Protocol for creation of a risk scoring system for acute type A aortic dissection surgery

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ARTICLE INFO

ABSTRACT

Stanford type A aortic dissection is a kind of cardiovascular disease which seriously threatens human life and health. It has the characteristics of rapid onset, rapid progress and high mortality. Surgical treatment is a recognized treatment for type A aortic dissection. There are many disputed places in the actual clinical work about the timing, prognosis and methods of the operation. This study aims to establish an early mortality risk scoring system for acute Stanford A aortic dissection surgery patients.

Methods and analysis: The structured data of patients with acute type A aortic dissection were collected. The primary outcome is death during hospitalization. Secondary outcomes will include re-operation and related complications. A risk scoring system of patients with acute type A aortic dissection undergoing surgical treatment will be established. Prospective data will be used to validate the risk stratification ability and accuracy of the model in operative risk prediction.

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1. Introduction

Acute aortic dissection (AAD) is a rare and extremely dangerous cardiovascular surgical disease with an annual incidence of 3–4 per 100,000. About two-thirds of the patients with AAD involve ascending aorta, which is classified as type A according in Stanford classification [1]. Mortality in patients with Stanford type A aortic dissection was significantly correlated with the extent of dissection, the time from onset to diagnosis, and the method of treatment. If only relying on conservative medical treatment, the mortality rate within 24 h of onset is as high as 20%, and up to 50% within 2 weeks. In recent IRAD database published data, the early hospital mortality rate is 59% [2]. Because the main cause of early death is aortic rupture, surgical repair before rupture is currently recognized as the main treatment of type A aortic dissection. According to the extent and progress of dissection, a variety of surgical methods can be selected for aortic repair. However, as a large-scale cardiac surgery requiring deep hypothermic circulatory arrest and selective cerebral perfusion, the hospital mortality rate of type A aortic dissection is higher than that of other types of cardiac surgery. Multicenter data show that the hospital mortality rate within 60 days or in the early stage is about 23% [3]. By establishing risk prediction model, we can not only comprehensively assess the risks of surgery before operation, but also distinguish the severity of patients' disease, stratify the risk levels, and help clinicians choose the best treatment strategies according to the individual characteristics of patients, so as to reduce the mortality and complication rate of surgery.

2. Methods and analysis

2.1. Aims and objectives

The primary aim of the study is to establish a risk scoring system for Stanford A aortic dissection patients based on the largest database of aortic dissection in northern China. Validate the scoring system in surgical risk assessment and provide the evidence-based medical basis for clinicians in treatment of acute type A aortic dissection.

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The aim will be achieved in following steps:

Sample size calculation.
Retrospective collection of data on acute type A AD surgery patients.
Establishment and internal validation of early mortality risk prediction model.
External validation of the established model using prospective data.
Assign score for each variable and create a clinical risk score.

2.2. Study design

This study is designed as a cohort study. The establish of model is conducted using retrospective cohort data, the validation of model is performed using prospective data in our center.

2.3. Participants

2.3.1. Inclusion criteria
Patients with acute type A aortic dissection (less than 2 weeks) over the age of 18, the dissection involves the ascending aorta or the arch of the aorta, receive surgical treatment in our center, informed consent by relatives or later on in during the hospital admission when patients regain mental capacity.

2.3.2. Exclusion criteria
The dissection tear was located lower than the left subclavian artery, patients with chronic aortic dissection.

2.3.3. Outcome measures
Primary endpoint events: death during hospitalization, both intraoperatively and postoperatively. Secondary endpoint events: Whether patients was discharged home; if patients was transferred to other hospitals, the reason for transfer need to be collected. Re-operation and hospitalization complications associated with surgery within 30 days of the procedure, such as MODS, sepsis, cardiovascular adverse events, respiratory failure, acute renal failure and nervous system complications (Table 1). The death and complications of the patients after discharge and the detailed time of occurrence were observed by special follow-up personnel through telephone and mail questionnaires.

2.4. Data validation and management

Only variables with less than 25% missing will be included in the univariate analysis [4], only variables with less than 10% missing will be included in the parsimonious regression model, and the missing values will be estimated by multiple imputation method (see Table 2).

