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The Interleukin-1 Axis and Risk of Death in Patients With Acutely Decompensated Heart Failure

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ABSTRACT

BACKGROUND Soluble ST2 (sST2), which is the soluble form of interleukin (IL)-1 receptor-like 1, identifies risk in acutely decompensated heart failure (ADHF). IL-1β is an inflammatory cytokine that has deleterious effects in myocardial remodeling and function. IL-1β inhibition has beneficial effects after acute myocardial infarction. However, the role of IL-1β in ADHF and its relationship to ST2 remain unclear.

OBJECTIVES This study sought to investigate the relationship between IL-1β and sST2, and the prognostic impact of such a relationship in patients with ADHF.

METHODS This study examined 316 consecutive patients who were hospitalized with ADHF (72 ± 12 years of age, 57% male, and left ventricular ejection fraction 45 ± 17%). Blood samples were collected at presentation, and IL-1β and sST2 levels were measured. All-cause mortality was obtained for all patients at 1 year.

RESULTS The IL-1β concentration at presentation was associated with prior HF hospitalizations, functional impairment, and higher N-terminal pro–B-type natriuretic peptide and high-sensitivity troponin T concentrations. IL-1β was higher in patients who died during the year after hospitalization (n = 52, 16.5%) (p = 0.005), and the optimal threshold was identified with levels over 49.1 pg/ml (hazard ratio: 2.5; 95% confidence interval: 1.43 to 4.49; p = 0.0014). Circulating IL-1β positively correlated with sST2 (ρ = 0.65; p < 0.001). Considering the prognostic thresholds of IL-1β (≥49.1 pg/ml) and sST2 (≥35.0 ng/ml) concentrations: all patients with low sST2 also presented with low IL-1β; among patients with high sST2, only those with also high IL-1β had a significantly higher risk of death (30% vs. 14%; hazard ratio: 2.52; 95% confidence interval: 1.40 to 4.56; p = 0.002).

CONCLUSIONS Circulating IL-1β concentrations are clinically meaningful in ADHF patients and interplay with the predictive ability of sST2. IL-1 axis-related inflammation signaling may represent a therapeutic target in ADHF. (J Am Coll Cardiol 2019;XXX) © 2019 by the American College of Cardiology Foundation.

The ST2 receptor belongs to the interleukin 1 (IL-1) receptor family, and there are both soluble (sST2) and transmembrane (ST2L) isoforms (1). Circulating levels of sST2 are increased in patients with acutely decompensated heart failure (ADHF) and represent an established predictor of worse prognosis in follow-up (2,3). sST2 is a well-acknowledged prognosis biomarker in heart failure

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(HF), approved by the Food and Drug Administration, and included in international guidelines (4). Studies suggest that sST2 plays a pathobiological role in HF progression by functioning as a decoy receptor that can sequester IL-33 and thereby prevent the cardioprotective interaction of IL-33 with transmembrane ST2L. Notably, IL-33 is a cytokine that belongs to the IL-1 family and is thought to function as an alarmin that is released by dying cells or in response to organ damage (5).

Like IL-33/ST2, IL-1β belongs to the IL-1 superfamily (6). IL-1β plays a central role in the inflammatory response and is found mainly in the circulation, where it is produced by activated macrophages. IL-1β has negative effects on myocardial remodeling and function in experimental models (7), but data about IL-1β in patients with HF are scarce because the focus has been on other cytokines. Indeed, the presence of elevated concentrations of IL-1β has only been reported in chronic HF (8-10). Inflammation is a hallmark of HF progression, but anti-inflammatory therapies directed against some cytokines, such as anti-tumor necrosis factor-α, have not been effective (11). Recently, the direct inhibition of IL-1β with a human monoclonal antibody, canakinumab, was shown to improve the prognosis of patients with myocardial infarction and elevated C-reactive protein (12).

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Although sST2 and IL-1β are both part of the IL-1 axis, little is known about their relationship. A better understanding of this relationship is likely to clarify the pathophysiological role of IL-33/ST2 and the potential of IL-1β inhibition as a therapeutic target in HF. Here, we investigated the potential relationship between sST2 and IL-1β, and the prognostic impact of such a relationship in patients with ADHF.

METHODS

STUDY POPULATION AND DESIGN. The study population was obtained from a prospective registry that enrolled 316 consecutive patients who were admitted to the Department of Cardiology at the University Hospital Virgen de la Arrixaca with a diagnosis of ADHF. ADHF was defined as rapid or gradual onset of signs and symptoms of HF resulting in unplanned hospitalization, including new-onset acute HF or decompensation of chronic HF. The presence of symptoms and signs of HF, including signs of lung congestion (pulmonary rales or signs on chest radiography), elevated concentrations of N-terminal pro-B-type natriuretic peptide (13), objective findings of LV systolic dysfunction or structural heart disease by echocardiography, and the need for intravenous furosemide within 24 h after admission were all required to be eligible for the study. Blood samples were collected from all patients upon their arrival at the emergency department. Detailed information about symptoms, clinical history, 12-lead electrocardiogram, and medication usage was collected prospectively. An echocardiographic evaluation was also performed on all patients during the hospitalization, and standardized measures were obtained according to the American Society of Echocardiography recommendations (14). Left ventricular ejection fraction (LVEF) was measured by Simpson's method, and reduced LVEF was defined as <40%. All patients received standard HF management as recommended by current guidelines (15). Clinical management decisions about each patient were made by the responsible cardiologist, who was unaware of the patient's sST2 and IL-1β concentrations. All patients were followed clinically, and no patients were lost. The primary study outcome was all-cause mortality at 1 year, which was collected from the National Insurance and Death Records. The study complied with the tenets of the Declaration of Helsinki and was approved by the local ethics committee. Written informed consent was obtained from each patient before inclusion.

