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CLINICAL RESEARCH

Combined Free Light Chains Are Novel Predictors of Prognosis in Heart Failure

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ABSTRACT

OBJECTIVES This study investigated the prevalence and potential incremental prognostic value of combined free light chains (cFLCs) in patients recently hospitalized with decompensated heart failure (HF).

BACKGROUND Inflammatory pathways are recognized in the pathogenesis and progression of HF. Free light chain (FLC) elevation is conventionally associated with monoclonal gammopathies, including multiple myeloma. Polyclonal increases in both kappa and lambda FLCs occur in autoimmune and other chronic inflammatory conditions. Recently, a novel assay for measuring kappa and lambda immunoglobulin FLCs together, known as combined free light chain (cFLC) has been developed.

METHODS Six hundred twenty-eight patients recently hospitalized with decompensated HF were studied. cFLCs were measured by turbidimetry using an immunoassay. The incremental prognostic value of cFLCs for mortality was evaluated using Cox proportional hazard models including 22 established predictors of outcome in HF.

RESULTS Of 628 patients, 290 (46%) died during a follow-up of 3.2 ± 1.5 years. Two hundred seventy patients (43%) had elevated cFLCs. There was a clear gradient in the risk of death according to cFLC quartile, with those in the top quartile having an unadjusted risk of mortality more than twice that of those in the lowest quartile (hazard ratio: 2.38; $p < 0.0001$). After multivariable analysis, cFLC remained an independent predictor of mortality, with an almost 50% higher adjusted risk for those in the top compared with bottom quartile. Older age, lower body mass index, New York Heart Association classification III/IV, previous myocardial infarction, current smoking and B-type natriuretic peptide, bilirubin, high-sensitivity C-reactive protein, glycated hemoglobin, and lymphocyte concentrations were also independent predictors of mortality.

CONCLUSIONS cFLCs are an independent predictor of mortality in patients recently hospitalized with decompensated HF. Further work is required to assess the effects of HF therapies on cFLC concentrations and whether or not directly targeting this marker of inflammation improves prognosis for patients with HF. (J Am Coll Cardiol HF 2015;3:618–25)

Inflammation is believed to play a role in the pathophysiology of heart failure (HF) and an association between levels of several inflammatory biomarkers, particularly cytokines, and fatal and non-fatal outcomes have been demonstrated in patients with HF (1). B cell–derived plasma cells are central to humoral immune defense, producing immunoglobulins (antibodies) against pathogens and

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pathogen-related toxins. When aberrant, this antibody response may lead to autoimmune disease. Immunoglobulins (antibodies) consist of heavy and light chains with the latter comprising either kappa or lambda variants. B cells, plasma blasts, and plasma cells produce surplus light chains; those not bound to heavy chains can be detected as soluble free light chains (FLCs) in plasma/serum. FLC elevation is conventionally associated with monoclonal gammopathies (2–5), including multiple myeloma. Polyclonal increases in both kappa and lambda FLCs occur in autoimmune and other chronic inflammatory conditions, characterized by chronic B cell maturation, activation, and consequent increased immunoglobulin production such as rheumatoid arthritis, systemic lupus erythematosus, and chronic obstructive pulmonary disease (6–8). Conditions impairing FLC clearance, such as renal or reticuloendothelial system diseases, may also result in elevation of polyclonal FLC concentrations (9–12).

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Traditional methods of measuring excess immunoglobulins, such as serum protein electrophoresis or immunofixation, may not detect minor increases in serum light chains. More sensitive nephelometric assays measuring individual kappa and lambda FLC concentrations have been available for approximately a decade (13). Recently, a sensitive and novel assay measuring both kappa and lambda FLCs, referred to as combined free light chains (cFLCs), has been developed (14). Using this new assay, we have studied the prevalence and prognostic value of elevated cFLC concentrations in HF.

METHODS

Our study complied with the Declaration of Helsinki and was approved by the Local Ethics Committee. All patients provided written informed consent.

