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# Elevated Soluble Suppressor of Tumorigenicity 2 Levels in Gout Patients and Its Association with Cardiovascular Disease Risk Indicators

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**Purpose:** To investigate the association between soluble suppressor of tumorigenicity 2 (sST2) levels and cardiovascular disease predictors in patients with gout.

**Materials and Methods:** We retrospectively reviewed the medical records of patients with gout who were tested for sST2 but did not receive uric acid-lowering therapy. These patients were classified into elevated and normal sST2 groups using a cut-off of >49.6 ng/mL and >35.4 ng/mL in males and females, respectively. Correlations between clinical and laboratory variables, sST2 levels, and elevated sST2 level predictors were assessed using linear and logistic regression analyses.

**Results:** Notably, 27 (11.3%) and 211 (88.7%) of the 238 identified patients had elevated and normal sST2 levels, respectively. Linear regression analysis revealed that male sex (β=-0.190, $p$=0.002), body mass index (BMI) (β=-0.184, $p$=0.002), white blood cell count (β=0.231, $p$<0.001), C-reactive protein (β=0.135, $p$=0.031), and fasting blood glucose (β=0.210, $p$<0.001) were independently associated with sST2 levels. In multivariate logistic regression analysis, male sex [odds ratio (OR) 0.112, $p$=0.001], BMI (OR 0.836, $p$=0.008), creatinine (OR 5.730, $p$=0.024), and fasting blood glucose (OR 1.042, $p$=0.002) predicted elevated sST2 levels. Patients with increased sST2 levels had a significantly higher atherosclerotic cardiovascular disease risk score and a greater proportion of high-risk Framingham Risk Score compared to the normal sST2 group ($p$=0.002 and $p$<0.001).

**Conclusion:** Patients with gout and elevated sST2 levels have a higher risk of future cardiovascular disorders, which may provide insights into risk stratification and the implementation of intervention strategies.

**Key Words:** Gout, suppressor of tumorigenicity 2, cardiovascular, risk, biomarker

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## INTRODUCTION

Gout is one of the most common types of chronic inflammatory arthritis, with an increasing global incidence and prevalence.[1] With a clear preference for males and older adults, the estimated global prevalence of gout reached 53.87 million in 2019, resulting in significant socioeconomic challenges for the affected patients and society.[2] Pathogenically, gout is induced by the formation of monosodium urate crystals, manifesting as acute and intense pain in the affected joints.[3] Gout was initially identified as a disease that mainly causes self-limiting inflammation within the joints of the lower extremities; however, growing evidence suggests that it is closely associated with the presence of components of metabolic syndrome, including

hypertension, diabetes mellitus, dyslipidemia, and obesity.[4] Notably, gout is associated with an increased risk of cardiovascular disease (CVD), particularly in the presence of hyperuricemia, regardless of other traditional CVD risk factors.[5,6] Nevertheless, the predictive factors for CVD in patients with gout have been poorly described in the literature, emphasizing the need for a biomarker that can assess CVD risk in these patients.

Suppressor of tumorigenicity 2 (ST2) belongs to the interleukin (IL)-1 receptor family and is a cognate receptor of IL-33.[7] It is encoded by IL-1 receptor-like 1, and the binding of the membrane-bound form of ST2 to IL-33 mitigates inflammation and promotes tissue repair. Meanwhile, the soluble form of ST2 (sST2) functions as a decoy receptor for IL-33, disrupting the balance of the IL-33 signaling pathway by counteracting its inherent physiological function.[8] Importantly, sST2 has recently been recognized as a novel biomarker of myocardial stress, injury, fibrosis, and systemic inflammation. Researchers have found that elevated sST2 levels are associated with a risk of various CVDs and increased disease activity in inflammatory disorders. In this context, there have been numerous reports highlighting the association between sST2 levels and heart failure and coronary artery diseases.[9] Accordingly, sST2 level evaluation was included in the 2017 American College of Cardiology/American Heart Association guidelines for risk stratification in patients with heart failure.[10] However, to our knowledge, the role of sST2 in patients with gout and its association with CVD risk have yet to be investigated. Therefore, this study aimed to 1) evaluate the differences in patient characteristics between patients with elevated and normal sST2 levels, 2) identify factors associated with sST2 levels, and 3) compare CVD risks based on sST2 levels using tools for assessing future CVD risk in patients with gout.

