Original Article

Early risk stratification of acute type A aortic dissection: development and validation of a predictive score

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Background: The performance of published preoperative risk scores for acute type A aortic dissection (aTAAD) is suboptimal. So, the predictive power of these scores were externally validated in order to develop and validate a more reliable preoperative score for identification of patients at high risk of mortality.

Methods: Potential preoperative risk variables of consecutively admitted patients with aTAAD were prospectively collected. Seven published risk scores were validated with our dataset. For derivation and internal validation, the original population was divided at a ratio of 7:3. Logistic regression was used to identify variables for the new score. A 50-patient retrospective dataset was used for external validation. The predictive accuracy for post-operative mortality was evaluated using the area under the receiver operating characteristic (AUROC) curve.

Results: During the study period, 225 patients with aTAAD were admitted preoperatively. Of these, 209 underwent surgical repair and 29 died postoperatively. The AUROCs of the seven published pre-operative risk scores for post-operative mortality ranged from 0.57 to 0.77. Four variables were derived for the new score system, i.e., Acute myocardial ischemia, Lactate, Iliac arteries involved, and CreatininE (the ALICE score). The AUROCs for post-operative mortality in the derivation, internal and external validation populations were 0.85, 0.88 and 0.83, respectively. At a cutoff value of 3, the ALICE score for post-operative mortality had a sensitivity of 71% to 88% and specificity of 78% to 86%.

Conclusions: The ALICE score comprising four components might help bedside clinicians in early detection of the most severe aTAAD patients.

Keywords: Acute type A aortic dissection (aTAAD); mortality; risk score

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Introduction

Acute type A aortic dissection (aTAAD) is a potentially fatal macrovascular emergency and critical illness with time-dependent high mortality (1,2). Ensuring survival requires intensive health-care resources, including accurate preoperative risk assessment, timely decision-making, and relevant interventions, as well as high-quality anesthesia and postoperative management (3). However, as successful surgery demands high technical expertise (4), patients are referred to regional cardiovascular centers. Our institution is one such center and is inundated with increasing numbers of aTAAD patients; hence, there is an urgent unmet need of a high-performing preoperative risk stratification tool to help clinicians to allocate priority to the most severe patients, and pay more attention to possible postoperative complications. On the other hand, a standardized risk score is needed to assess therapeutic effects of new emerging procedures.

Since 2000, seven predictive models have been proposed for aTAAD risk stratification (5-11). However, some flaws cannot be ignored: (I) the predictive accuracies were not optimal for relative low values of areas under the receiver operating characteristic (AUROC) curves (0.66 to 0.77); (II) the variables comprising these risk scores are highly heterogeneous; (III) these scores were all developed based on retrospective data; (IV) involvement of vessels, which is related to postoperative complications, was not considered; and (V) the score accuracies were not externally validated. Additionally, the mortality of untreated patients reportedly increases by 1% to 2% per hour after symptom onset during the first 24 to 48 h (2). Patients who died before surgical interventions, therefore, should have received more attention. Unfortunately, none of the risk models addressed the concern of preoperative deaths.

The aim of the present study was to externally validate these published risk scores based on prospectively collected data in order to develop and validate a novel preoperative risk score with adequate ability to identify the most severe aTAAD patients with high risk of both pre- and postoperative mortality. The authors present the study in accordance with the TRIPOD reporting checklist (available at http://dx.doi.org/10.21037/cdt-20-730).

Methods

Study population

This prospective cohort study was conducted in a 39-bed cardiac surgery intensive care unit (ICU) at a tertiary teaching hospital. From December 24, 2016 through February 12, 2019, patients admitted to the ICU with a diagnosis of TAAD and intended for surgery were eligible for inclusion. Patients who had contraindications to surgery (persistent coma, cerebral hemorrhage, ischemic intestinal necrosis, and other characteristics given the risks associated with heparinization and cardiopulmonary bypass) or refused surgical treatment were excluded. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol was approved by the Institutional Ethics Committee of Zhongshan Hospital affiliated to Fudan University (approval No. B2016-142R). Written informed consent was obtained from patients or their legally authorized representatives.

Data collection

For each patient, variables of previous risk models were considered as candidate elements in the present study. Demographic data, comorbidities, history of cardiac surgery, onset of symptoms, involvement of vessels, non-invasive blood pressures of upper limbs, echocardiography, electrocardiography (ECG), urinary output, and conventional laboratory data were collected. The Penn classification (12), a four-stage perfusion stratification for aTAAD, was also included. The surgical procedures, supportive therapies rendered in the ICU [mechanical ventilation (MV), renal replacement therapy (RRT), veno-arterial extracorporeal membrane oxygenation (V-A ECMO)], postoperative complications, lengths of hospital and ICU stay, and cause of death were also recorded.

Definitions

Acute myocardial ischemia was defined as abnormal ECG readings [pathologic Q waves, ST-segment deviation, new and deep T-wave inversions (7)] combined with elevation of cardiac biomarkers [cardiac troponin T (cTnT) in this study]. Oliguria was defined as urinary output ≤0.5 mL/kg/h. Liver malperfusion was defined as any elevation of liver function [aspartate aminotransferase (AST), alanine aminotransferase (ALT) or bilirubin] (10). Due to lack of baseline creatinine levels, the diagnoses of acute kidney injury and acute renal failure were based on the absolute value of Sequential Organ Failure Assessment score (13), i.e., ≥1.2 and 3.5 mg/dL, respectively. Shock was defined as hypotension (systolic pressure <90 mmHg or the need

of pharmacologic support to maintain SBP >90 mmHg) and tissue hypoperfusion (hyperlactacidemia, i.e., lactate ≥2 mmol/L).

Outcomes measures

The primary endpoint was post-operative mortality. The secondary endpoints were pre-operative, hospital mortality, and a composite endpoint of hospital mortality or prolonged ICU stay (i.e., >30 days).

Statistical analysis

Variables are expressed as medians [with interquartile range (IQR)] or numbers (and percentages) and compared with the Wilcoxon rank sum test or Fisher's exact test, respectively. For external validation of published risk scores, the scores (or logit values) were calculated with our dataset and then validated based on the AUROC. To construct a new risk score, the original cohort was randomly divided into two parts for derivation and internal validation at a ratio of 7:3. The randomization was deemed acceptable after comparing all the preoperative variables and outcome measures between the derivation and internal validation populations (*Table 1*; all P>0.05).

The score was constructed using the following steps: (I) univariable comparisons of the derivation population were performed in order to choose candidate risk factors for post-operative mortality; (II) multivariable logistic regression analysis was conducted using a backward stepwise method. Only variables with probability (P) values <0.05 were retained in the final model; (III) the likelihood ratios were used to assess goodness-of-fit; (IV) the variables in the final model were also confirmed by the Best Subset Selection Method (14) (Figure S1A,B); (V) a correlation matrix was created for collinearity diagnosis to ensure the independence of variables (Figure S1C). (VII) calibration plots were created and the Brier score was calculated to access the calibration of the final risk model (Figure S2); and (VII) a risk score system was constructed based on the regression β coefficient. The β coefficient of each factor retained in the final model was divided by the smallest coefficient and rounded to the nearest integer.

The new risk score was validated in two ways. (I) Internal validation was conducted by comparing AUROCs between derivation and internal validation populations. The sensitivity, specificity, positive and negative predictive values (PPV and NPV) were also calculated at the cutoff value determined by Youden index. To test the robustness of the cutoff value, grey zone analysis was performed (15). In addition, the score distribution was analyzed with clinical outcomes and Penn classification. (II) External validation was performed with a retrospective external dataset with 50 patients (July 2018 through December 2018; Table S1) provided by our collaborative partner Xijing Hospital (Xi'an, China). The new score was applied to the dataset to evaluate the predictive accuracy for post-operative mortality.

Statistical analysis was performed using R, version 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria). All statistical tests were two-tailed. A P value of <0.05 was considered statistically significant.

