Anzhen Risk Evaluation System for Acute Aortic Syndrome (AZSCORE-AAS): protocol for a multicentre prospective cohort study in northern China

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ABSTRACT
Introduction Acute aortic syndrome (AAS) is a group of acute and critical conditions, including acute aortic dissection (AAD), acute intramural haematoma and penetrating aortic ulcer. High mortality and morbidity rates result in a poor patient prognosis. Prompt diagnoses and timely interventions are paramount for saving patients’ lives. In recent years, risk models for AAD have been established worldwide; however, a risk evaluation system for AAS is still lacking in China. Therefore, this study aims to develop an early warning and risk scoring system in combination with the novel potential biomarker soluble ST2 (sST2) for AAS.

Methods and analysis This multicentre, prospective, observational study will recruit patients diagnosed with AAS at three tertiary referral centres from 1 January 2020 to 31 December 2023. We will analyse the discrepancies in sST2 levels in patients with different AAS types and explore the accuracy of sST2 in distinguishing between them. We will also incorporate potential risk factors and sST2 into a logistic regression model to establish a logistic risk scoring system for predicting postoperative death and prolonged intensive care unit stay in patients with AAS.

Ethics and dissemination This study was registered on the Chinese Clinical Trial Registry website (http://www.chictr.org.cn/). Ethical approval was obtained from the human research ethics committees of Beijing Anzhen Hospital (KS2019016). The ethics review board of each participating hospital agreed to participate. The final risk prediction model will be published in an appropriate journal and disseminated as a mobile app to facilitate clinical use. Approval and anonymised data will be shared.

Trial registration number ChiCTR1900027763.

STRENGTHS AND LIMITATIONS OF THIS STUDY
⇒ The prospective nature of the study reduces the possibility of missing data.
⇒ Cooperation with large tertiary referral centres will ensure high-volume data for model construction.
⇒ Presentation of Anzhen Risk Evaluation System for Acute Aortic Syndrome will be in the form of a mobile app to facilitate clinical use.
⇒ We will only derive and internally validate the surgical risk prediction model, and an external validation will be necessary to test its extrapolation.
⇒ The participating centres are from northern China; thus, the findings may have a selection bias.

INTRODUCTION
Acute aortic syndrome (AAS) is a group of critical aortic diseases, including acute aortic dissection (AAD), acute intramural haematoma (IMH) and penetrating aortic ulcer (PAU), that share similar clinical manifestations, diagnostic workups and therapeutic challenges. Classic AAD accounts for 80%–90% of AAS cases.1-3 Of these, type A AAD is the most fatal, with intimal tears involving the ascending aorta. The mortality rate increases by 1% for each additional hour from symptom onset, and the cumulative mortality can be as high as 50% within the first 48 hours.4 In comparison, the lesions of IMH signify haemorrhage within the medial layer, while the lesions of PAU signify a local intimal rupture, secondary to atherosclerotic plaque. Both conditions can stabilise or improve but may also progress to AAD.5 Based on reports from the 2022 American College of Cardiology guidelines,6 16%–47% of IMH cases may deteriorate to AAD, and up to 40% of PAU cases may involve ruptures. For patients with type A AAD and most patients with type B AAD with complications or high-risk features, timely intervention (including open surgery and endovascular management) can save their lives.2 Although treatment strategies and surgical techniques have made great strides over the past 20 years, with surgical mortality for type A decreasing from 25.0% to 18.4%, and that for type B from 30.2% to 21.1%,8,9 it remains significantly more fatal...
than other cardiac surgical procedures. Meanwhile, the high incidence of complications adversely affects patient prognoses. Therefore, a valid scoring system plays a key role in surgical risk assessment, cost control and treatment strategy formulation.