BIOCHEMICAL ANALYSIS. Blood samples were obtained by venipuncture when the patient arrived at the emergency department, and aliquots of serum were stored at −80°C until analysis. Serum concentrations of IL-1β were analyzed with Quantikine ELISA Kits (Boster Biological Technology, Pleasanton, California) according to the manufacturer's instructions. Blanks, diluted standards, or samples were added as appropriate into coated wells in 96-well plates and coincubated with horseradish peroxidase-conjugated antibody at 37°C for 30 min. The reaction system was terminated with stop solution, and the absorbance was determined at 450 nm using a microplate reader (CLARIOstar; BMG Labtech, Ortenberg, Germany). Concentrations of sST2 were determined using a high-sensitivity sandwich immunoassay (Presage ST2; Critical Diagnostics, San Diego, California). The ST2 assay had within-run and total coefficients of variation of <2.5% and 4.0%, respectively. High-sensitivity troponin T (hsTnT), N-terminal pro-B-type natriuretic peptide (NT-proBNP), C-reactive protein, and other biochemical measures were obtained with commercial assays using an Elecsys 2010 Analyzer (Roche Diagnostics, Mannheim, Germany).

ABBREVIATIONS AND ACRONYMS

ADHF = acutely decompensated heart failure

CI = confidence interval

HF = heart failure

HR = hazard ratio

hsTnT = high-sensitivity troponin T

IL = interleukin

IQR = interquartile range

LVEF = left ventricular ejection fraction

NT-proBNP = N-terminal pro-B-type natriuretic peptide

sST2 = soluble isoform of IL-1 receptor-like 1

TABLE 1 Population Characteristics According to IL-1β Quartiles

	Overall (N = 316)	IL-1β Quartiles, pg/ml (1.12-21.5) (n = 79)	(21.5-32.1) (n = 79)	(32.1-49.7) (n = 79)	(49.7-258.0) (n = 79)	p Value
sST2, ng/ml	58.13 ± 38.83	42.38 ± 26.53	35.72 ± 12.32	49.81 ± 2.92	104.61 ± 45.26	<0.001
IL-1β, pg/ml	45.91 ± 45.56	10.55 ± 6.21	27.20 ± 3.04	39.81 ± 4.83	106.07 ± 54.67	<0.001
Female	137 (43.4)	33 (41.8)	43 (54.4)	28 (35.4)	33 (41.8)	0.447
Age, yrs	71.8 ± 11.7	71.8 ± 11.6	72.3 ± 11.9	70.9 ± 11.7	72.1 ± 12.0	0.799
Weight, kg	80 ± 18	80 ± 20	77 ± 12	82 ± 19	81 ± 20	0.226
Height, cm	164 ± 9	164 ± 9	162 ± 9	165 ± 10	164 ± 10	0.589
Body mass index	29.8 ± 5.7	29.6 ± 6.3	29.3 ± 4.4	29.9 ± 4.9	30.2 ± 7.0	0.432
History						
Hypertension	235 (76.8)	58 (76.3)	58 (74.4)	60 (77.9)	59 (78.7)	0.624
Diabetes mellitus	151 (49.0)	36 (46.8)	38 (48.7)	39 (50.6)	38 (50.0)	0.647
Dyslipidemia	177 (57.3)	39 (50.6)	46 (59.0)	44 (57.1)	48 (62.3)	0.189
Smoking	57 (18.6)	18 (23.4)	10 (13.0)	18 (23.7)	11 (14.5)	0.422
Alcohol use disorder	20 (6.6)	5 (6.5)	2 (2.6)	6 (8.1)	7 (9.2)	0.284
Peripheral vasculopathy	17 (5.7)	2 (2.6)	6 (8.2)	6 (8.0)	3 (4.1)	0.705
Cerebrovascular disease	29 (9.4)	4 (5.2)	12 (15.4)	9 (11.7)	4 (5.3)	0.819
Pulmonary disease	49 (16.0)	16 (20.8)	4 (5.2)	17 (22.4)	12 (15.6)	0.936
Hypothyroidism	36 (12.0)	7 (9.2)	7 (9.3)	12 (16.2)	10 (13.5)	0.240
Atrial fibrillation	148 (49.3)	43 (57.3)	33 (43.4)	36 (48.0)	36 (48.6)	0.407
Coronary disease	102 (33.3)	20 (26.0)	29 (37.7)	27 (35.1)	26 (34.7)	0.328
Myocardial infarction	72 (23.5)	14 (18.2)	22 (28.6)	18 (23.4)	18 (24.0)	0.570
Revascularization	84 (27.6)	15 (19.5)	24 (31.2)	23 (29.9)	22 (30.1)	0.179
Prior HF diagnosis	140 (46.7)	28 (36.4)	35 (46.7)	39 (51.3)	38 (52.8)	0.036
Prior HF hospitalization	117 (39.0)	22 (28.9)	31 (40.8)	31 (41.3)	33 (45.2)	0.051
Number	1.0 (1.0-2.0)	1.0 (1.0-2.0)	1.0 (0.5-1.5)	1.0 (1.0-2.0)	2.0 (1.0-2.0)	0.031
NYHA functional class						0.031
I	61 (20.5)	17 (22.1)	21 (27.6)	14 (19.4)	9 (12.3)	
II	155 (52.0)	37 (48.1)	43 (56.6)	38 (52.8)	37 (50.7)	
III	79 (26.5)	23 (29.9)	12 (15.8)	19 (26.4)	25 (34.2)	
IV	3 (1.0)	0 (0.0)	0 (0.0)	1 (1.4)	2 (2.7)	