Results

Study population

During the study period, 261 patients with TAAD were admitted to our ICU prior to surgery. Of these, 225 patients were diagnosed with aTAAD and were willing to undergo surgical repair (Figure S3). The median time from initial symptom onset to admission was 17 hours. There were 209 (93%) patients with complaints of chest or back pain and 46 (20%) with neurological abnormalities (*Table 1*). The numbers of patients with involvements of supra-aortic, mesenteric, renal, and iliac arteries were 156 (69%), 42 (19%), 88 (39%), and 62 (28%), respectively (*Table 1*). Patients with involvement of the iliac arteries had more renal (69% *vs.* 28%, P<0.001), mesenteric (44% *vs.* 9%, P<0.001), and supra-aortic arteries (82% *vs.* 64%, P<0.010) implicated.

Before surgery, 16 (7%) patients died due to acute rupture (n=13) and post-myocardial infarction heart failure (n=3). Of those who died preoperatively, 12 (75%) presented with acute myocardial ischemia. Among the 209 patients who underwent surgery, 190 (91%) received ascending aorta and total arch replacement concomitant with descending aorta stent elephant trunk (Table S2). After surgery, 29 patients died at a median of 7 (IQR 3–14) days, due to refractory cardiogenic shock (n=16), major hemorrhage (n=3), severe cerebral infarction or hemorrhage (n=4), and septic shock (n=6). Of these, 27 patients died within 30 days (*Table 1*). Despite a relatively high rate of acute myocardial ischemia (19%) following surgery, only 7% of patients had acute coronary involvement. Forty-one (20%) and 12 (6%) patients received RRT and V-A ECMO for renal and circulatory failure, respectively. The median

Table 1 Comparison of characteristics between derivation and internal validation datasets

Variables	All patients (n=225)	Derivation (n=159)	Internal validation (n=66)	P value
Characteristics and medical history				
Age, years	53 [44–63]	54 [45–64]	50 [43–59]	0.134
Male gender	181 (80%)	129 (81%)	52 (79%)	0.714
Hypertension	150 (67%)	106 (67%)	44 (67%)	1.000
Coronary artery disease	19 (8%)	16 (10%)	3 (5%)	0.291
Remote myocardial infarction	7 (3%)	6 (4%)	1 (2%)	0.677
History of stroke	15 (7%)	10 (6%)	5 (8%)	0.771
Iatrogenic dissection	9 (4%)	6 (4%)	3 (5%)	0.724
Onset of symptoms				
Time of onset, hours	17 [10–41]	19 [10–41]	14 [7–46]	0.280
Chest or back pain	209 (93%)	150 (94%)	59 (89%)	0.353
Abdominal pain	28 (12%)	21 (13%)	7 (11%)	0.663
Neurological abnormalities	46 (20%)	31 (19%)	15 (23%)	0.590
Dyspnea	29 (13%)	17 (11%)	12 (18%)	0.132
Nausea and vomiting	18 (8%)	14 (9%)	4 (6%)	0.597
Painless AD	14 (6%)	8 (5%)	6 (9%)	0.362
Involvement of vessels				
Supra-aortic arteries involved	156 (69%)	110 (69%)	46 (70%)	1.000
Mesenteric arteries involved	42 (19%)	31 (19%)	11 (17%)	0.709
Renal arteries involved	88 (39%)	65 (41%)	23 (35%)	0.454
Iliac arteries involved	62 (28%)	44 (28%)	18 (27%)	1.000
Circulation variables				
SBP, mmHg	152 [131–168]	152 [134–168]	152 [128–169]	0.826
DBP, mmHg	87 [69–96]	88 [71–96]	85 [64–98]	0.765
MAP, mmHg	108 [92–118]	108 [95–118]	108 [88–119]	0.861
Difference in SBP, mmHg	10 [5–20]	10 [5–18]	11 [7–26]	0.124
Difference in PP, mmHg	11 [5–20]	10 [5–18]	13 [6–26]	0.167
Pulse deficit	16 (7%)	8 (5%)	8 (12%)	0.085
Lactate, mmol/L	1.6 [1.2–2.7]	1.6 [1.2–2.6]	1.7 [1.1–3.0]	0.752
Hyperlactacidemia	77 (34%)	51 (32%)	26 (39%)	0.355
Shock	4 (2%)	1 (1%)	3 (5%)	0.077
Cardiac and coronary artery variables				
LVEF, %	62 [60–66]	62 [60–66]	63 [60–66]	0.434
LVEF <50%	14 (6%)	10 (6%)	4 (6%)	1.000
Aortic root diameter, mm	40 [37–45]	40 [37–45]	41 [38–45]	0.805

Table 1 (*continued*)

Table 1 (*continued*)

Variables	All patients (n=225)	Derivation (n=159)	Internal validation (n=66)	P value
Massive pericardial effusion	19 (9%)	12 (8%)	7 (11%)	0.441
cTnT, ng/mL	0.02 [0.01–0.07]	0.02 [0.01–0.07]	0.02 [0.01–0.07]	0.804
abnormal ECG	63 (28%)	39 (25%)	24 (36%)	0.076
Acute myocardial ischemia	43 (19%)	29 (18%)	14 (21%)	0.583
Renal function				
Creatinine, mg/dL	1.01 [0.79–1.32]	1.01 [0.80–1.30]	0.94 [0.75–1.28]	0.156
UO, mL/kg/h	0.9 [0.7–1.3]	0.9 [0.7–1.3]	0.9 [0.7–1.2]	0.396
Oliguria	20 (9%)	15 (9%)	5 (8%)	0.800
Acute kidney injury	75 (33%)	55 (35%)	20 (30%)	0.642
Acute renal failure	12 (5%)	11 (7%)	1 (2%)	0.188
Liver function				
ALT, U/L	28 [18–53]	29 [19–48]	26 [17–68]	0.926
AST, U/L	26 [17–49]	27 [18–44]	23 [17–67]	0.968
Transaminase elevation	74 (33%)	51 (32%)	23 (35%)	0.756
Bilirubin, μmol/L	17 [12–24]	17 [12–24]	16 [12–23]	0.953
Liver malperfusion	119 (53%)	86 (54%)	33 (50%)	0.660
Others				
WBC, 10^9/L	11.9 [9.4–15.3]	11.8 [9.5–15.3]	12.4 [9.5–12.3]	0.716
PLT, 10^9/L	164 [125–203]	165 [127–202]	160 [122–205]	0.721
Preoperative CPR	3 (1%)	1 (1%)	2 (3%)	0.204
Pennsylvania classification				0.838
Penn class Aa	120 (53%)	85 (53%)	35 (53%)	
Penn class Ab	57 (25%)	41 (26%)	16 (24%)	
Penn class Ac	17 (8%)	13 (8%)	4 (6%)	
Penn class Abc	31 (14%)	20 (13%)	11 (17%)	
Clinical outcomes				
Pre-operative mortality	16 (7%)	10 (6%)	6 (9%)	0.569
Post-operative mortality	29 (13%)	21 (13%)	8 (12%)	1.000
Hospital mortality	45 (20%)	31 (19%)	14 (21%)	0.855
30-day mortality	27 (13%)	20 (13%)	7 (13%)	0.823
Composite endpoints	54 (24%)	38 (24%)	16 (24%)	1.000

Values are median [interquartile range] or number (%). AD, aortic dissection; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; LVEF, left ventricular ejection fraction; cTnT, cardiac troponin T; ECG, Electrocardiography; UO, urinary output; ALT, alanine aminotransferase; AST, aspartate aminotransferase; WBC, white blood cell; PLT, platelet; CPR, cardiopulmonary resuscitation. Difference in SBP or PP means the difference between measurements taken from both arms.

length of MV was 2 (IQR 1–5) days and 41 (20%) patients underwent tracheotomy. For patients who survived, the median lengths of stay in ICU and hospital stay were 8 (IQR 5–13) and 18 (IQR 14–25) days, respectively.

External validation of previous risk scores

Seven published preoperative risk scores for aTAAD were validated with our population (*Table 2*). The risk score proposed by Tan *et al.* (5) had the poorest AUROC (0.56) for post-operative mortality. The other six scores shared similar predictive performances for post-operative mortality, with AUROCs ranging from 0.69 to 0.77, which was in accordance with the reported values (0.66 to 0.77) (*Table 2*). All seven risk scores performed better for pre-operative mortality than post-operative mortality. The AUROCs of pre-operative mortality were 0.04 to 0.17 higher than post-operative mortality for the seven risk scores. Apart from risk scores reported by Tan *et al.* (5), the other six risk scores (6-11) had better AUROCs (0.73 to 0.80) for hospital mortality. The mortalities of each grade of score were close in the original populations and our cohort (Table S3).