STUDY DESIGN. The study design is described elsewhere (15). Briefly, we enrolled 1,003 near-consecutive patients with decompensated HF from 3 hospitals. HF was defined according to the criteria of the European Society of Cardiology (16). Eligible patients were also required to be 18 years of age or older and to have an elevated B-type natriuretic peptide (BNP >100 pg/ml). The main exclusion criteria were primary presentation with myocardial infarction (MI) and significant cognitive impairment or concurrent systemic disease likely to result in reduced life expectancy. Attendance for the study visit was planned 1 month post-discharge. Of 1,003 patients originally enrolled, 648 patients (65%) returned for the study visit. Failure to attend was due to death (n = 115, 11%), deterioration in health (n = 73, 7%), or withdrawal of consent (n = 167, 17%).

LABORATORY MEASUREMENTS. Whole blood was drawn from venipuncture into serum and plasma vacutainers. Samples were processed immediately by centrifugation at 3,000 g for 15 min and serum and plasma fractions were aliquoted for storage at -80°C until assay. cFLCs were measured by turbidimetry using the Combylite immunoassay on a SPAplus automated analyzer (The Binding Site Group Ltd., Birmingham, United Kingdom). Elevated concentrations of cFLCs were defined as >45.7 mg/l, above the 95% reference range for the combined kappa and lambda FLC assays (17). Combylite immunoassay has a limit of quantification of 0.63 mg/l on neat samples, and assay precision (coefficient of variation) of 5.5% around the upper reference interval (54 mg/l) (14). High-sensitivity C-reactive protein (hsCRP) was assayed using a Siemens immunoassay on a Siemens BN II nephelometer (Siemens Healthcare Diagnostics GmbH, Marburg, Germany). Plasma BNP was measured using an Abbott Architect assay (Abbott Diagnostics, Maidenhead, United Kingdom). cFLCs were measured by The Binding Site Group Ltd., who supplied the assay results to the study statistician (CH) but did not have access to any other data and were not involved in the data analysis. All other biomarker assays were performed in local laboratories in Glasgow, United Kingdom.

LEFT VENTRICULAR EJECTION FRACTION. Left ventricular ejection fraction (LVEF) was measured by 2-dimensional echocardiography. Analysis was performed offline, using the biplane method of discs (modified Simpson's rule) by a single operator blinded to patient information. Twenty-six patients had an incalculable LVEF by this method. Reduced systolic function was defined as LVEF <50% (18).

FOLLOW-UP. All enrolled patients consented to be "flagged" with the Information Services Division of the Scottish Health Service for data on in-hospital and out-of-hospital deaths, held by the General Register Office for Scotland. The primary outcome measure of this study was death from any cause.

STATISTICAL ANALYSIS. Differences in clinical characteristics according to quartiles of cFLC concentration were compared using 1-way analysis of variance for continuous variables and Fisher's test for categorical variables. All continuous variables were transformed as appropriate to normalize their distributions.

ABBREVIATIONS AND ACRONYMS

BMI = body mass index

BNP = B-type natriuretic peptide

cFLC = combined free light chains

HF = heart failure

hsCRP = high-sensitivity C-reactive protein

LVEF = left ventricular ejection fraction

MI = myocardial infarction

NYHA = New York Heart Association

RDW = red cell distribution width

Survival time was calculated from the date of the study visit (between January 16, 2007 and March 6, 2009) until death or censoring at August 31, 2012. Inter-group differences in mortality rates were investigated using a chi-squared test. Kaplan-Meier survival curves were constructed to show survival of patients according to cFLC concentration. Curves were compared using the log-rank test. The incremental prognostic value of cFLC was evaluated using Cox proportional hazard models including established predictors of outcome in HF. These predictors were prospectively selected from the clinical model derived by the CHARM investigators (Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity) (19) and routine hematological and biochemical variables predictive of outcome in the subsequent CHARM analyses (20,21). The established predictors of outcome included: age, sex (men vs. women), smoking habit (current vs. none or past), history of HF for more than 2 years, New York Heart Association (NYHA) functional class (III/IV vs. I/II), LVEF, medical history (MI, diabetes mellitus, chronic obstructive pulmonary disease, peripheral arterial disease), left bundle branch block on electrocardiogram, heart rate, systolic blood pressure, body mass index (BMI), peripheral edema, bilirubin, urate, creatinine, hemoglobin, glycosylated hemoglobin, lymphocytes, and red cell distribution width (RDW). BNP and hsCRP were also included. Restricted cubic splines with 5 knots were performed on all continuous variables and the data were log transformed to improve linearity if splines revealed a non-linear relationship. Log transformations were all natural logs, and improvement in linearity was determined by a combination of inspecting spline plots and an increased Wald linearity p value (with the null hypothesis being that data are linear). Cutpoints for continuous biomarkers were determined using survival receiver-operating characteristic (ROC) curves using the freely distributed R package Hmisc. All other statistical analyses were performed using R version 2.15.0 (R Foundation for Statistical Computing, Vienna, Austria) or SAS version 9.3 (SAS Institute, Cary, North Carolina), or later versions of these programs, and a p value <0.05 was considered statistically significant. Model performance and comparison was assessed using Harrel's c-statistic (22). The net reclassification index (NRI) (23), adapted for use in survival models (24), was used to assess if cFLCs improved the prediction of outcome, in addition to BNP. For model comparison, c-statistics were generated using ordinary non-parametric bootstrapping with 1,000 replicates, and then p values obtained from paired Student *t* tests. Internal validation was performed by bootstrapping, using Somers' Dxy rank correlation as the marker of validation, to evaluate the predictive performance of the data. No adjustment has been made for multiple comparisons.