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STATISTICAL ANALYSIS. Continuous variables were tested for normal distribution using the Kolmogorov-Smirnov test. Continuous variables are expressed as median (25th to 75th percentiles, interquartile range [IQR]) or as mean ± SD according to normality. Differences across quartiles of IL-1β were assessed using asymptotic linear-by-linear association tests for continuous or categorical variables. Differences between 1-year mortality groups were studied by analysis of variance, the Kruskal-Wallis test, or Fisher exact test, as appropriate. The correlation between IL-1β and sST2 was assessed using the Spearman correlation test. Receiver-operating characteristic curve analysis was used to assess the cutoff value for IL-1β (Youden index). A new categorical variable was created using all possible combinations of sST2 and IL-1β cutoff values: sST2 <35 ng/ml and IL-1β <49.1 pg/ml (low-low); sST2 ≥35 ng/ml and IL-1β <49.1 pg/ml (high-low); and sST2 ≥35 ng/ml and IL-1β ≥49.1 pg/ml (high-high). The case of sST2 <35 ng/ml and IL-1β ≥49.1 pg/ml (low-high) had no observations. Cox proportional hazards regression analysis was used to study the associations between baseline characteristics and 1-year mortality. Multivariable analysis was performed using 3 models: sST2 and IL-1β as continuous variables after natural logarithmic transformation (Ln), both sST2 and IL-1β as categorical variables, and the categories of the combination. For the last model (combination of categories), reverse Helmert contrasts were used in which each level was compared with all the previous ones: high-low versus low-low; high-high versus high-low + low-low. A stepwise method with bidirectional elimination was used to choose the best models that forced sST2 and IL-1β (or their combination) to be maintained. All of the covariates used in the complete models are listed in the Online Appendix. Due to missing values (<5% for all covariates), multivariate imputation by chained equations was used that considered 10 multiple imputations. Kaplan-Meier curves and log-rank tests were estimated for the categorized biomarkers. All

TABLE 1 Continued

	Overall (N = 316)	IL-1β Quartiles, pg/ml (1.12-21.5) (n = 79)	(21.5-32.1) (n = 79)	(32.1-49.7) (n = 79)	(49.7-258.0) (n = 79)	p Value
At admission						
LVED volume, ml	122 (88-178)	126 (88-181)	118 (87-178)	137 (99-179)	118 (84-171)	0.976
LVEF, %	44.8 ± 17.0	44.8 ± 15.9	44.9 ± 16.6	46.1 ± 17.7	43.2 ± 17.7	0.696
LVEF <40%	157 (57.5)	34 (54.0)	47 (63.5)	43 (58.9)	33 (52.4)	0.717
LA diameter, mm	45 (42-50)	47 (41-50)	45 (40-49)	46 (42-50)	46 (43-51)	0.330
Heart rate, beats/min	83 (68-105)	90 (70-110)	83 (66-100)	84 (68-108)	80 (66-106)	0.201
SBP, mm Hg	136 ± 30	136 ± 32	140 ± 29	135 ± 30	132 ± 27	0.353
DBP, mm Hg	74 ± 17	74 ± 17	76 ± 17	73 ± 16	72 ± 16	0.315
Sinus rhythm	153 (50.5)	40 (53.3)	43 (57.3)	36 (47.4)	34 (44.2)	0.144
Hemoglobin, g/dl	12.4 ± 2.1	12.5 ± 2.0	12.3 ± 1.9	12.3 ± 2.1	12.6 ± 2.2	0.764
Creatinine, mg/dl	1.11 (0.91-1.48)	1.07 (0.86-1.35)	1.12 (0.91-1.37)	1.12 (0.94-1.55)	1.14 (0.94-1.62)	0.076
Urea, mg/dl	51 (38-72)	47 (38-68)	52 (40-67)	51 (40-76)	53 (35-86)	0.385
Sodium, mmol/l	140 (136-142)	140 (138-142)	139 (136-141)	139 (136-142)	139 (135-141)	0.024
Potassium, mmol/l	4.4 (4.0-4.8)	4.5 (4.2-4.8)	4.4 (3.9-4.7)	4.5 (4.2-4.7)	4.4 (4.0-4.8)	0.785
NT-proBNP, pg/ml	3,569 (1,899-7,353)	4,003 (2,223-7,602)	2,725 (1,432-5,573)	3,295 (2,086-6,959)	5,114 (2,106-8,629)	0.010
hsTnT, ng/l	28 (18-52)	27 (19-42)	24 (13-54)	27 (19-41)	35 (22-97)	0.029
C-reactive protein, mg/l	9.8 (4.3-20.4)	8.8 (3.9-20.2)	9.0 (3.8-18.6)	9.5 (4.3-28.0)	10.2 (6.2-17.9)	0.235
Previous treatment						
Pacemaker	41 (13.9)	8 (10.8)	5 (6.8)	13 (18.1)	15 (20.0)	0.031
ICD	21 (7.1)	3 (4.1)	5 (6.7)	4 (5.7)	9 (12.0)	0.085
ACEI or ARB	199 (65.0)	43 (55.8)	55 (70.5)	48 (62.3)	53 (71.6)	0.112
Beta-blockers	168 (54.9)	43 (55.8)	42 (53.8)	41 (53.2)	42 (56.8)	0.939
Anti-aldosteronics	69 (22.6)	14 (18.2)	15 (19.5)	16 (20.8)	24 (32.4)	0.043
Digoxin	24 (8.0)	5 (6.6)	6 (7.8)	9 (12.3)	4 (5.4)	0.939
Amiodarone	21 (7.0)	6 (7.9)	4 (5.2)	1 (1.4)	10 (13.5)	0.327
Acetylsalicylic acid	117 (39.1)	28 (36.8)	33 (42.9)	32 (44.4)	24 (32.4)	0.646
Anticoagulation	120 (40.3)	34 (44.7)	24 (31.2)	30 (42.3)	32 (43.2)	0.799

Values are mean ± SD, n (%), or median (interquartile range).