Univariable analyses of potential preoperative variables

The original cohort was randomly divided into a derivation group (n=159) and a validation group (n=66). Univariable analysis was performed to identify potential factors associated with post-operative mortality (Table S4). Involvement of the iliac arteries (48% *vs.* 21%, P=0.014), remote myocardial infarction (14% *vs.* 2%, P=0.037), and acute myocardial ischemia (43% *vs.* 9%, P<0.001) occurred more often among patients who died after surgery than among those who survived. The post-operative mortality group also had higher levels of lactate, creatinine, cTnT, ALT and AST (Table S4).

Logistic regression and score derivation

Upon logistic regression, four preoperative variables were retained in the final model: Acute myocardial ischemia, Lactate, Iliac arteries involved, and CreatininE (abbreviated as ALICE score). The formal ALICE score was a 12-point risk stratification system (*Table 3*), with AUROCs of 0.85 (95% CI: 0.78–0.90), 0.92 (95% CI: 0.87–0.96), 0.89 (95% CI: 0.83–0.93), and 0.84 (95% CI: 0.78–0.90) for post-operative mortality, pre-operative mortality, hospital mortality, and composite outcome, respectively (*Table 4*). At a cutoff of 3, the ALICE score had a sensitivity of 71% and specificity of 86% for post-operative mortality, and a sensitivity of 100% and specificity of 78% for pre-operative mortality (*Table 4*). The grey zone ranged from 2 to 4 for post-operative mortality and from 3 to 5 for pre-operative mortality (*Table 4* and Figure S4). Of note, the possible scores are 0 to 10 and 12, as a score of 11 is an impossible permutation of the combinations from the four individual elements.

Internal validation of ALICE score

In the internal validation population, the AUROCs of ALICE scores were 0.88 (95% CI: 0.77–0.95), 0.86 (95% CI: 0.75–0.93), 0.89 (95% CI: 0.79–0.96), and 0.90 (95% CI: 0.80–0.96) for post-operative mortality, pre-operative mortality, hospital mortality, and composite outcome, respectively (*Table 4*). The grey zone ranged from 3 to 5 for post-operative mortality and from 2 to 5 for pre-operative mortality (*Table 4* and Figure S4). There were no significant differences between the AUROCs for clinical outcomes between the derivation and internal validation populations (*Figure 1A* and *Table 4*). Post-operative mortality increased along with the ALICE scores in both the derivation and internal validation populations (*Figure 1B*). Other predictive parameters (i.e., sensitivity, specificity, PPV and NPV) were similar among the derivation and internal validation populations (*Table 4*).

External validation of ALICE score

The post-operative mortality of the 50-patient retrospective external validation dataset was 20%. Of those in the external validation dataset, 41 (82%) underwent ascending aorta and total arch replacement + descending aorta stent (Table S1). The AUROC for post-operative mortality in the external validation population was 0.83 (95% CI: 0.69–0.97) with a grey zone ranging from 3 to 4 (*Table 4* and Figure S4). The sensitivity and specificity were 80% and 78%, respectively, with a cutoff value of 3, as determined by the Youden's index. The predictive performance, whether AUROC or other predictive parameters, was very close for the derivation and internal validation populations (*Table 4*).

Risk stratification of ALICE score

Mortality exhibited an evident gradient with the ALICE score (*Figure 2*). The hospital mortalities were 5%, 38%,

Table 2 Prior external validation of predictive scores using pre-operative variables

Study	Year	N	Pre-operative variables	Reported AUROC	AUROC for		
					Post-operative mortality	Pre-operative mortality	Hospital mortality
Tan *et al.* (5)	2001	252	Preoperative CPR, iatrogenic dissection, drained pericardial tamponade	NA	0.56 (0.49–0.63)	0.62 (0.55–0.68)	0.58 (0.62–0.65)
Spirito *et al.* (6)	2001	108	Remote myocardial infarction, preoperative renal dysfunction, shock, age>70	NA	0.70 (0.63–0.76)	0.75 (0.69–0.81)	0.73 (0.67–0.79)
Mehta *et al.* (7)	2002	547	Age >70 y, female, abrupt onset pain, abnormal ECG, any pulse deficit, kidney failure, hypotension/shock/tamponade	0.74	0.69 (0.62–0.75)	0.86 (0.81–0.90)	0.76 (0.70–0.81)
Santini *et al.* (8)	2007	311	Older age, cardiac tamponade, hypotension, acute myocardial ischemia, mesenteric ischemia, acute renal failure, neurologic injury	0.77	0.74 (0.67–0.80)	0.80 (0.74–0.85)	0.77 (0.71–0.82)
Leontyev *et al.* (9)	2016	534	Age <50, 50–70, >70, critical preoperative state, coronary malperfusion syndrome, extremity malperfusion syndrome, visceral malperfusion syndrome, coronary artery disease	0.77	0.74 (0.68–0.80)	0.87 (0.81–0.91)	0.80 (0.74–0.85)
Mejare-Berggren *et al.* (11)	2017	509	Critical preoperative state, Penn class non-Aa, coronary artery disease	0.66	0.73 (0.67–0.79)	0.82 (0.76–0.87)	0.78 (0.72–0.83)
Ghoreishi *et al.* (10)	2018	269	Lactate, creatinine, liver malperfusion	0.75	0.77 (0.71–0.83)	0.81 (0.75–0.86)	0.80 (0.74–0.85)

Data are presented as true value (95% CI). CPR, cardiopulmonary resuscitation; ECG, electrocardiography; AUROC, area under receiver operating characteristic.

Table 3 The ALICE score card

Risk factor	Categories	Reference value (W_{ij})	OR (95% CI)	β_i	$\beta_i(W_{ij}-W_{iREF})$	ALICE score $=\beta_i(W_{ij}-W_{iREF})/B$
Acute myocardial ischemia	No	0= W_{1REF}	4.16 (1.2–13.98)	1.43	0.00	0
	Yes	1			1.43	2
Lactate, mmol/L	<2	1= W_{2REF}	1.35 (1.08–1.73)	0.30	0.00	0
	2–5	3.5			0.75	1
	5–8	6.5			1.65	2
	>8	10			2.70	4
Iliac arteries involved	No	0= W_{3REF}	3.33 (1.05–10.67)	1.20	0.00	0
	Yes	1			1.20	2
Creatinine, mg/dL	<1.2	1= W_{4REF}	2.48 (1.29–6.48)	0.91	0.00	0
	1.2–1.9	1.6			0.54	1
	2.0–3.4	2.7			1.54	2
	>3.4	4.2			2.91	4

70%, and 100% among ALICE score intervals of 0 to 2, 3 to 4, 5 to 6, and ≥7, respectively (*Figure 2*), demonstrating an ideal risk stratification power. Kaplan-Meier analyses confirmed the statistical difference in survival between patients with various ALICE scores (Figure S5). Besides, the ALICE scores also exhibited a gradient with the different clinical outcomes. The highest ALICE score for pre-operative deaths, post-operative deaths, and survival in with ICU for more or less than 30 days were 5 (IQR 3–8), 4 (IQR 3–5), 2 (IQR 1–3) and 1 (IQR 0–2), respectively (P<0.001, Figure S6). Moreover, of 209 patients who underwent surgery, the risk of postoperative complications was much greater in ALICE-positive patients (Figure S7). This risk score was also related to the Penn classification and the Penn class Abc, defined as localized and generalized ischemia, had the highest ALICE score (Figure S8). To facilitate automatic calculations of preoperative and postoperative mortalities based on our model, we have also built a free webpage tool (http://www.aimedicallab.com/tool/alice_en.html).

Discussion

To the best of our knowledge, this is the first prospective study to validate previously published risk scores, and, therefore, create a novel and simple score for aTAAD risk stratification. The 12-point ALICE score, comprising four components, had good performances for either post-operative mortality or pre-operative mortality, in both derivation and validation populations.