RESULTS

STUDY COHORT AND CLINICAL CHARACTERISTICS ACCORDING TO cFLC CONCENTRATION. Of 648 patients completing the study, 628 (97%) had cFLC analysis performed on stored blood samples. The baseline clinical characteristics of the patients are summarized in **Table 1**, for both the overall cohort and per quartile of cFLC concentration. The mean (SD) age of the overall cohort was 71 ± 11 years and 367 (58%) were male. The median (interquartile range) cFLC concentration was 41.9 (29.5 to 62.2) mg/l. Of 628 patients, 270 (43%) had elevated cFLC concentrations (defined as >45.7 mg/l) (17).

Patients with an elevated cFLC concentration were older and more likely to be male. A history of HF before the index hospitalization was more common among those with increased cFLC concentration and the presence of peripheral edema at the baseline assessment more common among those with elevated cFLCs. Patients with an elevated cFLC concentration were more likely to have a history of hypertension, diabetes mellitus, and peripheral artery disease. There was no difference in LVEF according to cFLC concentration and the use of HF medications was similar between the 4 groups, although there was a trend towards patients with lower cFLC concentrations being more likely to be prescribed an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker than those with higher cFLC concentrations. There was no difference in blood pressure or heart rate between the groups.

BNP, hsCRP, RDW, urate, and glycosylated hemoglobin concentrations were higher in patients with elevated cFLCs. Renal dysfunction, anemia, and lymphopenia were also more common in these patients.

The prevalence of rheumatoid arthritis and connective tissue diseases was low in the patients overall and did not differ according to cFLC concentration. There were no patients with diagnosed monoclonal gammopathies (including monoclonal gammopathy of unknown significance, primary systemic amyloidosis, multiple myeloma, Waldenstrom macroglobulinemia, and light-chain-deposition disease); these conditions are conventionally associated with abnormal amounts of FLCs.

OVERALL SURVIVAL AFTER HOSPITAL ADMISSION WITH DECOMPENSATED HF. The mean follow-up was 3.2 ± 1.5 years. Of the 628 patients, 290 (46%) died during the follow-up period.

TABLE 1 Baseline Characteristics Overall and Stratified by Quartiles of cFLC Concentration