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor antagonist; DBP = diastolic blood pressure; HF = heart failure; hsTnT = high-sensitivity troponin T; ICD = implanted cardioverter-defibrillator; IL-1β = interleukin-1β; LA = left atrial; LVED = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; SBP = systolic blood pressure; sST2 = soluble ST2.

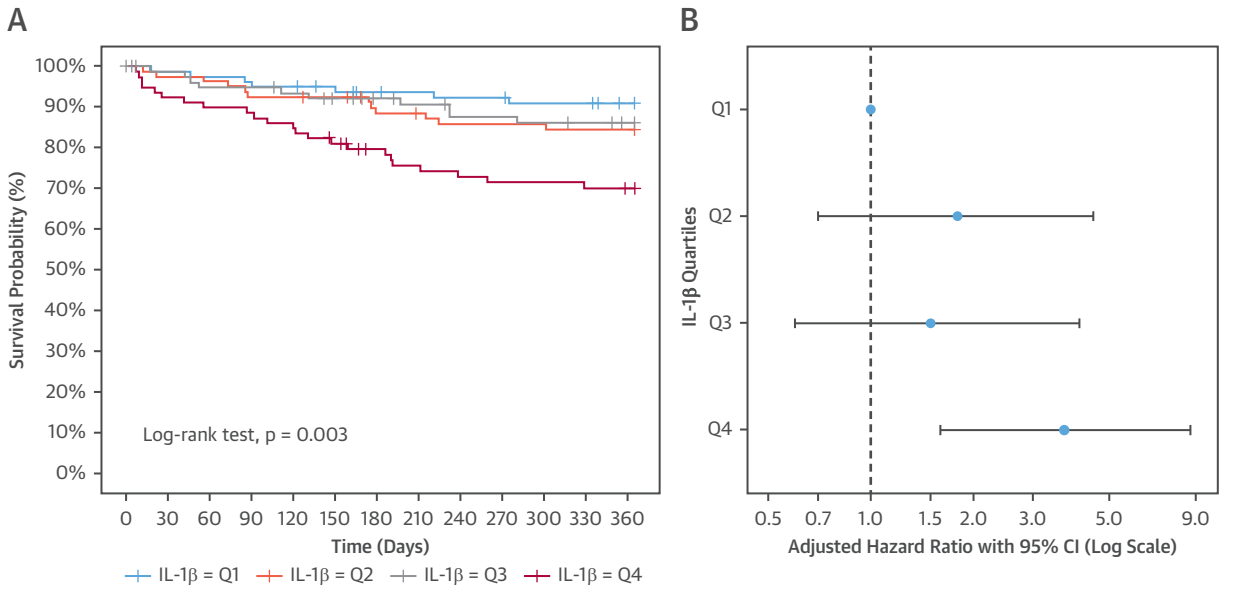
tests were 2-sided, and $p < 0.05$ was considered statistically significant.

RESULTS

STUDY POPULATION AND IL-1β. The characteristics of the study population at presentation are shown in Table 1, both for the entire population (N = 316) and by quartiles of serum IL-1β concentrations: 56.5% were male, the mean age was 71.78 ± 11.74 years, and the mean LVEF was 44.79 ± 16.95 (LVEF <40% in 42.5%). The median IL-1β concentration was 32.08 pg/ml (IQR: 21.50 to 49.70), and there were trends across quartiles of impaired functional capacity, higher number of previous hospitalizations, and lower sodium concentrations. In addition, patients in the highest quartile of IL-1β had higher concentrations of NT-proBNP (3,290 [IQR: 1,701 to 6,350] pg/ml vs. 5,114 [IQR: 2,106 to 8,629] pg/ml; p = 0.010) and hsTnT (26 [IQR: 17 to 43] ng/l vs. 35 [IQR: 22 to 97] ng/l; p = 0.004). No significant differences were found for other patient characteristics, including etiology, demographic and echocardiographic characteristics, and biochemical parameters such as renal function and C-reactive protein. The median sST2 concentration was 45.93 (IQR: 33.56 to 69.75) ng/ml, and there was a positive correlation between IL-1β and sST2 (Online Figure 1) ($\rho = 0.65$; $p < 0.001$).

