ORIGINAL RESEARCH ARTICLE

Magnitude of Soluble ST2 as a Novel Biomarker for Acute Aortic Dissection

Editorial, see p 270

BACKGROUND: Misdiagnosis of acute aortic dissection (AAD) can lead to significant morbidity and death. Soluble ST2 (sST2) is a cardiovascular injury–related biomarker. The extent to which sST2 is elevated in AAD and whether sST2 can discriminate AAD from other causes of sudden-onset severe chest pain are unknown.

METHODS: We measured plasma concentrations of sST2 (R&D Systems assay) in 1360 patients, including 1027 participants in the retrospective discovery set and 333 patients with initial suspicion of AAD enrolled in the prospective validation cohort. Measures of discrimination for differentiating AAD from other causes of chest pain were calculated.

RESULTS: In the acute phase, sST2 levels were higher in patients with AAD than those with either acute myocardial infarction in the first case-control discovery set within 24 hours of symptom onset or with patients with pulmonary embolism in the second discovery set (medians of 129.2 ng/mL versus 14.7 with $P<0.001$ for AAD versus acute myocardial infarction and 88.6 versus 9.3 with $P<0.001$ for AAD versus pulmonary embolism). In the prospective validation set, sST2 was most elevated in patients with AAD (median [25th, 75th percentile]: 76.4 [49.6, 130.3]) and modestly elevated in acute myocardial infarction (25.0 [15.5, 37.2]), pulmonary embolism (14.9 [10.2, 30.1]), and angina patients (21.5 [13.1, 27.6], all $P<0.001$ versus AAD). The area under receiver operating characteristic curve for patients with AAD versus all control patients within 24 hours of presenting at the emergency department was 0.97 (0.95, 0.98) for sST2, 0.91 (0.88, 0.94) for D-dimer, and 0.50 (0.44, 0.56) for cardiac troponin I, respectively. At a cutoff level of 34.6 ng/mL, sST2 had a sensitivity of 99.1%, specificity of 84.9%, positive predictive value of 68.7%, negative predictive value of 99.7%, positive likelihood ratio of 6.6, and negative likelihood ratio of 0.01.

CONCLUSIONS: Among patients with suspected aortic dissection in the emergency department, sST2 showed superior overall diagnostic performance to D-dimer or cardiac troponin I. Additional study is needed to determine whether sST2 might be a useful rule-out marker for AAD in the emergency room.

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Clinical Perspective

What Is New?

- In the acute phase, soluble ST2 was most elevated in patients with acute aortic dissection and modestly elevated in patients with other causes of acute chest pain.
- Soluble ST2 showed superior overall diagnostic performance for acute aortic dissection over D-dimer or cardiac troponin I within 24 hours of presentation to the emergency department.
- ST2 tests with levels <35ng/mL (measured by the R&D Systems assay) appear to reliably rule out acute aortic dissection in patients with suspicion of this disease if used within 24 hours after symptom onset.

What Are the Clinical Implications?

- Soluble ST2 could be a useful biomarker for aortic dissection, which can discriminate acute aortic dissection from other diseases presenting with acute chest pain.
- Soluble ST2 may provide fast and inexpensive diagnostic test to exclude early aortic dissection.

Aortic aneurysm and dissection results in ≈10 000 deaths in the United States annually.[1] As a life-threatening cardiovascular disease, acute aortic dissection (AAD) is a rapidly fatal clinical emergency, with an untreated mortality of ≈1% to 2% per hour after symptom onset.[2] Immediate early diagnosis is crucial and lifesaving for appropriate management of the condition.[3] One of the main challenges for a definitive diagnosis is to distinguish AAD from other sudden-onset severe chest pain diseases, especially acute myocardial infarction (AMI) and pulmonary embolism (PE), because these patients show similar symptoms but require different treatments. Misdiagnosis of AAD as myocardial infarction or PE often results in catastrophic hemorrhage or an exacerbation of AAD, especially when thrombolytic drugs are inappropriately used.[4–6] However, ECGs and chest x-ray films lack sensitivity and specificity in these circumstances.[7] Definitive confirmatory investigation (eg, computed tomography and magnetic resonance imaging) may be limited or not available in the emergency room. It is reported that variation in the presentation of AAD can result in misdiagnosis, with ≤40% of cases being established only at postmortem.[8,9]

To accelerate the diagnosis of AAD, which is a disease of the aortic medial layer, the search for potential biomarkers has focused on those markers associated with injury to vascular smooth muscle (smooth muscle myosin),[10] vascular interstitium (calponin),[11] elastic laminae of the aorta (soluble elastin fragments),[12] or endothelial turnover (CD40 ligand)[13] and markers associated

with exposure of blood to nonintimal vascular surfaces (D-dimer).[14] At present, only D-dimer has a clinically relevant role in suspected aortic dissection (AD).[14,15] However, low specificity was reported for D-dimer in patients with false lumen thrombosis, less extensive disease, and younger age groups.[16] Although significantly elevated D-dimer levels were reported in patients with AAD compared with AMI, D-dimer cannot discriminate patients with AAD from those with PE. A biomarker that can provide additional information to help in early diagnosis and to either reliably include or exclude AAD as a diagnostic possibility would be valuable, particularly if it can be assessed at the time of presentation.

