Tumor Necrosis Factor-α and Mortality in Heart Failure
A Community Study

Shannon M. Dunlay, MD; Susan A. Weston, MS; Margaret M. Redfield, MD; Jill M. Killian, BS; Véronique L. Roger, MD, MPH

Background—Tumor necrosis factor-α (TNFα), an inflammatory cytokine, was reported to be elevated in trials of heart failure (HF) with reduced ejection fraction (EF) and associated with mortality. Whether this is true for HF with preserved EF is unknown, and community data are lacking. We evaluated the distribution of TNFα, its association with baseline characteristics and mortality, and its benefit in assessing risk in community HF patients.

Methods and Results—Olmsted County residents with active HF from July 2004 to March 2007 (n=486; mean age, 76.7 years; EF ≥50%, 55%) were prospectively recruited. Clinical characteristics and TNFα were measured. Elevated TNFα (more than the assay limit of normal of 2.8 pg/mL) was present in 143 (29%). Higher TNFα was associated with decreased creatinine clearance, nonsmoking status, anemia, and greater comorbidity (P trend <0.05 for all). Mortality increased with increasing TNFα (P=0.016), with 1-year mortality estimates of 16%, 18%, 23%, and 32% from the lowest to highest quartile, respectively. After adjustment for age, sex, and EF, the hazard ratios for death were 1.24, 1.37, and 1.90 from the second to the highest TNFα quartile, respectively (P trend =0.007). TNFα contributed to risk assessment as indicated by increases in the area under the receiver operating characteristic curves in all models examined (P<0.05 for all). Results did not differ by EF (P=0.60 interaction term of TNFα and EF).

Conclusions—TNFα was elevated in a large portion of community HF patients, was associated with a large decrease in survival, and provided a significant incremental increase in risk assessment above established indicators. TNFα is useful for risk assessment in HF patients with preserved and reduced EF. (Circulation. 2008;118:625-631.)

Key Words: epidemiology ■ heart failure ■ inflammation ■ risk factors

Inflammation plays a key role in the pathogenesis of heart failure (HF). Tumor necrosis factor alpha-α (TNFα), an inflammatory cytokine, has been implicated in HF progression as a mediator of myocardial dysfunction and adverse remodeling. Studies to date have shown that some patients with HF have elevated circulating levels of TNFα compared with control subjects and have suggested that increased circulating levels are associated with increased mortality. However, attempts to use TNFα as a therapeutic target in patients with severe systolic dysfunction have resulted in an increase in all-cause mortality. To date, the role that TNFα plays in HF has not been fully elucidated and warrants further investigation.

Clinical Perspective p 631

Most published studies on TNFα are not generalizable to the entire HF population for several reasons. The vast majority of reports pertained to a small number of patients (<150) and focused on clinical trial populations. In addition, they have included only patients with severe systolic dysfunction (ejection fraction [EF] <30% to 35%), although HF with preserved EF accounts for approximately half of all HF cases. Substantial selection biases hinder the use of TNFα for risk prediction among all patients with HF.

In the present study, we aimed to address these gaps in knowledge by examining the distribution of TNFα and its association with baseline characteristics among all HF patients in a population-based setting. Next, we determined whether an association between serum TNFα level and mortality exists and whether this association differs by EF. Finally, we evaluated whether TNFα confers an incremental benefit in predicting risk above recognized predictors in community HF patients.

Methods

Study Design

This study is a population-based study conducted in Olmsted County, which is located in southeastern Minnesota and has a population of 124,277 (90% white, 51% female). This type of research is feasible in Olmsted County because nearly all medical care in virtually every specialty is provided by relatively few providers, including the Mayo Clinic, Olmsted Medical Center, and a few private practitioners. The records from each institution are...
Identification of Patients

To identify potential HF cases, natural language processing of the text of the electronic medical record is used.\textsuperscript{11} The vast majority of patient visits to the system are transcribed and appear in the record within 24 hours, making prompt ascertainment of newly diagnosed HF cases possible. Next, the complete records of potential cases are reviewed by trained abstractors to collect additional data and to verify HF cases using Framingham criteria.\textsuperscript{14} Patients are then contacted directly to obtain consent for participation in the study, which involves performing Doppler echocardiography and obtaining venous blood samples to measure biomarkers. Recruitment for the cohort is ongoing, allowing assessment of multiple factors in community HF patients over time. Hospitalized patients are contacted while in the hospital, and patients recruited from a clinical setting are contacted at their next clinic visit for consent, enrollment, and collection of data. All patients provided written authorization to participate in the study, which was approved by the Mayo Clinic Institutional Review Board.