	Overall (n = 628)	Q1 (<29.5 mg/l) (n = 157)	Q2 (29.5–41.9 mg/l) (n = 157)	Q3 (41.9–62.2 mg/l) (n = 157)	Q4 (>62.2 mg/l) (n = 157)	p Value
Demographic characteristics						
Age, yrs	70.8 ± 10.6	66.1 ± 12.2	71.3 ± 10.2	72.6 ± 9.1	73.3 ± 9.3	<0.0001
Male	367 ± 58.4	78 ± 49.7	81 ± 51.6	96 ± 61.1	112 ± 71.3	<0.001
Current smoker	137 ± 21.8	39 ± 24.8	37 ± 23.6	27 ± 17.2	34 ± 21.7	0.372
HF status						
Previous diagnosis HF	273 ± 43.5	58 ± 36.9	67 ± 42.7	66 ± 42.0	82 ± 52.2	0.052
HF >2 yrs	194 ± 30.9	40 ± 25.5	48 ± 30.6	51 ± 32.5	55 ± 35.0	0.309
NYHA functional class III/IV (vs. I/II)	208 ± 33.1	40 ± 25.5	55 ± 35.0	56 ± 35.7	57 ± 36.3	0.127
LVEF, %	40.1 ± 12.1	38.7 ± 11.7	41.6 ± 12.6	40.1 ± 12.8	39.9 ± 11.2	0.213
LVEF <50%	466 ± 77.4	123 ± 81.5	109 ± 71.2	114 ± 78.1	120 ± 78.9	0.184
Peripheral edema	421 ± 67.0	82 ± 52.2	99 ± 63.1	112 ± 71.3	128 ± 81.5	<0.0001
Medical history						
MI	285 ± 45.5	61 ± 38.9	76 ± 48.4	73 ± 46.5	75 ± 47.8	0.292
Hypertension	404 ± 64.3	82 ± 52.2	106 ± 67.5	102 ± 65.0	114 ± 72.6	0.002
Diabetes mellitus	195 ± 31.1	29 ± 18.5	45 ± 28.7	52 ± 33.1	69 ± 43.9	<0.0001
AF	334 ± 53.2	84 ± 53.5	66 ± 42.0	96 ± 61.1	88 ± 56.1	0.006
COPD	177 ± 28.2	35 ± 22.3	53 ± 33.8	47 ± 29.9	42 ± 26.8	0.141
PAD	102 ± 16.2	11 ± 7.0	26 ± 16.6	29 ± 18.5	36 ± 22.9	<0.001
Rheumatoid arthritis	17 ± 2.7	7 ± 4.5	3 ± 1.9	3 ± 1.9	4 ± 2.5	0.495
Connective tissue disease	12 ± 1.9	3 ± 1.9	5 ± 3.2	1 ± 0.6	3 ± 1.9	0.479
Physiological measurements						
HR, beats/min	77.1 ± 15.6	79.0 ± 16.9	77.6 ± 14.8	77.0 ± 16.0	74.8 ± 14.2	0.124
SBP, mm Hg	130.9 ± 23.4	129.2 ± 23.6	131.8 ± 24.2	131.8 ± 22.0	130.9 ± 23.9	0.727
DBP, mm Hg	67.8 ± 13.2	69.3 ± 13.5	67.6 ± 13.3	68.2 ± 12.9	66.1 ± 13.2	0.186
BMI, kg/m^2	28.6 ± 6.7	28.5 ± 6.8	28.6 ± 7.0	28.5 ± 6.0	28.9 ± 7.0	0.948
LBBB	120 ± 19.1	37 ± 23.6	28 ± 17.8	28 ± 17.8	27 ± 17.2	0.458
Laboratory measurements						
BNP, pg/ml	393 [201-796]	323 [164-697]	364 [188-733]	432 [207-870]	439 [235-926]	0.033
Urea, mmol/l	9.7 ± 5.1	7.2 ± 2.7	8.0 ± 3.3	9.8 ± 4.5	13.8 ± 6.2	<0.0001
Creatinine, μmol/l	117 ± 44	94 ± 21	102 ± 24	118 ± 33	156 ± 57	<0.0001
eGFR, ml/min/1.73 m^2	50 ± 17	55 ± 18	53 ± 16	51 ± 17	40 ± 15	<0.0001
eGFR, <60 ml/min/1.73 m^2	337 ± 54	41 ± 26.1	68 ± 43.3	95 ± 60.5	133 ± 84.7	<0.0001
eGFR, <30 ml/min/1.73 m^2	50 ± 8.0	0 ± 0	4 ± 2.5	8 ± 5.1	38 ± 24.2	<0.0001
Bilirubin, μmol/l	11.6 ± 8.0	11.5 ± 7.2	11.1 ± 7.3	11.9 ± 6.9	11.9 ± 10.0	0.774
hsCRP, mg/l	9.3 ± 13.2	5.3 ± 7.7	7.8 ± 10.9	9.5 ± 11.9	14.7 ± 18.3	<0.0001
Urate, mmol/l	0.47 ± 0.14	0.40 ± 0.12	0.44 ± 0.13	0.49 ± 0.14	0.53 ± 0.15	<0.0001
HbA1c, %	6.3 ± 1.3	6.1 ± 1.2	6.3 ± 1.3	6.4 ± 1.3	6.5 ± 1.5	0.049
Hemoglobin, g/l	12.5 ± 2.0	13.3 ± 2.0	12.7 ± 2.0	12.5 ± 1.8	11.7 ± 1.9	<0.0001
White cell count, × 10^9/l	7.9 ± 2.4	8.0 ± 2.9	7.8 ± 1.9	7.8 ± 2.2	8.1 ± 2.5	0.511
RDW, %	15.6 ± 2.5	15.0 ± 2.0	15.7 ± 2.6	15.5 ± 2.2	16.2 ± 2.9	<0.001
Lymphocytes, × 10^9/l	1.9 ± 1.3	2.2 ± 2.2	1.8 ± 0.7	1.8 ± 0.7	1.7 ± 0.8	0.007
Medical therapies						
Diuretic	603 ± 96.0	147 ± 93.6	151 ± 96.2	152 ± 96.8	153 ± 97.5	0.405
ACEI or ARB	501 ± 79.8	134 ± 85.4	129 ± 82.2	120 ± 76.4	118 ± 75.2	0.077
MRA	84 ± 13.4	21 ± 13.4	19 ± 12.1	22 ± 14.0	22 ± 14.0	0.955
Beta blocker	416 ± 66.2	107 ± 68.2	99 ± 63.1	107 ± 68.2	103 ± 65.6	0.744

