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STUDY PROTOCOL

The Anzhen Risk Scoring System for Acute Type A Aortic Dissection: A Prospective Observational Study Protocol

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Abstract

Introduction: Acute type A aortic dissection (ATAAD) is a catastrophic disease with fatal outcomes. Malperfusion syndrome (MPS) is a serious complication of ATAAD, with an incidence of 20–40%. Many studies have shown that MPS is the main risk factor for poor ATAAD prognosis. However, a risk scoring system for ATAAD based on MPS is lacking. Here, we designed a risk scoring system for ATAAD to assess mortality through quantitative assessment of relevant organ malperfusion and subsequently develop rational treatment strategies.

Methods and analysis: This was a prospective observational study. Patients' perioperative clinical data were collected to establish a database of ATAAD (N≥3000) and determine whether these patients had malperfusion complications. The Anzhen risk scoring system was established on the basis of organ malperfusion by using a random forest survival model and a logistics model. The better method was then chosen to establish a revised risk scoring system.

Ethics and dissemination: This study received ethical approval from the Ethics Committees of Beijing Anzhen Hospital, Capital Medical University (KS2019034-1). Patient consent was waived because biological samples were not collected, and no patient rights were violated. Findings will be disseminated at scientific conferences and in peer-reviewed publications.

Keywords: Acute type A Aortic Dissection; 30-Day mortality; Risk prediction; Random Forest survival; Malperfusion syndrome

Strengths and limitations of this study

There are currently no systematic studies in Asian patients with acute type A aortic dissection. This is the first such study with stratification of patients according to surgical risk to guide treatment decisions. Because this was a single-center observational prospective study, the generalizability of the

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results may be limited, and replication in other centers and patient populations is necessary.

Introduction

Acute type A aortic dissection (ATAAD) is a catastrophic disease that often requires emergency surgery [1]. With improvements in the diagnosis and treatment of ATAAD, more patients with ATAAD have received prompt treatment. Although the mortality rate for ATAAD has decreased to approximately 10–15% with advances in surgical techniques [2–4], it remains higher than the mortality rates for valvular and coronary surgery, which are approximately 1–3% [5–7]. Decreasing the rates of mortality and postoperative complications of ATAAD remains an urgent problem to be solved.

Preoperative ATAAD with organ malperfusion complications is very common, with an incidence of 20–40% [8, 9]. The poorly perfused regions include the coronary artery, cerebrovascular, spinal cord, celiac trunk, mesenteric artery, kidney, and lower extremities (Figure 1) (Refer to the Chinese expert consensus of standardized diagnosis and treatment for aortic dissection, the Committee of Great Vessels of Chinese Association of Cardiovascular Surgeons). Many studies have suggested that malperfusion syndrome (MPS) is the main risk factor affecting ATAAD prognosis [2, 9, 10]. ATAAD with, rather than without, MPS is associated with higher mortality, longer ICU stays, and higher costs in patients undergoing aortic surgery. However, the types of organs involved in malperfusion vary, and their influence on prognosis differs.

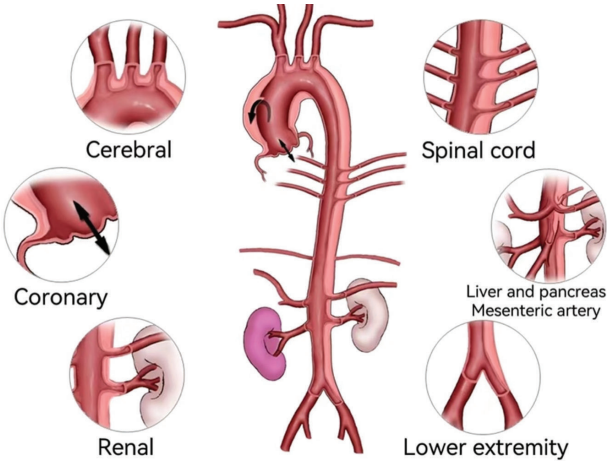

Figure 1 Acute Type A Aortic Dissection with Organ Malperfusion Complications.