## MATERIALS AND METHODS

### Patient selection

In this single-center retrospective analysis, we reviewed the electronic health records of patients with gout between February 2020 and September 2023. Patients with gout were diagnosed based on the 1977 American Rheumatism Association criteria.[11] The inclusion criteria were as follows: 1) available sST2 levels; 2) not using uric acid-lowering therapies; 3) clinical information on body mass index (BMI), alcohol, and smoking; and 4) available laboratory results of fasting glucose and cholesterol profiles of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides. We categorized the patients into normal and elevated sST2 groups based on the pre-specified sST2 cut-off of >49.6 ng/mL and >35.4 ng/mL in males and females, respectively.[12] In addition, the results of sST2 of 100 healthy controls, who were tested during routine health examination in the hospital database, were also collected to compare the level of sST2 between patients with gout and the controls. The Institutional Review Board of Severance Hospital approved this study, which followed the principles of the 1964 Declaration of Helsinki and its equivalent ethical standards (IRB approval no: 9-2024-0006). The requirement for informed consent from the patients was waived, as this was a retrospective study

### Data collection and definition of variables

Patient demographics and laboratory data were collected when sST2 levels were evaluated. sST2 level was measured by enzyme-linked immunosorbent assay (ELISA), which was performed in Seoul Clinical Laboratories using the Presage® ST2 ELISA Assay (Critical Diagnostics, San Diego, CA, USA), as previously described.[12]

Demographic data included age, sex, BMI, alcohol consumption status (yes/no), smoking status (yes/no), new-onset gout (disease duration of <1 month) (yes/no), and the presence of hypertension, diabetes mellitus, and dyslipidemia. The laboratory data included uric acid, white blood cell (WBC) count, C-reactive protein (CRP), creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), fasting glucose, TC, LDL-C, HDL-C, and triglyceride levels.

Hypertension was defined as taking antihypertensive medications or a measured systolic or diastolic blood pressure of ≥140 mm Hg or ≥90 mm Hg, respectively. Patients were defined as having diabetes mellitus when they were on anti-diabetic medication or when their glycated hemoglobin level was ≥6.5%. Dyslipidemia was also determined following the diagnostic criteria by the Korea National Health Screening Program (TC ≥240 mg/dL, LDL-C ≥160 mg/dL, HDL-C <40 mg/dL, or triglycerides ≥200 mg/dL) or when the patients were taking medications for dyslipidemia.[13] Hyperuricemia was defined based on serum uric acid levels >7.0 mg/dL and >6.0 mg/dL in males and females, respectively.[6]

### CVD risk assessment

We used the atherosclerotic cardiovascular disease (ASCVD) risk score and Framingham Risk Score (FRS) to estimate CVD risk in patients.[14,15] The ASCVD risk score calculates the 10-year ASCVD risk by considering age, sex, race, TC and HDL-C levels, systolic blood pressure, antihypertensive medication use, diabetes mellitus, and smoking status. Conversely, the FRS is a validated tool for assessing CVD risk based on risk factors such as age, sex, smoking status, systolic blood pressure, hypertension treatment status, diabetes mellitus, TC, HDL-C level, and known vascular disease. As previously described, the 10-year risk factors were calculated as low, moderate, or high risk.

### Statistical analysis

Continuous and categorical variables are expressed as medians with interquartile ranges and numbers with percentages, respectively. The Mann–Whitney U, chi-square, or Fisher's ex-


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act tests were performed to compare the differences between groups. Pearson's correlation analysis was used to assess the correlation coefficients between sST2 levels and continuous variables. Multivariate linear regression analyses were conducted to identify variables associated with sST2 levels, and logistic regression analyses were applied to determine the predictive factors for high sST2 levels using a forward entry method based on the Akaike information criterion.[16] The relative risk according to sST2 levels was calculated using a contingency table and the chi-square test. All statistical analyses were performed using SPSS Statistics for Windows (version 21.0; IBM Corp., Armonk, NY, USA). Statistical significance was set at two-tailed $p<0.05$.

## RESULTS

### Patients' baseline characteristics

In total, 238 patients with a median age of 44.0 years were included in this study; most were male (93.3%), and new-onset disease was documented in 75 (31.5%) of the patients. Of the enrolled patients, 108 (45.4%) had a clinical gout attack. The median level of sST2 was 26.8 ng/mL, and according to the predefined sST2 levels, 27 (11.3%) patients had elevated sST2 levels, while the remaining 211 (88.7%) were assigned to the normal sST2 group. Patients with elevated sST2 levels were older, less likely to be male, had a lower BMI, and had lower rates of alcohol consumption and smoking. However, diabetes mellitus was more commonly diagnosed in the elevated sST2 level group. Regarding laboratory variables, significantly higher WBC count, CRP, creatinine, and fasting blood glucose levels were observed; however, the ALT, TC, LDL-C, and triglyceride levels were lower (Table 1).

When categorizing the patients according to sex, male patients were younger, had higher BMI, and had greater proportion of alcohol consumption and smoking; however, the proportion of those with new-onset disease was lower than in the female group. On the other hand, male patients had higher levels of ALT, TC, LDL-C, and TG, whereas their level of sST2 was lower (Supplementary Table 1, only online). Furthermore, compared to healthy controls, patients with gout demonstrated significantly higher sST2 levels ($p=0.013$) (Supplementary Fig. 1, only online).