The European System for Cardiac Operative Risk Evaluation II (EuroSCORE II), which is widely used in Western countries, has satisfactory predictive efficacy in valve-related surgery and coronary artery bypass grafting, while Poullis pointed that it cannot predict surgical risk accurately in high-risk patients. Additionally, there are few literature reports on aortic surgeries. The German Registry for Acute Aortic Dissection Type A is a risk prediction model developed recently, especially for type A AAD, with acceptable predictive efficacy demonstrated in external validation. However, the latest results showed that its predictive power is lower than that of EuroSCORE II. Our team used EuroSCORE II to predict in-hospital mortality and the length of intensive care unit (ICU) stay in 384 patients with type A AAD who underwent total aortic arch replacement with stented elephant trunk implantation. However, the prediction efficiency was poor (area under the curve (AUC)=0.49). The conflicting findings may lie in the fact that the risk model study participants being mainly from Western countries and thoracic aortic surgery accounting for only 7.3% of total operations. Therefore, some of the variables in its prediction model are somewhat contradictory to the pathophysiology of aortic diseases. The first Registry of Aortic Dissection in China compared our data with the International Registry of Acute Aortic Dissection, finding that the onset of type A AAD in our patients was a decade earlier (51.8±11.4 years vs 63.1±14.0 years, p<0.01). Axitell and colleagues performed a comparative study in which Chinese patients were much younger (52±14 years vs 61±13 years, p<0.001) with more complex preoperative pathophysiology. The aforementioned results required us to consider possible regional differences. Therefore, a new risk assessment system suitable for the disease characteristics of Chinese patients with AAS is urgently required.

In addition, currently established risk models are based on routine clinical data and do not incorporate novel indexes to increase reliability. Biomarkers are characterised by easy access to samples and fast reading of results. Except for D-dimer, other biomarkers have not been widely used. Of note, D-dimer has low specificity in patients with AAS, especially those with false lumen thrombosis or limited range of involvement. As the circulating isoform of ST2, soluble ST2 (sST2) is a member of the interleukin (IL)-1 receptor family and is produced primarily by endothelial and immune cells, but also to a lesser extent by cardiac fibroblasts and cardiomyocytes. sST2 acts as a decoy receptor for IL-33, preventing it from binding directly to ST2-ligand, and as a regulator to modulate downstream inflammatory processes. In addition, sST2 concentration can be an independent predictor of poor prognosis in patients with heart failure. Our previous study found that sST2 had improved sensitivity and specificity compared with D-dimer at a cut-off point of 34.6 ng/mL, serving as a potential diagnostic biomarker for AAD. Given our team’s previous significant findings, we hypothesise that sST2 can be used not only as a molecular marker for the early diagnosis of AAS but also as a basis for risk stratification in critical patients before intervention. Finally, a multimodal AAS risk model will be developed in combination with this potential biomarker.

OBJECTIVES

The primary objective of this study is to explore a risk scoring model incorporating sST2 to predict surgical mortality and ICU stay >48 hour in patients with AAS based on a prospective multicentre database.

The secondary objective is to investigate the ability of sST2 to distinguish and predict the surgical outcomes of different types of AAS.

METHODS

Study design

The research is a prospective, multicentre, observational study. This study was conceived and initiated by the Department of Cardiovascular Surgery, Beijing Anzhen Hospital, Capital Medical University. Participating centres include The Third Hospital of Peking University in Beijing and The First Affiliated Hospital of Zhengzhou University in Zhengzhou, Henan Province. For all patients enrolled in the study, venous blood will be collected on admission to the hospital. Then blood samples will be drawn into anticoagulation tubes, marked with numbers instead of names, centrifuged at 3000 rpm for 15 min into plasma, and stored in the medical cryogenic refrigerator at −80°C. A Duoset ELISA kit (DY523B-05; R&D Systems, Minneapolis, Minnesota, USA) will be used to measure circulating sST2 levels following the instructions. We will cover the costs of laboratory tests and inform patients of their results on availability. Moreover, different treatment plans will be selected, and effective interventions for some risk factors will be implemented to reduce mortality and complication rates. To do so, we will use the risk scoring system for aortic surgery established by a logistic mathematical model. We used the Strengthening the Reporting of Observational Studies in Epidemiology checklist when writing our report.

Participants

We plan to recruit Chinese patients with AAS who meet the inclusion and exclusion criteria listed as follows from 1 January 2020 to 31 December 2023 to participate in this study. Recruitment is non-obligatory and will not influence clinical decisions. The research teams consist of clinicians experienced in the diagnosis and treatment of AAS. Furthermore, all investigators will undergo appropriate training on all relevant information regarding this study.

Criteria

Inclusion criteria
- Age 18 or older.
- Patients diagnosed with AAS by CT angiography.
- From symptom onset to surgery ≤14 days.
- Signed informed consent.

Exclusion criteria
- Traumatic or iatrogenic AAS.
- Women with AAS in pregnancy.
- No surgical intervention.

Data collection
A standardised case report form (CRF) is designed to collect a set of primary variables. Each participant will be provided with a unique identity code; the data will be written on printed CRFs in real time; and well-trained investigators will input the collected data into a secure, password-protected, electronic database to avoid errors. Only the researchers involved will have access to the identity information. The CRF will be retained for a minimum of 10 years.