The ALICE score inherited three valid elements of previous risk scores. Renal dysfunction and lactate, two strong predictors of aTAAD (6-8,10,16,17), were also retained in the model. Acute myocardial ischemia, which is also considered a high-risk event, occurred in 15% and 6% to 27% of patients following surgery in the present study and previous studies, respectively (7-9,17). The causes of acute myocardial ischemia included hypotension, coronary involvement, dynamic flap occlusion, and pre-existing coronary disease (18). Chen *et al.* reported an incidence of coronary involvement of 14.1% based on surgical findings (19), which was two-fold greater than for our population (7%). Evaluation of coronary involvement prior to surgery is difficult. In the present study, 12 patients with concomitant acute myocardial ischemia died preoperatively. These patients could potentially have had coronary involvement, thereby accounting for a lower incidence of coronary involvement among the patients who underwent surgery.

In the proposed model, the involvement of the iliac arteries was introduced as a new predictor. TAAD extending to the iliac arteries is the most severe Debakey type I aortic dissection. In this prospective study, involvement of iliac artery was associated with more tearing of renal, mesenteric,

Table 4 The predictive parameters for clinical outcomes of ALICE score in derivation and validation populations

Endpoints	Post-operative mortality			Pre-operative mortality		Hospital mortality	
	Derivation	Internal validation	External validation	Derivation	Internal validation	Derivation	Internal validation
AUROC	0.85 [0.78–0.90]	0.88 [0.77–0.95]	0.83 [0.69–0.97]	0.92 [0.87–0.96]	0.86 [0.75–0.93]	0.89 [0.83–0.93]	0.89 [0.79–0.96]
Best threshold	3	3	3	3	3	3	3
Gray zone	2–4	3–5	3–4	3–5	2–5	3–4	3–5
Patients in the gray zone	32%	22%	26%	21%	32%	14%	23%
Sensitivity	71 [48–89]	88 [47–100]	80 [44–97]	100 [69–100]	83 [36–100]	81 [63–93]	86 [57–98]
Specificity	86 [79–91]	83 [70–92]	78 [62–89]	78 [70–84]	73 [60–84]	86 [79–91]	83 [70–92]
PPV	45 [28–64]	44 [20–70]	47 [23–72]	23 [12–39]	24 [8–47]	58 [42–73]	57 [34–78]
NPV	95 [89–98]	98 [88–100]	94 [80–99]	100 [97–100]	98 [88–100]	95 [89–98]	96 [85–99]

Data are presented as true value [95% CI]. The predictive parameters were determined at a cutoff of 3.

and supra-aortic arteries, and could be considered as a parameter of dissection progression. Recently, Czerny *et al.* (20) developed a scoring system to predict the postoperative 30-day mortality based on a German Registry database (GERAADA score). In this study, dissection extending to descending or further downstream was also confirmed as a significant risk factor (OR: 1.443, P=0.005). Some reported variables were not adopted in our model. On the one hand, collinearity widely exists among candidate variables (Figure S1). For instance, cTnT improved the accuracy of predictive model, despite correlation with transaminases. On the other hand, very specific high-risk events, such as iatrogenic dissection (5), massive pericardial effusion (21), resuscitation (5,8,20), intubation and vasopressors (20), would increase specificity at the cost of lowering sensitivity. Although the GERAADA score (20) used many specific events as risk factors, this score did not generate better performance (AUROC: 0.73), comparing with previous works (AUROC: 0.74–0.77) (7-11).

Following surgery, the predictive accuracy of the ALICE score was better than that of previous models with AUROCs >0.83. For in-depth interpretation, the ALICE score was compared with the Penn classification, a popular but subjective classification of malperfusion in aortic dissection (12,22). The ALICE score was positively correlated with the Penn classification, implying reliable and quantitative evaluation of malperfusion. The definition of the ALICE score was, however, clearer and more objective. Moreover, because of the evident gradient with mortality (Figure S5), the ALICE score is a robust quantitative tool for risk stratification. Of note, none of the patients had an ALICE score of 12 because such a high score is predictive of extremely high mortality and death would occur before arriving at our institution. Additionally, much higher incidence of postoperative complications were observed among ALICE score-positive patients, which serves as a reminder of the importance of timely prevention and intervention measurements soon after surgery.

As the mortality of TAAD is time-dependent, time delay in the process of pre-hospital transfer, definitive diagnosis, and surgery preparation can lead to preoperative loss of lives (23). Unfortunately, there were no precise data on the incidence of preoperative deaths, let alone a tool to evaluate such a risk. The relatively low population ratio and potential selection bias made it difficult for us to establish an accurate risk score for pre-operative mortality. Therefore, we chose to create a risk score for post-operative mortality, and then verified the risk stratification for pre-operative mortality.

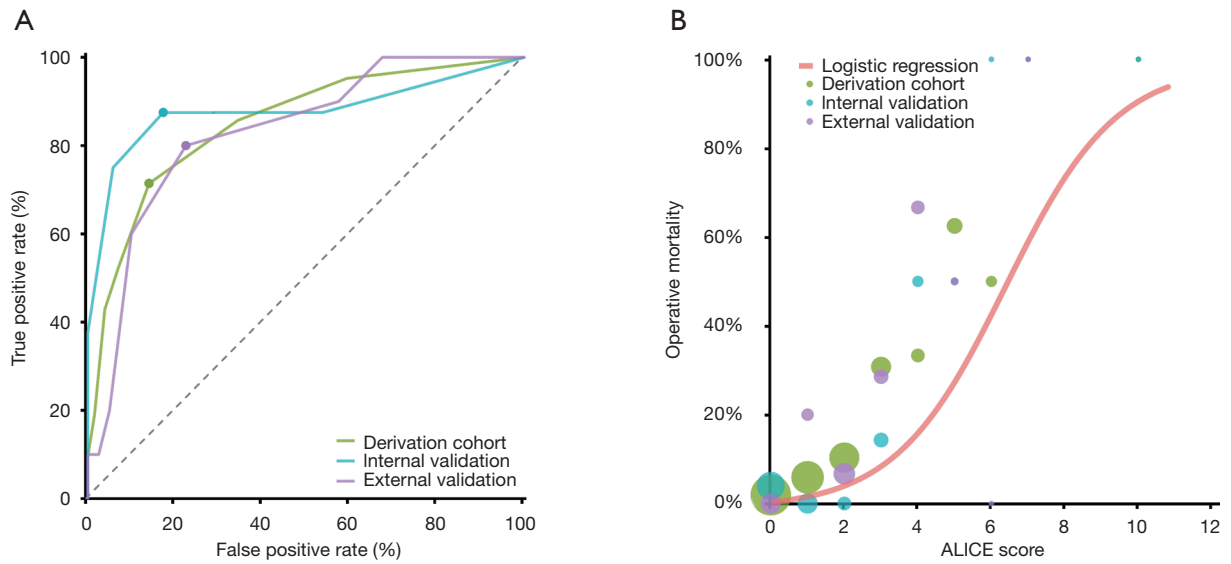

Figure 1 Receiver operating characteristic curves of ALICE scores for post-operative mortality. The AUROCs were 0.86 (95% CI, 0.80–0.90), 0.85 (95% CI, 0.78–0.90), and 0.88 (95% CI, 0.77–0.95) for the derivation, internal validation and external validation populations, respectively. The solid dots indicate the cutoff points with the best Youden's index. AUROC, area under the receiver operating characteristic.

