Lack of Diagnostic and Prognostic Utility of Circulating Plasma Myeloperoxidase Concentrations in Patients Presenting with Dyspnea

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BACKGROUND: Serum myeloperoxidase (MPO), an inflammatory biomarker, is associated with increased mortality in patients with acute coronary syndrome or chronic left ventricular systolic dysfunction. We sought to assess the diagnostic accuracy of MPO for acute decompensated heart failure (ADHF) and its prognostic value for patients with acute dyspnea.

METHODS: In a prospective, observational study conducted in 5 US centers, 412 patients [mean (SD) age, 58 (14) years; 39% women] presenting with dyspnea to the emergency department were enrolled and followed for 1 year. Clinical, serum biomarker [MPO, B-type natriuretic peptide (BNP), N-terminal proBNP (NT-proBNP)], and transthoracic echocardiographic data were obtained.

RESULTS: We observed no differences in MPO concentration (P = 0.07) between patients with ADHF [n = 147; median, 553 pmol/L; interquartile range (IQR), 413–738 pmol/L] and those without ADHF (n = 265; median, 576 pmol/L; IQR, 413–884 pmol/L). The diagnostic accuracy for ADHF was excellent for BNP [area under the ROC curve (AUC), 0.90; P < 0.001] and NT-proBNP (AUC, 0.90; P < 0.001) but poor for MPO (AUC, 0.46; P = 0.18). MPO appeared uncorrelated with echocardiographic measures of cardiac structure or function. The observed 1-year mortality rate was 12%. MPO concentration also appeared unrelated to mortality [odds ratio, 1.25 (above vs below the median); 95% CI, 0.71–2.18], whereas BNP (P = 0.001) and NT-proBNP (P < 0.001) were significant predictors of mortality. MPO concentration provided no prognostic information in addition to that of BNP or NT-proBNP concentration.

CONCLUSIONS: Unlike natriuretic peptides, MPO concentration was not predictive of ADHF diagnosis or 1-year mortality in a heterogeneous sample of emergency department patients with acute dyspnea.

Inflammatory mediators that coordinate the innate immune response play key roles in the pathophysiology of coronary disease and heart failure. Myeloperoxidase (MPO) is released from activated neutrophils and monocytes during inflammation and has been identified as a novel inflammatory marker (1). MPO increases the oxidative potential of hydrogen peroxide by generating hydrochlorous acid through the peroxidation of chloride, providing a powerful bactericidal antagonist to a wide range of pathogens.

In coronary artery disease, MPO has been implicated in initiating and propagating atherosclerosis. The enzyme promotes LDL oxidation, which leads to the formation of foam cells, fatty streaks, and atheromas (2, 3). MPO may also increase plaque vulnerability and promote thrombosis (4, 5). Consequently, the serum concentration of MPO has prognostic utility for patients with chest pain or acute coronary syndromes and may serve as an early diagnostic marker in this setting (6, 7). An increased MPO concentration is a predictor of higher mortality after myocardial infarction, independent of left ventricular ejection fraction (LVEF).
and serum N-terminal pro–B-type natriuretic peptide (NT-proBNP) concentration (8).

The role of inflammation and MPO in heart failure is less well defined. It is clear that inflammatory mediators generate reactive oxygen species, which may worsen myocardial function by causing protein dysfunction, fibrosis, nitric oxide depletion, and myocyte apoptosis (9). Serum MPO concentrations are increased in compensated chronic systolic dysfunction, and higher concentrations are predictive of mortality and adverse outcomes, such as the necessity for cardiac transplantation (10, 11). Higher MPO concentrations are also associated with an increased prevalence of severe diastolic dysfunction and right ventricular systolic dysfunction (11). Furthermore, serum markers of oxidative stress are increased in acute decompensated heart failure (ADHF) (12, 13). The purposes of this study were first to investigate the diagnostic and prognostic value of circulating MPO concentrations in patients presenting with dyspnea to the emergency department (ED) and, second, to evaluate the additive prognostic value of MPO concentration in combination with established natriuretic peptide biomarkers and measures of cardiac function.