The European System for Cardiac Operative Risk Evaluation II (EuroSCOREII) is one of the most frequently used risk assessment systems in clinical practice. However, its main component is coronary heart disease, whereas aortic disease accounts for only 7.3%; moreover, it does not consider the effects of malperfusion on prognosis [11]. Our previous study has indicated that the area under the EuroSCOREII ROC curve to predict ATAAD mortality is only 0.49, thus indicating a poor predictive ability [12]. The German Registry for Acute Type A Aortic Dissection (GERAADA) score is another commonly used scoring system [13], but it is based on European populations, whose ages and disease characteristics significantly differ from those in Asian populations.

Thus, a quantitative evaluation system for MPS is lacking to enable fine-grained classification of the operative risk of patients with ATAAD. Therefore, we created the Anzhen risk scoring system for ATAAD, which we propose for identifying high-risk populations, cost control, and formulation of treatment strategies.

Objective

The main objective of this study was to establish a scoring system for ATAAD with MPS, which assigns points to each poorly perfused organ. Patients were divided into low risk ($P < 10\%$), moderate risk ($10\% < P < 20\%$), high risk ($20\% < P < 40\%$), and very high risk ($P > 40\%$) groups according to the probability of postoperative death, as measured by the scoring system.

Methods

Definition of MPS

Some previous studies have defined MPS as tissue and organ ischemia, because dissection involves the aorta and its related branch vessels, and ultimately leads to necrosis and functional failure of related tissues and organs [13, 14]. Our definition of MPS was based on imaging evidence, combined with clinical manifestations of organ ischemia and/or laboratory evidence of organ malperfusion (Table 1) [15].

Table 1 Diagnosis of Malperfusion of Relevant Tissues and Organs.

Relevant tissues and organs	Diagnosis
Coronary	Diagnosis can be made if one or more of the following items occur: 1. electrocardiography showing ST-segment elevation; 2. echocardiography revealing motion abnormalities of the ventricular wall; 3. laboratory examination indicating myocardial ischemia (CK-MB, troponin); 4. imaging of the aortic CTA indicating no/low contrast filling in the coronary artery.
Cerebral	Diagnosis can be made if one of the following items occurs: 1. somnolence, coma, disorders of consciousness, other symptoms, or physical examination indicating hemiplegia or other positive signs; 2. aortic CTA indicating no/low contrast filling in the left common carotid artery or innominate artery [16, 17].
Spinal cord	Spinal cord injury can be diagnosed if the patient presents with paraplegia or paresis.
Liver and pancreas	Diagnosis can be made if two or more of the following items occur: 1. clinical manifestations of nausea or vomiting; 2. laboratory examination indicating increased liver function indexes (ALT, AST, TBIL, DBIL, LDH, etc.), elevated trypsin (serum amylase, lipase, urinary amylase, etc.), hyperlactatemia, etc.; 3. aortic CTA indicating decreased spleen and liver perfusion, or peripancreatic edema; 4. aortic CTA indicating no/low contrast filling in the celiac trunk.
Mesenteric artery	Diagnosis can be made if one of the first two of the following items occur, with or without the last two items: 1. aortic CTA indicating intestinal dilatation or mesenteric exudation; 2. aortic CTA indicating filling with no/low contrast in the superior mesenteric artery; 3. abdominal pain, abdominal distension, bloody stools, or other symptoms, or physical examination indicating abdominal tenderness, plate-shaped abdomen, and other positive signs; 4. laboratory examinations indicating hyperlactatemia [18, 19].
Renal	Diagnosis can be made if one of the first two items occur, with or without the addition of last two items: 1. imaging for aortic CTA: unilateral or bilateral renal cortical perfusion decreased; 2. imaging for aortic CTA: no/low contrast filling in the lumen of one or both renal arteries; 3. Anuria, oliguria or poor blood pressure control; 4. Laboratory examination indicated renal abnormalities (Cr, urea, eGFR etc.) [20].
Lower extremity	Diagnosis can be made if the first item occurs, with or without the addition of the last items: 1. clinical manifestations: unilateral or bilateral lower extremity paresthesia, weakness accompanied by the corresponding lateral extremity pulseless, pallor, low skin temperature; 2. laboratory tests suggested myoglobin was elevated; 3. imaging for aortic CTA: no/low contrast filling in the lumen of iliac artery or external iliac artery or femoral artery.

CK-MB, creatinine kinases MB isoenzyme; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; DBIL, direct bilirubin; LDH, lactate dehydrogenase; CTA, computed tomography angiography; eGFR, estimated glomerular filtration rate; Cr, creatinine.