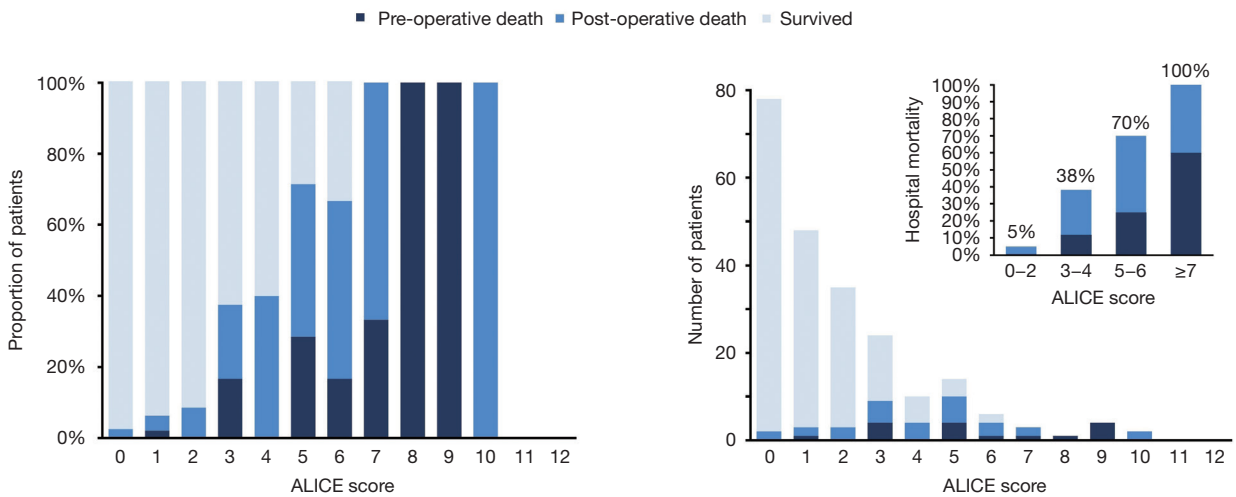

Figure 2 Distribution of clinical outcomes according to the ALICE score. The mortality rose sharply at a cutoff value of 3. Moreover, the mortality of patients with an ALICE of ≥7 was 100%.

Fortunately, the performance of the ALICE score for pre-operative mortality was good, with an AUROC of 0.86 to 0.92, enabling us to recognize patients with the most severe TAAD and to accordingly allocate health-care resource to the highest priority patients.

Over the past two decades, surgical procedures for aTAAD have evolved immensely (3). In our center, total arch replacement + frozen stented elephant trunk surgery is preferred. There are geographical differences in procedures for aTAAD (24). Hence, the predictive accuracy of the proposed ALICE score should be re-examined for a population with very different compositions of surgical procedures. Besides, a very high ALICE scores is associated with a lower probability of survival after aggressive 1-stage surgery, thus procedures for high-risk patients should be carefully considered. Moreover, since many new procedures

have emerged in recent years (25), the proposed ALICE score enables standardization for the assessment of disease severity in order to improve the therapeutic effects with non-randomized control data.

Study limitations

There were several limitations to this study. First, a cohort with 29 post-operative death events was used to validate previous scores externally. Despite good agreement, the small sample size should not be overlooked. Second, the ALICE score was derived based on a single-center cohort, which may limit the generalizability of these results. Nonetheless, the predictive accuracy of the ALICE score was confirmed by both internal and external validations. Third, the ALICE score did not contain any intra-operative parameters, which may have improved accuracy. However, the main purpose of the ALICE score was to recognize the most severe patients preoperatively. Fourth, in this population, a few patients had scores of ≥7. A perfect risk scale, however, should be able to form a gradient of risk within a homogeneous distribution of patients. Finally, despite external validation with a dataset from another Chinese cardiovascular center, it is necessary to further validate the accuracy of the model with an external, large dataset, preferably from other geographic locations.

Conclusions

The present prospective cohort study derived a novel ALICE score comprising four components (i.e., acute myocardial ischemia, lactate, iliac arteries' involvement, and creatinine. The ALICE score is a reproducible and simple tool with good accuracy, which might help bedside clinicians with early risk stratification of patients with aTAAD and, therefore, improve the decision-making on surgical procedures and perioperative managements in ICU ward.

Acknowledgments

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/cdt-20-730). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol was approved by the Institutional Ethics Committee of Zhongshan Hospital affiliated to Fudan University (approval No. B2016-142R). Written informed consent was obtained from patients or their legally authorized representatives.

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Supplementary

Table S1 Operative and post-operative conditions of the external validation dataset (n=50)

Intra and post-operative conditions	Values
Age, years	50 [40–58]
Gender	40 (80%)
Time of onset, days	1.0 [0.7–1.1]
Surgical procedures	
Conservative repair of the aortic root + ascending aorta and total arch replacement+ descending aorta stent	12 (24%)
Conservative repair of the aortic root + ascending aorta and total arch replacement	1 (2%)
Conservative repair of the aortic root + ascending aorta replacement	5 (10%)
Ascending aorta and total arch replacement + descending aorta stent	29 (58%)
Total arch replacement + descending aorta stent	2 (4%)
Ascending aorta replacement	1 (2%)
Concomitant	
CABG	3 (6%)
Bentall/aortic valve replacement/modified Cabrol	8 (16%)
Acute myocardial ischemia	14 (28%)
Iliac arteries involved	23 (46%)
Lactate, mmol/L	1.4 [1.0–2.1]
Creatinine, mg/dL	0.9 [0.8–1.1]
Hospital mortality	10 (20%)

Data are presented as median [interquartile range], means ± SD or number (%). CABG, coronary artery bypass grafting.

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Table S2 Operative and post-operative conditions of the prospective cohort (n=209)

Intra and post-operative conditions	Values
Intraoperative conditions	
Operation time, min	461±65
CPB time, min	208±38
Aortic cross-clamping time, min	112±21
DHCA time, min	25±7
Surgical procedures	
Ascending aorta and total arch replacement+ descending aorta stent	190 (91%)
Ascending aorta and total arch replacement	6 (3%)
Hemi-arch replacement + descending aorta stent	3 (1%)
Hemi-arch replacement	6 (3%)
Ascending aorta replacement	4 (2%)
Concomitant	
CABG	14 (7%)
Bentall/David/Wheats/aortic valve replacement/aortic valve plasty	71 (34%)
Supportive therapies	
Renal replacement therapy	41 (20%)
V-A ECMO	12 (6%)
Tracheotomy	41 (20%)
Length of mechanical ventilation, days	2 [1–5]
Length of ICU stay, days	8 [5–13]
Length of hospital stay, days	17 [13–25]
Post-operative complications	
Cerebral infarction or hemorrhage	35 (17%)
Hospital acquired infection	44 (21%)
Heart failure	28 (13%)
Renal failure	61 (29%)
Liver injury	42 (20%)
Major bleeding	20 (10%)

Data are presented as median [interquartile range], means ± SD or number (%). CPB, cardiopulmonary bypass; DHCA, deep hypothermic circulatory arrest; CABG, coronary artery bypass grafting; V-A ECMO, venoarterial extracorporeal membrane oxygenation.

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Table S3 The mortalities of each grade of published scores in their original populations and our cohort

Risk models	Variables used for classification	Grade of score	Mortality	
			Reported	Our cohort
Augoustides *et al.* (Penn classification)	Localized ischemia and generalized ischemia	Penn class Aa	3%	6%
		Penn class Ab	26%	11%
		Penn class Ac	18%	24%
		Penn class Abc	40%	63%
Ghoreishi *et al.*	Lactate, creatinine, liver malperfusion	Risk score <7	4%	0%
		Risk score 7–20	14%	10%
		Risk score >20	37%	21%
Mejare-Berggren *et al.* (Leipzig-Halifax Scorecard)	Critical preoperative state, Penn class non-Aa, coronary artery disease	Risk score 0–5	12%	6%
		Risk score 10–15	23%	16%
		Risk score 20–25	43%	56%
Leontyev *et al.*	Age <50, age 50–70, age >70, critical preoperative state, coronary malperfusion syndrome, extremity malperfusion syndrome, visceral malperfusion syndrome, coronary artery disease	Risk score 0–3	7%	6%
		Risk score 4–6	13%	8%
		Risk score 7–10	39%	18%
		Risk score >10	75%	64%
Santini *et al.*	Older age, cardiac tamponade, hypotension, acute myocardial ischemia, mesenteric ischemia, acute renal failure, neurologic injury	Risk score 10–14	<15%	7%
		Risk score 15–27	15–30%	18%
		Risk score 28–36	30–45%	9%
		Risk score 37–115	>45%	52%