**Materials and Methods**

**STUDY DESIGN AND PATIENTS**

The study was a prospective cohort study conducted in 5 centers in the US. The research was approved by the institutional review boards of the participating study centers. The study enrolled a convenience sample of 412 patients from May 2003 through December 2006.

Patients were included if they were ≥18 years old and had presented to an ED setting with a primary complaint of dyspnea. We excluded both patients with overt causes of dyspnea, including trauma, pneumothorax, or upper airway obstruction, and patients with acute coronary syndromes. Acute coronary syndrome was defined as a clinical suspicion of cardiac ischemia or infarction accompanied by either (a) an ST-segment deviation of ≥1 mm or (b) a serum troponin concentration increased above the upper limit of the reference interval for the local laboratory. Written informed consent was obtained from all patients enrolled in the study.

A designated study coordinator obtained data from the medical record and by querying patients directly. Pertinent data included demographic information, symptoms, physical examination findings, vital signs, medical history, electrocardiograms, chest x-ray reports, and medication status. Information about the patient’s race was entered if the patient reported it. We used these data to adjust multivariate models of prognosis and to calculate the estimated glomerular filtration rate, which was calculated from the Modification of Diet in Renal Disease equation (14). The patient’s status at the 12-month follow-up was assessed by telephone interview, a review of medical records, and a search of the Social Security Death Index to identify the time to death, if applicable.

**BLOOD SAMPLES AND ASSAYS**

At the time of patient enrollment, 20 mL of blood was collected into glass tubes [EDTA-containing, heparin-coated, and plain (for serum) tubes], centrifuged within 2 h, and stored at −20 °C or colder. The frozen samples were shipped on dry ice to the Core Laboratory at the University of Maryland Medical Center and maintained at −70 °C until measurement. The samples were thawed once in a room-temperature water bath and assayed within 1 h.

MPO in EDTA-containing plasma was measured by immunoassay on the Dimension RxL system (Siemens Healthcare Diagnostics). We carried out a 20-day precision in-house study according to the CLSI EP5-A2 standard and obtained MPO within-run and total imprecision values of 3.8% and 4.8%, respectively, at 428 pmol/L (n = 80) and 3.3% and 3.6%, respectively, at 3643 pmol/L. The detection limit was 13 pmol/L, and the assay was linear to 5223 pmol/L. The concentration of BNP in EDTA-containing plasma was measured with a fluorescence immunoassay kit on a Beckman Coulter Access 2 instrument. The concentration of NT-proBNP in plain serum was measured on a Dimension RxL system with a 1-step immunometric sandwich assay. All blood samples were processed by personnel blinded from any patient data.

NT-proBNP and BNP values were divided into classes that were “negative,” “gray-zone” (intermediate), or “positive” for predicting cardiac dyspnea. For NT-proBNP, the age-based cutoffs for diagnosing heart failure have been established elsewhere (≥450 ng/L for patients <50 years, > 900 ng/L for patients 50–70 years, and >1800 ng/L for patients >70 years). NT-proBNP concentrations <300 ng/L are considered negative for cardiac dyspnea, and values between 300 ng/L and the age-based cutoff value represent gray-zone concentrations (15). For BNP, concentrations <100 ng/L have been shown to have a strong negative predictive value for ADHF, whereas values >500 ng/L strongly predict ADHF (16). Values of 100–500 ng/L were considered intermediate (17).

**ECHOCARDIOGRAPHY**

Prospective echocardiography evaluations were planned for all patients within 96 h of enrollment. The echocardiograms were performed by an experienced sonographer, and the VHS tapes or digital images were sent to the core laboratory (University of Maryland).
To minimize interobserver variability, we had a single investigator blinded from the clinical data and performed all of the measurements.