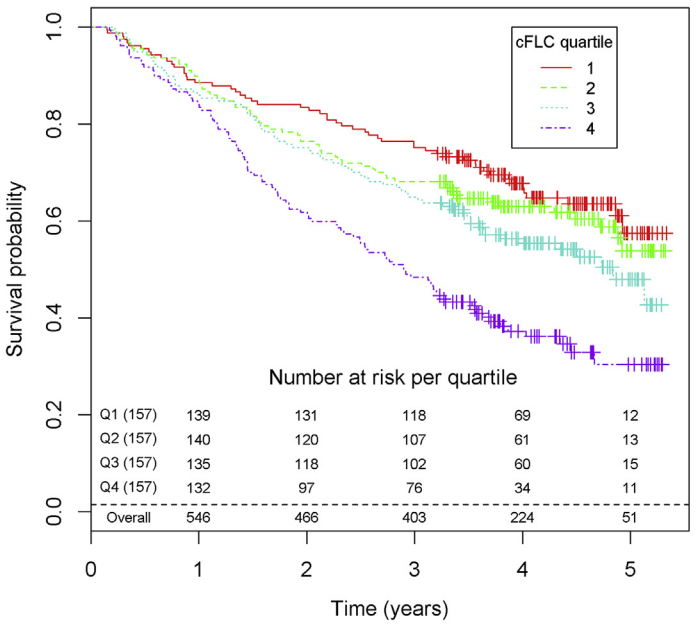
Values are mean ± SD or median [interquartile range].

ACEI = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin receptor blocker; BMI = body mass index; BNP = B-type natriuretic peptide; cFLC = combined free light chains; COPD = chronic obstructive pulmonary disease; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; HBA1c = glycosylated hemoglobin; HF = heart failure; HR = heart rate; hsCRP = high-sensitivity C-reactive protein; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; MI = myocardial infarction; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association classification; PAD = peripheral arterial disease; Q = quartile; RDW = red cell distribution width; SBP = systolic blood pressure.

UNADJUSTED OUTCOMES ACCORDING TO cFLC CONCENTRATION. Patients with higher cFLC concentrations had higher mortality rates during the follow-up period (Figure 1). There was a clear gradient in the risk of death according to cFLC quartile (Q) with the highest risk in patients with the highest cFLC concentration. There were 55 (35%), 62 (39%), and 73 (46%) deaths among patients in Q1, Q2, and Q3, respectively. Of 157 patients in the top quartile (Q4), 100 (64%) died, and the unadjusted risk of mortality for these patients was more than twice that of those in Q1 (hazard ratio [HR]: 2.38; $p < 0.0001$). Patients were stratified according to BNP and cFLC concentration using ROC curve cutoff values of 441 pg/ml and 51.8 mg/l, respectively. Patients with low BNP and low cFLC concentrations were at lowest risk of mortality and patients with high BNP and high cFLC concentrations were at greatest risk, whereas elevation of either biomarker was associated with an intermediate risk during follow-up ($p < 0.0001$) (Figure 2).

When analyzed as a continuous variable, the HR for all-cause mortality was 1.37 (95% confidence interval [CI]: 1.24 to 1.52) per SD of log cFLC per SD ($p < 0.001$).