ST2 is an interleukin (IL)–1 receptor family member with transmembrane (ST2L) and soluble (sST2) isoforms. sST2, a soluble truncated form of ST2L, is secreted into the circulation and functions as a decoy receptor for IL-33. Blood concentrations of sST2 increase in many inflammatory diseases and heart diseases,[17,18] emerging as a clinically useful prognostic biomarker in patients with heart failure.[19–24] However, the extent to which sST2 is elevated in AAD is unknown.

We measured plasma concentrations of sST2 in patients with aortic dissection and other acute chest pain diseases (eg, AMI, PE, or angina). We then compared them with healthy participants to evaluate the diagnostic performance of different levels of sST2 at discriminating AAD from other diagnoses and assess whether sST2 is a potential novel biomarker for AAD under different circumstances.

METHODS

Study Sample

The overall study design is shown in Figure 1. The study comprised a retrospective discovery set and a prospective validation cohort. The data that support the findings of this study are available from the corresponding author on reasonable request. The detailed study design and population samples of the discovery set are described in Appendix I and Figure IA in the online-only Data Supplement. In short, 2 case-control sets were established to evaluate the diagnostic performance of sST2 for discriminating AAD from AMI or PE, respectively. The reason for setting up 2 separate case-control groups was mainly the consideration of time from symptom onset and number of patients available. To discriminate AAD from AMI, all patients with AAD within 24-hour symptom onset were enrolled and frequency matched with patients with AMI within the same time frame. Because of the limited number of PE cases within 24-hour symptom onset, we established the second retrospective case-control study set, including all patients with AAD or PE available within 14-day symptom onset, to evaluate the diagnostic performance of sST2 at discriminating AAD from PE. All patients were subject to the same exclusion criteria described in Appendix I in the online-only Data Supplement. All patients with AAD in the study set for AAD versus AMI were also eligible and included in the study set for AD versus PE.

Figure 1. Overall study design.
*Detailed population information and the corresponding objectives in the discovery set are shown in Appendix I in the online-only Data Supplement. †Detailed population information of the validation cohort is shown in Figure I in the online-only Data Supplement. AAD indicates acute aortic dissection; AD, aortic dissection; AMI, acute myocardial infarction; PE, pulmonary embolism; and sST2, soluble ST2.

To further evaluate the diagnostic value of sST2, we designed a validation cohort, including all consenting patients with a suspicion of acute AD within the first 24 hours of presentation to the emergency department at Anzhen Hospital (Beijing, China). Patients with initial suspicion of having AAD were prospectively enrolled in the validation cohort between October 2016 and March 2017. From the total 3618 chest pain patients presenting in the emergency department, we excluded patients in whom there was little or no suspicion of a life-threatening disease (1386 patients), patients with confirmed AMI when presenting (656 patients, eg, those transferred from other hospitals or diagnosed by ECG), confirmed angina (974 patients), confirmed PE (30 patients), confirmed AAD (126 patients), and those whose symptoms were clearly not related to AD (113 patients, eg, pleurisy, pneumonia, acute abdominal diseases) (Figure I in the online-only Data Supplement). Exclusion of these patients was based on the guidelines on the diagnosis and treatment of aortic diseases.[25–27] The remaining 333 patients (ie, suspected AAD or AAD not immediately ruled out) were finally eligible and included for the validation cohort without further selection of patients based on the final diagnosis. Patients suspected to have heart failure were included. The suspicion of AAD generally causes clinicians to order a D-dimer test, which is currently recommended in the Chinese clinical guidelines for diagnosing AAD[27] and implemented in our hospital emergency department, although this practice may not be routine in other countries. All patients in our validation cohort had confirmatory medical imaging examination regardless of the result of the D-dimer test.

For all participants, whole blood was drawn into sodium citrate tubes, processed immediately into plasma, and stored at –80°C. Blood samples were handled using the same procedures for the different case-control groups. We used the first blood sample from participants after they entered the hospital and before surgery. Baseline characteristics and surgical information of patients were collected from medical records and confirmed by the study physicians.

The study was approved by the Beijing Anzhen Hospital Ethics Review Board. All patients provided written informed consent. For patients with AAD with sudden death soon after admission or diagnosed at autopsy, consent was obtained from family members.

Outcome

All patients with AD had image information from ECGs and computed tomography to confirm the final diagnosis. D-dimer was not used for confirmation of the final diagnosis of AD. Patients with AD were classified according to the site of the intimal tear or the part of the aorta affected, irrespective of the position of the tear. Anatomic classification was made using the Stanford system. Patients with AD were classified as having acute dissection if their time from onset of symptoms was ≤14 days. In unusual circumstances, in which the time of symptom onset was unclear, acuteness of dissection was determined from other clinical features, such as the characteristics of the dissecting membrane on imaging and the appearance of the aortic wall during the operation. Patients were diagnosed with AMI if they had chest pain lasting >20 minutes, diagnostic serial ECG changes comprising new pathological Q waves or ST-segment and T-wave changes, and a plasma creatine kinase-myocardial band elevation more than twice the normal level or cardiac troponin I (cTnI) level >0.1 ng/mL. Diagnosis of PE was confirmed by positive spiral computed tomography or pulmonary angiography, a high probability on ventilation perfusion scintigraphy, or a proximal deep vein thrombosis documented on

compression ultrasonography or angiography. Patients with AMI with suspected heart failure were based on the Killip classification, where Killip class >1 indicates patients with certain clinical signs of heart failure. Patients with PE with the ratio of right over left ventricle ≥0.9 implies the presence of right ventricle strain.