Data Collection

Echocardiography

All echocardiograms were obtained and analyzed at the Mayo Clinic Echocardiography Laboratory according to the guidelines of the American Society of Echocardiography.\textsuperscript{15} Left ventricular EF was measured with M-mode, quantitative, and semiquantitative methods as previously described and validated\textsuperscript{16} with excellent correlation between methods. EF values were averaged when multiple measurements were performed. Although EF was dichotomized (<50%, ≥50%)\textsuperscript{10} for descriptive purposes, it was examined as a continuous variable in all analyses. Diastolic function was assessed by an approach that integrates Doppler measurements of the mitral inflow and Doppler tissue imaging of the mitral annulus using the medial annulus velocity, a method that has previously been validated.\textsuperscript{17} Diastolic function was then classified on the basis of these results into 4 categories: normal diastolic function, mild diastolic dysfunction (impaired relaxation or pseudonormal), moderate diastolic dysfunction (impaired relaxation without increased filling pressures), and severe diastolic dysfunction (severely reduced compliance). In the case of severe mitral stenosis, mitral valve prosthesis, or missing data, diastolic function was classified as indeterminate.

TNFα Measurement

Venous samples were obtained as soon as possible after recruitment of patients in both the inpatient and outpatient setting. All venous samples were stored in EDTA tubes, processed, and stored at −70°C until TNFα measurement took place (samples were not thawed in the interim). The TNFα level was quantified by enzyme-linked immunonassay (TNFSF1A Immunoassay, R&D Systems, Minneapolis, Minn). Samples were incubated in microtiter plate wells with a monoclonal antibody specific for TNFα. After a wash, an enzyme-linked polyclonal antibody specific for TNFα was added. After incubation and a second wash, an amplifier solution was added, and the color was developed in proportion to the amount of TNFα bound in the first step. The optical density of each well was measured to determine the concentration of TNFα present in each sample. The reference range for the assay is 0.550 to 2.816 pg/mL. All of the assays were performed in the Mayo Clinic Immunochromal Core Laboratory, and technicians were blinded to the clinical characteristics and outcomes of the patients.

Additional Patient Data

Data pertaining to baseline patient characteristics were obtained by review of medical records by trained nurse-abstractors. Prior myocardial infarction occurring in Olmsted County was defined through the use of standardized myocardial infarction criteria, which have previously been described and validated.\textsuperscript{18} Physician’s diagnosis was used to document history of coronary artery disease, history of chronic obstructive pulmonary disease, and history of atrial fibrillation/flutter. Hypertension was defined as systolic blood pressure >140 mm Hg, diastolic blood pressure >90 mm Hg, or use of antihypertensive medications. Smoking status was classified as current, former (quit at least 6 months ago), or never on the basis of documentation. Hyperlipidemia was defined by use of the American Diabetes Association criteria.\textsuperscript{20} The height and weight documented at the time of HF diagnosis were used to calculate body mass index. Creatinine clearance was calculated from the last outpatient creatinine value with the Cockcroft-Gault\textsuperscript{21} equation. Severe renal disease was defined as a creatinine clearance <30 mL/min. The hemoglobin value nearest the date of HF diagnosis was used to diagnose anemia through the use of World Health Organization criteria (hemoglobin <13 mg/dL in men or 12 mg/dL in women).\textsuperscript{22} The Charlson Index, a comorbidity score reflecting the cumulative increased likelihood of 1-year mortality, also was collected.\textsuperscript{23} New York Heart Association (NYHA) functional class also was collected.

Mortality Follow-Up

Follow-up took place through passive surveillance of the community medical records. The ascertainment of death included death certificates filed in Olmsted County, obituary notices, and electronic files of death certificates obtained from the state of Minnesota Department of Vital and Health Statistics.\textsuperscript{12} All-cause mortality was used as the end point in all analyses.

