 to cTnI did not significantly impact overall accuracy from 0.92 with cTnI alone to 0.93 ($p = 0.18$).

Diagnostic performance (EDTA Plasma)

MRP-8/14 concentration in plasma did not differentiate patients with a diagnosis of MI at any timepoint (Table 2). There was no utility of plasma MRP-8/14 for diagnosis of MI (baseline AUC = 0.51 (95% CI 0.48–0.53)).

Discussion

Our study demonstrates that in a typical cohort of patients who presented to the emergency room with non-traumatic chest pain, MRP-8/14 did not aid in the diagnosis of MI. Although the peak serum concentration of MRP-8/14 was associated with the presence of MI and delivered a very high negative predictive value (0.95) when coupled with a negative troponin, the overall diagnostic performance was poor with an AUC <0.65. These findings were consistent across multiple pertinent subgroups, including patients with an initially negative cTnI, and patients that presented within six hours of symptom onset.

Our study adds an important negative result to the assessment of pro-thrombotic/inflammatory biomarkers for diagnostic assessment in patients with suspected ACS. The notion of using multiple biomarkers reflecting different pathobiological contributors to ACS has remained conceptually attractive and has proven to enhance risk assessment [14], but to date has failed to substantially enhance *diagnosis*. For example, several biomarkers of inflammatory processes in ACS, including hsCRP, sCD40L, and pregnancy-associated plasma protein-A, have been associated with poor prognosis [15–17] but their diagnostic utility is diminished due to a lack of clinical specificity [18]. MRP-8/14 has been shown in genetic knock-down approaches to reduce vascular inflammation and thrombosis in models of atherosclerosis, vasculitis and restenosis [11], and thus, had the potential to offer greater specificity and diagnostic accuracy than non-specific bio-markers of inflammation. In addition, in a pilot study including 39 patients with ACS, serum MRP-8/14 appeared to offer high discrimination with a sensitivity of 95% and specificity of 92% [19]. Notably, this study was performed with recruitment of selected patients undergoing coronary angiography in a step-wise fashion of separate cohorts over time, in which it is possible that differential sample handling may have contributed to marked elevation of MRP-8/14 in serum samples from patients with ACS. When tested prospectively using the same assay in our larger and more heterogeneous cohort of patients presenting to the emergency department, we found serum MRP-8/14 not to provide robust clinical specificity or sensitivity. Because MRP-8/14 is released by inflammatory cells, including neutrophils and monocytes as well as platelets, it is possible that the lack of specificity observed in our study derives from the inflammatory response to other conditions, particularly in the broader group of patients presenting with non-traumatic chest pain. The search for useful platelet-associated biomarkers for the diagnostic assessment of suspected ACS, reflecting the important interaction between leukocytes and platelets in the initiation, progression, and complications of atherosclerosis, is of great interest [20]. For example platelet-monocyte aggregates detected by flow cytometry have been reported to be helpful in the diagnosis of MI in patients presenting with chest pain [21]. However, flow cytometric-based tests are impractical in the emergency department setting.

MRP-8/14 is expressed in leukocytes (monocytes, neutrophils), platelets, and endothelial cells and capable of being secreted by these cells in response to cellular activation. Others have found MRP-8/14 only within macrophages and granulocytes [19]. However, our group has shown platelets to also be a source [12]. Therefore, the predominant source(s) of MRP-8/14 in plasma is unknown. It is intriguing that serum testing revealed an association with MI, where as plasma testing did not. In serum, the concentration of MRP-8/14 would

be expected to reflect both circulating MRP-8/14 and the ex vivo release from platelet and leukocyte secretion during coagulation. The notion that measurement of the “total” concentration of platelet- and leukocyte-secreted biomarkers in serum may offer information incremental to that from the circulating concentration in platelet-poor plasma may warrant additional investigation for this and other platelet-related biomarkers.

Although newer assays for troponin offer dramatically increased analytical and clinical sensitivity, their clinical specificity has been diminished [22]. We explored conjoint testing of MRP-8/14 as a biomarker of thrombosis along with cTnI as a marker of necrosis with the aim of potentially improving the diagnostic specificity of troponin. However, we found that MRP-8/14 was not useful for this aim due to its poor clinical specificity in this population.

Our present study was not designed to assess the relationship between MRP-8/14 and clinical outcomes. We note that prior work from our group as well as others has demonstrated an independent relationship between MRP-8/14 and cardiovascular outcomes both in individuals at risk for atherosclerosis [12, 23] and those stabilized after ACS [8]. Specifically, we have previously observed that patients post-ACS with MRP-8/14 in the highest quartile had a 2.0-fold increased odds of a recurrent event after adjusting for standard risk indicators, and C-reactive protein [8]. Our present study expands on these findings, indicating that the strongest potential for clinical application of MRP-8/14 is likely to derive from its prognostic associations and not from a diagnostic use in ACS.

Conclusion

Although elevated in patients with MI and delivering a high negative predictive value in conjunction with troponin, MRP 8/14 performed poorly overall as a diagnostic biomarker in patients presenting to the emergency room with chest pain concerning for ACS. Future investigation of this biomarker is likely to focus on its prognostic and possibly therapeutic applications.