Measurements of sST2 and D-Dimer

Circulating sST2 was measured using a DuoSet ELISA kit (DY523B-05; R&D Systems) according to the manufacturer's instructions.[28–32] The limit of detection for sST2 is 0.019 ng/mL, with mean intraassay coefficient of variation of <6.0% and mean interassay coefficient of variation of <9.5%. Detailed procedures as well as the comparison between assay methods for sST2 are described in Appendix II and Figure IB in the online-only Data Supplement). Levels of D-dimer were measured using the commercially available automated latex-enhanced immunoturbidimetric assay (HemosIL D-dimer HS; Instrumentation Laboratory). The limit of detection for D-dimer is 21 ng/mL, with mean intraassay coefficient of variation of <8.3% and mean interassay coefficient of variation of <11.0%. Technicians were blind to the settings of the different case-control groups.

Statistical Analysis

Demographic and medical information of AAD and other chest pain diseases were summarized by mean (SD) or median (interquartile range [IQR]) for skewed variables (eg, sST2 and D-dimer). A 2-sample t test was used to compare mean levels of log-transformed sST2 or other continuous risk factors (log-transformed where appropriate) by different disease outcomes. The χ^2 test was used for assessing difference in distribution of a categorical variable by different disease outcomes. For the time course of sST2 levels according to the time from symptom onset, we fit the linear regression model on log-sST2 with the continuous time from symptom onset. A linear trend test was used to test the association. Compared with D-dimer, the diagnostic performance of sST2 for distinguishing AAD from all other diseases, AMI, PE, or angina was assessed using receiver operating characteristic curve (ROC) analysis. The area under the ROC, sensitivity, specificity, accuracy, 2 likelihood ratios suggested by Choi[33] for positive and negative test results, positive predictive value, and negative predictive value were calculated. Nonparametric ROC analyses were performed using only a continuous variable of sST2, D-dimer, or cTnI without the adjustment of other risk factors. The Wald test was used to assess the significance of the difference between areas under the ROC. Because the prevalence of AD in patients presenting with a suspicion of AD is poorly understood, to ease the generalization of our estimations, we used 25% (ie, 1 in 4 patients) for calculating positive predictive value and negative predictive value, as applied in other studies with similar study design for D-dimer.[14] The optimal cutoff point from the study was the threshold leading to the maximum summation of sensitivity and specificity (ie, the Youden index).[34] The recommended predefined cutoff point for D-dimer was 500 ng/mL, which is widely used in the published literature.[14] Analyses were made using Stata (version 14.0) software (Stata Statistical Software). All P values were 2-tailed and have not been adjusted for multiple testing.

A P value <0.05 was considered statistically significant. Two-sided P values and 95% confidence intervals were used.

RESULTS

Patient Demographics and sST2 Distribution

In the discovery set, data were available for 1027 participants, including 677 AD cases (443 acute AD cases), 234 AMI cases, 49 PE cases, and 67 healthy control participants (Figure 1). In the first case-control set to discriminate AAD from AMI within 24 hours of symptom onset, baseline characteristics of patients are shown in Table I in the online-only Data Supplement. There were 245 patients with AAD and 234 patients with AMI. Both sST2 and D-dimer were significantly higher in patients with AAD compared with AMI. Levels of sST2 in patients with AMI were also higher than those of healthy participants (Figure 2a). sST2 levels were elevated at 129.2 ng/mL (median, IQR: 71.3–197.5) in patients with AAD compared with 14.7 ng/mL (median, IQR: 9.9–23.3) in patients with AMI (P<0.001). Of 234 patients with AMI, 184 had Killip class I, which indicated no sign of heart failure, and 50 patients had Killip class II, III, or IV. The sST2 concentration was higher in patients with AMI with Killip class >1 at 23.9 (median, IQR: 15.6–44.7) than those with Killip = 1 at 13.3 (median, IQR: 8.6–19.8) (P<0.001). However, both were significantly lower than those with AAD (both P<0.001 versus AAD). sST2 concentrations positively correlated with D-dimer concentrations. Pearson's correlation coefficients were highest at 0.39 in patients with dissection and 0.27 in patients with AMI (Figure II in the online-only Data Supplement). Meanwhile, sST2 concentrations were positively correlated with brain natriuretic peptide in patients with AMI but not in patients with AD (Figure III in the online-only Data Supplement). Pearson's correlation coefficients were 0.30 in patients with AMI and only –0.04 in patients with AD.