Statistical Analysis

Subjects were divided into quartiles based on TNFα level (<1.5, 1.5≤TNFα<2.1, 2.1≤TNFα<3.1, ≥3.1 pg/mL). Because the TNFα distribution was skewed, log TNFα was used for all analyses of TNFα as a continuous variable. Baseline characteristics are presented as frequencies or means with SDs. Trends in baseline characteristics across quartiles were analyzed with generalized linear models for continuous variables and Mantel-Haenszel χ² for categorical variables. In addition, log TNFα was analyzed as a continuous variable with all baseline characteristics to ensure that a significant association was not missed by quartile analysis. All patients had TNFα measurements and echocardiography performed. Data were complete in all other areas except smoking status (n=1 missing), prior history of myocardial infarction (n=11 missing, also used to calculate the Charlson Index), hemoglobin (n=1 missing), and creatinine clearance (n=14 missing).

Mortality was assessed with the Kaplan-Meier method with censoring at the time of the last follow-up. Cox proportional-hazards regression analysis was used to estimate both unadjusted and adjusted hazard ratios for mortality by TNFα group using the lowest quartile as the reference. Baseline clinical characteristics were adjusted for in the multivariable models with forced entry. Individual comorbidities were adjusted for rather than Charlson Index score. In an ancillary analysis, to investigate whether the association between TNFαs and mortality differed among those with incident or prevalent HF, we restricted the sample to those with incident HF and performed Cox proportional-hazards regression analysis. Finally, logistic regression analysis was performed to assess the incremental value of TNFα in determining the risk of death in HF patients. Models before and after the addition of TNFα were compared by use of the area under the receiver operating characteristic curve with methods previously described\textsuperscript{24} and were 1 tailed. A value of P<0.05 was used as the level of significance. Analyses were performed with SAS 9.1 software (SAS Institute Inc, Cary, NC) and JMP version 6.0.0 (SAS Institute).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.
Table 1. Baseline Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Overall (n=486)</th>
<th>Quartile 1, TNFα&lt;1.5 pg/mL (n=130)</th>
<th>Quartile 2, 1.5&lt;TNFα&lt;2.1 pg/mL (n=130)</th>
<th>Quartile 3, 2.1&lt;TNFα&lt;3.1 pg/mL (n=130)</th>
<th>Quartile 4, TNFα≥3.1 pg/mL (n=130)</th>
<th>(P_{\text{test}})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>76.7 (13.0)</td>
<td>74.4 (12.5)</td>
<td>77.0 (14.0)</td>
<td>78.2 (11.8)</td>
<td>77.1 (13.2)</td>
<td>0.09</td>
</tr>
<tr>
<td>Male sex</td>
<td>236 (48.6)</td>
<td>52 (44.1)</td>
<td>65 (50.0)</td>
<td>64 (53.3)</td>
<td>55 (46.6)</td>
<td>0.60</td>
</tr>
<tr>
<td>EF, %</td>
<td>49.2 (16.4)</td>
<td>47.9 (17.4)</td>
<td>47.7 (16.4)</td>
<td>50.3 (16.2)</td>
<td>51.1 (15.6)</td>
<td>0.07</td>
</tr>
<tr>
<td>EF ≥50%, n (%)</td>
<td>266 (54.8)</td>
<td>61 (51.7)</td>
<td>66 (50.8)</td>
<td>69 (58.0)</td>
<td>70 (59.3)</td>
<td>0.14</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>391 (80.4)</td>
<td>86 (72.9)</td>
<td>109 (83.8)</td>