Simpson biplane analysis was used to determine the LV end-systolic volume (LVESV) and the LV end-diastolic volume (LVEDV) \((18)\). The LVEF was calculated as: \([\text{LVEDV} - \text{LVESV}] / \text{LVEDV} \times 100\%\).

LV mass was measured according to the M-mode criteria recommended by the American Society of Echocardiography and the formula proposed by Devereux et al. \((19)\). The LV mass was indexed to body surface area.

Diastolic function was assessed in the apical 4-chamber view. Doppler evaluations of inflow velocities and tissue Doppler imaging sampling from the lateral mitral annulus were obtained to grade the severity of diastolic dysfunction as stage I [impaired relaxation, ratio of transmitial peak flow velocity in early diastole to peak flow velocity in late diastole (E/A ratio) < 1, deceleration time (Dt) > 220 ms], stage II [pseudonormal, E/A ratio between 1 and 2, Dt < 220 ms, early diastolic mitral annular velocity (Em') < 8.5 m/s], or stage III (restrictive, E/A ratio > 2, Dt < 150 ms) \((20)\).

**DIAGNOSIS OF HEART FAILURE AND STRUCTURAL CARDIAC DEFECTS**

An expert panel of physicians trained in cardiovascular medicine diagnosed ADHF by means of a standardized adjudication form. The physicians were not directly involved in the care of the patients and were blinded to the biomarker results and the diagnosis of the ED physician. Two panel members reviewed the presenting signs and symptoms, the medical history, medications, and echocardiography and electrocardiography results and diagnosed ADHF according to the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial criteria \((21)\). A third expert was used to determine the final diagnosis if the 2 experts disagreed. The panel of physicians also identified patients with structural heart disease from the clinical data and assessments of echocardiographic variables of LV systolic function (LVEF ≤ 40%), valvular disease, and the presence of myocardial hypertrophy.

**STATISTICAL ANALYSIS**

Continuous variables are presented as the mean \((SD)\), and categorical variables are presented as percentages. MPO values were not normally distributed and were therefore logarithmically transformed before parametric analyses. Patients with ADHF, patients with cardiac structural defects without ADHF, and patients with neither ADHF nor cardiac structural defects were compared with 1-way ANOVA and subsequent between-group \(t\)-tests. Variances were not pooled across groups if heterogeneity of variances was observed \((\text{Levene} \, P < 0.01)\). Associations of MPO concentration with clinical, biochemical, and echocardiographic variables were evaluated with Spearman nonparametric correlation coefficients. Linear regression analysis was used to adjust for clinical characteristics, including age, race, sex, and body mass index (BMI). To examine diagnostic properties, we used ROC curves to examine whether MPO and other biomarkers were associated with ADHF and structural cardiac abnormalities, and we used the area under the ROC curve \((\text{AUC})\) and the \(c\) statistic as indicators of accuracy.

We used Cox proportional hazards models to assess the predictive value of the biomarkers for mortality and adjusted for the same clinical characteristics used in the linear regression analysis. Separate models were examined for MPO, BNP, and NT-proBNP, and the final multivariate model examined the relative contribution of all biomarkers and covariates. Statistical analysis was performed with SPSS software, version 14.0.

**Results**

**PATIENTS**

Table 1 summarizes the characteristics of the 412 patients \(\text{[mean age, 58 (14) years; 61% men; 64% African American]}\). Patients with ADHF (n = 147) were more often men \((P < 0.001)\) and were older \((P < 0.001)\) than patients in the comparison groups. ADHF patients had a lower mean estimated glomerular filtration rate \([56 (26) \text{mL} \cdot \text{min}^{-1} \cdot (1.73 \text{m}^2)^{-1}]\) than those with structural heart disease \([62 (30) \text{mL} \cdot \text{min}^{-1} \cdot (1.73 \text{m}^2)^{-1}]\) and those with nonpathologic hearts and without ADHF \([86 (29) \text{mL} \cdot \text{min}^{-1} \cdot (1.73 \text{m}^2)^{-1}]\) \((P < 0.001)\). Although the history of prior myocardial infarction or heart failure was more prevalent in patients with ADHF (29% and 42%, respectively) or structural heart disease (29% and 39%) than in those without cardiac abnormalities (19% and 31%), these differences between groups did not reach statistical significance \((P = 0.07, \text{and } P = 0.11, \text{respectively})\). The prevalences of heart failure risk factors diabetes mellitus (30%) and hypertension (65%) did not differ when the groups were compared on the basis of the presence or absence of ADHF \((P = 0.53, \text{and } P = 0.86, \text{respectively})\).