In the second case-control set to discriminate AAD from PE, baseline characteristics of 443 patients with AAD and 49 patients with PE are shown in Table II in the online-only Data Supplement. Levels of D-dimer were similar among patients with both AAD and PE (median: 1431 versus 1594, P=0.19). sST2 was significantly elevated in patients with AAD compared with PE (median: 88.6 versus 9.3, P<0.001) regardless of whether patients underwent a type A or type B dissection (Figure 2b). sST2 levels in patients with PE were also higher than those in healthy participants. Pearson's correlation coefficients in patients with PE were 0.14 for sST2 with D-dimer and 0.21 for sST2 with brain natriuretic peptide, respectively (Figures II and III in the online-only Data Supplement). Among 49 patients with PE, 12 (24.5%) had right ventricle/left ventricle ≥0.9, which indicated
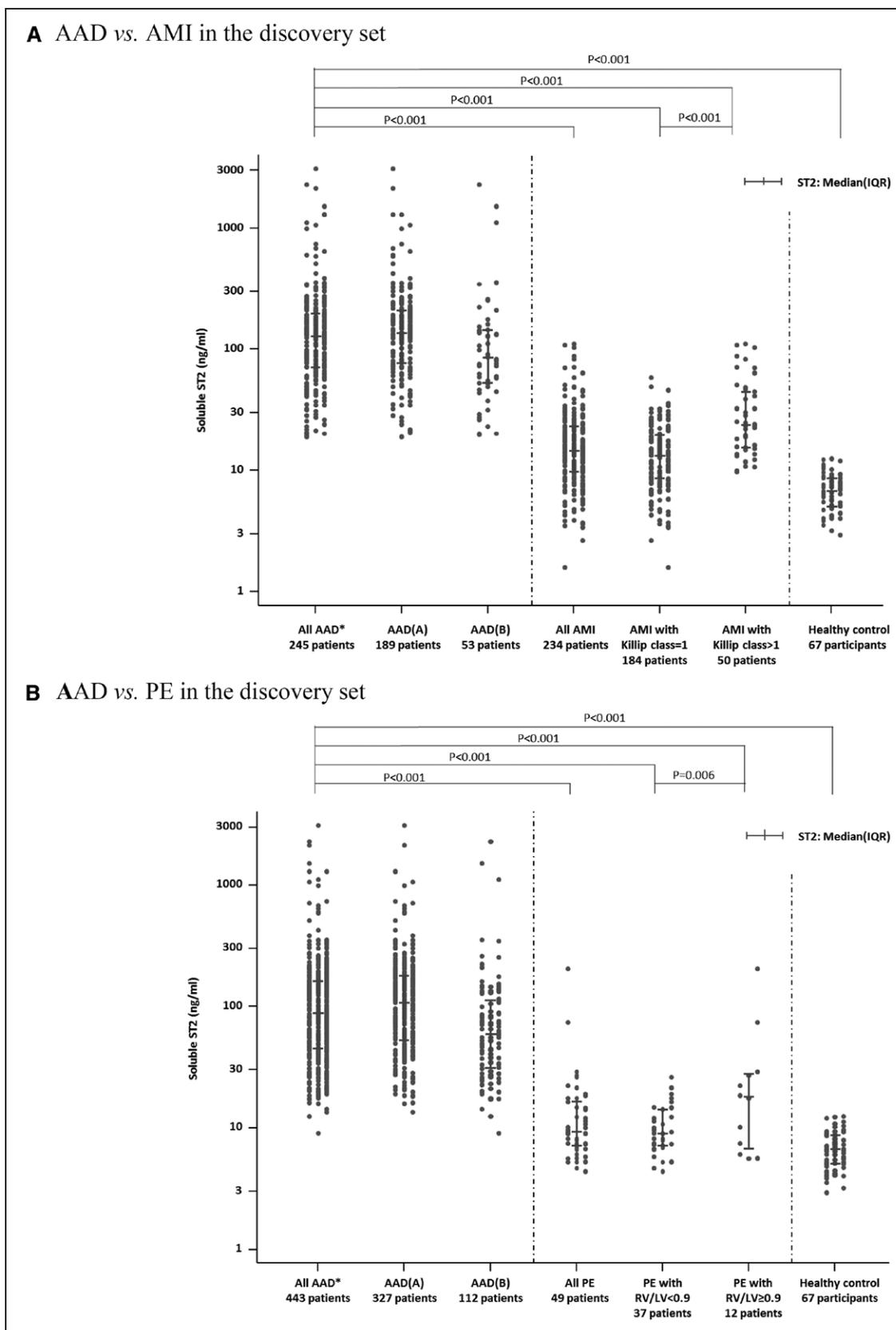
Figure 2. Distribution of sST2 according to disease status.
A, AAD vs AMI in the discovery set. *Including 189 patients with type A AAD, 53 patients with type B AAD, and 3 patients with acute abdominal AAD. Analysis included all patients within 24 hours of time of onset. **B,** AAD vs PE in the discovery set. *Including 327 patients with type A AAD, 112 patients with type B AAD, and 4 patients with acute abdominal (*Continued*)
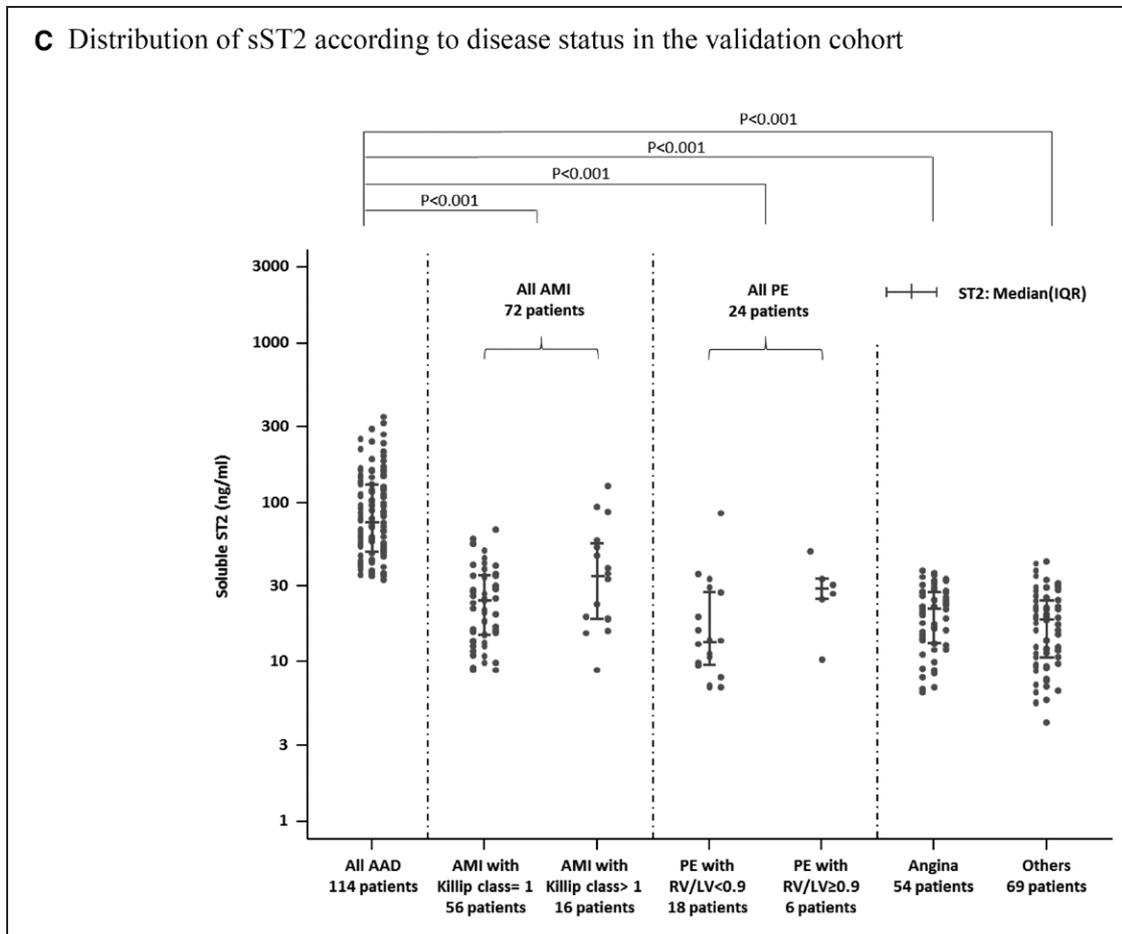
Figure 2 Continued. AAD. Analysis included all patients within 14 days of time of onset. **C,** Distribution of sST2 according to disease status in the validation cohort. Medians of sST2 concentrations were 25.0 ng/mL (IQR: 15.5–37.2) in all patients with AMI and 14.9 ng/mL (IQR: 10.2–30.1) in all patients with PE. AAD indicates acute aortic dissection; AMI, acute myocardial infarction; IQR, interquartile range; LV, left ventricle; PE, pulmonary embolism; and RV, right ventricle.