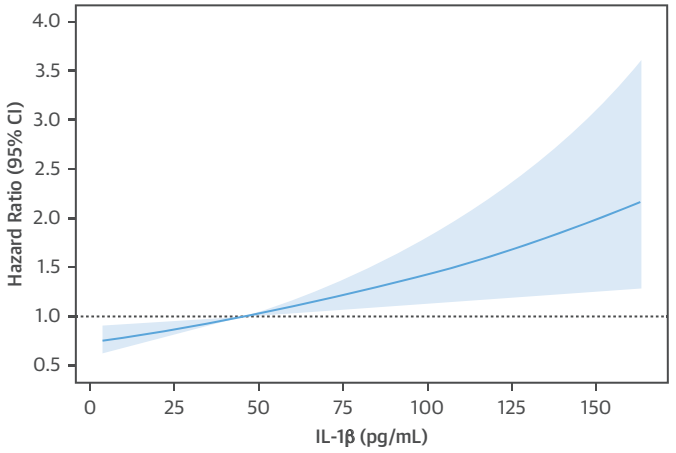
IL-1β AND ALL-CAUSE MORTALITY. All patients had a 1-year follow-up and among deceased patients (n = 52, 16.5%) survival had a median of 116 days (IQR: 46 to 193 days). IL-1β concentrations were significantly higher in patients who died (38.67 pg/ml [IQR: 26.74 to 71.71 pg/ml] vs. 31.20 pg/ml [IQR: 20.36 to 46.04 pg/ml]; p = 0.005). The distributions of variables according to survival status at 1-year and the results of univariate Cox regression analysis are shown in Online Tables 1 and 2. As continuous Ln-transformed variables, IL-1β (per 1 SD, hazard ratio [HR]: 1.47; 95% confidence interval [CI]: 1.09 to 1.97; p = 0.012) and sST2 concentrations (per 1 SD, HR: 1.56;

FIGURE 1 Kaplan-Meier Survival Analysis and Adjusted Hazard Risk of Death by Quartiles of IL-1β



Kaplan-Meier survival analysis **(A)** and adjusted hazard risk of death **(B)** by quartiles of IL-1β, during the first year after hospitalization are shown. Patients were grouped into quartiles based on admission concentrations of IL-1β. Patients in the highest quartile (≥49.7 pg/ml) had a significant lower survival in the Kaplan-Meier analysis **(A)**. The adjusted hazard risk of death was significantly higher in the highest quartile, compared with the lowest quartile **(B)**. Adjusted by age, coronary revascularization, cerebrovascular disease, prior HF, prior HF hospitalization, NYHA functional class, blood pressure, hemoglobin, urea, creatinine, NT-proBNP, hsTnT, beta-blockers, and mineralocorticoid receptor antagonists. CI = confidence interval; HF = heart failure; IL = interleukin; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; Q = quartile; hsTnT = high-sensitivity troponin T.

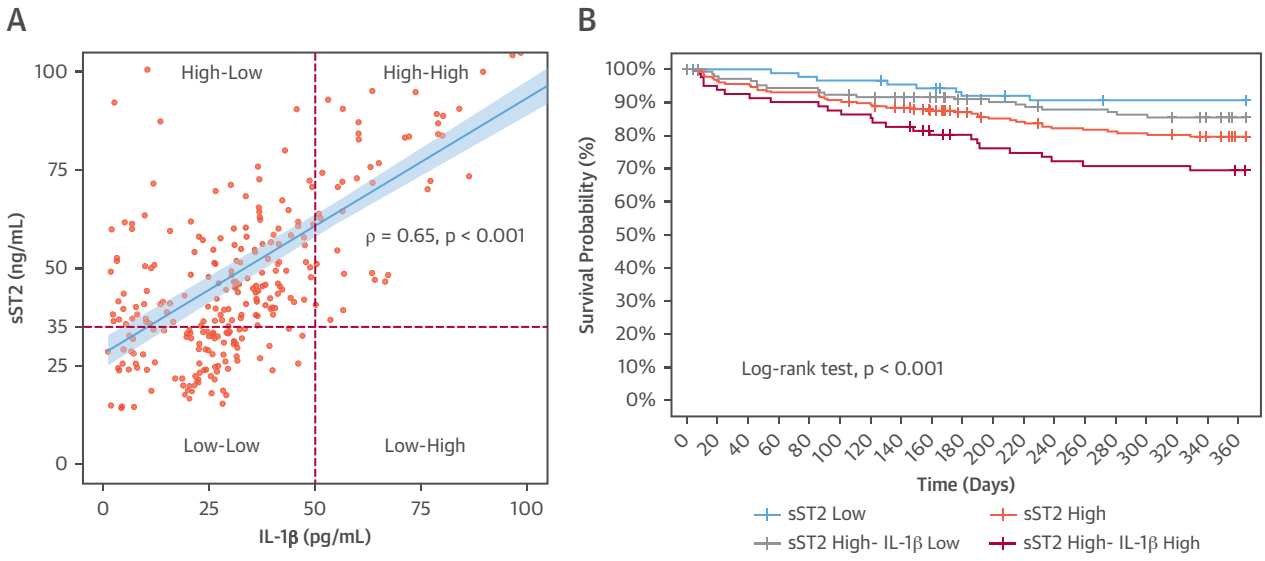
FIGURE 2 Adjusted Cox Proportional Hazards Regression Analysis of Mortality Risk by Concentrations of IL-1β



The association between IL-1β concentrations and death was examined using adjusted hazard ratios **(blue line)** and 95% confidence interval **(shaded area)**. Concentrations above the value of 49.1 pg/ml were associated with a significant higher risk of death. Adjusted by age, coronary revascularization, cerebrovascular disease, prior HF, prior HF hospitalization, NYHA functional class, blood pressure, hemoglobin, urea, creatinine, NT-proBNP, hsTnT, beta-blockers, and mineralocorticoid receptor antagonists. Abbreviations as in Figure 1.