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Table S4 Comparison of pre-operative variables among patients with different clinical outcomes in derivation population

Variables	Derivation population (n=159)	Died before surgery (n=10)	Operative patients (n=149)	Survived (n=128)	Died after surgery (n=21)	P value
Characteristics and medical history						
Age, years	54 [45–64]	60 [54–65]	53 [44–64]	52 [44–64]	54 [46–63]	0.680
Male gender	129 (81%)	7 (70%)	122 (82%)	102 (80%)	20 (95%)	0.125
Hypertension	106 (67%)	9 (90%)	97 (65%)	82 (64%)	15 (71%)	0.625
Coronary artery disease	16 (10%)	0 (0%)	16 (11%)	13 (10%)	3 (14%)	0.702
Remote myocardial infarction	6 (4%)	0 (0%)	6 (4%)	3 (2%)	3 (14%)	0.037
History of stroke	10 (6%)	1 (10%)	9 (6%)	8 (6%)	1 (5%)	1.000
Iatrogenic dissection	6 (4%)	0 (0%)	6 (4%)	5 (4%)	1 (5%)	1.000
Onset symptoms						
Time of onset, hours	19 [10–41]	12 [10–29]	19 [10–41]	19 [10–41]	17 [10–31]	0.677
Chest or back pain	150 (94%)	10 (100%)	140 (94%)	120 (94%)	20 (95%)	1.000
Abdominal pain	21 (13%)	1 (10%)	20 (13%)	15 (12%)	5 (24%)	0.163
Neurological abnormalities	31 (19%)	2 (20%)	29 (19%)	23 (18%)	6 (29%)	0.248
Dyspnea	17 (11%)	1 (10%)	16 (11%)	13 (10%)	3 (14%)	0.702
Nausea and vomiting	14 (9%)	0 (0%)	14 (9%)	12 (9%)	2 (10%)	1.000
Painless AD	8 (5%)	0 (0%)	8 (5%)	7 (5%)	1 (5%)	1.000
Involvement of vessels						
Supra-aortic arteries involved	110 (69%)	8 (80%)	102 (68%)	84 (66%)	18 (86%)	0.079
Mesenteric arteries involved	31 (19%)	4 (40%)	27 (18%)	20 (16%)	7 (33%)	0.066
Renal arteries involved	65 (41%)	5 (50%)	60 (40%)	51 (40%)	9 (43%)	0.814
Iliac arteries involved	44 (28%)	7 (70%)	37 (25%)	27 (21%)	10 (48%)	0.014
Circulation variables						
SBP, mmHg	152 [134–168]	133 [103–145]	154 [136–169]	155 [136–169]	151 [124–165]	0.365
DBP, mmHg	88 [71–96]	81 [50–93]	88 [73–96]	88 [73–97]	85 [65–91]	0.195
MAP, mmHg	108 [95–118]	95 [70–107]	108 [95–118]	109 [96–120]	108 [76–116]	0.336
Difference in SBP, mmHg	10 [5–18]	7 [6–13]	10 [4–18]	10 [4–17]	15 [7–20]	0.155
Difference in PP, mmHg	10 [5–18]	4 [1–20]	11 [5–17]	11 [6–17]	9 [3–13]	0.142
Pulse deficit	8 (5%)	3 (30%)	5 (3%)	3 (2%)	2 (10%)	0.146
Lactate, mmol/L	1.6 [1.2–2.6]	2.9 [2.1–6.3]	1.5 [1.1–2.3]	1.4 [1.1–2.2]	1.8 [1.2–4.3]	0.050
Hyperlactacidemia	51 (32%)	7 (70%)	44 (30%)	35 (27%)	9 (43%)	0.196
Shock	1 (1%)	1 (10%)	0 (0%)	0 (0%)	0 (0%)	1.000
Cardiac and coronary artery variables						
LVEF, %	62 [60–66]	54 [37–59]	62 [60–66]	62 [60–66]	63 [60–66]	0.983
LVEF <50%	10 (6%)	4 (40%)	6 (4%)	4 (3%)	2 (10%)	0.200
Aortic root diameter, mm	40 [37–45]	48 [42–52]	40 [37–45]	40 [37–45]	42 [39–44]	0.121
Massive pericardial effusion	12 (8%)	3 (30%)	9 (6%)	6 (5%)	2 (14%)	0.116
cTnT, ng/mL	0.02 [0.01–0.07]	0.29 [0.16–1.09]	0.02 [0.01–0.05]	0.02 [0.01–0.05]	0.04 [0.02–0.93]	0.012
Abnormal ECG	39 (25%)	8 (80%)	31 (21%)	21 (16%)	10 (48%)	0.003
Acute myocardial ischemia	29 (18%)	8 (80%)	21 (14%)	12 (9%)	9 (43%)	<0.001
Renal function						
Creatinine mg/dL	1.01 [0.80–1.30]	1.68 [1.46–1.97]	1.01 [0.79–1.27]	0.95 [0.79–1.16]	1.44 [1.22–1.89]	<0.001
UO, ml/kg/h	0.9 [0.7–1.3]	0.8 [0.5–1.0]	0.9 [0.7–1.3]	1.0 [0.7–1.3]	0.9 [0.4–1.1]	0.144
Oliguria	15 (9%)	3 (30%)	12 (8%)	6 (5%)	6 (29%)	0.002
Acute kidney injury	55 (35%)	8 (80%)	47 (32%)	33 (26%)	14 (67%)	<0.001
Acute renal failure	11 (7%)	4 (40%)	7 (5%)	4 (3%)	3 (14%)	0.059
Liver function						
ALT, U/L	29 [19–48]	66 [35–130]	28 [18–46]	26 [18–44]	33 [23–75]	0.038
AST, U/L	27 [18–44]	63 [42–213]	26 [18–39]	25 [17–35]	59 [29–110]	<0.001
Transaminase elevation	51 (32%)	7 (70%)	44 (30%)	32 (25%)	12 (57%)	0.005
Bilirubin, μmol/L	17 [12–24]	21 [12–40]	17 [12–24]	17 [12–24]	12 [9–21]	0.133
Liver malperfusion	86 (54%)	8 (80%)	78 (52%)	62 (48%)	16 (76%)	0.020
Others						
WBC, 10^9/L	11.8 [9.5–15.3]	12.7 [11.0–15.1]	11.8 [9.2–15.3]	11.6 [9.0–15.1]	12.9 [10.7–18.6]	0.069
PLT, 10^9/L	165 [127–202]	114 [95–145]	166 [129–205]	166 [129–201]	179 [124–210]	0.787
Pre-operative CPR	1 (1%)	0 (0%)	1 (1%)	1 (1%)	0 (0%)	1.000

Data are presented as median [interquartile range] or number (%). Difference in SBP or PP means the difference between measurements taken from both arms. AD, aortic dissection; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; LVEF, left ventricular ejection fraction; cTnT, cardiac troponin T; ECG, electrocardiography; UO, urinary output; ALT, alanine aminotransferase; AST, aspartate aminotransferase; WBC, white blood cell; PLT, platelet; CPR, cardiopulmonary resuscitation.