### Relationship between sST2 level and variables

The sST2 level was positively correlated with age, WBC count, CRP, creatinine, and fasting blood glucose, whereas it was negatively correlated with BMI, TC, and LDL-C (Table 2). sST2 level comparisons based on demographic data indicated significant differences in sex, alcohol consumption pattern, and the presence of diabetes mellitus ($p<0.001$, $p=0.003$, and $p=0.002$, respectively) (Fig. 1).

The linear regression analysis demonstrated that age, male sex, BMI, alcohol consumption, presence of diabetes mellitus,

**Table 1.** Comparison of Patient Demographics and Laboratory Data between the Two Groups

| Characteristics | Total (n=238) | Elevated sST2 (n=27) | Normal sST2 (n=211) | *p* value |
|---|---|---|---|---|
| Age (yr) | 44.0 (36.0–57.0) | 66.0 (46.8–81.0) | 42.0 (35.3–54.8) | <0.001 |
| Sex, male | 222 (93.3) | 18 (66.7) | 204 (96.7) | <0.001 |
| BMI (kg/m$^2$) | 26.8 (24.3–29.5) | 24.7 (20.9–26.9) | 27.1 (24.6–29.7) | 0.002 |
| Alcohol | 148 (62.2) | 9 (33.3) | 139 (65.9) | 0.001 |
| Smoking | 81 (34.0) | 4 (14.8) | 77 (36.5) | 0.030 |
| New-onset gout | 75 (31.5) | 12 (44.4) | 63 (29.9) | 0.125 |
| Hypertension | 151 (63.4) | 19 (70.4) | 132 (62.6) | 0.428 |
| DM | 28 (11.8) | 9 (33.3) | 19 (9.0) | <0.001 |
| Dyslipidemia | 165 (69.3) | 21 (77.8) | 144 (68.2) | 0.313 |
| Uric acid (mg/dL) | 7.8 (6.8–8.8) | 8.5 (8.0–9.1) | 7.6 (6.8–8.8) | 0.051 |
| WBC count (/mm$^3$) | 7360.0 (6170.0–9000.0) | 8400 (7137.5–10155.0) | 7200.0 (6082.5–8830.0) | 0.013 |
| CRP (mg/L) | 3.0 (1.1–11.0) | 10.5 (1.8–50.8) | 2.8 (1.1–9.6) | 0.009 |
| Creatinine (mg/dL) | 1.0 (0.9–1.1) | 1.1 (0.9–1.5) | 1.0 (0.9–1.1) | 0.019 |
| AST (IU/L) | 22.0 (18.0–29.0) | 20.0 (15.0–26.8) | 22.0 (18.0–29.0) | 0.053 |
| ALT (IU/L) | 25.5 (17.0–42.0) | 18.0 (10.0–31.8) | 27.0 (18.0–44.8) | 0.005 |
| Fasting glucose (mg/dL) | 97.0 (92.0–106.0) | 111.0 (96.3–130.0) | 96.0 (91.0–104.0) | <0.001 |
| TC (mg/dL) | 190.0 (151.0–217.0) | 171.0 (122.0–195.8) | 192.0 (154.5–219.3) | 0.032 |
| LDL-C (mg/dL) | 125.5 (91.0–150.0) | 95.0 (68.3–143.3) | 126.0 (98.9–150.0) | 0.039 |
| HDL-C (mg/dL) | 44.5 (37.0–52.0) | 42.0 (34.3–52.0) | 45.0 (38.0–52.0) | 0.328 |
| Triglyceride (mg/dL) | 151.0 (104.0–214.0) | 118.0 (79.0–182.5) | 158.0 (109.0–220.3) | 0.011 |

sST2, soluble suppressor of tumorigenicity 2; BMI, body mass index; DM, diabetes mellitus; WBC, white blood cell; CRP, C-reactive protein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.
Data are expressed as median (interquartile range) or number (%), as appropriate.