Study Design

This was a single-center, prospective, observational study. We collected preoperative, intraoperative, and postoperative data for 3000 consecutive patients with ATAAD diagnosed at the Beijing Anzhen Hospital since January 2009, and established a large database of aortic dissection surgery. A mathematical model was used to assign scores to the included preoperative, intraoperative, and postoperative data to establish the scoring system. We then conducted internal and external validation of the scoring system. Finally, the Anzhen risk scoring system for aortic dissection was developed. The study flowchart is shown in Figure 2.

Participants

We screened 3000 consecutive patients with ATAAD who underwent surgery since February 2009. The inclusion criteria were as follows: 1. confirmation with computed tomography angiography (CTA); 2. onset time less than 14 days; and 3. age >18 years. The exclusion criteria were as follows: 1. connective tissue diseases; 2. traumatic, iatrogenic, or infected aortic dissection; 3. previous history of

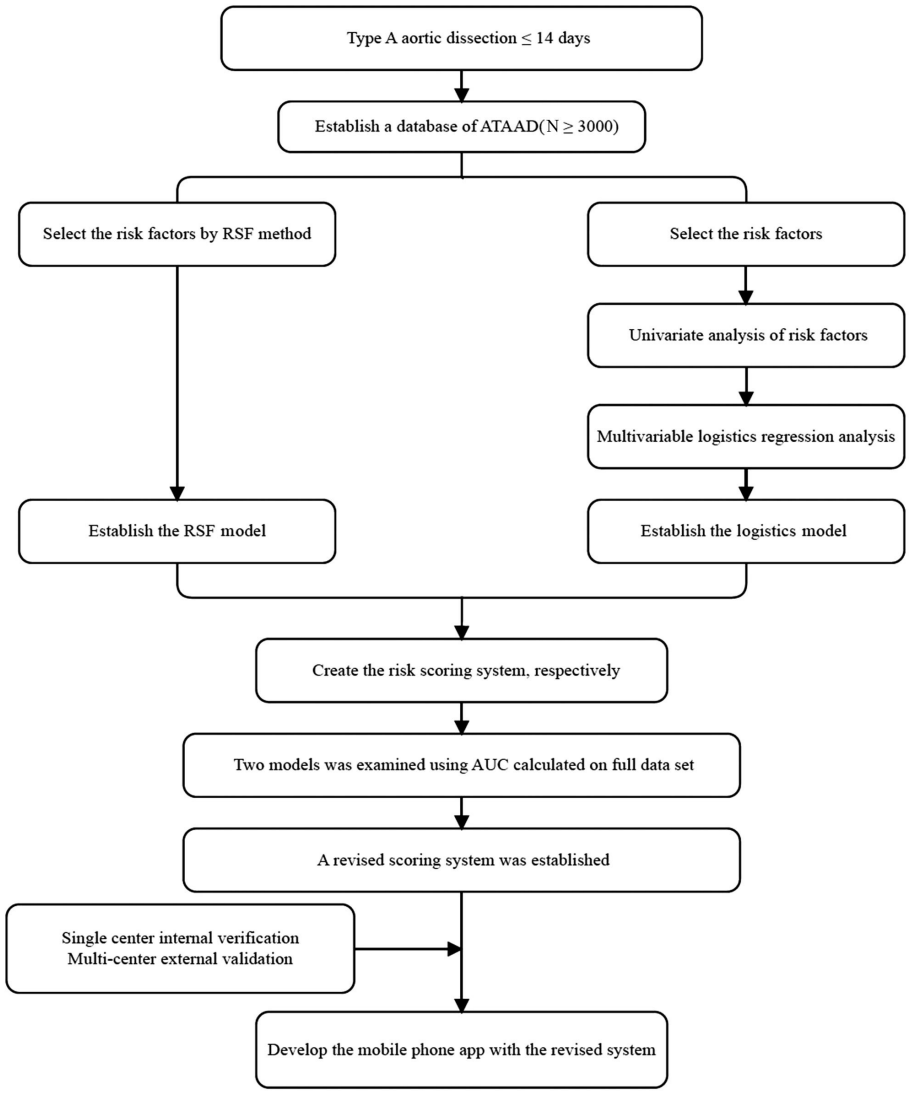

Figure 2 Flow Chart for Creation of a Risk Scoring System of Acute Type A Aortic Dissection with Malperfusion Syndrome. RSF, random survival forest; AUC, area under the curve.

organ failure; 4. history of coronary heart disease; 5. previous history of severe cerebral infarction (with sequelae) and paraplegia; and 6. pregnancy.

