



Peri-operative risk factors for in-hospital mortality in acute type A aortic dissection

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Background: Acute type A aortic dissection (TAAD) is cardiovascular emergency and requires surgical interventions. In-hospital mortality rate of surgical-treated TAAD patients remains high. We aim to examine the prognostic implications of peri-operative parameters to identify high-risk patient for in-hospital mortality.

Methods: A total of 264 surgically treated TAAD patients were included in this study. The association between in-hospital mortality and peri-operative parameters were examined.

Results: Thirty patients (11.36%) died during hospitalization. Patients with higher Apache II score had a significantly higher rate of in-hospital mortality when compared with patients scored ≤ 20 in unadjusted model [Score 21–25: HR =12.9 (1.7–100.8), $P=0.0148$; Score >25: HR =94.5 (12.6–707.6), $P<0.0001$]. Patients with Sbp >120 mmHg, Cr >200 mmol/L (both at admission and after surgery), BUN >8.2 mmol/L (both at admission and after surgery), AST >80 μL , aortic cross-clamping time >120 min and cardiopulmonary bypass time (CPBT) >230 min were also significantly related to higher rate of in-hospital mortality in univariate analysis. In multivariable analysis, APACHE II score [Score 21–25: HR =9.5 (1.2–74.4), $P=0.032$; Score >25: HR =51.0 (6.7–387.7), $P=0.0001$], AST >80 $\mu\text{mol/L}$ [HR =2.3 (1.1–4.8), $P=0.0251$], aortic cross-clamping time >120 min (HR =2.9 (1.1–7.7), $P=0.0315$) remained significant in predicting TAAD in-hospital mortality.

Conclusions: APACHE II score could be a useful tool to predict TAAD in-hospital mortality. AST >80 μL and aortic cross-clamping time >120 min were also independent predictors.

Keywords: Acute type A aortic dissection (TAAD); in-hospital mortality; APACHE II score; peri-operative risk factor

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Introduction

Acute type A aortic dissection (TAAD) is cardiovascular emergency that is often fatal. American Heart Association guidelines recommend that surgical interventions should be given to TAAD patients to resect all aneurysmal aorta

and the proximal extent of the dissection (1). TAAD surgical managements had been increased and improved in recent years. In 2015, international registry of acute aortic dissection (IRAD) reported that in-hospital mortality of surgical treated TAAD patients has decreased over time, but the rate remained high (from 25% to 18% over

17 years, $P=0.003$) (2). Identifying patients with high-risk feature is clinically relevant. IRAD researchers reported that the principal independent pre-operative predictors of mortality were history of aortic valve replacement, migrating chest pain, hypotension as sign of TAAD, shock or tamponade, preoperative cardiac tamponade, and preoperative limb ischemia (3). Age greater than 70 years, prior cardiac surgery, intraoperative hypotension, a right ventricle dysfunction at surgery, a necessity to perform coronary revascularization, pre-existing cardiac disease, and cardiopulmonary resuscitation were also reported as risk factors for TAAD in-hospital mortality in other studies (4,5).

Since TAAD is an acute condition and often progresses rapidly, it could be hard to gather all the relevant data during hospitalization. Studies were lacking to explore potential prognostic values of biomarkers, traditional disease severity measurement system (e.g., APACHE II score), and intra-operative parameters. In the current study, we aim to examine the prognostic implications of such parameters to identify high-risk patient for in-hospital mortality.

Methods

Study design and patients' selection

This is a retrospective analysis of consecutive TAAD patients in Guangdong General Hospital from March 2012 to April 2016. All patient data were collected by chart review. Patients who died before and during surgery were excluded ($n=4$), and a total of 264 patients were analyzed. This retrospective study did not require ethics approval.

Measurement and outcome

Diagnosis of TAAD was by contrast-enhanced computed tomography scan and identified by dissections involving the ascending aorta. The primary endpoint of the study is in-hospital mortality, which is defined as death within first TAAD related hospitalization during which surgical treatment was rendered. In-hospital mortality in this study included 30-day mortality and after 30-day mortality (but in-hospital mortality). Pre-operative parameters [age, sex, history of hypertension, APACHEII score, systolic blood pressure (Sbp), diastolic blood pressure (Dbp), mean arterial pressure (MAP), temperature, heart rate (HR), hemoglobin count (Hbg), white blood cell count (WBC), albumin level (Alb), blood creatinine level (Cr), blood urea nitrogen level (BUN), alanine aminotransferase level (Alt), aspartate transaminase (AST), serum total bilirubin (TBil), direct

bilirubin (DBil)], intra-operative parameters [aortic cross-clamping time (XCT) and cardiopulmonary bypass time (CPBT)], and post-operative parameters (Cr immediate after surgery, BUN immediate after surgery, ICU stay) were prospectively entered in electronic health medical system and retrospectively collected. Pre-operative parameters were recorded by physicians and nurses at admission. APACHE II score was calculated by emergency room physicians. XCT and CPBT were recorded by perfusionist during surgery.