<td>98 (81.7)</td>
<td>98 (83.1)</td>
<td>0.09</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>40 (8.2)</td>
<td>20 (17.1)</td>
<td>5 (3.8)</td>
<td>10 (8.3)</td>
<td>5 (4.2)</td>
<td>0.003</td>
</tr>
<tr>
<td>Hyperlipidemia, n (%)</td>
<td>326 (67.1)</td>
<td>78 (66.1)</td>
<td>89 (68.5)</td>
<td>79 (65.8)</td>
<td>80 (67.8)</td>
<td>0.91</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>148 (30.5)</td>
<td>30 (25.4)</td>
<td>42 (32.3)</td>
<td>42 (35.0)</td>
<td>34 (28.8)</td>
<td>0.50</td>
</tr>
<tr>
<td>BMI, mean (SD), kg/m²</td>
<td>29.2 (7.9)</td>
<td>29.5 (8.3)</td>
<td>29.3 (7.9)</td>
<td>28.8 (7.7)</td>
<td>29.2 (7.8)</td>
<td>0.64</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior MI, n (%)</td>
<td>118 (24.8)</td>
<td>26 (22.0)</td>
<td>36 (28.3)</td>
<td>23 (19.3)</td>
<td>33 (29.7)</td>
<td>0.46</td>
</tr>
<tr>
<td>Prior CAD, n (%)</td>
<td>261 (53.7)</td>
<td>58 (49.2)</td>
<td>66 (50.8)</td>
<td>66 (55.0)</td>
<td>71 (60.2)</td>
<td>0.07</td>
</tr>
<tr>
<td>COPD, n (%)</td>
<td>140 (28.8)</td>
<td>42 (35.6)</td>
<td>29 (22.3)</td>
<td>39 (32.5)</td>
<td>30 (25.4)</td>
<td>0.30</td>
</tr>
<tr>
<td>Anemia, n (%)</td>
<td>258 (53.2)</td>
<td>42 (35.6)</td>
<td>63 (48.8)</td>
<td>74 (61.7)</td>
<td>79 (66.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Severe renal disease, n (%)</td>
<td>81 (17.2)</td>
<td>4 (3.5)</td>
<td>16 (12.6)</td>
<td>25 (21.6)</td>
<td>36 (31.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Creatinine clearance, mean (SD), ml/min</td>
<td>58.8 (33.9)</td>
<td>70.2 (33.2)</td>
<td>61.0 (33.4)</td>
<td>56.2 (35.0)</td>
<td>47.7 (30.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>C-reactive protein (mg/dL)</td>
<td>4.34 (6.61)</td>
<td>2.41 (4.39)</td>
<td>3.64 (5.48)</td>
<td>4.39 (6.17)</td>
<td>7.01 (8.91)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Atrial fibrillation/flutter, n (%)</td>
<td>155 (31.9)</td>
<td>44 (37.3)</td>
<td>43 (33.1)</td>
<td>37 (30.8)</td>
<td>31 (26.3)</td>
<td>0.07</td>
</tr>
<tr>
<td>NYHA class 3 or 4, n (%)</td>
<td>355 (73.0)</td>
<td>89 (75.4)</td>
<td>101 (77.7)</td>
<td>81 (67.5)</td>
<td>84 (71.2)</td>
<td>0.20</td>
</tr>
<tr>
<td>Charlson Index ≥3, n (%)</td>
<td>316 (66.5)</td>
<td>64 (54.2)</td>
<td>83 (65.4)</td>
<td>87 (73.1)</td>
<td>82 (73.9)</td>
<td>0.001</td>
</tr>
<tr>
<td>Moderate or severe diastolic dysfunction, n (%)</td>
<td>369 (75.9)</td>
<td>84 (71.2)</td>
<td>98 (75.4)</td>
<td>95 (79.2)</td>
<td>92 (78.0)</td>
<td>0.17</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; MI, myocardial infarction; CAD, coronary artery disease; and COPD, chronic obstructive pulmonary disease.

Results

Patient Identification and Baseline Characteristics

Four hundred eighty-six consecutive patients with active HF were enrolled in the study between July 29, 2004, and March 7, 2007, and underwent echocardiography and TNFα assay. The consent rate for the study during this time period was 71%. The mean age of participants was 76.7 ± 13.0 years; 236 (48.6%) were male; and 266 (54.8%) had preserved EF (≥50%) (Table 1). The population had a high index of comorbidity, with 316 (66.5%) having a Charlson Index ≥3, and overall poor functional status, with 355 (73.0%) having NYHA class III/IV HF symptoms.