Outcome Measurement

The primary outcome of this study was 30-day mortality. The secondary outcomes were ICU stay > 7 days, length of hospital stay > 14 days, and hospital charges.

Data Collection

Data were input into the web version of the aortic dissection database (https://adda.mdruby.cn/, Figure 3), which our team had previously developed. Patient data were obtained from the medical records inpatient system. Patients admitted during the study period were strictly followed. Six clinical study technicians, comprising three supervisors and three data collectors, were recruited and received professional training before data entry. The supervisors checked the data entered by the data collectors and compared them with the medical records. If the data error rate exceeded 5%, the data were re-entered.

Data Elements

To address the objectives, we used the above methods to collect the necessary information.

Figure 3 Web Version of the Aortic Dissection Database (https://adda.mdruby.cn/).

The database consisted of three parts, and the variables compiled within the study included the following.

1. Preoperative characteristics: clinical manifestations, age, sex, height, weight, NYHA cardiac function classification, hypertension, diabetes, hyperlipidemia, smoking, alcohol consumption, coronary artery disease, stroke, history of tuberculosis, history of cardiac surgery, carotid stenosis, chronic obstructive pulmonary disease, blood gas analysis, leucocyte concentration, laboratory examinations of renal function and liver function, myocardial enzymes, type of aortic dissection, onset time, primary tear location, pleural effusion, branch artery involvement, resuscitation, false lumen thrombosis status, and left ventricular ejection fraction.
2. Operative indicators: operative time, cardiopulmonary bypass time, aortic cross-clamping time, circulatory arrest time, lowest nasopharyngeal temperature, lowest rectal temperature, operative technique, secondary cardiopulmonary bypass, arterial cannulation site for cardiopulmonary bypass time, and cerebral perfusion technique.
3. Postoperative indicators: IABP, ECMO, CRRT, blood gas analysis, duration of intubation, length of ICU stay, death, cause of death, hospitalization cost, length of hospital admission, renal function, liver function, paraplegia, ischemic stroke, and limb ischemia.

Sample Size and Statistical Analysis

The calculation of the minimal sample size was performed according to Riley et al. [21, 22]. Using the pmsampsize package in R, we determined the minimum sample size required for developing a multivariable prediction model. We estimated that 10–20 variables would need to be included in the model.

The mortality rate for ATAAD was set at 5%. The minimum sample size for 10 candidate predictors was calculated to be 850, and that for 20 candidate predictors was calculated to be 1699 participants. This study included ≥ 3000 patients, thus fully meeting the sample size requirements.

Categorical data are reported as frequencies (percentages), and continuous data are reported as mean ± standard deviation or median (interquartile range). χ^2 test with the exact method was used for categorical variables, and t-test or Mann-Whitney U-test was used for continuous variables. A P-value < 0.05 indicated a statistically significant difference. The variable selection process was performed multiple times with the logistic regression model and random forest survival model (R-package randomForestSRC). The performance of the final risk models was examined on the basis of the area under the curve calculated on the full dataset. The Hosmer-Lemeshow goodness-of-fit test was used to assess the fit of the model (Hosmer-Lemeshow statistic > 0.05). All analyses were performed in the statistical software R version 4.1.2.

Ethics and dissemination

This study received ethical clearance from The Ethics Committees of Beijing Anzhen Hospital, Capital Medical University (KS2019034-1). Patient consent was waived because the study did not violate patient privacy, endanger patient safety, collect biological samples, or violate patient rights. The results of this study will be published in peer-reviewed journals and presented at international scientific meetings.

Patient and public involvement

Neither patients nor the public was involved in the design, conduct, reporting, or dissemination plans of this research.

Author Contributions

BJ and CL contributed to conception, data collection, and analysis, and drafted the manuscript. CL, YZ, and YG contributed to analysis. CL, ZQ, and SC contributed to data collection. LS contributed to conception and editing of the manuscript. JZ contributed to conception, design, and acquisition of data, and critically reviewed the manuscript. All authors approved the final manuscript.

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Conflicts of interest

The authors report no proprietary or commercial interest in any product described or concept discussed in this article.

Data availability statement

Data are available upon reasonable request to the corresponding author.

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