A data monitoring committee is independent of the investigators, and the members have sufficient expertise in statistical analysis and aortic surgery. They will hold meetings periodically to review the reliability of the accumulated data and to determine whether the trial should make any modifications.

Predictor variables
The CRF includes demographic information, disease history, laboratory results, imaging features and surgical details of patients. All variables are selected based on clinical practice and are collected prospectively.

Preoperative predictors
- The demographic information includes age (years), sex and body mass index (kg/m²).
- Disease history including hypertension, diabetes mellitus, hyperlipidaemia, heart failure, coronary artery disease, chronic pulmonary disease, chronic kidney disease, previous cerebrovascular accident, history of myocardial infarction, previous cardiac/aortic surgery and Marfan syndrome.
- sST2 (ng/mL), SpO₂ (%), PaO₂ (mm Hg), PaCO₂ (mm Hg), pH, lactate acid (mmol/L), white blood cell (1×10⁹/L), neutrophil (1×10⁹/L), platelet (1×10⁹/L), haemoglobin (g/L); creatine kinase-MB (ng/mL), lactate dehydrogenase (U/L), hsTnI (pg/mL), myoglobin (mg/L), fasting blood glucose (g/L), serum creatinine (µmol/L), estimated glomerular filtration rate (mL/min), uric acid (µmol/L), blood urea nitrogen (mg/dL), glutamic–pyruvic transaminase (U/L), glutamic–oxalacetic transaminase (U/L), albumin (g/L), D-dimer (ng/mL) and fibrin degradation product (µg/mL).
- AAS type (AAD, IMH or PAU), organ malperfusion (brain, coronary artery, spinal cord, vissus, kidney or extremity), and left ventricular ejection fraction (%).

Intraoperative predictors
- Status of operation (emergent or elective).
- Procedure type: aortic valve procedures (replacement or repair), proximal aorta procedures (Bentall, David, Wheat or ascending aorta replacement), arch procedures (total arch replacement or hemiarch replacement), descending aorta procedure (elephant trunk or thoracic endovascular aortic repair), and concomitant procedures (coronary artery bypass grafting, extra-anatomical bypass or other valve operations).
- Cardiopulmonary bypass time (min), cross-clamp time (min), selective cerebral perfusion (retrograde, antegrade or both), circulatory arrest time (min) and redo cardiopulmonary bypass.

Outcomes and definitions
The primary endpoint in the present study is postoperative mortality, regardless of the cause, during hospitalisation or within 30 days of surgery. The secondary endpoint is defined as a prolonged length of ICU stay (>48 hours).

Coronary artery disease is based on (1) preoperative CT angiography or coronary angiography or (2) previous procedures related to the coronary artery or history of myocardial infarction. Chronic pulmonary disease mainly refers to chronic obstructive pulmonary disease in need of long-term use of bronchodilators and/or steroid anti-inflammatory drugs. Chronic kidney disease is defined as serum creatinine concentration of ≥133µmol/L or requirement for renal replacement therapy. Organ malperfusion is defined as compromised blood flow in the relevant organs due to the dissection process, as supported by radiological evidence and/or laboratory data, and clinical symptoms and/or organ impairment. Definitions of postoperative complications are presented in table 1.

Sample size and statistical analysis
The sample size calculation was based on Riley et al.²⁵ using the pmsampsize package in Stata V.15.1 software (StataCorp LLC, College Station, Texas, USA). We estimated that 10–15 variables needed to be included in our model. The incidence of compound outcomes was set at 20%.²³²⁰ The conservative estimate of the variation that could be explained by the prediction model was 15%, with a corresponding R² of 0.0945. The minimum sample sizes for the 10 candidate predictors were calculated as 902, and 1353 for the 15 predictors. Our cohort will enrol about 2000 patients, fully meeting the sample size requirements. A random split-sample method will be used to divide data into a training dataset for modelling and a validation dataset for internal validation (split ratio=0.8:0.2).

Missing data are identified to be at random and dealt with using multiple imputation technique.²⁷ Considering our prospective nature, the likelihood of missing data is not significant.

The diagnostic value of sST2 in distinguishing AD, IMH and PAU will be assessed by the receiver operating characteristic (ROC) curve. Optimal cut-off points are identified.
as the threshold values corresponding to the maximum Youden Index (sensitivity=specificity=1).

