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ST2 in Emergency Department Patients With Noncardiac Dyspnea

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Abstract

Objectives: Serum levels of soluble ST2, a member of the interleukin-1 receptor family, predict mortality in emergency department (ED) patients with dyspnea secondary to acute heart failure and acute coronary syndrome. Elevated levels of ST2 have also been described in pulmonary disease, but it is unclear if these are associated with adverse outcomes. The hypothesis for this study was that elevated ST2 levels would be associated with 180-day mortality and 180-day return ED visits or hospital readmission in patients presenting to the ED with noncardiac causes of dyspnea.

Methods: This prospective observational cohort study enrolled a convenience sample of patients presenting to a single academic tertiary care ED with a chief complaint of dyspnea. Exclusion criteria included dyspnea due to chest wall trauma, airway obstruction, and known cardiac etiology (new onset heart failure, prior heart failure with current brain natriuretic peptide > 500 pg/mL, presumed ischemic chest pain, elevated troponin, electrocardiogram changes indicating myocardial infarction or ischemia, heart transplant). ST2 levels were measured at ED presentation and compared between those with and without adverse outcomes. Staff were blinded to ST2 levels. Differences between groups were assessed using the Mann-Whitney U test.

Results: Of the 82 patients enrolled, 45 (55%) were female, 48 (59%) were African American, and 34 (42%) were hospitalized. The most frequent ED or hospital diagnosis was chronic obstructive pulmonary disease (COPD) or asthma, in 29 (35%) patients. At 180 days, 36 of 81 patients (44%) had return ED visits, 21 of 81 patients (26%) were readmitted, and five of 82 patients (6%) were deceased. Median ST2 level was 227 ng/mL in patients who died versus 32 ng/mL in those who survived (difference = 195 ng/mL, 95% confidence interval [CI] = 48 to 342 ng/mL, $p = 0.006$). Median ST2 level was 59 ng/mL in readmitted patients versus 31 ng/mL in

nonreadmitted patients (difference = 28 ng/mL, 95% CI = -3 to 60 ng/mL, $p = 0.036$). Median ST2 levels were 41 ng/mL in patients with return ED visits versus 31 ng/mL in those without return visits (difference = 10 ng/mL, 95% CI = -10 to 20 ng/mL, $p = 0.23$).

Conclusions: Patients with noncardiac dyspnea who died or required readmission to the hospital within 180 days had higher levels of ST2 compared with nonadmitted survivors. Further research into ST2 as a prognostic tool in pathologic processes not involving the heart, such as pulmonary disease, is warranted.

ST2, a member of the interleukin-1 receptor family, exists in transmembrane (ST2L) and soluble (sST2) isoforms. Originally discovered in fibro-blasts, ST2 expression occurs in cardiomyocytes and pulmonary endothelial cells. The soluble isoform (hereto referred to as ST2) functions as a decoy receptor for interleukin-33, down regulating the inflammatory response.^{1,2} ST2 has been studied extensively as a cardiac biomarker for heart failure and acute coronary syndrome, as it is released by cardiomyocytes in response to mechanical wall strain.³⁻⁵ Elevated levels have also been reported in patients with pulmonary disease, such as chronic obstructive pulmonary disease (COPD), pulmonary hypertension, asthma, pulmonary embolism, and pneumonia, but it is unclear if these are associated with adverse outcomes.⁶⁻⁸

Few biomarkers have prognostic value in diseases with a primarily pulmonary etiology. The purpose of this pilot study was to evaluate whether ST2 is associated with adverse outcomes outside of cardiac disease in patients presenting to the emergency department (ED) with dyspnea. We hypothesized that within this patient population, plasma levels of ST2 would be elevated in patients with increased morbidity and mortality.

METHODS

Study Design

This was a prospective observational cohort study. Institutional review board approval was obtained, and the study was registered at [ClinicalTrials.gov](https://clinicaltrials.gov), NCT0070 7811. Informed consent was obtained from all subjects for the blood draws, follow-up phone calls, and review of medical records.