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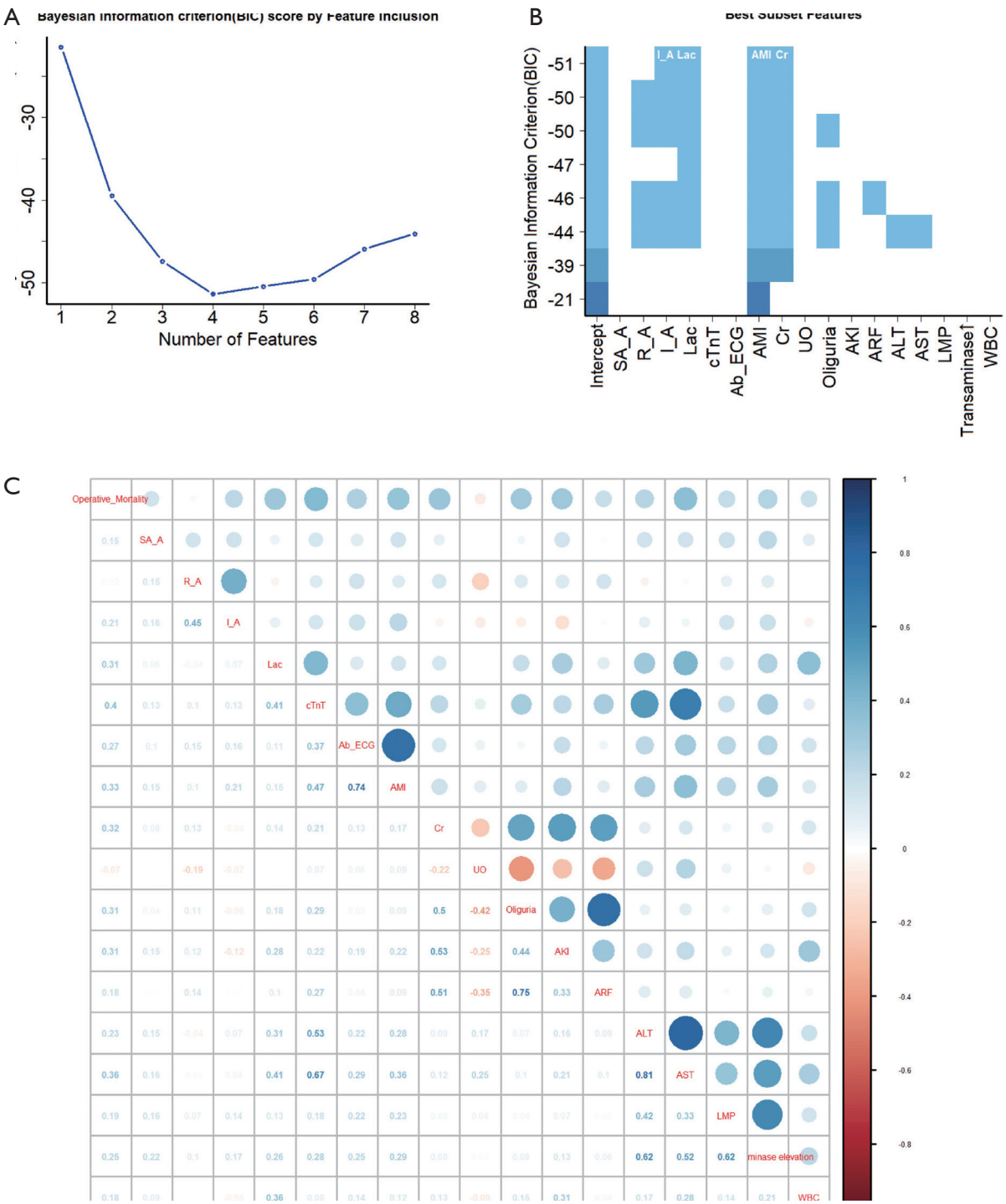

Figure S1 Collinearity diagnosis and variables selection. (A) Correlation matrix among post-operative mortality and candidate variables. Collinearities existed among same kinds of variables, such as renal function, liver function and cardiac parameters. In addition, the cTnT had strong correlation with aminotransferases. (B) Best subset selection based on BIC also suggested a subset comprising of 4 variables. (C) The best subset with the highest BIC was consisted of lactate, creatinine, acute myocardial ischemia and involvement of Iliac arteries.

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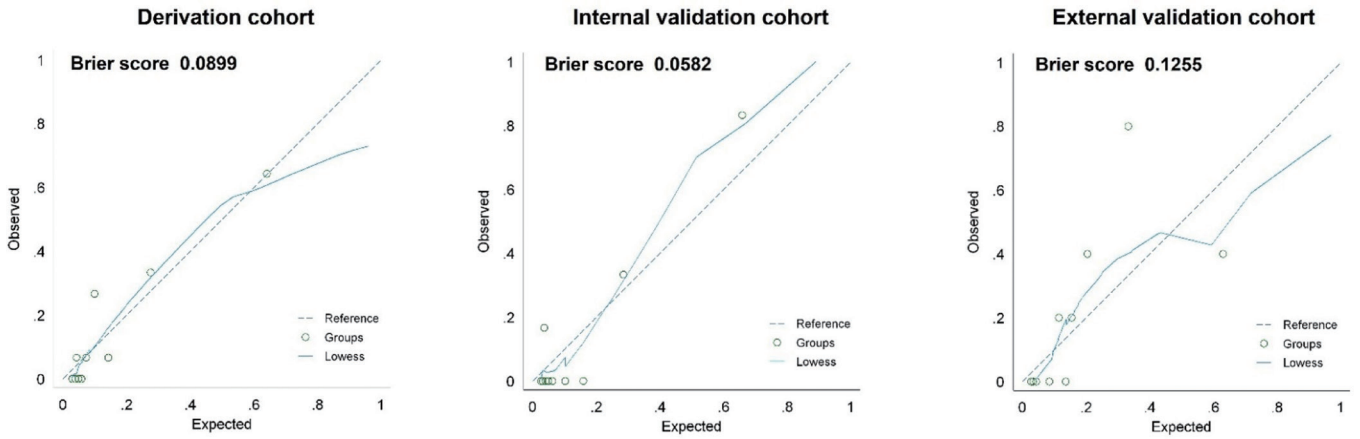

Figure S2 Calibration plots and Brier score for post-operative mortalities among derivation, internal validation and external validation cohorts.

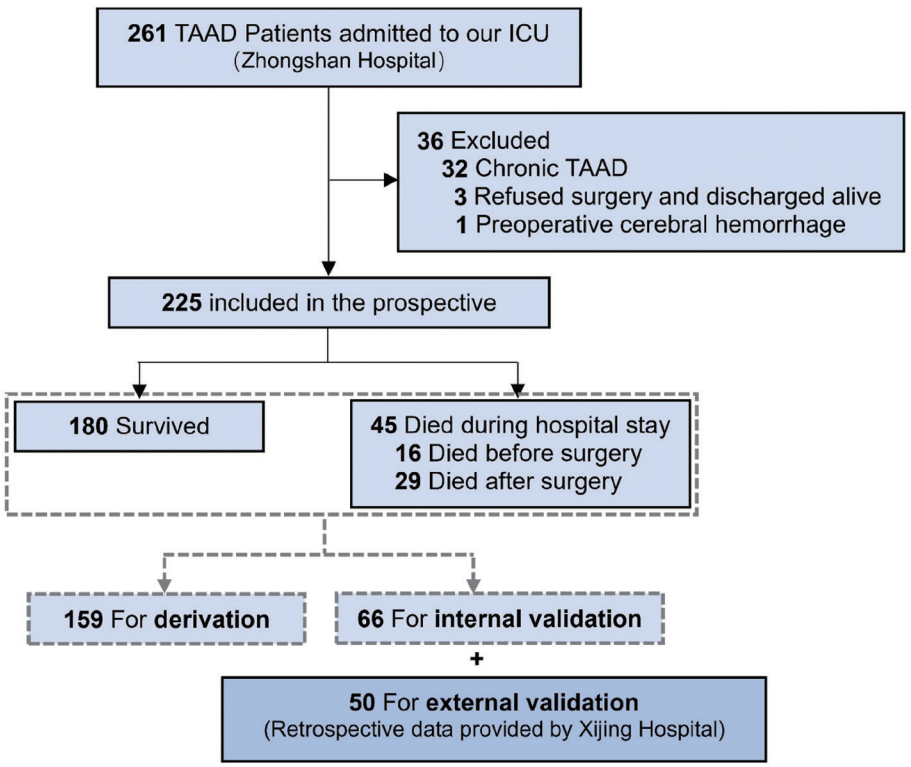

Figure S3 Study flowchart. The original prospective cohort was divided into two parts in a ratio of 7:3 for derivation and internal validation. A 50-patient retrospective cohort was used for external validation.