the presence of right ventricle strain.[35] Similar to patients with AMI with Killip class >1, sST2 concentrations were higher in patients with PE with right ventricle/left ventricle ≥0.9 at 18.1 (median, IQR: 6.8–27.9) than others at 9.0 (median, IQR: 7.2–14.3) (P=0.006). Again, both were significantly lower than those with AAD (both P<0.001 versus AAD). The additional dissection patients in the AAD versus PE set were generally comparable to those in the AAD versus AMI set, except that levels of both sST2 and D-dimer were slightly lower, probably because of the longer time from symptom onset of these patients (Table III in the online-only Data Supplement).

Time course was examined in the discovery set using box plot analysis according to time from symptom onset. Of the 677 patients who underwent dissection, the peak level of sST2 was within 24 hours from symptom onset. A moderate decline was observed over time (linear trend test P<0.001) (Figure 3).

The validation cohort consisted of 333 patients, including 114 with AAD and 219 with different final diagnoses. Of the non-AD controls, 72, 24, 54, and

69 patients had AMI, PE, angina, and other diseases, respectively (Figure 1). Baseline characteristics of patients are shown in Table IV in the online-only Data Supplement. sST2 levels were elevated in AAD at 76.4 ng/mL (median, IQR: 49.6–130.3). These were 3-fold, 5-fold, 3.6-fold, and 4-fold higher than levels for AMI (median at 25.0 ng/mL), PE (median at 14.9 ng/mL), angina (median at 21.5 ng/mL), and other diseases (median at 18.6 ng/mL), respectively (Figure 2c). Similar to the results in the discovery set, 22% of patients with AMI (n=16) had Killip class >1, and 25% of patients with PE (n=6) had right ventricle/left ventricle ≥0.9. Although sST2 levels were higher in those patients with suspected heart failure than other patients, they were still lower than those patients with AAD (Figure 2c).