**CLINICAL CORRELATES OF MPO**

The median MPO concentration was 566 pmol/L \([\text{interquartile range (IQR), 414–827 pmol/L}]\). MPO was weakly but significantly associated with New York Heart Association class–based dyspnea severity \((r = 0.17; P = 0.001)\). In a subgroup analysis, MPO concentration was weakly associated with dyspnea severity in
patients without ADHF or structural heart disease ($r = 0.23; P = 0.001$), but not in patients with ADHF ($r = 0.09; P = 0.28$) or structural heart disease ($r = 0.11; P = 0.45$). MPO concentration was also weakly associated with female sex ($r = 0.12; P = 0.02$), BMI ($r = 0.14; P = 0.005$), and heart rate ($r = 0.16; P = 0.002$) (Table 2). Multivariate analyses indicated that the relationship between the severity of dyspnea and MPO concentration remained significant ($r = 0.13; P = 0.014$), whereas associations with age, sex, and BMI were no longer significant.

**MPO AND DIAGNOSIS OF HEART FAILURE AND STRUCTURAL HEART DISEASE**

MPO concentrations in patients without ADHF (median, 576 pmol/L; IQR, 413–884 pmol/L) were similar to those of ADHF patients (median, 553 pmol/L; IQR, 415–738 pmol/L) ($P = 0.07$). In contrast, BNP and NT-proBNP concentrations were significantly higher in ADHF patients ($P < 0.001$ for both BNP and NT-proBNP; Fig. 1). For the entire patient cohort, MPO concentration was correlated with neither NT-proBNP concentration ($r = 0.02; P = 0.72$) nor BNP concentration ($r = 0.04; P = 0.56$). ROC curves for the diagnosis of ADHF indicated that BNP (AUC = 0.90; $P < 0.001$) and NT-proBNP (AUC = 0.90; $P < 0.001$) had excellent diagnostic value as markers for ADHF, whereas MPO was not useful in this regard (AUC = 0.46; $P = 0.18$) (Fig. 2). For patients without ADHF, the MPO values of patients with and without structural heart disease did not differ ($P = 0.93$).

Echocardiography results were obtained for 338 patients (82%). MPO concentration was not correlated with LVEF, LVEDV, or LVESV (Table 3). MPO con-

| Table 1. Characteristics of the patients in the studied diagnostic groups. 