TNFα Levels

TNFα levels ranged from 0.3 to 28.0 pg/mL, with a mean value of 3.1 ± 3.4 pg/mL and median value of 2.1 pg/mL (25th to 75th percentile, 1.5 to 3.1 pg/mL). We found that 143 (29%) had TNFα levels above the reference range for the test (>2.8 pg/mL). The distribution of TNFα did not differ significantly between patients recruited in an inpatient and outpatient setting (\(P=0.31\)). Higher TNFα was associated with current nonsmoking status, increased prevalence of anemia, and a higher level of comorbidity (Table 1). In addition, higher TNFα was associated with decreasing creatinine clearance (Figure 1A) and decreasing hemoglobin (Figure 1B). The graded association is suggestive of a “dose-response” effect. No association was found between TNFα and body mass index or NYHA functional class. The distribution of TNFα (median, 2.2 pg/mL [25th to 75th percentile, 1.5 to 3.2 pg/mL] and 1.9 pg/mL [25th to 75th percentile, 1.4 to 2.9 pg/mL]) among those with preserved and reduced EF, respectively. Although nonsignificant trends toward increasing age and EF with higher TNFα quartile were noted, both relationships remained nonsignificant when TNFα was examined as a continuous variable (\(P=0.13\), age versus log TNFα; \(P=0.15\), EF versus log TNFα; data not shown), indicating that no significant association existed between age and TNFα or EF and TNFα. No sex-based differences were present. Finally, a trend toward increased frequency of coronary artery disease was found among those with higher TNFα, but it was not significant (\(P=0.069\)).

TNFα Level and Association With Mortality

After a mean follow-up of 17 ± 10 months, 147 patients (30.2%) were dead. The 1-year Kaplan-Meier mortality estimate was 22% (95% confidence interval [CI] 18% to 26%) overall and increased from lowest to highest quartile (16% [95% CI 9% to 22%], 18% [95% CI 11% to 25%], 23% [95% CI 15% to 29%], and 32% [95% CI 23% to 40%], respectively; \(P=0.016\); Figure 2). The unadjusted hazard ratios for death were 1.34 (95% CI 0.82 to 2.21), 1.47 (95%...
CI 0.89 to 2.44), and 2.10 (95% CI 1.30 to 3.38) from lowest to highest quartile, respectively, with the lowest quartile used as the referent (P\textsubscript{trend}=0.002; Table 2). After adjustment for age, sex, EF, and comorbidities, this relationship held, with a hazard ratio for death of 1.88 (95% confidence interval, 1.09 to 3.25) in the highest versus lowest quartile (P\textsubscript{trend across quartiles}=0.028). The largest impact on the increase in hazard ratios observed from model 1 to 2 was due to adjustment for smoking status, whereas adjustment for creatinine clearance and anemia attenuated the association between TNF\(\alpha\) and mortality. Adding C-reactive protein to the model did not appreciably change the association between TNF\(\alpha\) and mortality. The relationship between TNF\(\alpha\) and mortality was similar among those with incident HF compared with the overall population. No interaction between TNF\(\alpha\) and EF was noted (P=0.60 for interaction term), indicating that associations between TNF\(\alpha\) and death did not differ significantly for patients with preserved versus reduced EF.

**Addition of TNF\(\alpha\) Level to Mortality Risk Assessment**

Inclusion of TNF\(\alpha\) in the model resulted in a notable increase in predictive value of mortality in patients with HF (Table 3). For instance, the area under the receiver operating characteristic curve increased from 0.67 to 0.70 in a model that included age and sex (P=0.035) and from 0.74 to 0.78 in a model that include age, sex, EF, NYHA functional class, and traditional risk factors (P=0.018).

**Discussion**

In the present study, we demonstrated that serum TNF\(\alpha\) is elevated in a large proportion of community HF patients with a wide range of EF and that elevated circulating TNF\(\alpha\) was strongly associated with decreased creatinine clearance, anemia, and a high degree of comorbidity. Second, we identified a strong independent association between elevated TNF\(\alpha\) and mortality in HF patients regardless of EF. Finally, we have demonstrated that TNF\(\alpha\) improved risk prediction in HF above traditional risk indicators.