95% CI: 1.20 to 2.03; $p < 0.001$) were associated with a higher risk of death. After multivariate adjustment, considering Ln(IL-1β) and Ln(sST2) separately as continuous variables, sST2 retained statistical significance (per 1 SD, adjusted HR: 1.39; 95% CI: 1.05 to 1.84; $p = 0.021$), whereas IL-1β did not reach significance (per 1 SD, adjusted HR: 1.31; 95% CI: 0.97 to 1.76; $p = 0.083$). The analysis for quartiles of IL-1β (Figure 1) showed the survival was lower in patients at the highest quartile (49.7 pg/ml; log rank $p = 0.003$) and the adjusted risk of death was significantly higher in the highest quartile compared with the lowest quartile (adjusted HR: 2.98; 95% CI: 1.23 to 7.18; $p < 0.001$). A threshold of IL-1β of ≥49.1 pg/ml, close to the highest quartile, was identified as the optimal cutoff point for predicting mortality in receiver-operating characteristic curve analysis (area under the curve of 0.62; 95% CI: 0.53 to 0.70). The Cox proportional hazards regression analysis confirmed that concentrations below and above this value of IL-1β were associated with significant lower and higher risk of death, respectively (Figure 2), and patients above this value were at increased risk compared with those below it (adjusted HR: 2.7; 95% CI: 1.58 to 4.71; $p < 0.001$).

FIGURE 3 Distribution of sST2 and IL-1β Concentrations and Survival Analysis According to Categories of Risk



Distribution of sST2 and IL-1β concentrations **(A)** and survival analysis **(B)** according to the combination of categories of risk (high and/or low) is shown. Concentrations of IL-1β and sST2 were classified as high/low according to the prognostic thresholds: sST2 ≥35.0 ng/ml (high) and IL-1β ≥49.1 pg/ml (high). All patients with low sST2 had also low IL-1β, whereas patients with high sST2 presented low or high IL-1β **(A)**. Patients were grouped on the basis of categories of sST2 and IL-1β. In the Kaplan-Meier analysis, patients with high sST2 **(orange line)** were reclassified as low risk **(gray line)** and high risk **(red line)** according to the presence of high IL-1β **(B)**. IL = interleukin; sST2 = soluble ST2.

IL-1β/sST2 CATEGORIES AND PROGNOSIS. We used the established prognostic threshold of 35.0 pg/ml for sST2 and the identified prognostic value of 49.1 pg/ml for IL-1β to categorize the levels of both interleukins as being high or low. As shown in Figure 3A, all patients with low concentrations of sST2 also had low IL-1β concentrations; in other words, no patients had low sST2 and high IL-1β levels. At 1 year, mortality was 9.0% for patients with low sST2 and 19.4% for patients with high sST2. The use of IL-1β (high or low) reclassified patients with high levels of sST2 into high-risk and low-risk groups, with 1-year mortality rates of 29.6% versus 13.7%, respectively (Figure 3B). Therefore, only patients with elevated concentrations of both sST2 and IL-1β exhibited a lower survival during the follow-up. Indeed, multivariable Cox regression modeling for predicting 1-year death (Table 2, model 1) showed that high IL-1β retained higher predictive value (adjusted HR: 2.36; 95% CI: 1.27 to 4.40; p = 0.007) than high sST2. In addition, patients with high sST2 and low IL-1β had a similar risk as patients with low sST2; whereas patients with both high sST2 and high IL-1β had a significantly higher risk compared with all other groups (adjusted HR: 2.52; 95% CI: 1.40 to 4.56; p = 0.002) (Table 2, model 2) or low sST2 (Online Table 3).

DISCUSSION

This study evaluated the relationship between IL-1β and sST2 in patients with ADHF, as well as the prognostic significance of elevated concentrations of IL-1β and sST2. This is the first study to our knowledge to show a very close relationship between IL-1β and

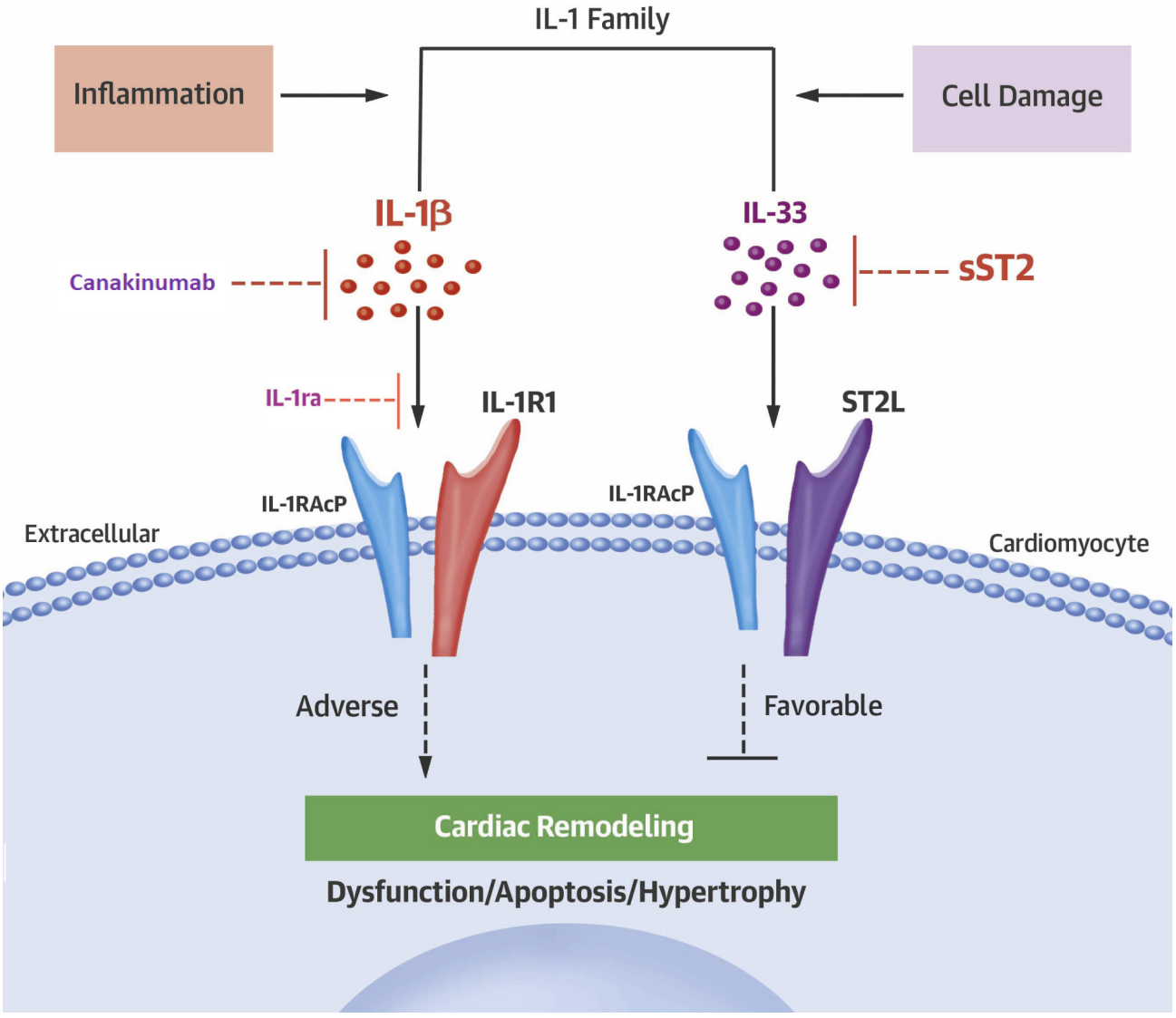
TABLE 2 Adjusted Cox Regression Multivariable Model for Prediction of Death at 1 Year Considering Categories of Risk of sST2 and IL-1β