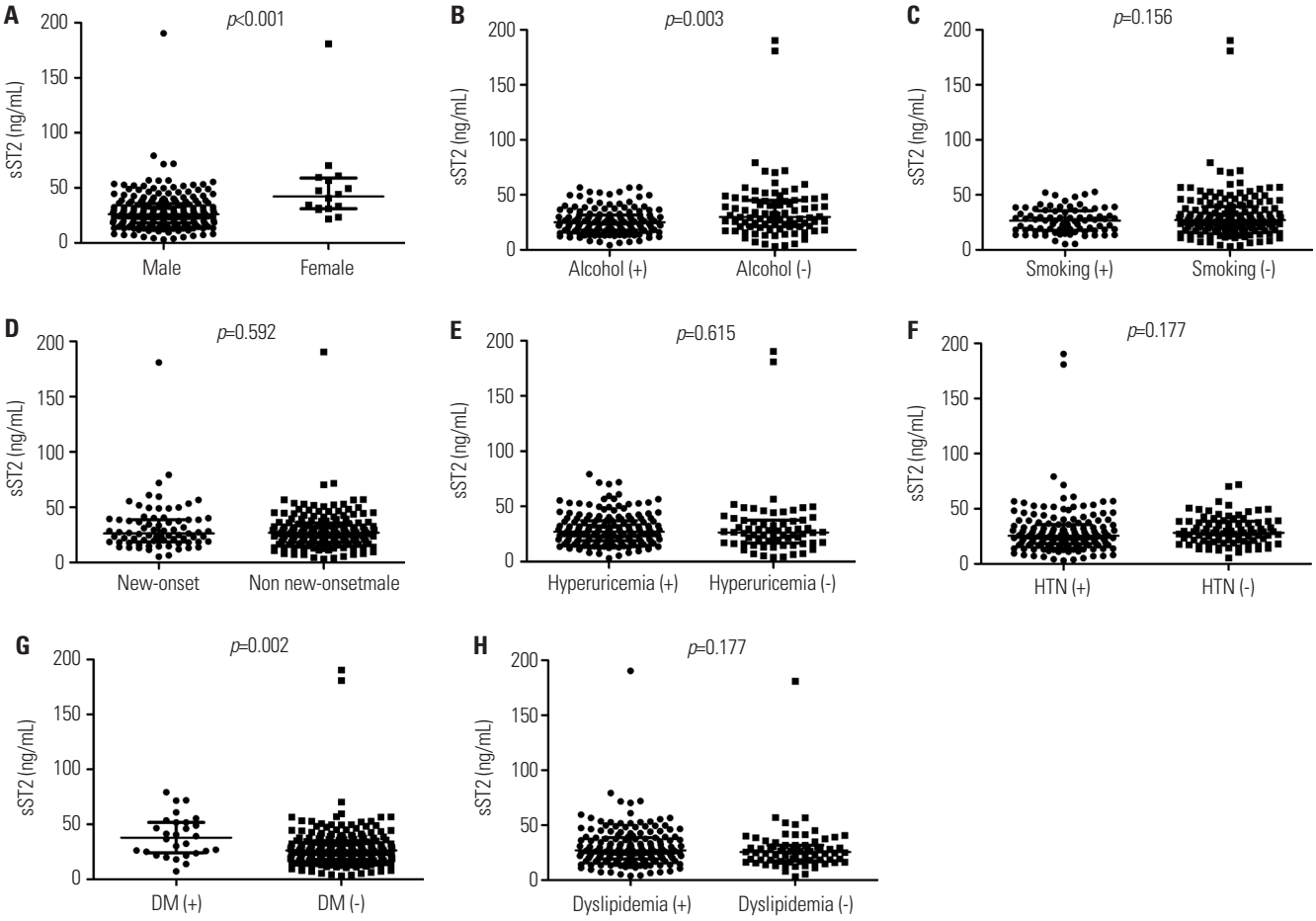


**Fig. 1.** Comparison of sST2 levels based on (A) sex, (B) alcohol consumption, (C) smoking status, (D) new-onset disease, presence of (E) hyperuricemia, (F) hypertension, (G) DM, and (H) dyslipidemia. Error bars represent the median with interquartile range. sST2, soluble suppressor of tumorigenicity 2; HTN, hypertension; DM, diabetes mellitus.

**Table 2.** Correlation between sST2 Levels and Continuous Variables

| Characteristics | Correlation coefficient (r) | 95% CI | *p* value |
|---|---|---|---|
| Age | 0.278 | 0.156 to 0.391 | <0.001 |
| BMI | -0.223 | -0.341 to 0.099 | <0.001 |
| Uric acid | 0.005 | -0.123 to 0.132 | 0.943 |
| WBC count | 0.265 | 0.143 to 0.380 | <0.001 |
| CRP | 0.303 | 0.182 to 0.414 | <0.001 |
| Creatinine | 0.204 | 0.078 to 0.322 | 0.002 |
| AST | -0.001 | -0.128 to 0.127 | 0.992 |
| ALT | -0.121 | -0.244 to 0.007 | 0.063 |
| Fasting glucose | 0.246 | 0.123 to 0.362 | <0.001 |
| TC | -0.136 | -0.258 to 0.009 | 0.037 |
| LDL-C | -0.145 | -0.267 to 0.018 | 0.026 |
| HDL-C | 0.011 | -0.116 to 0.138 | 0.865 |
| Triglyceride | -0.103 | -0.227 to 0.025 | 0.114 |

sST2, soluble suppressor of tumorigenicity 2; CI, confidence interval; BMI, body mass index; WBC, white blood cell; CRP, C-reactive protein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

WBC count, CRP, creatinine, fasting glucose, TC, and LDL-C levels were associated with sST2 levels in univariate analysis. After adjustment, male sex [β=-0.190, 95% confidence interval (CI): -0.306–-0.074, $p$=0.002], BMI (β=-0.184, 95% CI: -0.299–-0.070, $p$=0.002), WBC count (β=0.231, 95% CI: 0.116–0.346, $p$<0.001), CRP (β=0.135, 95% CI: 0.015–0.256, $p$=0.031), and fasting blood glucose (β=0.210, 95% CI: 0.100–0.319, $p$<0.001) were independently associated with sST2 level (Table 3).

