



## Soluble ST2 and troponin I combination: Useful biomarker for predicting development of stress cardiomyopathy in patients admitted to the medical intensive care unit



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### ABSTRACT

**Objective:** Stress cardiomyopathy (SCM) sometimes develops in patients with non-cardiac medical illness. We hypothesized that soluble suppression of tumorigenicity 2 (sST2) can predict SCM.

**Methods:** In 76 patients admitted to non-cardiac medical intensive care unit (MICU), echocardiography and sST2 were assessed on admission day (D0) and on the third day (D2). Cardiac troponin I (cTnI) and B-type natriuretic peptide (BNP) were measured on D0.

**Results:** The SCM group (21%, 16/76) showed significantly higher cTnI, BNP, sST2 (D2), and sST2 changes than the non-SCM group. In receiver operator characteristics curve analysis, they equally predicted SCM. In 65 patients with normal cTnI, sST2 (D2) and sST2 changes predicted SCM better than cTnI or BNP.

**Conclusion:** Follow-up sST2 and the change in sST2 have additional predictive value for SCM in patients with normal cTnI. A combination strategy of sST2 and cTnI would be useful to predict SCM in patients admitted to the MICU.

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### Introduction

Stress cardiomyopathy (SCM), also known as Takotsubo cardiomyopathy or apical ballooning syndrome, was first described in Japan in 1990.<sup>1</sup> SCM is an enigmatic disease with multifactorial pathogenesis, and various stressors, either physical or emotional, can work as a trigger. Its prevalence was reported as 0.02% in the United States,<sup>2</sup> but it is more common in Japan and Korea<sup>3,4</sup>—a single tertiary care university hospital in Seoul, Korea, reported an incidence as 28% in patients with non-cardiac medical illness.<sup>4</sup>

**Abbreviations:** SCM, stress cardiomyopathy (Takotsubo cardiomyopathy); MICU, medical intensive care unit; ACS, acute coronary syndrome; cTnI, cardiac troponin I; BNP, B-type natriuretic peptide; sST2, soluble suppression of tumorigenicity 2; 2D, two-dimensional; LV, left ventricular/ left ventricle; hs-CRP, high-sensitivity C-reactive protein; CK-MB, creatine kinase-MB isoenzyme.

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SCM is one of the possible reversible acute heart failure syndromes, typically regarded as a benign disease with a favorable prognosis. However, a variety of serious complications or even death may occur during the acute clinical course, especially in patients with sepsis as a stressor.<sup>4,5</sup> In a non-cardiac medical intensive care unit (MICU), the prevalence of SCM can be underestimated if the physician is not looking for it or lacks heart surveillance, unless there was a previous cardiac medical history. Therefore, active suspicion, rapid diagnosis, and close monitoring of acute heart conditions are especially necessary in non-cardiac MICUs, which would then facilitate detection of SCM and its cardiac complications, ensuring adequate support in a timely manner.

SCM is still diagnostically challenging. It is easily missed entirely by focusing on only non-cardiac medical stress conditions, or it is misdiagnosed as an acute coronary syndrome (ACS) if noticing only chest pain, electrocardiographic changes, or elevated cardiac troponin I (cTnI). About 0.9% of patients presenting with ACS-like symptoms and percutaneous coronary angiograms were ultimately diagnosed as having SCM.<sup>6</sup> While myocardial histopathological findings have not been studied in great detail, high catecholamine secretion may be one of the key

findings in the onset of SCM. Non-invasive cardiac imaging studies are good diagnostic tools to evaluate apical ballooning. Cardiovascular magnetic resonance imaging (MRI) at initial clinical presentation may provide relevant functional and tissue information that might aid in the establishment of SCM diagnosis.<sup>7</sup> However, radiologic cardiac imaging, such as CT or cardiac MRI, might not be feasible in hemodynamically unstable, critically ill patients with other non-cardiac comorbidities. Portable echocardiography is useful to assess systolic and diastolic hemodynamics and mitral valve insufficiency<sup>8</sup> but it cannot be routinely performed in all patients admitted to non-cardiac MICUs, especially due to its high cost. In Korea, echocardiography is covered by National Health Insurance only in cases with coronary stent insertion or open heart surgery; if not covered by insurance, its cost varies across institutions and is around \$250–\$350 US dollars (about 10 times more expensive than blood biomarkers in Korea: B-type natriuretic peptide (BNP), \$40; cTnI, \$11).

A specific biomarker for SCM screening is required, but until now, no single biomarker has been established. Elevation of cTnI is reportedly less prominent in SCM than in ACS.<sup>9</sup> BNP and myoglobin or troponin T ratios also have been suggested to discriminate SCM from ACS<sup>10,11</sup>; yet this was a retrospectively retrieved, case-controlled design to compare between ACS and SCM, and it is questionable as a screening tool for SCM in medically ill patients. In reality, a panel or profile of specific biomarkers for SCM screening may be necessary depending on research findings.