Data collection will follow Caldicott II principles (http://systems.hscic.gov.uk/infogov/caldicott/). The data of the patients were obtained by inquiring the medical record system by specialized collectors. Study data will be stored and managed using an electronic data capture tools (http://r.empowerstats.cn/dataweb/), including demographic data, co-morbidity, and prior medical history. Echocardiography and aortic computed tomography angiography data was evaluation by experienced ultrasound physicians and imaging specialists in our hospital.

To ensure the realness of data collection, 10% of the patients were randomly selected from the database, and the contents and the original data were checked. Check all patient data entered by the researcher if the error rate of variables entered by the researcher exceeds 5%.

Table 1
Definition of operation related complication.

Complication	Definition
MODS	The failure of two or more organs 24 h after the onset of the symptom
Sepsis	Significant elevation of white blood cell and neutrophil counts, blood culture is positive, or infection that is difficult to control using antibacterial therapy
Respiratory failure	Severe impairment of pulmonary ventilation or ventilation due to various causes, resulting in arterial partial oxygen pressure less than 60 mmHg
Cardiovascular adverse events	Cardiovascular adverse events were defined as low cardiac output syndrome, malignant arrhythmia, and aortic rupture
Nervous system complications	Cerebral hemorrhage, cerebral infarction, paraplegia, hemiplegia and spinal cord ischemia diagnosed by physical examination or brain imaging examination
ARF	The estimated GFR decreased by at least 25% in the 48–72 h period after surgery
Re-operation	Reason for re-operation is classified into major bleeding, implant infection, tamponade, anastomotic leakage

MODS = Multiple organ dysfunction syndrome, ARF = acute renal failure.

2.5. Anticipated recruitment

By collecting retrospective cohort data, 890 patients with acute type A aortic dissection who underwent surgical treatment at our hospital from January 2015 to December 2018 were consecutively collected to form a modeling cohort. Through a prospective cohort study, 890 consecutive surgery patients with acute type A aortic dissection in our center from January 2019 to July 2021 were selected to form a model validation cohort.

2.6. Study timelines

Data collection and analysis will be conducted following the time line below

1. From January 2019 to June 2019, collect 890 consecutive patients from 2015 to 2018 retrospectively
2. June 2019, complet the establishment of risk scoring system
3. From January 2019 to June 2021, collect data of validation cohort patients
4. June 2021, Validate and adjust the risk scoring system

2.7. Statistical analysis

The area under ROC curve for predicting mortality risk of patients with acute type A aortic dissection was obtained as the main index and the sample size was estimated. According to previous reports, the early surgery mortality rate of acute type A aortic dissection is 10–30%. As the area under ROC curve predicted by European Score System is 0.79. The area under ROC curve is set 0.8 as the reference standard and 0.7 as the acceptable threshold. PASS 11.0 software was used to estimate the sample size needed to establish a mortality prediction model. The significance level (a) is set as 0.05, the grasp degree (1-beta) is set as 0.9, using the bilateral test, the research needs at least. The results showed that at least 890 acute type A aortic dissection who underwent surgery needed to be enrolled in the study.

Continuous variables are expressed as mean ± standard deviation and categorized variables as percentage. T-test, One-Way ANOVA test, Kruscal Whallis H test and chi-square test (categorical variables) were used to determine any statistical difference between different outcome groups. Univariate analysis was used to evaluate the relationship between variables and outcomes,

Table 2
Data fields for the study.