	Model 1		Model 2	
	HR (95% CI)	p Value	HR (95% CI)	p Value
IL-1β >49.1 pg/ml	2.36 (1.27-4.40)	0.007	–	–
sST2 >35 ng/ml	1.14 (0.49-2.65)	0.760	–	–
sST2-IL-1β				
High-low (vs. low-low)	–	–	1.14 (0.49-2.65)	0.760
High-high (vs. low-low + high-low)	–	–	2.52 (1.40-4.56)	0.002
Age, per yr	1.04 (1.01-1.07)	0.015	1.04 (1.01-1.07)	0.015
NYHA functional class				
II	2.07 (0.61-7.09)	0.246	2.07 (0.61-7.09)	0.246
III	4.71 (1.39-15.90)	0.012	4.71 (1.39-15.90)	0.013
IV	12.90 (1.77-94.24)	0.012	12.90 (1.77-94.24)	0.012
Cerebrovascular disease	3.60 (1.73-7.51)	<0.001	3.60 (1.73-7.51)	<0.001
Urea	1.01 (1.01-1.02)	<0.001	1.01 (1.01-1.02)	<0.001

Adjusted by coronary revascularization, prior HF diagnosis, prior HF hospitalization, blood pressure, hemoglobin, creatinine, NT-proBNP, hsTnT, beta blockers and mineralocorticoid receptor antagonists. Model 1 considers separately IL-1β and sST2 categories. Model 2 considers the combination of categories of IL-1β/sST2.

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

CENTRAL ILLUSTRATION **Mechanistic Link Between IL-1β and ST2 Signaling Systems in Heart Failure**



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Both IL-1β and IL-33 belong to the IL-1 family: IL-1β is mainly secreted in response to inflammation by activated macrophages and has deleterious effects on myocardial cells by binding its receptor IL-1R1, forming a complex with its accessory protein (IL-1RAcP). Conversely, IL-33 is secreted by cells in response to damage, and exerts favorable effects by binding the transmembrane receptor ST2L. Each signaling has its own counter-regulator: the IL-1 receptor antagonist (IL-1ra) binds the IL-1R and avoids the interaction with IL-1β; Canakinumab is recombinant human monoclonal antibody that binds IL-1β and avoids the interaction with IL-1R1. sST2 binds to IL-33 and prevents the interaction with ST2L. Our study, from a clinical perspective, shows that both systems are closely related, and the presence of high levels of IL-1β adds synergistic information over the presence of high sST2 concentrations, by identifying the highest risk of death in the follow-up. Therefore, the antagonism of IL-1β could have a favorable effect on cardiac remodeling and prognosis of patients with heart failure. IL = interleukin.

sST2, and to suggest that IL-1β might be a player in acute HF syndromes.

In contrast to other inflammatory cytokines, IL-1β has received little attention in the setting of HF (10). This lack of clinical data contrasts with the large amount of experimental evidence that links IL-1β with adverse remodeling and HF progression (16,17). Just 3 studies have measured IL-1β along with many other cytokines, and all found that IL-1β levels are elevated in patients with chronic HF compared with

control patients (8,9,18). In another study, IL-1β was significantly higher in patients with ADHF compared with non-HF and control groups (19). A population study of 1,292 participants also found that IL-1β concentrations were associated with HF (20). Although inflammation is clearly present in HF pro-gression and identifies a worse prognosis, more attention has been paid to other cytokines, such as tumor necrosis factor-alpha and IL-6 (10). Regarding prognosis, there are no previous data about the ability of IL-1β to identify higher risk in HF pop-ulations. However, in a population of patients with idiopathic dilated cardiomyopathy, IL-1β was a strong and independent predictor of all-cause mor-tality in long-term follow-up (21). Therefore, our study provides valuable data about the possible role of this cytokine in HF. Specifically, we found that in a representative population of ADHF, elevated con-centrations of IL-1β upon arrival at an emergency room identified a higher risk of death in the following year. In addition, we found that IL-1β had a very close relationship with sST2, which is a well-established prognostic marker in acute and chronic HF.