Statistical analysis

Categorical variables and continuous variables are analyzed with Chi-square test and *t*-test respectively. Cox proportional hazard model was used for univariate and multivariable regression. Survival was estimated using Kaplan-Meier curve (and compared using log-rank test). A two-sided P value <0.05 was considered statistically significant. SAS 9.4 was used to perform all statistical analysis.

Results

Patients' characteristics

From March 2012 to April 2016, a total of 264 TAAD patients were surgically treated in Guangdong General Hospital. The demographic and disease characteristics were summarized in *Table 1*. Mean hospitalization duration was 31.96 ± 19.26 days. Reasons of long hospital stay (more than 30 days) included ($n=100$): infection ($n=63$), impaired wound healing ($n=9$), kidney failure ($n=15$), respiratory failure ($n=6$), liver failure ($n=6$), heart failure ($n=5$), pleural effusion ($n=3$), pericardial effusion ($n=3$), post-operation bleeding ($n=3$), stroke ($n=3$), gastrointestinal bleeding ($n=2$), unconsciousness ($n=2$), vocal cord injury ($n=2$), renal arterial thrombosis ($n=1$), nerve injury ($n=1$), and paraplegia ($n=1$). Patients who did not survive during hospitalization had an average higher APACHE II score ($P<0.0001$), WBC ($P=0.0006$), BUN ($P=0.0274$), longer XCT ($P=0.0002$) and CPBT ($P<0.0001$). Thirty patients (11.36%) died during hospitalization: 7 from septic shock (23.33%), 5 from malignant arrhythmia (16.67%), 5 from brain death (16.67%), 3 from low cardiac output (10.00%), 3 from severe pneumonia (10.00%), 2 from gastrointestinal hemorrhage (6.67%), 1 from aortic dissection rupture (3.33%), 1 from cardiac tamponade (3.33%), 1 from hematogenic shock (3.33%), 1 from acute kidney failure

Table 1 Patients' characteristics

Characteristics	All patients (n=264)	Survived (n=234)	Not survived (n=30)	P value
Hospitalization, day	31.96±19.26	34.15±18.90	14.90±12.49	<0.0001
Pre-operative factors				
Age, year	47.75±9.98	47.61±10.07	48.83±9.40	0.5274
Male, n (%)	230 [87]	205 [88]	25 [83]	0.5606
History of Hypertension, n (%)	149 [56]	130 [56]	19 [63]	0.4422
APACHE II Score	20.89±4.04	20.09±3.18	27.17±4.57	<0.0001
Sbp, mmHg	132.41±19.48	131.90±20.29	136.10±10.90	0.0898
Dbp, mmHg	72.78±13.83	72.71±14.00	73.27±12.57	0.8371
MAP, mmHg	92.65±13.93	92.46±14.27	94.20±11.06	0.5196
Temperature, °C	36.79±0.50	36.78±0.49	36.88±0.58	0.2585
HR, /min	80.92±12.41	80.83±12.51	81.63±11.78	0.7402
Hbg, g/L	120.52±19.84	121.00±19.95	116.40±18.76	0.23
WBC, ×10 ⁹ /L	12.01±4.89	11.64±4.69	14.89±5.55	0.0006
Alb, g/L	32.81±5.73	32.95±5.86	31.75±4.50	0.2813
Cr, mmol/L	131.13±97.46	127.00±98.54	163.60±83.05	0.0528
BUN, mmol/L	9.15±5.78	8.87±5.86	11.34±4.65	0.0274
ALT, μ/L	109.30±489.26	78.81±315.80	347.10±1,141.70	0.2102
AST, μ/L	119.48±481.33	97.63±346.30	290.00±1,050.60	0.3274
Tbil, mmol/L	26.22±18.27	25.47±17.75	32.05±21.31	0.0634
Dbil, mmol/L	9.95±10.17	9.65±9.99	12.24±11.40	0.1902
Intra-operative factors				
XCT, min	123.00±40.57	119.70±38.65	148.40±46.60	0.0002
CPBT, min	231.64±52.17	224.50±44.77	287.20±70.60	<0.0001

Values are mean ± SD or n (%). Alb, albumin level; ALT, alanine aminotransferase level; AST, aspartate transaminase; BUN, blood urea nitrogen level; CPBT, cardiopulmonary bypass time; Cr, blood creatinine level; DBil, direct bilirubin; Dbp, diastolic blood pressure; Hbg, hemoglobin count; HR, heart rate; MAP, mean arterial pressure; Sbp, systolic blood pressure; TBil, serum total bilirubin; WBC, white blood cell count; XCT, aortic cross-clamping time.