In a subgroup analysis of patients with new-onset disease, age, sex, BMI, alcohol consumption, presence of diabetes mellitus, WBC count, CRP level, and fasting glucose level were associated with sST2 levels in univariate analysis. Multivariate analysis revealed that WBC count (β=0.161, 95% CI: 0.015–0.307, $p$=0.038), CRP (β=0.589, 95% CI: 0.448–0.730, $p$<0.001), and fasting glucose (β=0.167, 95% CI: 0.019–0.315, $p$=0.033) levels were significantly associated with sST2 levels (Table 4).

On the other hand, in a subset of males, a linear association was found between sST2 and BMI (β=-0.166, 95% CI: -0.286–-0.047, $p$=0.008), WBC count (β=0.259, 95% CI: 0.142–0.375, $p$<0.001), and fasting glucose (β=0.214, 95% CI: 0.080–0.348, $p$=0.003) in the multivariate analysis (Supplementary Table 2,


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**Table 3.** Linear Regression Analyses of Variables and sST2 Levels in Oatients with Gout

| Characteristics | Univariate analysis | | | Multivariate analysis (forward) | | |
|---|---|---|---|---|---|---|
| | β | 95% CI | *p* value | β | 95% CI | *p* value |
| Age | 0.278 | 0.160 to 0.395 | <0.001 | | | |
| Sex, male | -0.285 | -0.402 to -0.168 | <0.001 | -0.190 | -0.306 to -0.074 | 0.002 |
| BMI | -0.223 | -0.344 to -0.102 | <0.001 | -0.184 | -0.299 to -0.070 | 0.002 |
| Alcohol | -0.233 | -0.354 to -0.112 | <0.001 | | | |
| Smoking | -0.124 | -0.250 to 0.002 | 0.056 | | | |
| Hypertension | -0.003 | -0.131 to 0.124 | 0.963 | | | |
| DM | 0.166 | 0.042 to 0.290 | 0.011 | | | |
| Dyslipidemia | 0.054 | -0.073 to 0.181 | 0.407 | | | |
| Uric acid | 0.005 | -0.123 to 0.132 | 0.943 | | | |
| WBC count | 0.265 | 0.147 to 0.384 | <0.001 | 0.231 | 0.116 to 0.346 | <0.001 |
| CRP | 0.302 | 0.187 to 0.418 | <0.001 | 0.135 | 0.015 to 0.256 | 0.031 |
| Creatinine | 0.202 | 0.080 to 0.324 | 0.002 | | | |
| AST | -0.001 | -0.128 to 0.127 | 0.992 | | | |
| ALT | -0.120 | -0.246 to 0.005 | 0.063 | | | |
| Fasting glucose | 0.246 | 0.126 to 0.366 | <0.001 | 0.210 | 0.100 to 0.319 | <0.001 |
| TC | -0.136 | -0.261 to -0.010 | 0.037 | | | |
| LDL-C | -0.145 | -0.270 to -0.019 | 0.026 | | | |
| HDL-C | 0.011 | -0.117 to 0.139 | 0.865 | | | |
| Triglyceride | -0.103 | -0.229 to 0.024 | 0.114 | | | |

sST2, soluble suppressor of tumorigenicity 2; CI, confidence interval; BMI, body mass index; DM, diabetes mellitus; WBC, white blood cell; CRP, C-reactive protein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

**Table 4.** Linear Regression Analyses of Variables and sST2 Levels in Patients with New-Onset Gout

| Characteristics | Univariate analysis | | | Multivariate analysis (forward) | | |
|---|---|---|---|---|---|---|
| | β | 95% CI | *p* value | β | 95% CI | *p* value |
| Age | 0.408 | 0.217 to 0.600 | <0.001 | | | |
| Sex, male | -0.428 | -0.616 to -0.240 | <0.001 | -0.147 | -0.307, 0.012 | 0.081 |
| BMI | -0.309 | -0.519 to -0.103 | 0.007 | | | |
| Alcohol | -0.377 | -0.575 to -0.180 | 0.001 | -0.117 | -0.274, 0.040 | 0.159 |
| Smoking | -0.147 | -0.373 to 0.078 | 0.207 | | | |
| Hypertension | 0.033 | -0.197 to 0.263 | 0.780 | | | |
| DM | 0.303 | 0.094 to 0.512 | 0.008 | | | |
| Dyslipidemia | -0.046 | -0.276 to 0.184 | 0.696 | | | |
| Uric acid | -0.030 | -0.259 to 0.200 | 0.802 | | | |
| WBC count | 0.280 | 0.068 to 0.492 | 0.015 | 0.161 | 0.015, 0.307 | 0.038 |
| CRP | 0.718 | 0.606 to 0.829 | <0.001 | 0.589 | 0.448, 0.730 | <0.001 |
| Creatinine | 0.203 | -0.018 to 0.424 | 0.081 | | | |
| AST | -0.197 | -0.418 to 0.024 | 0.090 | | | |
| ALT | -0.226 | -0.445 to -0.008 | 0.051 | | | |
| Fasting glucose | 0.268 | 0.054 to 0.482 | 0.020 | 0.167 | 0.019, 0.315 | 0.033 |
| TC | -0.156 | -0.380 to 0.069 | 0.183 | | | |
| LDL-C | -0.186 | -0.408 to 0.036 | 0.110 | | | |
| HDL-C | 0.172 | -0.052 to 0.395 | 0.141 | | | |
| Triglyceride | -0.164 | -0.388 to 0.060 | 0.160 | | | |