<table>
<thead>
<tr>
<th>Variable</th>
<th>All (n = 412)</th>
<th>ADHF (n = 147)</th>
<th>Structural heart disease (n = 52)</th>
<th>No cardiac abnormality (n = 213)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>61%</td>
<td>73%</td>
<td>65%</td>
<td>52%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age, years</td>
<td>58 (14)</td>
<td>61 (13)</td>
<td>65 (12)</td>
<td>53 (14)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>33%</td>
<td>39%</td>
<td>33%</td>
<td>29%</td>
<td>0.09</td>
</tr>
<tr>
<td>Black</td>
<td>64%</td>
<td>57%</td>
<td>67%</td>
<td>69%</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>3%</td>
<td>4%</td>
<td>0%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Blood pressure, mmHg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>140 (25)</td>
<td>142 (27)</td>
<td>143 (26)</td>
<td>138 (23)</td>
<td>0.25</td>
</tr>
<tr>
<td>Diastolic</td>
<td>81 (17)</td>
<td>83 (19)</td>
<td>81 (18)</td>
<td>80 (15)</td>
<td>0.31</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>88 (19)</td>
<td>87 (20)</td>
<td>86 (18)</td>
<td>90 (19)</td>
<td>0.19</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>31 (10)</td>
<td>31 (9)</td>
<td>32 (11)</td>
<td>31 (10)</td>
<td>0.85</td>
</tr>
<tr>
<td>eGFR, mL · min⁻¹ · (1.73 m²)⁻¹</td>
<td>73 (32)</td>
<td>56 (26)</td>
<td>62 (30)</td>
<td>86 (29)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NYHA class</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I–II</td>
<td>30%</td>
<td>26%</td>
<td>26%</td>
<td>34%</td>
<td>0.06</td>
</tr>
<tr>
<td>III</td>
<td>54%</td>
<td>52%</td>
<td>58%</td>
<td>54%</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>16%</td>
<td>23%</td>
<td>16%</td>
<td>12%</td>
<td></td>
</tr>
<tr>
<td>Chronic medical conditions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAD</td>
<td>43%</td>
<td>48%</td>
<td>46%</td>
<td>39%</td>
<td>0.23</td>
</tr>
<tr>
<td>MI</td>
<td>24%</td>
<td>29%</td>
<td>29%</td>
<td>19%</td>
<td>0.07</td>
</tr>
<tr>
<td>HF</td>
<td>36%</td>
<td>42%</td>
<td>39%</td>
<td>31%</td>
<td>0.11</td>
</tr>
<tr>
<td>eGFR &lt;60 mL · min⁻¹ · (1.73 m²)⁻¹</td>
<td>34%</td>
<td>57%</td>
<td>48%</td>
<td>15%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>65%</td>
<td>66%</td>
<td>64%</td>
<td>64%</td>
<td>0.86</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>30%</td>
<td>33%</td>
<td>25%</td>
<td>29%</td>
<td>0.53</td>
</tr>
</tbody>
</table>

* Data are presented as the mean (SD) or as percentages. 
* bpm, beats per minute; eGFR, estimated glomerular filtration rate; NYHA, New York Heart Association; CAD, coronary artery disease; MI, myocardial infarction; HF, heart failure.
centration showed a weak inverse association with LV mass index that was statistically significant only in patients with neither structural heart disease nor ADHF ($r = -0.18; P = 0.03$). MPO concentrations in patients with diastolic dysfunction (median, 539 pmol/L; IQR, 415–799 pmol/L) were not significantly different from those in patients without diastolic dysfunction (median, 589 pmol/L; IQR, 413–896 pmol/L) ($P = 0.22$),