Diagnostic Performance for Discriminating AAD

In the prospective validation cohort, the area under the ROC for 114 patients with AAD versus all non-AD con-
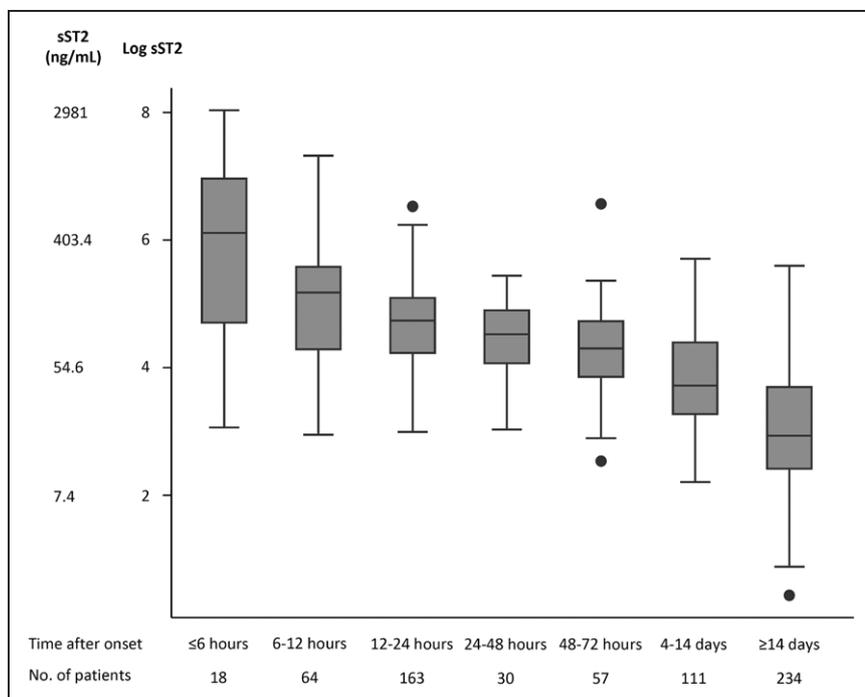
Figure 3. Levels of sST2 according to the time after onset in patients with dissection in the discovery set.
sST2 indicates soluble ST2.

trol patients within 24 hours presenting at the emergency department were 0.97 (0.95, 0.98) for sST2, 0.91 (0.88, 0.94) for D-dimer, and 0.50 (0.44, 0.56) for cTnI, respectively (Figure 4a). For different control diseases, the area under the ROC of sST2 to discriminate AAD were 0.92 (0.88, 0.96) from patients with AMI, 0.96 (0.91, 1) from patients with PE, and 0.995 (0.990, 1) from patients with angina, respectively (Figure 4b). Thus, sST2 showed superior overall diagnostic performance compared with D-dimer and cTnI when all these conditions with sudden-onset severe chest pain were present in the emergency department.

Classification of Patients Using Levels of sST2

In the validation cohort, sST2 at cutoff levels of 34.6 ng/mL and D-dimer at 323 ng/mL were the thresholds leading to the maximum summation of sensitivity and specificity in discriminating AAD from all other control diagnoses (Figure 4 and Table). Corresponding sensitivities were 99.1% for sST2 and 93.9% for D-dimer, and specificities were 84.9% for sST2 and 78.5% for D-dimer, resulting in 89.8% of patients for sST2 and 83.8% of patients for D-dimer being correctly classified. Although predictive values are widely used from a clinical perspective, their estimations relied on a known prevalence in the tested population (ie, proportion of confirmed AD in all patients with suspicion of AAD). Assuming 1 in 4 patients would have AD as used in other studies,[14] positive and negative predictive values for sST2 at 34.6 ng/mL were 68.7% and 99.7%, respectively. Positive and negative likelihood ratios for

sST2 were 6.6 and 0.01, respectively. Negative predictive value was >90% and negative likelihood ratio was <0.1, indicating that sST2 at ≈35 ng/mL was a good rule-out tool for AAD. Moreover, higher cutoff values were associated with higher positive predictive values. For an sST2 of 40 ng/mL, sST2 had the highest accuracy of 90.1% with sensitivity of 87.7%, specificity of 91.3%, positive predictive value of 77.1%, negative predictive value of 95.7%, positive likelihood ratio of 10.1, and negative likelihood ratio of 0.13. Diagnostic performance of sST2 at 34.6, 36, or 40 ng/mL was also superior to D-dimer at a predefined cutoff level of 500 ng/mL.

DISCUSSION

This study analyzed data from 1360 participants, including 1027 participants in the retrospective discovery set and 333 patients with initial suspicion of having AAD in the prospective validation cohort. Several promising results suggest that the sST2 may be a potential novel biomarker for discriminating AAD from other severe chest pain diseases, and therefore it might help in the early diagnosis of AAD.