sST2, soluble suppressor of tumorigenicity 2; CI, confidence interval; BMI, body mass index; DM, diabetes mellitus; WBC, white blood cell; CRP, C-reactive protein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

only online).

### Predictors of elevated sST2 level and CVD risk based on sST2 levels

Logistic regression analysis revealed that age, male sex, BMI, alcohol consumption, smoking, presence of diabetes mellitus, WBC count, CRP, creatinine, ALT, fasting glucose, TC, and triglycerides were associated with elevated sST2 levels. However, multivariate analysis indicated that male sex [odds ratio (OR): 0.112, 95% CI: 0.028–0.428, $p$=0.001], BMI (OR: 0.836, 95% CI: 0.725–0.947, $p$=0.008), WBC count (OR: 1.000, 95% CI: 1.000–1.000, $p$=0.024), creatinine (OR: 5.730, 95% CI: 1.348–27.856, $p$=0.024), and fasting glucose (OR: 1.042, 95% CI: 1.016–1.070, $p$=0.002) predicted elevated sST2 levels (Table 5).

When a separate analysis was performed in patients with new-onset disease, CRP (OR: 1.096, 95% CI: 1.023–1.232, $p$=0.038) was significantly associated with elevated sST2 levels (Table 6). Meanwhile, BMI (β=0.838, 95% CI: 0.710–0.967, $p$=0.025), WBC count (β=1.000, 95% CI: 1.000–1.001, $p$=0.036), creatinine (β=5.941, 95% CI: 1.117–33.929, $p$=0.039), and fasting glucose (β=1.037, 95% CI: 1.009–1.068, $p$=0.011) were identified to be independent predictors of elevated sST2 level in male patients with gout (Supplementary Table 3, only online).

In addition, comparing the CVD risk scores between patients with elevated and normal sST2 levels revealed that those with elevated sST2 levels had significantly higher ASCVD risk scores than those in the group with normal sST2 levels ($p$=0.002). Furthermore, patients in the elevated sST2 group had a significantly higher risk (relative risk: 2.021, 95% CI: 1.352–3.022, $p$<0.001) of having high-risk FRS compared to those with normal sST2 levels (Fig. 2).

## DISCUSSION

Emerging evidence clearly indicates a relationship between higher sST2 levels and increased CVD risk in the general population.[17] Considering that gout is increasingly understood as a disease with greater risk of cardiovascular events, investigating the clinical significance of sST2 in this CVD risk-enriched population is worthwhile. The present study demonstrated significant clinical and laboratory feature differences in patients with elevated and normal sST2 levels. Notably, the linear regression analysis demonstrated that sex, BMI, WBC count, CRP, and fasting blood glucose influenced sST2 levels, with a different pattern observed in patients with new-onset disease and males. Moreover, logistic regression showed that the predictors of elevated sST2 levels differed from those identified in the linear regression. Finally, patients with gout and elevated sST2 levels had a significantly higher ASCVD risk score and higher probability of being included in the FRS high-risk group than those in the normal sST2 group.

The increased CVD risk in patients with elevated sST2 levels could be primarily explained by the fact that the main sources

**Table 5.** Logistic Regression of Variables Associated with Elevated sST2 Levels

| Characteristics | Univariate analysis | | | Multivariate analysis (forward) | | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | *p* value | OR | 95% CI | *p* value |
| Age | 1.053 | 1.030 to 1.079 | <0.001 | | | |
| Sex, male | 0.068 | 0.022 to 0.203 | <0.001 | 0.112 | 0.028 to 0.428 | 0.001 |
| BMI | 0.817 | 0.728 to 0.907 | <0.001 | 0.836 | 0.725 to 0.947 | 0.008 |
| Alcohol | 0.259 | 0.106 to 0.592 | 0.002 | | | |
| Smoking | 0.303 | 0.086 to 0.822 | 0.033 | | | |
| Hypertension | 1.411 | 0.609 to 3.558 | 0.439 | | | |
| DM | 5.079 | 1.950 to 12.725 | <0.001 | | | |
| Dyslipidemia | 1.653 | 0.674 to 4.671 | 0.301 | | | |
| Uric acid | 1.183 | 0.934 to 1.499 | 0.162 | | | |
| WBC count | 1.000 | 1.000 to 1.000 | 0.013 | 1.000 | 1.000 to 1.000 | 0.024 |
| CRP | 1.015 | 1.005 to 1.027 | 0.003 | | | |
| Creatinine | 10.328 | 3.544 to 40.694 | <0.001 | 5.730 | 1.348 to 27.856 | 0.024 |
| AST | 0.964 | 0.916 to 1.000 | 0.107 | | | |
| ALT | 0.969 | 0.940 to 0.993 | 0.026 | | | |
| Fasting glucose | 1.043 | 1.023 to 1.066 | <0.001 | 1.042 | 1.016 to 1.070 | 0.002 |
| TC | 0.991 | 0.982 to 0.999 | 0.035 | | | |
| LDL-C | 0.990 | 0.980 to 1.000 | 0.051 | | | |
| HDL-C | 1.002 | 0.970 to 1.032 | 0.901 | | | |
| Triglyceride | 0.993 | 0.987 to 0.999 | 0.027 | | | |