FIGURE 1 Survival Curves for All-Cause Mortality Stratified by cFLC Concentration in Quartiles



Kaplan-Meier analyses show an increasing gradient of risk with increasing quartile, with patients in the top quartile (Q4) having the highest mortality rates ($p < 0.0001$). cFLC = combined free light chain concentration.

MULTIVARIABLE ANALYSIS INCLUDING cFLC CONCENTRATION. Univariate and multivariable analyses are shown in Table 2. The majority of variables were significant univariate predictors of mortality. cFLC concentration was also a significant independent predictor of mortality (HR: 1.49; $p = 0.01$ for Q4 vs. Q1 to Q3) in the multivariable analysis. Age, previous MI, NYHA III/IV, BMI, current smoking and BNP, bilirubin, hsCRP, glycated hemoglobin, and lymphocyte concentration were also independent predictors of mortality. The multivariable model was repeated with cystatin C (data not shown), a more sensitive marker of renal function, substituted for creatinine, and cFLC remained an independent predictor of risk of death (HR: 1.45; $p = 0.03$).

The c-statistic for the model (with creatinine) increased from 0.728 to 0.734 with the addition of cFLC as Q1 to Q3 versus Q4 ($p < 0.0001$).

When analyzed as a continuous variable, the HR for all-cause mortality was 1.17 (95% CI: 1.01 to 1.36) per SD of log cFLC per SD ($p = 0.042$). The c-statistic increased from 0.728 to 0.730 ($p < 0.0001$).

NRI for the addition of cFLC (Q4 vs. Q1 to Q3) to BNP (dichotomized according to ROC cutpoint 441 pg/ml) was high with an overall NRI of 0.439 (95% CI: 0.292 to 0.586; $p < 0.0001$). Compared with the model using just BNP, the predicted probability of an event (death) using the model with both BNP and cFLCs was higher for 46.21% of patients with an event and lower for the other 53.79%, resulting in an NRI of -7.6% (95% CI: -19.1% to 3.9%; $p = 0.195$) for those patients who died. Using the same model, the predicted probability was lower for 75.74% of patients who did not have an event (i.e., did not die) and higher for the other 24.26%, resulting in an NRI of 51.5% (95% CI: 42.3% to 60.6%; $p < 0.0001$) for those who survived. The overall NRI was therefore 43.9% (95% CI: 29.2% to 58.6%; $p < 0.0001$). Validation by bootstrap (300 replicates) resulted in an optimism of 5%.

DISCUSSION

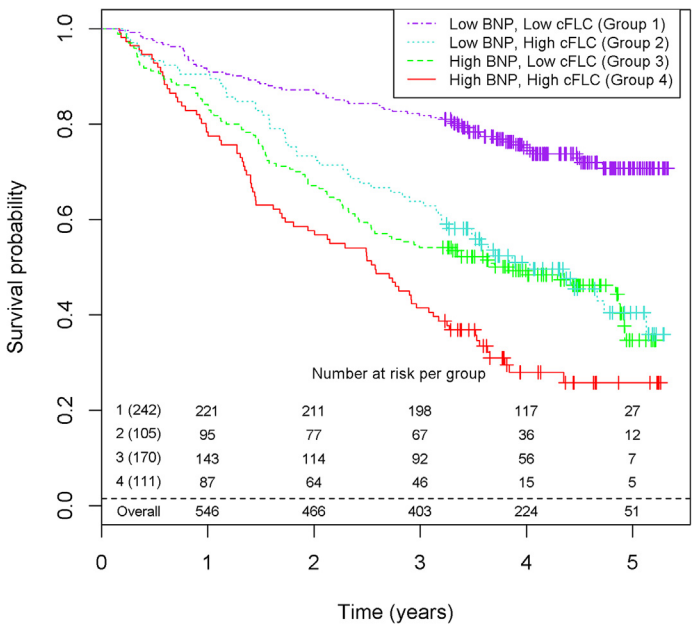
To our knowledge this is the first study to describe the prevalence and prognostic significance of elevated cFLC concentrations in a large group of patients recently hospitalized with decompensated HF. The first notable finding was that almost one-half of these patients had an elevated cFLC concentration. The second important finding was that patients with elevated cFLC concentrations were at increased risk of death. Moreover, after adjustment for other prognostic factors in a multivariable model,

elevated cFLC concentration remained an independent predictor of mortality with a 30% higher adjusted risk of death. The prognostic variables prospectively included in the multivariable model incorporated a comprehensive list of established predictors of risk in HF (19–21). This list included BNP, which is consistently found to be the most powerful prognostic marker in HF and to which few, if any, new markers add incremental predictive information. Furthermore, cFLC improved net reclassification in addition to BNP.