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**Table 2. Correlation of MPO concentration with clinical variables.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>All patients</th>
<th>ADHF</th>
<th>Structural heart disease</th>
<th>No ADHF</th>
<th>No cardiac abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Spearman correlation, $r$</td>
<td>$P$</td>
<td>Spearman correlation, $r$</td>
<td>$P$</td>
<td>Spearman correlation, $r$</td>
</tr>
<tr>
<td>Age</td>
<td>0.01</td>
<td>0.84</td>
<td>0.07</td>
<td>0.40</td>
<td>-0.15</td>
</tr>
<tr>
<td>BMI</td>
<td>0.14</td>
<td>0.005</td>
<td>0.17</td>
<td>&lt;0.05</td>
<td>0.21</td>
</tr>
<tr>
<td>Race</td>
<td>0.02</td>
<td>0.69</td>
<td>-0.03</td>
<td>0.71</td>
<td>0.07</td>
</tr>
<tr>
<td>Female sex</td>
<td>0.12</td>
<td>0.02</td>
<td>0.15</td>
<td>0.08</td>
<td>-0.04</td>
</tr>
<tr>
<td>Systolic BP*</td>
<td>-0.01</td>
<td>0.84</td>
<td>0.07</td>
<td>0.38</td>
<td>-0.02</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>-0.06</td>
<td>0.22</td>
<td>-0.05</td>
<td>0.54</td>
<td>-0.01</td>
</tr>
<tr>
<td>Heart rate</td>
<td>0.16</td>
<td>0.002</td>
<td>0.08</td>
<td>0.37</td>
<td>0.24</td>
</tr>
<tr>
<td>NYHA class</td>
<td>0.17</td>
<td>0.001</td>
<td>0.09</td>
<td>0.28</td>
<td>0.11</td>
</tr>
<tr>
<td>Chronic medical conditions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAD</td>
<td>0.01</td>
<td>0.85</td>
<td>0.004</td>
<td>0.97</td>
<td>-0.26</td>
</tr>
<tr>
<td>MI</td>
<td>-0.03</td>
<td>0.58</td>
<td>-0.004</td>
<td>0.96</td>
<td>-0.18</td>
</tr>
<tr>
<td>HF</td>
<td>0.04</td>
<td>0.38</td>
<td>0.11</td>
<td>0.20</td>
<td>-0.06</td>
</tr>
<tr>
<td>Hypertension</td>
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<td>0.39</td>
<td>0.03</td>
<td>0.77</td>
<td>-0.22</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>-0.03</td>
<td>0.60</td>
<td>-0.01</td>
<td>0.89</td>
<td>-0.03</td>
</tr>
<tr>
<td>eGFR</td>
<td>-0.04</td>
<td>0.44</td>
<td>0.03</td>
<td>0.76</td>
<td>-0.09</td>
</tr>
<tr>
<td>BNP</td>
<td>-0.04</td>
<td>0.46</td>
<td>-0.18</td>
<td>0.03</td>
<td>-0.25</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>-0.02</td>
<td>0.72</td>
<td>-0.12</td>
<td>0.17</td>
<td>-0.14</td>
</tr>
</tbody>
</table>

* BP, blood pressure; NYHA, New York Heart Association; CAD, coronary artery disease; MI, myocardial infarction; HF, heart failure; eGFR, estimated glomerular filtration rate.

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**Fig. 1.** Box-and-whisker plots of MPO (A), BNP (B), and NT-proBNP (C) biomarker concentrations according to diagnosis.
nor was MPO concentration associated with the stage of diastolic dysfunction ($r = -0.06; P = 0.32$).

**PROGNOSIS OF MPO FOR 1-YEAR MORTALITY**
Complete follow-up data were available for 401 (97%) of 412 patients. Fifty-one patients (12%) with a validated follow-up status died. The $c$ statistic value for MPO prediction of mortality was not significant (AUC, 0.52; $P = 0.58$) (Fig. 3). MPO did not appear to be a significant predictor of mortality [hazard ratio, 1.25 (comparing groups above vs below the MPO median); 95% CI, 0.71–2.18]. Stratified analyses for the 3 patient groups revealed no relationships between MPO concentration and mortality ($P$ values $>0.20$).

In contrast, BNP [hazard ratio, 2.87 (above vs below the median); 95% CI, 1.55–5.30] and NT-proBNP [hazard ratio, 3.11 (above vs below the median); 95% CI, 1.66–5.87] were significantly related to mortality. Furthermore, both natriuretic peptide tests remained significant predictors of mortality in Cox proportional hazards analysis after adjustment for age, race, sex, and BMI. The addition of MPO concentration to the prognostic models provided no added predictive value ($P$ values $>0.20$; see Fig. 1 in the Data Supplement that accompanies the online version of this article at http://www.clinchem.org/content/vol55/issue1), even when natriuretic peptide values were stratified into known diagnostic/prognostic subgroups (negative vs gray zone vs positive).