(3.33%), 1 from alveolar hemorrhage (3.33%).

APACHE II score and in-hospital mortality

The range of APACHE II score of these patients was 13 to 40. *Table 2* showed the percentage of death by APACHE II score. There was an abrupt increase in in-hospital mortality when APACHE II score was more than 25. *Figure 1* showed that the in-hospital survival rate of all the patients was 82.86%. When stratifying by APACHE II score, patients with score higher than 25 had a significant lower in-hospital

survival (35.67%) than patient with lower score (score <20: 99.1%; 21–25: 86.76%, $P<0.0001$)

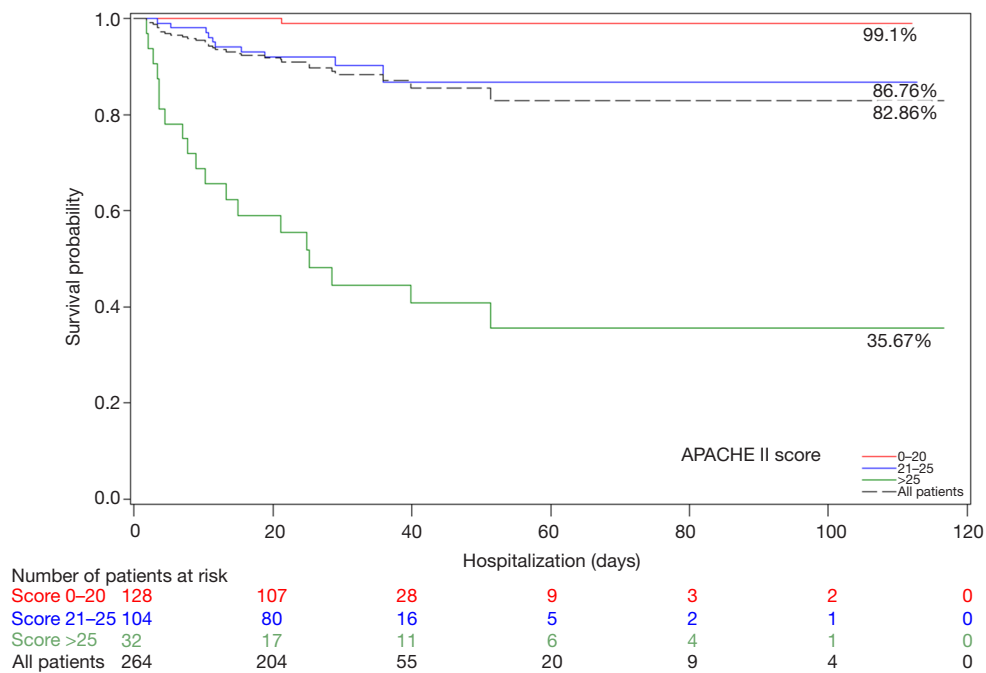
Table 3 showed that, compared with patients with score ≤20, patients with higher score had a significantly higher rate of in-hospital mortality in unadjusted model [21–25: HR =12.9 (1.7–100.8), $P=0.0148$; Score >25: HR =94.5 (12.6–707.6), $P<0.0001$].

Univariate analysis

Besides APACHE II score, SBP >120 mmHg, Cr

Table 2 APACHE II score and mortality distribution

APACHE II score	Total	Death	Percentage
0–15	11	0	0.0
16–20	117	1	0.9
21–25	104	10	9.6
26–30	24	13	54.2
31–35	6	4	66.7
36–40	2	2	100.0
Total	264	30	11.4

**Figure 1** Surgical-treated type A aortic dissection patients' in-hospital survival probability by APACHE II score.

>200 mmol/L (both at admission and after surgery), BUN >8.2 mmol/L (both at admission and after surgery), AST >80 μ/L, XCT >120 min and CPBT >230 min were also significantly associated with higher rate of in-hospital mortality in univariable analysis (*Table 3*).

Multivariable analysis

In multivariable analysis (*Table 4*), using variables which were available and related to APACHE II score (age, temperature, HR, Cr at admission, MAP) and other important factors (Sbp, AST and aortic cross-clamping

time) (model 1), we found that SBP >120 mmHg, AST >80 μ/L, and XCT >120 min were independent predictors of in-hospital mortality.

After adjusting for APACHE II score (model 2), AST >80 μ/L and XCT >120 min remained significant.