We found that the magnitude of elevated sST2 can distinguish patients with AAD from patients with AMI within 24 hours after symptom onset. When aortic dissection occurs, disruption to the aortic media immediately changes aorta hemodynamics, with intramural hemorrhage leading to propagation (especially when the intimal layer is also disrupted) and tracking of blood within the media. Vascular smooth muscle cells are directly exposed to blood flow, shear stress, and lo-
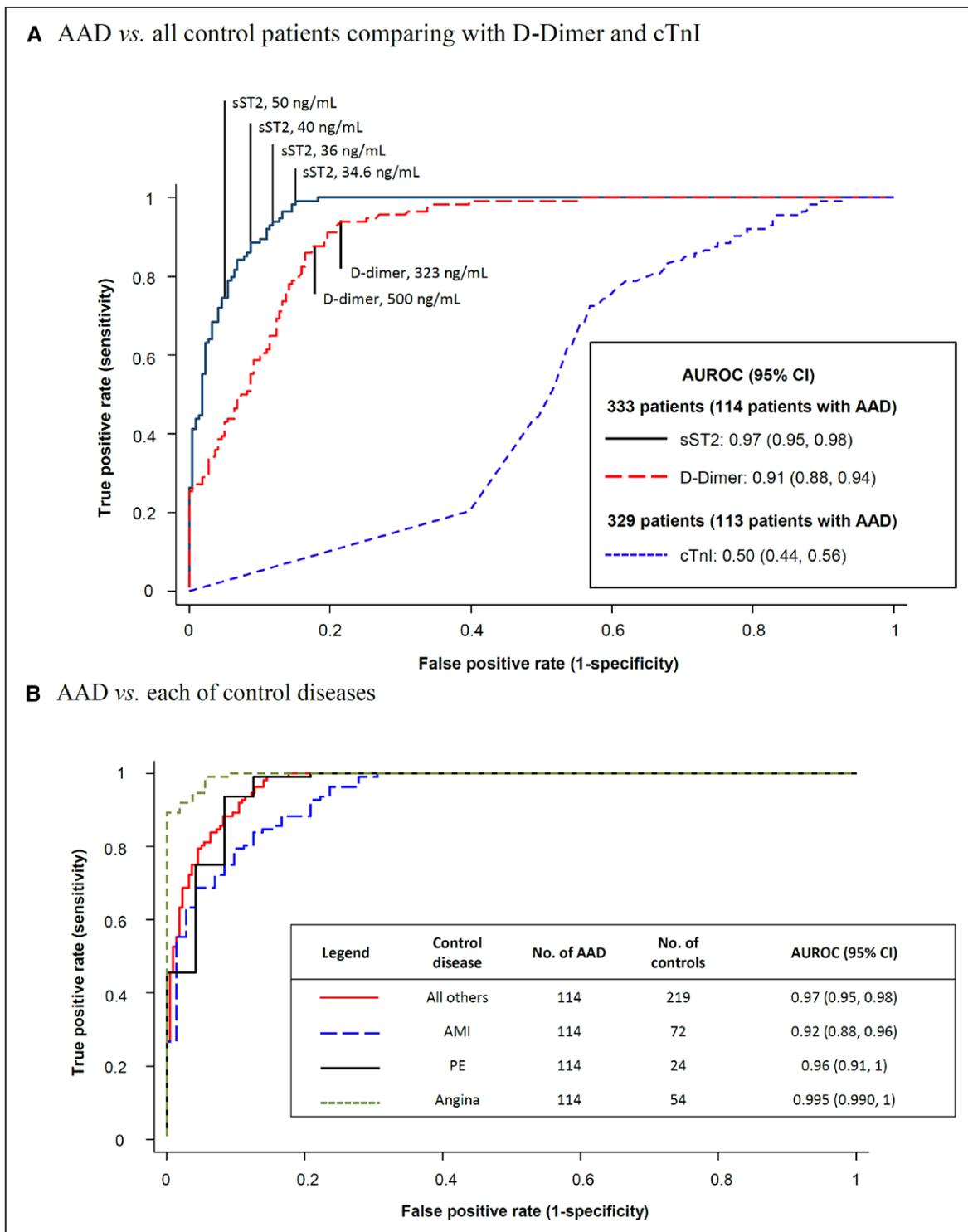
Figure 4. Receiver operating characteristic curves of sST2 in the validation cohort.
A, AAD vs all control patients comparing with D-dimer and cTnI. **B,** AAD vs each of the control diseases. AAD indicates acute aortic dissection; AMI, acute myocardial infarction; AUROC, area under the receiver operating characteristic curve; CI, confidence interval; cTnI, cardiac troponin I; PE, pulmonary embolism; and sST2, soluble ST2.

cal inflammation.[36] In patients with dissection, smooth muscle cell stretch and vascular injury occurred in the large area of the aorta, the largest artery, which may induce higher levels of sST2 in the circulation than in the small or medium vessels of AMI or PE. Our results

suggested that the degree of the elevation of sST2 levels is associated with the different magnitudes of vascular injury among AAD, AMI, and PE. In fact, although sST2 levels were higher in patients with AMI or PE with suspected heart failure, they were still lower than that

Table. Diagnostic Performance of Patients With AAD Versus Others Using sST2 Compared With D-Dimer in the Validation Cohort

	Threshold	Sensitivity, %	Specificity, %	Accuracy, %	PLR	NLR	PPV, %‡	NPV, %‡
Patients (n=333, with AAD n=114)								
sST2, ng/mL	34.6*	99.1	84.9	89.8	6.6	0.01	68.7	99.7
	36	93.0	88.1	89.8	7.8	0.08	72.3	97.4
	40	87.7	91.3	90.1	10.1	0.13	77.1	95.7
	50	74.6	95.0	88.0	16.3	0.27	83.2	91.8
D-dimer, ng/mL	323*	93.9	78.5	83.8	4.4	0.08	59.3	97.5
	500 (recommended)†	87.7	82.2	84.1	4.9	0.15	62.2	95.3

AAD indicates acute aortic dissection; NLR, negative likelihood ratio; NPV, negative predictive value; PLR positive likelihood ratio; PPV, positive predictive value; and sST2, soluble ST2.

*Optimal threshold value obtained from the data, which was the threshold leading to the maximum summation of sensitivity and specificity (ie, the Youden index).

†Predefined threshold values based on information from previous literature.

‡Because the prevalence of aortic dissection in patients presenting with suspicion of aortic dissection is poorly understood, to ease the generalization of our estimations, we used 25% (ie, 1 in 4 patients) as suggested in the previous literature.

in patients with AAD in our study, suggesting that the increment of sST2 in AAD may mainly be a result of smooth muscle cell stretch and vascular injury rather than myocardial strain.