Study Setting and Population

This study was performed at a single academic, tertiary care ED, and a convenience sample of patients reporting dyspnea during the preceding 24 hours was enrolled. Patients were 18 years or older and enrolled within 3 hours of presentation to the ED. Exclusion criteria included dyspnea due to chest wall trauma, airway obstruction, and known cardiac etiology (new-onset heart failure, prior heart failure with current brain natriuretic peptide > 500 pg/mL, presumed ischemic chest pain, elevated troponin, electrocardiogram changes indicating myocardial infarction or ischemia, or heart transplant).

Study Protocol

Blood samples were obtained using standard venipuncture techniques at enrollment and repeated 3 to 6 hours later, when possible. Samples were centrifuged, and plasma was isolated and stored at -80°C within 1 hour of being drawn. Samples were thawed and ST2 levels measured using an enzyme-linked immunosorbent assay (Presage ST2 assay, Critical Diagnostics, San Diego, CA).

Patient information was gathered from medical records, treating physicians, and by research interviews. Outcomes were followed via electronic medical records for 180 days after discharge from the index visits. Follow-up phone calls were made at 30 and 180 days. The

vital status of each patient was checked using the social security death index. Researchers were blinded to ST2 levels until outcomes assessment.

Data Analysis

Data analyses used SPSS 18.0 for Windows (IBM, Armonk, NY). Mann-Whitney U test and Wilcoxon signed ranks test were used to test for differences between and within groups, respectively. Differences in medians were computed with corresponding 95% confidence intervals (CIs). Area under the receiver operating characteristic curve (AUC) was used to quantify prognostic accuracy. Only a single ST2 observation from each participant was included.

RESULTS

We enrolled 82 patients; 45 (55%) were female, and the median age was 57 years (range = 20 to 88 years). Forty-eight (59%) were African American, 33 (40%) were white, and one (1%) was Hispanic. Past medical history included asthma in 39 patients (48%), followed by pneumonia in 31 (38%) and COPD/emphysema in 30 (37%). Patients had a median of 3 days of symptoms prior to presentation (interquartile range [IQR] = 1 to 7 days). Supplemental oxygen was required for 36 patients (44%), and 34 (42%) were admitted following their index presentations. The most common diagnosis was asthma/bronchospasm/COPD, with 29 patients (35%).

One patient died during the index hospitalization. Within 30 days of discharge, 13 (16%) had return ED visits, 10 (12%) were readmitted to the hospital, and two (3%) had died. Between 30 and 180 days, 30 patients (38%) had return ED visits, and 16 (20%) were readmitted to the hospital. An additional two patients (3%) died between 30 and 180 days, for a total of five (6%) deaths during the study period. Two patients could not be reached by phone and had no records in the hospital's electronic medical records at 180 days, but were still alive based on the social security death index query.

The median ST2 level at enrollment was 33 ng/mL (IQR = 22 to 74 ng/mL), and 30 patients had second blood draws 3 to 6 hours after enrollment, with a median of 42 ng/mL (IQR = 20 to 149 ng/mL). The median initial ST2 level for the 30 patients with 3- to 6-hour blood draws was 37 ng/mL (IQR = 22 to 118 ng/mL), such that the change in ST2 over 3 to 6 hours in this subgroup did not reach statistical significance ($p = 0.088$).

Patients who died had higher median ST2 levels than those who survived (median = 227 ng/mL vs. 32 ng/mL, difference = 195 ng/mL, 95% CI = 48 to 342 ng/mL, $p = 0.006$; Figure 1). Additionally, patients readmitted to the hospital at least once had a higher median ST2 level than those who were not readmitted (median = 59 ng/mL vs. 31 ng/mL, difference = 28 ng/mL, 95% CI = -3 to 60 ng/mL, $p = 0.036$). Patients with one or more repeat ED visits had similar ST2 levels to those without repeat ED visits (median = 41 vs. 31 ng/mL, difference = 10 ng/mL, 95% CI = -10 ng/mL to 20 ng/mL, $p = 0.23$). ROC analysis was performed on ST2 and death within 180 days, with an AUC of 0.87 (95% CI = 0.72 to 1.00).