Recently, emerging cardiac mechanical stress biomarkers, such as soluble suppression of tumorigenicity 2 (sST2), have been evaluated. sST2 is a member of the Toll-like/interleukin-1 receptor superfamily.<sup>12,13</sup> New insight into sST2 signaling was provided only after the discovery of interleukin-33 (IL-33) as a functional ligand for ST2 in 2005.<sup>14</sup> Both transmembrane and soluble forms of ST2 were upregulated in mechanically-stimulated cardiac myocytes, with the soluble form displaying more robust expression. Stress or strain of cardiac myocytes releases both IL-33 and sST2; elevated IL-33 has cardio-protective effects to reduce fibrosis or hypertrophy, but elevated sST2 blunts that protective effect.<sup>12,13</sup> There have been several studies regarding diagnostic and prognostic values of sST2 in certain cardiac pathologic conditions, such as loss of myocardial tissue (acute myocardial infarction)<sup>15,16</sup> and mechanical overload of the myocardium (heart failure).<sup>17,18</sup> However, none of the previous studies tested sST2 as a cardiac biomarker for SCM, which is also an acute myocardial stress condition. We hypothesized that sST2 has incremental predictive value over other suggested cardiac biomarkers (BNP or cTnI) for SCM in patients admitted to a non-cardiac MICU.

## Materials and methods

### Study design and human subjects

Between May and August in 2014, we prospectively enrolled patients entering the MICU of our single tertiary referral hospital either from the emergency department or from the general ward to manage acute medical illnesses. We included patients who agreed with this study and could undergo echocardiography and biomarker testing on the day of MICU admission (D0) and on the third day of the MICU stay (D2). We excluded all patients referred to the cardiac ICU. We also excluded patients admitted for short-term monitoring, with a previous history of ischemic heart disease, or with a poor echo window for routine transthoracic echocardiography. Considering the usual number of MICU patients in our hospital and the reported incidence of SCM (28%) in the Korean population,<sup>4</sup> we assumed that approximately 80–100 patients would be a reasonable sample size for this study.

SCM was discerned using transthoracic echocardiography from apical hypokinesia or akinesia with normal basal left ventricular (LV) wall motions and without evidence of left anterior descending coronary artery stenosis. Not all the screened patients admitted to the non-cardiac MICU underwent routine coronary angiography—that depended on individual-clinician judgments (generally in this institution, if there is a suspicion of ACS, subsequent coronary angiography is routine). In patients without a coronary angiogram, normal electrocardiograms or the recovery of apical wall motion without coronary revascularization were clues to diagnose SCM. The study protocol followed the World Medical Association Declaration of Helsinki regarding ethical conduct of research involving human subjects and got an approval by the institutional review board of Konkuk University Medical Center. Written informed consents were obtained from all enrolled patients.

### Measurement of biomarkers

Serum samples for sST2 were obtained on D0 and D2, and were stored at  $-80^{\circ}\text{C}$  until being analyzed. The sST2 concentrations were measured using a commercial enzyme-linked immunosorbent assay, Presage ST2 assay (Critical Diagnostics, San Diego, CA, USA), according to the manufacturer's instruction. This assay has been validated with minimal variation (within-run CV < 2.5% and total CV < 4.0%) across a wide assay measurement range. All samples were measured in duplicate, and the average value of two measurements was used for the analysis. Plasma samples were obtained on D0 for the measurement of BNP and cTnI. They were measured using a chemiluminescent microparticle immunoassay on an Architect i2000 analyzer (Abbott Laboratories, Abbott Park, IL, USA), according to the manufacturer's instructions.

### Echocardiographic evaluation

We performed echocardiography using the portable Vivid Q platform (GE Healthcare, Milwaukee, WI, USA) on D0 and D2. SCM was diagnosed by two experienced cardiologists independently based on echocardiographic apical ballooning patterns without proven coronary artery disease. Two-dimensional (2D) imaging of parasternal, apical, and subcostal views, PW Doppler imaging of mitral inflow, tissue Doppler imaging of septal mitral annular motion, and CW Doppler imaging of tricuspid regurgitation were performed. As an offline analysis, the LV ejection fraction (EF) was calculated by the modified Simpson's method from apical four- and two-chamber views.<sup>19</sup> LV filling pressure was assessed from mitral inflow E velocity over mitral septal annular e prime velocity.<sup>20</sup> Resting pulmonary hypertension was assessed via a tricuspid regurgitation jet peak velocity using the simplified Bernoulli equation.<sup>21</sup> Doppler-independent longitudinal strain (LV global as well as apical segmental strain) was assessed using semi-automated speckle-tracking post-processing techniques from a 2D apical four-chamber view image of the LV (EchoPAC version 10, GE Healthcare).<sup>22</sup> The average frame rate was  $58 \pm 10$  frames per second.

### Statistical analysis

We performed statistical analysis using dBSTAT (DBSTAT Version 5. Chuncheon, Korea: DBSTAT Co.; 2010. <http://dbstat.com>). Data were expressed as mean  $\pm$  standard deviation (SD) or median and interquartile range (IQR) for continuous variables and as number (percentage) for categorical or binary variables. All continuous variables were tested for normality using Kolmogorov–Smirnov nonparametric tests. We compared clinical, echocardiographic, and

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