Besides AMI, we discovered that the magnitude of elevated sST2 can distinguish patients with AAD from patients with PE, whereas D-dimer, as a fibrin degradation product present in the circulation after fibrinolysis of thrombus, was found to be significantly increased similarly in a number of diseases, including both PE and AAD. Currently, D-dimer aids clinical diagnosis for PE only as a rule-out tool when the test result is negative.

In contrast, sST2 is not considerably elevated in patients with PE. This observation suggests that sST2 could be a potential biomarker for discriminating AAD from PE, providing additional valuable information beyond that provided by D-dimer. This is strongly supported by our results from the prospective validation cohort, which included all patients with suspected of AD with acute chest pain within the first 24 hours of presenting to the emergency department. A high proportion of patients with PE would limit the performance of D-dimer for evaluation of AAD but cause no influence on sST2.

In addition, we found that using sST2 at around 35 ng/mL can exclude aortic dissection with a negative likelihood ratio <0.1 and a negative predictive value of >90%. It is noted that the cutoff point of 35 ng/mL for sST2 was also recommended in the emergency department for heart failure. However, this value for heart failure is proposed using the Presage assay, currently recommended by the US Food and Drug Administration. The Presage assay was not used in our study because it is not validated with our retrospective citrated plasma. We therefore compared sST2 plasma concentrations measured with the R&D Systems assay versus the Presage assay in the evaluation set with 67 patients available (Appendix II in the online-only Data Supplement). The 35 ng/mL using the R&D Systems assay was equivalent to 71 ng/mL using the Presage assay in our evaluation set. Furthermore, higher cutoff values of sST2 were associated with higher positive predictive values. sST2 at 40 ng/mL had the highest accuracy of 90% in our study with positive predictive value of 77% and positive likelihood ratio of 10. Therefore, sST2 could be a practical and promising tool to guide the need for further imaging diagnoses of AAD.

Two isoforms, sST2 and ST2L, are produced from a dual promoter system through differential mRNA processing.[37] Both ST2 forms are expressed in vascular cells and thoracic aorta tissues, with sST2 residing in the extracellular matrix of the integumentary system.[38] ST2 mRNA expression is induced by mechanical strain, tumor necrosis factor, IL-1α, and IL-1β. With stress and proinflammatory stimuli, the proximal promoter (active sST2), not the distal promoter (active ST2L), is responsible for transcriptional activation. Therefore, sST2, and not ST2L, is highly upregulated in the first hour. sST2 is rapidly secreted into the circulation and functions as a decoy receptor for IL-33. It then inhibits IL-33/ST2L signaling, which represents a crucial protective mechanism in case of mechanical overload. In this way, sST2 may extend the dissection and perhaps leads to further release.[17] These findings raise the possibility that the IL-33/ST2 system could be a potential pathophysiological mediator of dissection and includes the involvement of sST2 and ST2L in several different cellular processes, including cell alignment and differentiation, migration, survival or apoptosis, vascular remodeling, and cell-mediated inflammatory reactions in dissection progression. The role of sST2 and ST2L in these specific pathologies remains to be addressed in future studies.

To our knowledge, this study provides the first evidence that sST2 is associated with aortic dissection and could be a novel biomarker for AD in the acute phase. One strength of this study is that we discovered and validated the diagnostic performance of sST2 for AAD. We simultaneously measured D-dimer and sST2 for direct comparison to enhance the validity of our estimates of the diagnostic performance. The relatively large numbers of patients also allowed us to evaluate the corresponding results according to different clinically relevant subgroups (eg, patients with AMI or PE with or without suspected heart failure). This study had some limitations. Although this study had a relatively large number of patients to examine AAD, it was a single-center study. Although the prevalence of 1 in 3 suspected patients with AAD in our validation cohort was comparable to several published studies for D-dimer with similar study designs,[14] it may still be enriched compared with the Western population in general clinical practice (ie, not large referral centers). Therefore, we excluded patients transferred from other hospitals with confirmed disease outcomes (Figure I in the online-only Data Supplement). A comparable prevalence of disease (ie, 25% used in other studies) was applied in the estimation of positive and negative predictive values to avoid inflation. However, the area under the ROC and the positive and negative predictive values observed in our study are likely exaggerated by the design of our derivation and validation cohorts. In particular, our validation cohort is not an all-comers cohort of patients with undifferentiated chest pain. Future validation studies evaluating sST2, and comparing sST2 with D-dimer, are thus needed. As a single-center study, the generalizability of our findings should also be verified by a large prospective multicenter study to confirm the diagnostic efficacy and accuracy of this novel assay. The absolute values for the concentrations of sST2 may be varied according to the assay method used, which may affect the cutoff levels proposed. Calibration across different assay methods could be applied where appropriate. Finally, other diseases (eg, acute respiratory distress syndrome) can also cause the elevation of sST2 levels,[39] although they may not often be confused with AD according to the symptoms of the disease. Further medical image-based confirmatory diagnoses are still essential in clinical practice.

Conclusions

sST2 showed superior overall diagnostic performance for acute AD over D-dimer or cTnI in patients with suspected AD in the emergency department. sST2 might be a useful rule-out marker for AAD, but the utility of a positive prediction is less clear. Therefore, sST2 could be a sensitive candidate that may provide fast and cost-effective diagnostic testing to determine early AAD.

DISCLOSURES

None.

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