**Discussion**
Our results demonstrated that circulating MPO concentrations provided no diagnostic or prognostic information in the evaluation of ED patients presenting with dyspnea. Importantly, MPO concentration con-
tributed no added predictive value to a clinical model that included demographic variables and natriuretic peptide assessment. This finding is of particular interest because accumulated data have shown a potential diagnostic and prognostic role for inflammatory markers in patients with LV systolic dysfunction (10, 11, 22, 23). Furthermore, MPO concentration was not significantly correlated with findings of structural heart disease, systolic dysfunction, or diastolic dysfunction.

Other investigators have shown markers of inflammation and oxidative stress to be increased acutely in patients with ADHF (12, 13, 22, 23). MPO is an inflammatory marker of particular interest, given its availability for clinical use and the accumulating data supporting a prognostic role for MPO in patients with cardiovascular disease. The present findings, however, suggest that previous observations by Ng et al. demonstrating a diagnostic utility for inflammatory markers, including C-reactive protein and MPO, are potentially limited to the identification of nonacute patients with undiagnosed LV dysfunction (24). Asthma, chronic obstructive pulmonary disease, smoking, bronchitis, and pneumonia have all been associated with increased MPO concentrations (25–27).

Inflammation has been linked to myocyte dysfunction, adverse LV remodeling, and poor outcomes in heart failure (28, 29). Studies of mouse models of infarction and ischemia/reperfusion have shown that LV dilation and dysfunction are limited in MPO-null mice, implying that MPO plays a mechanistic role in remodeling (30, 31). In fact, Tang and colleagues have shown that patients with stable chronic heart failure have higher serum concentrations of MPO than healthy controls (10). In patients with advanced cardiomyopathy, higher MPO concentrations were associated with a higher prevalence of the combined endpoint of death or heart transplantation (11); however, the MPO values that were obtained (median, 303 pmol/L; IQR, 256–530 pmol/L) were lower than the concentrations we observed (median, 566 pmol/L; IQR, 414–827 pmol/L). Although MPO seems to have a viable role for prognosis in stable patients with an established diagnosis of heart failure with severe systolic dysfunction, MPO concentration appears to be increased erratically in patients with acute dyspnea.

When applied to a population with dyspnea as a primary presentation, MPO did not predict 1-year survival. Even when we limited the analysis to patients with diagnosed heart failure, MPO was still not associated with mortality. Conversely, the established natriuretic peptide markers BNP and NT-proBNP and the soluble ST2 receptor are known to be significant predictors of death at 1 year in dyspnea populations (22, 32–34). One explanation is that although inflammation may play a prominent role in late-stage heart failure and advanced stages of ventricular remodeling, its prognostic potential is limited in a general dyspnea population, in which more benign, reversible etiologies may also play a role in increasing the MPO concentration (35). Prior studies support the prognostic role of inflammatory markers, such as C-reactive protein or growth differentiation factor 15, in chronic heart failure (36, 37).

Our study had several limitations. Echocardiography evaluations were not performed for all of the participants, although we believe the 82% completion rate compares favorably with other dyspnea studies (16, 38). Although the 1-year follow-up data for the study population were complete for 97% of the patients, we did not report cause of death. Although unlikely, a longer follow-up might have unmasked a longer-term prognostic value for this marker. The strengths of the present study are its large, ethnically diverse cohort of patients for which the diagnosis and prognosis of ADHF were validated with strong correlation to established biomarkers, structural cardiac abnormalities, and an adjudicated diagnosis of heart failure.

In conclusion, the circulating serum MPO concentration, unlike natriuretic peptides, did not appear useful for establishing the etiology of dyspnea in patients presenting to an ED setting. In addition, MPO concentration was not correlated with LVEF or other cardiac structural abnormalities. Lastly, MPO concentrations did not provide significant prognostic infor-

![Fig. 3. ROC curves for BNP (AUC, 0.70; P < 0.001), NT-proBNP (AUC, 0.68; P < 0.001), and MPO (AUC, 0.53; P = 0.55) for predicting 1-year mortality.](https://example.com/fig3.png)
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