DISCUSSION

ST2 is a down regulator of inflammation, and plasma levels elevate after a disease process has developed.² As such, ST2 has been used to predict mortality in patients with acute exacerbations of disease, although a clear clinical application is still under investigation. ST2 has known prognostic utility in cardiac disease, including acute heart failure, chronic heart failure, myocardial infarction, and acute heart transplant rejection.^{5,9} Pulmonary disease has been less studied with ST2 elevation seen in laboratory models and small studies

of asthma, pneumonia, pulmonary fibrosis, and a single blood bank substudy of ED patients with cardiopulmonary dyspnea.^{7,8} Here we show that patients with undifferentiated dyspnea without any known cardiac etiology who died or required readmission to the hospital had higher levels of ST2 upon initial presentation to the ED compared to those with no adverse outcome. Thus, the prognostic accuracy suggests a sufficiently strong association to warrant further research into the clinical utility of ST2 in risk stratification and/or disease classification outside of cardiac disease.

This study was not designed to formally estimate sensitivity or specificity of ST2 or to determine the optimal operating point. However, trends in our data are consistent with studies that show ST2 to be a sensitive but nonspecific marker of mortality, as there were several patients with elevated ST2 levels who did not go on to have adverse outcomes.⁷ As such, one potential application in the acute setting could be to identify low-risk patients with dyspnea who could be discharged home. Studies in heart failure and acute coronary syndrome have shown cutoff values for increased risk between 15 and 35 ng/mL.^{5,10} In our study, those cohorts who were alive and did not required readmission within 180 days had a median ST2 level below 35 ng/mL. The AUC for death at 180 days reported here is similar to those of earlier studies of heart disease (AUC = 0.72 to 0.8).^{5,7,10}

ST2 elevation in a mechanical heart strain model showed ST2 transcription starting 2 to 15 hours after stress initiation.³ The patients described here had a median of 3 days of symptoms before presentation. It is unknown whether patients with sudden onset of dyspnea who present immediately to EDs will have elevated ST2 levels. Early presentation of disease was thought to explain poor prognostic utility in ED chest pain patients.⁶ ST2 varies throughout a hospital stay, and studies following ST2 levels longitudinally have shown levels may initially rise but then decrease with disease resolution.^{4,6,9} Our data show that within the time frame of an ED visit (3 to 6 hours), ST2 levels are stable.

LIMITATIONS

Fundamentally, this was a pilot study and a preliminary step in investigating a possible association between ST2 and outcomes in dyspneic patients without acute cardiac disease. We cannot conclude that the pathology leading to ST2 elevation in our patient population directly caused the increased need for hospitalization or deaths, nor did we adjust for possible noncardiac confounders. The true nature of this association and description of the underlying pathophysiology will need to be evaluated in future studies.

An a priori power analysis was not done due to lack of data on ST2 in noncardiac patients at study design. The data presented here could be used to determine appropriate sample size for subsequent studies. Additionally, 13 patients had nonspecific diagnoses, such as “acute coronary syndrome rule-out,” so the exact etiology of their dyspnea was unclear. Finally, should a reader choose to interpret the findings assuming a conservative Bonferroni correction, the critical significance level would be 0.0167.

CONCLUSIONS

ST2 may have prognostic utility for death and readmission to the hospital in ED patients with dyspnea with no known cardiac etiology for their symptoms. Additionally, serum levels of ST2 appear to be stable during a 3- to 6-hour ED visit. Although most studies of ST2 have investigated this biomarker’s ability to predict death in cardiac disease, given these results, further research into ST2 as a prognostic tool in other pathologic processes, such as pulmonary disease, is warranted.

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Figure 1. ST2 levels (ng/mL) compared to outcomes at 180 days. Boxes represent the IQR; whiskers represent the limit for outliers, shown as *circles* (○) for values 1.5–3 box lengths from the end of the box and *stars* (★) for values >3 box lengths from the end of the box. IQR = interquartile range.