HF is characterized by an inflammatory state with reports of elevation of several inflammatory cytokines, including TNF\(\alpha\), in selected patients with HF.\(^1\)\(^,\)^\(^2\)^\(^5\) TNF\(\alpha\) is an inflammatory cytokine produced mainly by monocytes and macrophages with pleiotropic effects. It binds to cell surface receptors, preventing the usual rise in intracellular calcium concentrations and resulting in activation of multiple signal transduction pathways, kinases, and transcription factors.\(^2\)\(^6\)\(^,\)\(^2\)\(^7\) TNF\(\alpha\) was first recognized as a possible mediator of cardiac dysfunction in sepsis after exposure to endotoxin.\(^2\)\(^8\)\(^,\)\(^2\)\(^9\) Since that time, elevated TNF\(\alpha\) has been demonstrated in many cardiac conditions, including myocarditis, hypertrophic car-
TNFα has been implicated in HF disease progression. Animal studies have demonstrated increased cardiac expression of TNFα in failing myocardium and noted that overexpression of myocardial TNFα resulted in left ventricular dysfunction and dilatation.43–47 TNFα also has been shown to be a mediator of hypertrophy and to contribute to adverse left ventricular remodeling.48 Despite its many deleterious effects, TNFα was demonstrated to have some protective effects, namely against acute ischemic injury.49,50 Overall, TNFα has a complex role in the inflammatory processes that is still incompletely elucidated.

Human studies of TNFα were performed in specific populations such as those enrolled in a randomized controlled trial of the inotropic drug vesnarinone and thus are not generalizable to the majority of HF patients. Specifically, clinical studies evaluating serum TNFα and clinical trials targeting TNFα were restricted to patients with severe systolic dysfunction (EF ≤30% to 35%). Thus, although more than half of all HF patients have preserved EF, there have been no clinical studies examining the role of TNFα in these patients. Furthermore, although prior studies reported that TNFα was elevated in the setting of systolic dysfunction, its distribution and determinants remain incompletely defined. Indeed, reports conflict on the association of TNFα level with HF severity, with some studies demonstrating increased levels with worsening NYHA functional class and other studies demonstrating no association.5,44 Similarly, studies noted that higher TNFα may be associated with older age, decreased renal function, and decreased body weight, whereas another failed to do so.53 Finally, the need for community studies examining the role of TNFα was recognized but up to now not addressed.

The present study contributes to addressing these gaps in knowledge in that it demonstrates that elevated circulating TNFα is present in approximately one third of community HF patients with a wide range of EF and is associated with decreasing hemoglobin and creatinine clearance, greater comorbidity, and current nonsmoking status. Although we identified a marginal trend toward higher TNFα levels with older age, we found no association between TNFα and NYHA functional class. In addition, the present data challenge the prior notion that TNFα may be a marker of “cardiac cachexia” given the lack of association with body mass index.

In clinical trials of HF with severe systolic dysfunction, elevated TNFα was associated with increased mortality.5,6 However, data from HF patients in the community and with preserved EF were lacking. The present study demonstrated that elevated TNFα is independently associated with mortality in patients with both preserved and reduced EF, thereby underscoring the relevance of this biomarker for risk prediction in all categories of the HF syndrome.

Furthermore, the data presented here indicated that TNFα makes a substantial contribution to risk prediction. Indeed, as recently underscored, hazard ratios and probability values are useful in determining statistical significance, but to demonstrate clinical utility in risk prediction, further measures must be reported.44 One established way of examining incremental changes in predictive ability involves measuring the area under the receiver operating characteristic curve. By using receiver operating characteristic analysis, we demonstrated that TNFα provides an improved risk prediction over established indicators.

### Study Strengths and Limitations

Although Olmsted County is becoming more diverse, the population studied was primarily white, so these data should be replicated in other racial and ethnic groups. The participation rate for the study was 71%, which is similar to rates reported in other community studies of cardiovascular disease.53,44 Furthermore, it should be noted that blood specimens are stored for future research as part of the present study, and assessment of other factors, including biomarkers, is likely in future investigations. The present study has several notable strengths. First, we examined TNFα in a large community HF population, which has not previously been reported.