sST2, soluble suppressor of tumorigenicity 2; OR, odds ratio; CI, confidence interval; BMI, body mass index; DM, diabetes mellitus; WBC, white blood cell; CRP, C-reactive protein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.


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**Table 6.** Factors Associated with Elevated sST2 Level in Patients with New-Onset Gout

| Characteristics | Univariate analysis | | | Multivariate analysis (forward) | | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | *p* value | OR | 95% CI | *p* value |
| Age | 1.074 | 1.037 to 1.123 | <0.001 | | | |
| Sex, male | 0.068 | 0.014 to 0.298 | <0.001 | 0.029 | 0.000 to 0.861 | 0.061 |
| BMI | 0.808 | 0.664 to 0.957 | 0.021 | | | |
| Alcohol | 0.042 | 0.002 to 0.239 | 0.003 | | | |
| Smoking* | | n/a | | | | |
| Hypertension | 1.316 | 0.372 to 5.358 | 0.680 | | | |
| DM | 20.000 | 4.234 to 117.067 | <0.001 | 16.853 | 0.618 to 1721.495 | 0.124 |
| Dyslipidemia | 2.159 | 0.506 to 14.927 | 0.349 | | | |
| Uric acid | 1.252 | 0.826 to 1.951 | 0.295 | | | |
| WBC count | 1.000 | 1.000 to 1.001 | 0.043 | 1.001 | 1.000 to 1.002 | 0.068 |
| CRP | 1.061 | 1.027 to 1.105 | 0.002 | 1.096 | 1.023 to 1.232 | 0.038 |
| Creatinine | 6.840 | 2.017 to 52.154 | 0.012 | 13.332 | 1.072 to 783.155 | 0.108 |
| AST | 0.919 | 0.826 to 0.995 | 0.073 | | | |
| ALT | 0.925 | 0.856 to 0.977 | 0.020 | | | |
| Fasting glucose | 1.080 | 1.034 to 1.145 | 0.002 | 1.025 | 0.977 to 1.124 | 0.553 |
| TC | 0.990 | 0.976 to 1.003 | 0.138 | | | |
| LDL-C | 0.986 | 0.970 to 1.001 | 0.082 | | | |
| HDL-C | 1.021 | 0.974 to 1.067 | 0.370 | | | |
| Triglyceride | 0.993 | 0.982 to 1.000 | 0.127 | | | |

sST2, soluble suppressor of tumorigenicity 2; OR, odds ratio; CI, confidence interval; BMI, body mass index; n/a, not applicable; DM, diabetes mellitus; WBC, white blood cell; CRP, C-reactive protein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.
*Odd ratios were not calculated due to the small number of events.

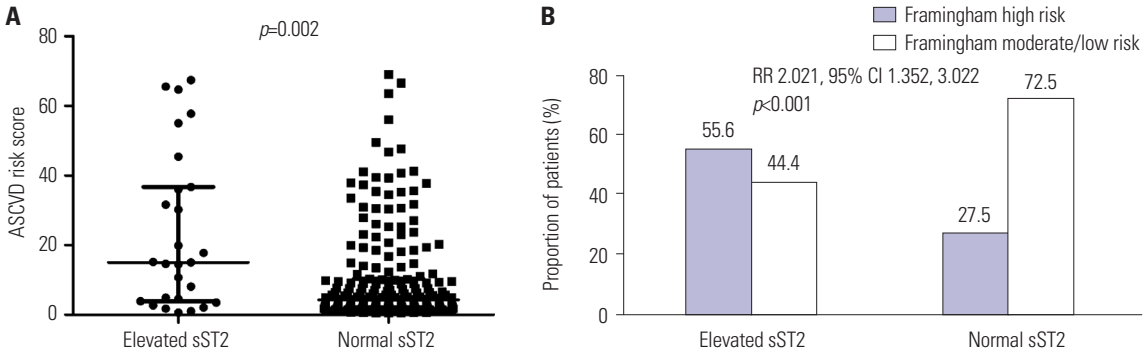


**Fig. 2.** Comparison of (A) ASCVD and (B) Framingham Risk Score in patients with normal and elevated sST2 level groups. Error bars represent the median with interquartile range. ASCVD, atherosclerotic cardiovascular disease; sST2, soluble suppressor of tumorigenicity 2; RR, relative risk; CI, confidence interval.