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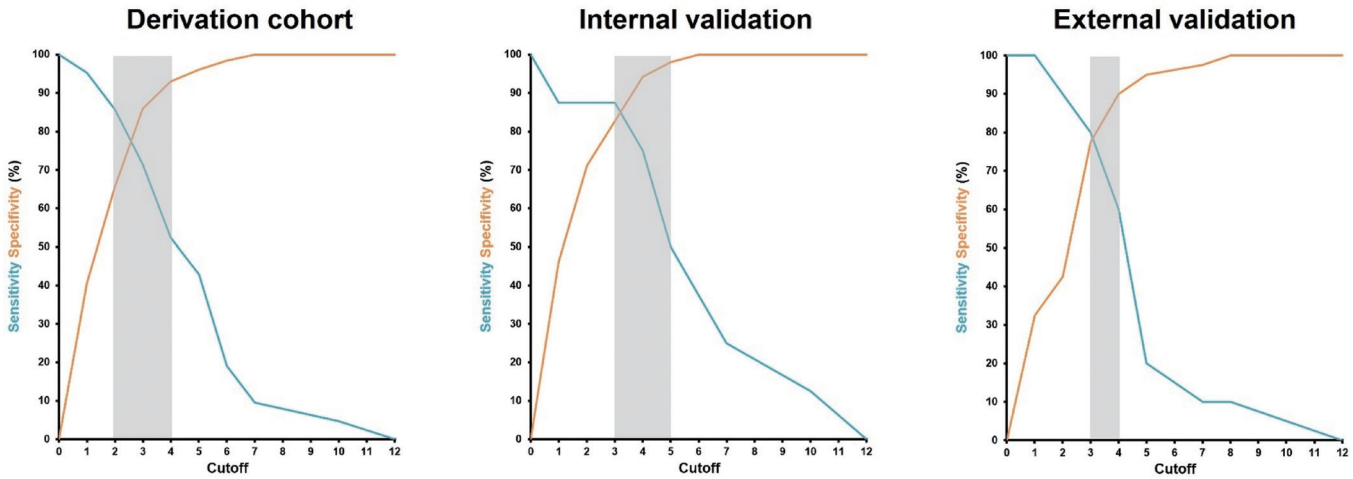

Figure S4 Gray zones by ALICE score to predict post-operative mortalities among derivation, internal validation and external validation cohorts.

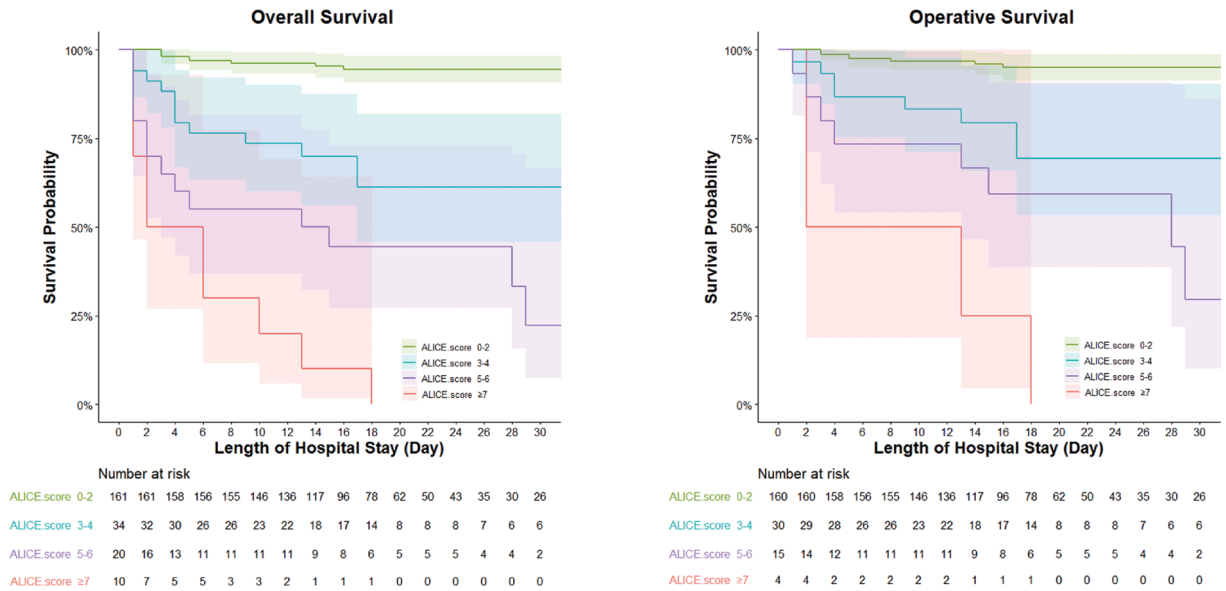

Figure S5 Overall survival and post-operative survival according to ALICE score. The solid lines and the corresponding shades indicated the cumulative survival probabilities and confidence limits. The ALICE score shown great discrimination power for overall hospital mortality and post-operative mortality (all P<0.001).

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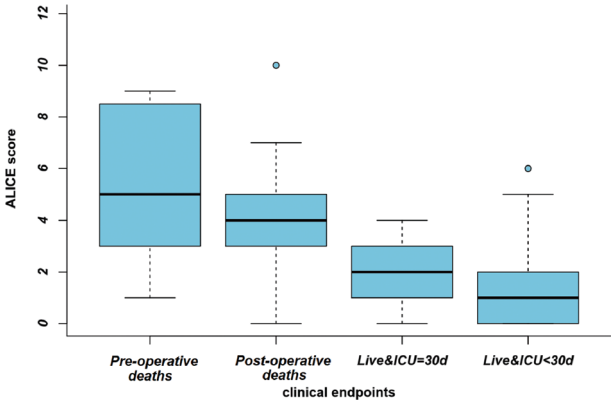

Figure S6 Distribution of ALICE scores according to different clinical endpoints. The middle horizontal line represents the median while the upper and lower borders of the box represent the upper and lower quartiles. The upper and lower whiskers represent the maximum and minimum values of non-outliers. Extra dots represent outliers. The ALICE score distributed in a gradient among different outcome groups. Both patients with early deaths and post-operative deaths had higher ALICE scores than patients who survived and stayed in ICU <30 days (P<0.001).

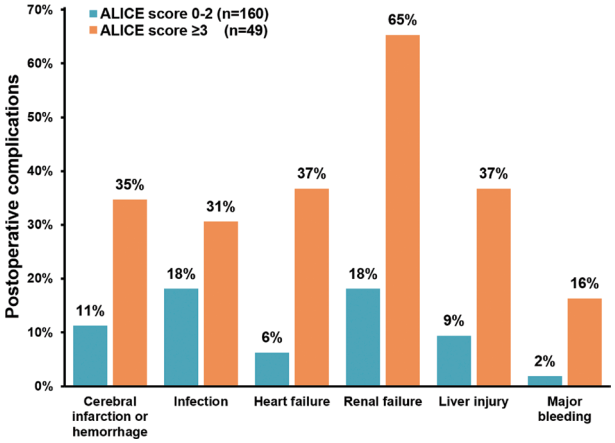

Figure S7 ALICE score positive patients suffered much higher incidence of post-operative complications. The P values were 0.072 for infection and <0.001 for other complications.

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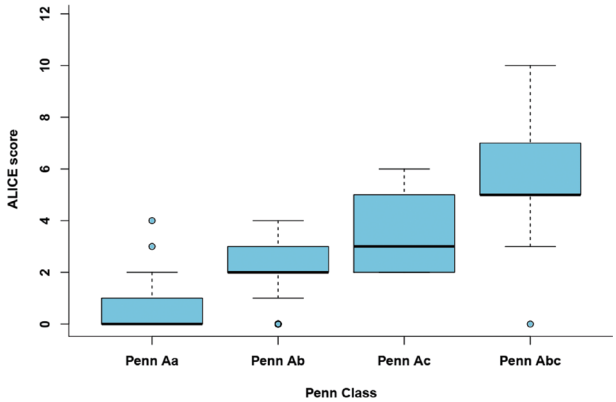

Figure S8 Distribution of ALICE scores according to Penn class. The middle horizontal line represents the median while the upper and lower borders of the box represent the upper and lower quartiles. The upper and lower whiskers represent the maximum and minimum values of non-outliers. Extra dots represent outliers. The ALICE score distributed in a gradient among different degree of Penn class ($P<0.001$).

http://dx.doi.org/10.21037/cdt-20-730