IL-1β and ST2 are both members of the IL-1 axis; however, their roles in cardiovascular pathophysiology and in HF in particular have not been linked previously. The IL-1 family is a group of pleiotropic cytokines that have multiple local and systemic effects. Its members are grouped into subfamilies according to the length of their precursors. The IL-1 subfamily comprises the IL-1α, IL-1β, and IL-33 cytokines. IL-1β is a multifunctional proinflammatory cytokine that binds to the IL1-R receptor on target cells (6). ST2 acts as a receptor for IL-33, which is released during necrotic cell death as an alarmin that signals tissue injury. The effects of IL-33 are driven by its binding to the transmembrane receptor ST2L; by contrast, the soluble form of sST2 acts as a decoy receptor that sequesters IL-33 and prevents it from exerting its effects (1). Therefore, the IL-1β and ST2 systems are close to each other (**Central Illustration**).

Data from experimental studies show that both IL-1β and sST2 have negative myocardial effects. The administration of IL-1β induces a reversible contractile dysfunction and impairs β1-adrenergic responsiveness, supporting the idea that IL-1β has an active role in the pathophysiology of ADHF (7). By contrast, IL-1β blockade improves contractile dysfunction and prevents adverse cardiac remodeling (22-24). Similarly, sST2 acts as a decoy receptor that inhibits the cardioprotective effects of IL-33/ST2L signaling and impairs the remodeling processes (25), resulting in myocardial hypertrophy, fibrosis, and apoptosis (26). In the clinical setting, sST2 levels predict a more adverse cardiac phenotype in ADHF patients and future progression of adverse remodeling after myocardial infarction (27,28). In the same way, IL-1β levels after ST-segment elevation myocardial infarction are strongly associated with impaired myocardial function and noninfarct left ventricular mass after 1 year, suggesting a potential role for IL-1β as a predictor of maladaptive myocardial remodeling following myocardial infarction (29). Therefore, both IL-1β and sST2 are linked to myocardial fibrosis, adverse remodeling, and HF progression (**Central Illustration**). In our study, NT-proBNP and hsTnT were the only biomarkers to show correlations with IL-1β levels, which suggests that IL-1β has a relationship with ongoing myocardial processes of stretch (NT-proBNP) and injury (hsTnT) in the acute setting of ADHF.

Despite these data, no previous clinical studies have linked IL-1β and ST2. Our study indicates that they have a close relationship. First, we found that sST2 and IL-1β have a similar response to ADHF, with a strong correlation. In addition, we found that IL-1β was elevated only in the presence of high concentrations of sST2 and added prognostic information to that of sST2. Specifically, high sST2 is prognostic only when IL-1β is also elevated. These findings suggest a pathophysiological link between the 2 cytokines in the setting of ADHF. Although some experimental studies of inflammatory disease have suggested a relationship between IL-1β and the IL-33/ST2 signaling pathway (30,31), only 1 study has investigated this interaction in cardiac disease (32). In the study by Chen et al. (32), administration of anakinra, a recombinant antagonist of the IL-1 human receptor, reduced the levels of sST2, was associated with reduced markers of fibrosis and inflammation, and improved left ventricular volume and mass values. That study suggested that IL-1β could induce sST2 and that both cytokines participated in the progression of adverse remodeling. No other studies have explored this interaction.

In a pilot study, the IL-1 receptor antagonist anakinra showed contradictory results in terms of improvement of functional capacity in patients with systolic HF (33,34). However, after observing the benefit obtained in CANTOS (Canakinumab

Anti-Inflammatory Thrombosis Outcomes Study) (12) with the use of canakinumab, a direct blocker of IL-1β, it seems reasonable to question whether the use of a direct IL-1β blocker is a better approach than receptor antagonism (**Central Illustration**). Indeed, the experimental data support the use of a direct blocker of IL-1β, because IL-1β modulation has repeatedly been shown to prevent adverse cardiac remodeling and systolic dysfunction following acute myocardial infarction in the mouse (22,23). In CANTOS, therapy was addressed by levels of C-reactive protein, which did not show a correlation with IL-1β in our study. The different clinical scenario (ADHF vs. chronic coronary disease) and the presence of C-reactive protein levels in higher range (median 9.8 mg/l vs. 4.2 mg/l), eventually influenced by acute extracardiac conditions, could account for the lack of association.

STUDY LIMITATIONS. This study has limitations due to the observational nature, the lack of serial measures, the limited sample power, and the use of electronic medical records instead of clinical events adjudication. However, it describes for the first time a link between IL-1β and sST2, which could be meaningful in HF progression and a relevant therapeutic target.

CONCLUSIONS

We report that the IL-1β cytokine has prognostic implications for ADHF and also has a meaningful relationship with ST2. These findings suggest an interplay between IL-1β and ST2 in the pathophysiology of ADHF and that available therapies that target IL-1β may have clinical benefits.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In patients with ADHF, elevated blood levels of IL-1β are associated with a heightened risk of death.

TRANSLATIONAL OUTLOOK: Future research should focus on the mechanisms relating IL-1β to survival in patients with HF and on the potential therapeutic value of that targeting this axis.

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KEY WORDS acute, heart failure, IL-1β, interleukin-1, ST2

APPENDIX For a supplemental figure and tables, please see the online version of this paper.