To investigate the sST2 thresholds for predicting surgical outcomes, we will use Cutoff Finder,28 which is a bundle of optimisation methods designed specifically for biomarkers.

Continuous variables will be denoted as mean±SD or median (IQR), and compared by Student’s t-test or Mann-Whitney U test, respectively. Categorical variables will be represented as number (%) and compared using χ2 test or Fisher’s exact test. Univariate and multivariate logistic regression analyses will be used to select risk factors that have an impact on surgical outcomes. Variables with a p value of <0.05 are considered statistically significant. All identified conventional clinical covariates and sST2 will be included to obtain regression coefficients, ORs and 95% CIs. A simple risk score will be calculated for each patient as follows: $B_0 + B_1X_1 + B_2X_2 + \ldots + B_iX_i$ to a validation dataset. The capacity to differentiate patients at a higher risk of endpoint events from those at a lower risk is described as discriminative ability. We will use the area under the ROC curve to quantify, taking sensitivity and specificity into account, considering AUC of >0.8 provides strong discrimination, while AUC of <0.7 is of limited help for clinical assistance.29 The calibration ability or goodness of fit refers to the similarity between predicted risk and observed risk, and will be assessed visually using the calibration plot.

**Patient and public involvement**

The patients and/or the public will not be involved in the recruitment, design, conduct, reporting or dissemination plans of the study.

**ETHICS AND DISSEMINATION**

Ethics approval was obtained from the human research ethics committees of Beijing Anzhen Hospital (KS2019016). Ethic review boards in each participating hospital agreed to participate. The study has also been registered at Chictrc.org.cn. Clinical data will only be collected after patients have fully understood the study content and signed relevant consent forms. Patients will also be informed of their freedom to withdraw from this study at any time without discrimination or retaliation. Findings of the trial will be presented at conferences and published in peer-reviewed journals. Based on the aforementioned findings, a mobile app will be developed, covering an early warning and surgical risk scoring system, and clinicians will have free access. We will commission a professional software company for app development and maintenance.

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**Table 1  Definitions of postoperative complications**

<table>
<thead>
<tr>
<th>Complications</th>
<th>Definitions</th>
</tr>
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<tbody>
<tr>
<td>Stroke</td>
<td>Abrupt onset of any neurological deficit for ≥24 hours caused by insufficient blood supply to the brain20</td>
</tr>
<tr>
<td>Spinal cord injury</td>
<td>Different motor function impairment of the lower extremities including paraparesis and paraplegia</td>
</tr>
<tr>
<td>Heart failure</td>
<td>Require prolonged use of positive inotropic drugs for ≥48 hours and/or the assistance of mechanical circulatory support device</td>
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<tr>
<td>Pneumonia</td>
<td>Presence of new and/or progressive pulmonary infiltrates on chest radiograph in combination of two or more of the following features: fever &gt;38°C or hypothermia &lt;36°C, white blood cell &gt;12×10^9/L or &lt;4×10^9/L, or purulent tracheobronchial secretions29</td>
</tr>
<tr>
<td>Respiratory insufficiency</td>
<td>Need for reintubation, tracheotomy, non-invasive positive ventilation or mechanical ventilation for longer than 48 hours</td>
</tr>
<tr>
<td>Acute liver injury</td>
<td>Acute and massive elevation of serum aminotransferases, reaching more than 10 times the upper limit of normal31</td>
</tr>
<tr>
<td>Mesenteric ischaemia</td>
<td>Abdominal pain with or without nausea and vomiting and rectal bleeding or bloody diarrhoea, diagnosed by imaging, endoscopy and/or surgery32</td>
</tr>
<tr>
<td>Acute kidney ischaemia</td>
<td>Changes in serum creatinine concentration or glomerular filtration rate using the KDIGO criteria33</td>
</tr>
<tr>
<td>Re-exploration for bleeding</td>
<td>Chest reopening for excessive bleeding with a persistent fall in haemoglobin and unstable haemodynamics</td>
</tr>
</tbody>
</table>

KDIGO, Kidney Disease: Improving Global Outcomes.

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Contributors H-ZW and S-WC conceived the basic concepts and framework of the study and wrote the first protocol manuscript, with further contributions from C-NL, Z-YQ, and Y-PG. J-MZ, ZZ and C-HO provided expert clinical guidelines. Y-LZ and R-TG contributed to the statistical consultation and literature search. All authors critically reviewed the drafts and agreed to submit the final edition.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

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