of ST2 are cardiomyocytes and cardiac fibroblasts, although its secretion has also been reported in extra-cardiac organs.[18] Therefore, increased sST2 levels in the circulation system could indicate higher subclinical myocardial injury and cardiovascular stress, represented by a greater ASCVD risk score and a higher proportion of patients with high-risk FRS. Alternatively, sST2 could predict greater CVD risk as it mitigates the anti-inflammatory effect of the IL-33/ST2 axis pathway,[19] which is supported by the fact that sST2 was linearly associated with the WBC count and CRP in our study population. Higher inflammation is linked to a greater risk of CVD; therefore, it is plausible that elevated sST2 levels disrupt the protective effects of IL-33, contributing to increased inflammatory processes and potentially worsening cardiovascular outcomes.[20] Supporting this "inflammatory hypothesis," sST2 has been shown to reflect disease activity in rheumatic disorders, such as rheumatoid arthritis, systemic lupus erythematosus, and systemic sclerosis with vascular injury, with frequent cardiovascular events observed in patients with heightened disease activity.[21] Notably, a substantial proportion (45.4%) of our patients experienced a clinical gout attack when sST2 level was assessed, which could have contributed to the elevation of sST2 concentration.

Our linear and logistic regression analyses revealed differences in demographic and laboratory factors associated with sST2. For example, male sex, BMI, WBC count, and fasting blood glucose were identified as common factors associated with sST2 in both analyses; however, only CRP levels and creatinine significantly affected linear and logistic regression, respectively. This study adopted the pre-specified normal value of sST2 based on the laboratory threshold established based on a previous study; however, several studies have proposed that the sST2 normal value should be defined individually based on the study population.[12,22,23] Intriguingly, it has generally been reported that age, sex, BMI, and renal function do not significantly impact sST2,[24] with discrepant results observed in the present study. Nonetheless, given that there is also evidence suggesting sST2 is related to age, glomerular filtration rate, and BMI,[25-28] our data do not appear to contradict the existing literature. Moreover, as gout is a disease that predominantly affects males and is associated with a complex interplay of factors, including metabolic dysregulation and the onset of acute inflammation, the diversity of the disease microenvironment should also be considered when interpreting the determinants of sST2. Finally, the discordance of variables showing significance in a subset of patients with new-onset disease and males emphasizes that the biology of sST2 in gout requires a better understanding, and additional efforts are needed to establish the optimal thresholds of sST2 for stratifying cardiovascular events in gout.

The ASCVD risk score and FRS used in this study are powerful tools for evaluating subsequent CVD risk based on population-based studies.[14,15] However, these conventional scoring systems may have limitations compared to using sST2 when assessing the severity of the cardiovascular injury, stratifying patient risk, and implementing intervention strategies. Unlike the conventional scoring systems, sST2 is not a scoring mechanism but a biomarker for ongoing cardiovascular processes that indicate myocardial stress and fibrosis. Moreover, its dynamic features following disease intervention and its prognostic value may identify patients who require active treatment to reduce the risk of cardiovascular events.[9,29] In addition, compared with the calculation and additional patient information required for ASCVD scores and FRS, sST2 measurement is simple and accessible through a single blood test. The finding that patients with elevated sST2 had higher ASCVD scores and were more frequently classified as a high-risk FRS group implies that sST2 may be a valuable biomarker for CVD risk assessment and prognosis in patients with gout. However, the clinical implications and precise disease-specific mechanisms associated with sST2 require further investigation.

The present study had some limitations. First, this retrospective study reviewed patients' clinical and laboratory records. Furthermore, since the assessment of sST2 was performed based on the physician's judgment, this could have led to bias in patient selection. Second, the number of patients with new-onset disease and elevated sST2 levels was small, which may have affected the identification of relevant factors. Third, there is no established ideal value of sST2 levels in patients with gout for detecting cardiovascular events; therefore, the arbitrary definition of increased sST2 as >49.6 ng/mL in males and >35.4 ng/mL in females could have affected the study's results. Fourth, as this was a retrospective and cross-sectional study, serial sST2 level changes in patients with gout based on modifications of CVD risk factors and uric acid levels could not be assessed. In addition, the follow-up period was too short to analyze the differences in cardiovascular events predicted by sST2 levels, which should be verified through large-sized studies.

In conclusion, patients with gout and elevated sST2 levels had higher CVD risk scores compared to those with normal sST2 levels. Furthermore, we identified a close linear association between sST2 and male sex, BMI, inflammatory markers of WBC count and CRP level, as well as fasting blood glucose level. These findings suggest that sST2 may be a useful biomarker for assessing CVD risk in individuals with gout and may provide insights that aid in high-risk patient stratification and recommendations for optimal management strategies.

## DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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## AUTHOR CONTRIBUTIONS

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