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Fig. 1.
Time course of Serum MRP-8/14 in MI

Table 1

Baseline characteristics

Variable	Overall (<i>n</i> = 412)	MRP-8/14 >3 (<i>n</i> = 90)	MRP-8/14 <3 (<i>n</i> = 321)	<i>p</i> value
Demographics				
Age ≥ 65 years (%) (<i>n</i> = 410)	146 (36)	35 (42)	111 (34)	0.19
Male (%)	254 (62)	56 (67)	198 (61)	0.30
Weight (kg), median (IQR) (<i>n</i> = 375)	85.3 (74.4–99.8)	83.9 (72.8–97.5)	86.2 (75.7–99.8)	0.37
Risk factors				
Diabetes mellitus (%) (<i>n</i> = 409)	117 (29)	24 (29)	93 (29)	0.94
Current smoker (%) (<i>n</i> = 410)	70 (17)	24 (29)	46 (14)	0.002
History of hypertension (%)	271 (66)	54 (64)	217 (66)	0.72
History of hypercholesterolemia (%)	266 (65)	54 (64)	212 (65)	0.92
History of MI (%) (<i>n</i> = 410)	118 (29)	23 (27)	95 (29)	0.75
History of PCI (%) (<i>n</i> = 408)	140 (34)	23 (27)	117 (36)	0.13
History of CABG (%) (<i>n</i> = 409)	61 (15)	14 (17)	47 (14)	0.61
History of CHF (%) (<i>n</i> = 410)	39 (10)	11 (13)	28 (9)	0.21
History of PAD (%) (<i>n</i> = 409)	41 (10)	13 (16)	28 (9)	0.06
History of CVA (%) (<i>n</i> = 389)	40 (10)	13 (16)	27 (9)	0.06
Previous CAD (%) (<i>n</i> = 189)	165 (87)	35 (81)	130 (89)	0.19
Creatinine clearance <60 ml/min (%) (<i>n</i> = 354)	56 (16)	18 (24)	38 (14)	0.03
Presentation and treatment				
ECG changes at presentation (%) (<i>n</i> = 405)	95 (23)	23 (27)	72 (22)	0.31
ST segment elevation (%) (<i>n</i> = 405)	24 (6)	5 (6)	19 (6)	0.96
Symptom onset to baseline (h) median (IQR) (<i>n</i> = 355)	8.5 (5.5–14.3)	7.88 (5–13)	8.9 (5.5–14.8)	0.25

Table 2

Diagnostic utility of serum/plasma MRP 8/14

	Sensitivity %	Specificity %	PPV %	NPV %	AUC
Serum—entire cohort					
Baseline	28.3 (20–37.9)	82.3 (77.5–86.4)	35.7 (25.6–46.9)	76.8 (71.8–81.2)	0.55 (0.51–0.60)
4–6 h	48.8 (37.6–60.1)	71.4 (64.7–77.4)	40.4 (30.7–50.7)	77.8 (71.2–83.5)	0.60 (0.54–0.66)
12–24 h	38.7 (27.6–50.6)	76.1 (68.8–82.4)	42.6 (30.7–55.2)	72.9 (65.6–79.5)	0.57 (0.51–0.64)
Peak	58.2 (48.4–67.5)	67 (61.5–72.1)	37.9 (30.5–45.6)	82.2 (77–86.7)	0.63 (0.57–0.68)
EDTA plasma—entire cohort					
Baseline	4.7 (1.6–10.7)	96.4 (93.6–98.2)	31.3 (11–58.7)	74.4 (69.8–78.7)	0.51 (0.48–0.53)
4–6 h	6.1 (2.0–13.7)	97.6 (94.4–99.2)	50 (18.7–81.3)	72.3 (66.6–77.5)	0.52 (0.49–0.55)
12–24 h	10.7 (4.7–19.9)	96.3 (92.2–98.6)	57.1 (28.9–82.3)	70.1 (63.6–76)	0.54 (0.50–0.57)
Peak	10 (5.1–17.2)	95 (92–97)	40.7 (22.4–61.2)	75.3 (70.8–79.5)	0.53 (0.49–0.56)

Table 3

Serum, Troponin negative at baseline, EDTA plasma, Troponin negative at baseline

	Sensitivity	Specificity	PPV	NPV	AUC
Serum, troponin negative at baseline					
Baseline	22.7 (7.8–45.4)	82.9 (78–87.1)	9.4 (3.1–20.7)	93.2 (89.3–96)	0.53 (0.44–0.62)
4–6 h	45 (23.1–68.5)	71.4 (64.4–77.8)	14.3 (6.8–25.4)	92.5 (86.9–96.2)	0.58 (0.47–0.70)
12–24 h	35.3 (14.2–61.7)	75.7 (67.9–82.3)	15.3 (5.43–28.5)	91.1 (84.6–95.5)	0.56 (0.43–0.68)
Peak	54.2 (32.8–74.4)	66.8 (61.1–72.2)	11.8 (6.5–19.4)	94.7 (90.6–97.3)	0.61 (0.50–0.71)
EDTA plasma, troponin negative at baseline					
Baseline	9.1 (1.1–29.2)	96.4 (93.6–98.3)	16.7 (2.1–48.4)	93.1 (89.6–95.8)	0.53 (0.47–0.59)
4–6 h	10 (1.2–31.7)	97.9 (94.7–99.4)	33.3 (4.3–77.7)	91.1 (86.3–94.7)	0.54 (0.47–0.61)
12–24 h	17.6 (3.8–43.4)	97.3 (93.2–99.3)	42.9 (9.9–81.6)	91.1 (85.6–95.1)	0.58 (0.48–0.67)
Peak	16.7 (4.7–37.4)	95.5 (92.5–97.6)	23.5 (6.8–49.9)	93.3 (89.9–95.9)	0.56 (0.48–0.64)