Data field	Option (definition)
Section 1–Demographic data	
Age	In years
Height	In meters
Weight	In kilograms
Body mass index	In kg/m^2
Body surface area	In m^2
Time from the onset	In days
Smoking status	Current smoker/Quit > 6 weeks/Non-smoker
Cardiovascular history	Yes/No
COPD history	Yes/No
Diabetes	Yes/No
Hypertension	Class I/Class II/Class III/Class IV
Diabetes	Yes/No
Previous Aortic surgery	Yes/No
Previous valve surgery	Yes/No
Previous coronary bypass surgery	Yes/No
Previous history of cerebrovascular disease	Yes/No
If yes -	
New neurological deficit	Transient syncope/lethargy/coma/limb/sensory/disorder/hemiplegia/paraplegia/limb movement disorder
Section 2–Baseline blood test results	
White blood cell count	In 1 * 10^9/L
Red blood cell count	In 1 * 10^9/L
Platelet count	In 1 * 10^9/L
Hemoglobin	In mg/L
Neutrophil percentage	In %
MCHC	In g/L
ESR	In cm/min
BUN	In mg/dL
SCr	In mmol/L
TnI	In ng/mL
Albumin	In g/L
ALT	In U/L
AST	In U/L
D-Dimer	In mmol/L
INR	
Fibrinogen	In g/L
FDP	In ug/mL
Lactate	In mmol/L
Section 3–Perioperative characteristics	
Time of operation	In hours
Bentall procedure	Yes/No
Total arch replacement combined with stented elephant trunk implant procedure	Yes/No
Combined valve surgery	Yes/No
Combined coronary bypass surgery	Yes/No
Time of cardiopulmonary bypass	In minutes
Time of aorta clamping	In minutes
Selective cerebral perfusion performed	Yes/No
ASA grade	1 – Normal healthy individual
	2 – Mild systemic disease that does not limit activities
	3 – Severe systemic disease that limits activities but is not incapacitating
	4 – Incapacitating systemic disease which is constantly life threatening
hypothermia circulatory arrest lowest anal temperature	In °C
Amount of intraoperative suspended frozen plasma infusion	In mL
Amount of intraoperative platelet infusion	In unit
Status of operation	Emergency/Urgent/Elective
Section 4–Ultrasonic correlation parameters	
Aortic sinus diameter	In mm
Ascending aorta diameter	In mm
Eject fraction	In % Classified into <30%/30–50%/>50%
LVEDD	In mm
Aortic vale regurgitation	Mild/Moderate/Severe
Mitral vale regurgitation	Mild/Moderate/Severe
Bicuspid aortic valve	Yes/No
Pericardial effusion	Mild/Moderate/Severe
Pulmonary hypertension	Mild/Moderate/Severe
Section 5–Post-operative outcomes	
Re-operation	Yes/No
If yes – reason for re-operation	Major bleeding/Implant infection/Tamponade/Anastomotic leakage
Discharged home	Yes/No
If not – reason for transfer	
Neurological complications	Yes/No
If yes – details of complications	Cerebral hemorrhage/Cerebral infarction/Diffuse encephalopathy/Spinal cord injury/Limb paralysis

Table 2 (*continued*)

Data field	Option (definition)
Cardiovascular complications	Yes/No
If yes – details of complications	Pericardial tamponade/Perioperative myocardial infarction/Low cardiac output syndrome/Arrhythmia/Rupture of aorta
Respiratory complications	Yes/No
If yes – details of complications	Atelectasis/Pulmonary infection/Pulmonary embolism/Pneumothorax Pleural effusion/Respiratory failure
Incision-related complications	Yes/No
If yes – details of complications	Incisional infection/Poor healing of sternum
Peripheral organ ischemia	Osteofascial compartment symptoms/Limb ischemia symptoms
Renal complications	Yes/No
If yes – stage of renal complications	ARF − 48–72 h after surgery, eGFR decreased by more than 25% AKI – Stage 1: SCr is 1.5–1.9 times baseline level/Stage 2: SCr is 2.0–2.9 times baseline level/SCr is more than three times the baseline level
Postoperative dialysis	Yes/No
MODS	The failure of two or more organs 24 h after the onset of the symptom
Sepsis	Significant elevation of white blood cell and neutrophil counts, blood culture is positive, or infection that is difficult to control using antibacterial therapy
Section 6 –Aortic computed tomography Angiography data	
Aortic arch involvement	Yes/No
If yes – involved branch	Brachiocephalic artery/Left common carotid artery/Left subclavian artery
Coronary artery involvement	Yes/No
If yes – involved branch	Left/Right
Branch involvement of abdominal viscera	Yes/No
If yes – involved branch	Renal artery/Superior mesenteric artery/Celiac trunk

MCHC = Mean erythrocyte hemoglobin concentration, ESR = Erythrocyte sedimentation rate, BUN = blood urea nitrogen, SCr = serum creatinine, TnI = cardiac troponin I, ALT = glutamic-pyruvic transaminase, AST = glutamic oxalacetic transaminase, INR = International Normalized Ratio, FDP = fibrin degradation products, LVEDD = left ventricular end diastolic diameter, ASA = American society of Anesthesiology, ARF = acute renal failure, eGFR = estimated glomerular filtration rate, AKI = acute kidney injury.