### Table 2. Hazard Ratios (95% Confidence Intervals) for Death Associated With TNFα Quartile

<table>
<thead>
<tr>
<th>Quartile 1, TNFα ≤1.5 pg/mL</th>
<th>Quartile 2, 1.5 ≤TNFα &lt; 3.1 pg/mL</th>
<th>Quartile 3, 2.1 ≤TNFα &lt; 3.1 pg/mL</th>
<th>Quartile 4, TNFα ≥3.1 pg/mL</th>
<th>P\textsubscript{trend}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted 1 (Reference)</td>
<td>1.34 (0.82–2.19)</td>
<td>1.47 (0.89–2.44)</td>
<td>2.010 (1.30–3.38)†</td>
<td>0.002</td>
</tr>
<tr>
<td>Model 1</td>
<td>1.24 (0.76–2.04)</td>
<td>1.37 (0.83–2.28)</td>
<td>1.90 (1.18–3.08)†</td>
<td>0.007</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.46 (0.87–2.43)</td>
<td>1.57 (0.92–2.64)</td>
<td>2.37 (1.43–3.93)†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Model 3</td>
<td>1.27 (0.75–2.14)</td>
<td>1.26 (0.73–2.16)</td>
<td>1.88 (1.09–3.25)∗</td>
<td>0.028</td>
</tr>
</tbody>
</table>

Model 1 was adjusted for age, sex, and EF. Model 2 was adjusted also for hypertension, hyperlipidemia, smoking status, body mass index, diabetes mellitus, coronary artery disease, chronic obstructive pulmonary disease, NYHA functional class, and atrial fibrillation/flutter. Model 3 was adjusted also for creatinine clearance and anemia.

\*P<0.05; †P<0.01.

### Table 3. Area Under Receiver Operating Characteristic Curves Predicting 6-Month Mortality

<table>
<thead>
<tr>
<th>Area Under the Curve, Overall (n=486)</th>
<th>Model Without TNFα</th>
<th>Model With TNFα</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td>0.500</td>
<td>0.600 (0.534–0.666)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Model 1</td>
<td>0.671 (0.610–0.732)</td>
<td>0.700 (0.642–0.758)</td>
<td>0.035</td>
</tr>
<tr>
<td>Model 2</td>
<td>0.687 (0.627–0.747)</td>
<td>0.723 (0.667–0.779)</td>
<td>0.030</td>
</tr>
<tr>
<td>Model 3</td>
<td>0.742 (0.689–0.795)</td>
<td>0.777 (0.728–0.826)</td>
<td>0.018</td>
</tr>
</tbody>
</table>

*Model 1 was adjusted for age and sex. Model 2 was adjusted also for risk factors (hypertension, hyperlipidemia, diabetes mellitus, tobacco use, and prior coronary artery disease). Model 3 was adjusted also for NYHA functional class and EF.
reported. Second, patients with the full spectrum of EF were examined, and complete EF ascertainment was present. This enabled the evaluation of the role of TNFα in patients with preserved EF for the first time.

Conclusions
Elevated levels of the inflammatory cytokine TNFα are present in a large subset of community patients with HF with both preserved and reduced EF. TNFα is independently associated with increased mortality. Furthermore, TNFα improves risk prediction above other established indicators and can be useful for risk stratification in patients with HF.

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Disclosures
None.

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Mortality among patients with heart failure is high. Interest has risen recently in the use of biomarkers to aid in identifying heart failure patients at increased mortality risk. Tumor necrosis factor-α (TNFα), an inflammatory cytokine, has previously been reported to be elevated in heart failure clinical trial patients with reduced ejection fraction and associated with increased mortality. However, data on patients with preserved EF and those living in the community were lacking. Among community heart failure patients with both preserved and reduced ejection fraction, our study findings indicate that TNFα is elevated in 29% of patients and that higher levels are more common in patients with increased comorbidity, including renal insufficiency and anemia. Higher TNFα was associated with increased mortality, and TNFα significantly improved mortality risk prediction. These findings suggest that measurement of TNFα in patients presenting with heart failure may aid in the identification of patients at highest mortality risk regardless of ejection fraction.
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Shannon M. Dunlay, Susan A. Weston, Margaret M. Redfield, Jill M. Killian and Véronique L. Roger

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