CAUSE OF ELEVATED cFLCs IN HF. The cause of elevated cFLCs in patients with HF is unknown. It may reflect generalized immune system activation or represent a more specific inflammatory response, as seen in viral myocarditis (25). The hazard related to increased cFLC concentration in the present study was independent of hsCRP. Although several other inflammatory biomarkers have also been shown to have independent prognostic value in HF (e.g., serum soluble ST2) (26), it may be that the mechanism underlying cFLC elevation in HF may be more than just simply generalized immune system activation. FLC concentrations also reflect renal clearance, which may be reduced in HF. However, the ability of this biomarker to provide risk stratification independent of creatinine, and cystatin C, suggests that elevated cFLCs is not simply a surrogate for reduced kidney function. Our finding of elevated cFLCs also suggests it may be of interest to study other B cell–related cytokines such as interleukin-6, B-lymphocyte stimulator, and proliferation-inducing ligand in HF.

ASSOCIATION BETWEEN cFLCs AND PROGNOSIS. There are a number of ways in which elevated FLCs might be associated with worse prognosis. Elevated FLCs may represent an immune response to endotoxins, which have entered the circulation through a leaky intestinal tract, as is believed to occur in patients with advanced HF and which may contribute to progression of the syndrome through cytokine activation and other inflammatory mechanisms. Alternatively, FLCs might reflect autoantibody production to myocyte proteins, as seen in myocarditis and transplant rejection, or to beta-adrenoceptors. FLCs may themselves have a direct and adverse biological effect. FLCs are believed to activate mast cells, which play a central role in the inflammatory process (27), producing mediators such as cytokines, which may have a deleterious role in HF. Mast cells have been shown to cause apoptosis of cardiac myocytes and proliferation of non-myocardial cells in an animal model of HF and increased mast cell density is recognized in hearts with left ventricular systolic dysfunction compared with normal hearts (28,29). This study suggested that the initial compensatory effect of the immune system response might lead to cardiac remodeling and ultimately progression of HF severity. Whether or not a similar potential pathophysiological process underlies chronic elevation of FLCs in HF is unknown. On the other hand, it is also possible that cFLCs may simply represent a non-specific marker of widespread immune system activation, rather than directly being involved in the pathogenesis of HF.

FIGURE 2 Survival Curves for All-Cause Mortality Stratified According to Receiver Operating Characteristic Curves for BNP and cFLC Concentrations



Kaplan-Meier analyses show patients with elevated BNP and elevated cFLC to be at greatest risk, patients with low BNP and low cFLC at lowest risk, and patients with either biomarker elevated to have an intermediate risk ($p < 0.0001$). BNP = B-type natriuretic peptide; cFLC = combined free light chain concentration.

POTENTIAL ROLE OF cFLCs IN THE MANAGEMENT OF HF? cFLC measurement is a simple, readily available blood test that identifies patients at increased mortality risk in this study. A single measurement of cFLCs led to a significant improvement in net reclassification but longitudinal monitoring of this biomarker may be even more useful for risk stratification and identifying patients at particularly high risk. However, the effect of disease progression on cFLC concentrations is unknown.

The effects of HF therapies on cFLC concentrations is unknown, as is the effect of immune modulating