and stepwise method was used to eliminate variables with P > 0.20. Cox proportional hazard model is applied for multivariate analysis and adjusted for the potential confounding. Final models were selected based upon Akaike Information Criterion (AIC) measures of model quality and performance. Hosmer-Lemeshow method was used to test the goodness of fit, c-statistics was used to test the discriminant ability of the model, and NRI was used to test the classification ability of the model.

Score assignment is conducted by rounding the adjusted odds ratio for each variable and then a clinical risk score is created. The association between the clinical risk score and the probability for mortality was determined.

3. Discussion

Because of the particularity, complexity and high perioperative mortality of cardiac surgery, many models for post-operative complications and mortality risk prediction have been designed. For example, the first surgical risk prediction method used in cardiovascular surgery field, the Parsonnet's score in 1989 [14], due to the existence of related items influenced by subjective judgment of physician, the performance of prediction model is not enough. Similarly, the European System for Cardiac Operative Risk Evaluation (EuroSCORE) [5], EuroSCORE II updated in 2012 [6], Ontario Province Risk (OPR) established in 1991, the Society of Thoracic Surgeons score (STS score) [7], and Cleveland model established in 1992 are also widely used scoring systems to predict early and in-hospital mortality in a variety of cardiac surgery, including aortic dissection. However, these scoring systems for patients undergoing conventional cardiac surgery are not suitable for patients with acute type A aortic dissection [8]. On the other hand, the average age of onset of aortic dissection in China is lower than that in western countries for 10–15 years [9], and it takes longer from onset to surgical treatment than in developed countries (average 4.5 h in developed countries and 2–7 days in developing countries likes China). Therefore, a scoring system suitable for patients in developing countries is needed to predict their risk of early death and to guide their choice of further treatment strategies. There

have been some risk prediction models for aortic related surgery based on limited sample [10–14]. However, due to inappropriate selection of variables included in the model: most of the models included only medical history and clinical symptoms while not many blood test variables or imaging characteristics was included, their predictive performance is doubtful.

Under the current condition of improved blood test and image examination methods (consequently, there will be fewer patients lack these variables), we urgently need an early death risk prediction model for patients with acute type A aortic dissection receiving surgical treatment in developing countries, which can predict early death and complication risk accurately enough. Although emergency surgery is still the preferred treatment for acute type A aortic dissection, the subgroup of high-risk population identified by this risk prediction model will remind clinicians to take preventive measures for specific complications.

Our center has the largest single-center sample of aortic dissection in northern China, most of which were transferred from neighbouring provinces. As the immense sample size advantage – to our knowledge most European centers can only achieve one-tenth of the number of operations in our center within the same time frame, the experience gained in this study will be more convincing and applicable to developing countries.

Ethical approval

This study was approved by the Ethics Committee of Beijing Anzhen Hospital. For prospective validation cohort patients, patients will be recruited and their clinical data will be collected after being informed of the study protocol and obtained consent. Dissemination of the study protocol will be via the Capital Health Development Project and Results will be published in clinical research journals when the study is finished.

Funding

Author contribution

Contributions: (I) Conception and design: H Zhang, M Gong; (II) Statistical method design: Z Wu, S Xu; (III) Modification suggestion: X Wang, H Li; (IV) Manuscript writing: All authors.

Conflicts of interest

The authors declare that there is no conflict of interests regarding the publication of this article.

Guarantor

Hongjia Zhang, the corresponding author, accept full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

Research registration number

This study have not been registered.

Acknowledgments

Thanks to J Liu for the guidance of the statistical method in this paper. All the authors agree with the opinions proposed in this paper.

CRediT authorship contribution statement

Ming Gong: Conceptualization. **Zining Wu:** Writing - original draft. **Shijun Xu:** Data curation. **Xinliang Guan:** Writing - review & editing. **Haiyang Li:** Resources. **Xiaolong Wang:** Resources. **Hongjia Zhang:** Conceptualization.

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