TABLE 2 Univariate Analysis and Multivariable Model for All-Cause Mortality

	Univariate Analysis HR (95% CI); p Value	Multivariable Model HR (95% CI); p Value
Clinical variables		
Age, yrs, per SD	1.60 (1.40-1.83); <0.0001	1.42 (1.19-1.63); <0.001
Female	0.88 (0.70-1.12); 0.30	–
Current smoker	1.14 (0.87-1.50); 0.36	1.57 (1.12-2.19); 0.008
HF >2 yrs	1.50 (1.18-1.90); <0.001	–
NYHA functional class III/IV	1.83 (1.45-2.31); <0.0001	1.33 (1.02-1.73); 0.033
LVEF, per SD <50%	1.20 (1.07-1.34); 0.002	–
MI	1.75 (1.39-2.21); <0.0001	1.54 (1.19-2.00); 0.001
Diabetes mellitus	1.17 (0.92-1.50); 0.199	–
COPD	1.37 (1.07-1.75); 0.012	–
PAD	1.04 (0.76-1.42); 0.811	–
LBBB	1.51 (1.15-1.98); 0.003	–
HR, per SD	1.00 (0.88-1.12); 0.904	–
SBP, per SD	0.95 (0.84-1.06); 0.352	–
BMI, per SD <30 kg/m^2	1.36 (1.22-1.52); <0.0001	1.24 (1.08-1.42); 0.002
Peripheral edema	1.38 (1.07-1.78); 0.013	–
Laboratory parameters		
cFLC Q4 (vs. Q1-Q3)	1.97 (1.55-2.52); <0.0001	1.49 (1.09-2.03); 0.012
Log (BNP), per SD	1.62 (1.43-1.83); <0.0001	1.28 (1.10-1.49); 0.002
Bilirubin, per SD	1.29 (1.16-1.43); <0.0001	1.24 (1.10-1.41); <0.001
Urate, per SD	1.22 (1.09-1.37); <0.001	–
hsCRP, per SD	1.30 (1.18-1.42); <0.0001	1.19 (1.06-1.32); 0.003
Creatinine, per SD	1.19 (1.08-1.32); <0.001	–
Hemoglobin, per SD	0.80 (0.71-0.89); <0.0001	–
HbA1c, per SD	1.06 (0.95-1.19); 0.312	1.25 (1.07-1.46); 0.005
Log (lymphocytes), per SD	0.74 (0.66-0.82); <0.0001	0.84 (0.73-0.97); 0.019
Log (RDW), per SD	1.21 (1.10-1.34); <0.001	–

CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1.

treatments on cFLC concentrations in patients with HF. Reduction in immunoglobulin G by immunoadsorption in a small randomized study (n = 34) of patients with nonischemic dilated cardiomyopathy and β_1-adrenoceptor autoantibodies was associated with an improvement in LVEF compared with standard HF therapy (30). The effect on mortality was not reported. Only 1 previous study has reported on reduction in individual concentrations of kappa and lambda FLCs in patients with HF. In this small trial (n = 59) of patients with advanced decompensated HF, patients were randomized to receive levosimendan or standard HF treatment (31). Those receiving levosimendan had a reduction in both kappa and lambda FLC concentrations compared with those receiving standard therapy. However, no outcome data were reported. Whether or not therapeutic reduction in cFLC concentrations in patients with HF improves clinical outcomes is unknown but would seem to be of interest given the results reported herein.

STUDY LIMITATIONS. Only a single baseline measurement of cFLC concentration was available for the patients in this study. It is not known whether cFLC concentrations change over time or in response to treatment in patients with HF. Our patients were studied approximately 1 month post-hospitalization for decompensated HF; cFLC levels may differ between acutely decompensated and chronically stable patients (and ours was a survivor cohort). Nonfatal outcomes, such as hospitalization for worsening HF, and mode of death were not available. We did not have a validation cohort.

CONCLUSIONS

cFLC concentration is an independent predictor of mortality in patients recently hospitalized with decompensated HF. This simple blood test is readily available in clinical practice. Further work is required to assess the role of cFLC level as a biomarker in HF, including evaluation of the effects of HF treatment and anti-inflammatory disease modifying therapies on cFLC concentrations. Ultimately, it may be of interest to test whether directly targeting this marker of inflammation improves prognosis.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Inflammatory pathways are recognized in the pathogenesis and progression of HF. Increases in both kappa and lambda FLCs occur in autoimmune and other chronic inflammatory conditions. cFLCs are an independent predictor of mortality in patients recently hospitalized with decompensated HF.

TRANSLATIONAL OUTLOOK 1: Although an isolated measurement of cFLCs identified patients at greatest risk of death in this study, longitudinal monitoring of this biomarker may be more useful for risk stratification and identifying patients at particularly high risk.

TRANSLATIONAL OUTLOOK 2: The effects of HF therapies and immune modulating treatments on cFLC concentrations are unknown, but should be studied as these may improve risk stratification for patients with HF.

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