Discussion

TAAD is a cardiovascular emergency that requires prompt surgical intervention. Despite advances in surgical technique, the disease is still fatal, with in-hospital mortality reported between 10.6% to 26.6% (3,5-10). Identifying

Table 3 Univariate analysis

Risk factors	Hazard ratio	P value
Apache II score		
Score ≤ 20	Ref.	Ref.
20 < Score ≤ 25	12.9 (1.7–100.8)	0.0148
Score >25	94.5 (12.6–707.6)	<0.0001
Male	0.8 (0.3–2.1)	0.6606
Age >50	1.5 (0.7–3.0)	0.3049
Alb ≤ 25 g/L	1.2 (0.4–4.1)	0.7156
WBC $>10 \times 10^9$ /L	2.2 (0.9–5.0)	0.0748
Hbg ≤ 130 g/L	1.7 (0.7–3.9)	0.2407
Temperature	1.4 (0.7–2.6)	0.3426
HR >65/min	1.9 (0.6–6.4)	0.2785
Hypertension	1.4 (0.7–2.9)	0.3864
Sbp >120 mmHg	11.6 (1.6–85.1)	0.0160
Dbp >90 mmHg	1.4 (0.4–4.7)	0.5542
MAP >110 mmHg	1.8 (0.63–5.19)	0.2727
Cr at admission		
Cr ≤ 115 mmol/L	Ref.	Ref.
115 < Cr ≤ 200 mmol/L	1.6 (0.7–3.8)	0.2843
Cr >200 mmol/L	3.6 (1.5–8.7)	0.0035
Cr after surgery		
Cr ≤ 115 mmol/L	Ref.	Ref.
115 < Cr ≤ 200 mmol/L	2.3 (0.9–6.4)	0.0967
Cr >200 mmol/L	4.0 (1.3–11.8)	0.0137
BUN at admission		
BUN >8.2 mmol/L	3.2 (1.5–7.1)	0.0032
BUN after surgery		
BUN >8.2 mmol/L	3.7 (1.5–9.1)	0.0041
AST >80 μ /L	4.0 (2.0–8.2)	0.0001
XCT >120 min	5.2 (2.0–13.5)	0.0008
CPBT ≤ 230 min	Ref.	Ref.
230 < CPBT ≤ 260 min	3.6 (1.1–11.9)	0.0370
CPBT >260 min	9.7 (3.3–28.8)	<0.0001
ICU stay ≤ 5 days	Ref.	Ref.
5 < ICU stay ≤ 10 days	0.5 (0.2–1.2)	0.1311
ICU stay >10 days	0.7 (0.3–1.7)	0.4437

Alb, albumin level; AST, aspartate transaminase; BUN, blood urea nitrogen level; CPBT, cardiopulmonary bypass time; Cr, blood creatinine level; Dbp, diastolic blood pressure; Hbg, hemoglobin count; HR, heart rate; MAP, mean arterial pressure; Sbp, systolic blood pressure; WBC, white blood cell count; XCT, aortic cross-clamping time.

Table 4 Multivariable analysis

Risk factors	Hazard ratio	P value
Model 1		
Age >50	1.9 (0.9–4.1)	0.0995
Temperature	1.5 (0.7–3.2)	0.289
HR >65/min	1.2 (0.4–4.2)	0.7398
Cr [†] ≤115 mmol/L	Ref.	Ref.
115 < Cr ≤200 mmol/L	1.3 (0.5–3.1)	0.5834
Cr >200 mmol/L	1.8 (0.7–4.8)	0.2442
WBC >10×10 ⁹ /L	1.1 (0.4–2.7)	0.8885
MAP >110 mmHg	1.2 (0.4–3.5)	0.7616
SBP >120 mmHg	9.4 (1.3–70.7)	0.0288
AST >80 μ/L	2.8 (1.3–6.2)	0.0123
XCT >120 min	4.2 (1.5–11.2)	0.0048
Model 2		
APACHE II Score ≤20	Ref.	Ref.
20 < Score ≤25	9.5 (1.2–74.4)	0.032
Score >25	51.0 (6.7–387.7)	0.0001
SBP >120 mmHg	6.5 (0.9–48.1)	0.0668
AST >80 μ/L	2.3 (1.1–4.8)	0.0251
XCT >120 min	2.9 (1.1–7.7)	0.0315

[†], Cr at admission. AST, aspartate transaminase; CPBT, cardiopulmonary bypass time; Cr, blood creatinine level; HR, heart rate; MAP, mean arterial pressure; Sbp, systolic blood pressure; WBC, white blood cell count; XCT, aortic cross-clamping time.

high risk patients is thus clinically relevant as clinical trials may target those patients for innovation in surgical techniques and peri-operative management.

In the current study, we analyzed the outcome of 264 TAAD patients who received surgical treatment in Guangdong General Hospital. The in-hospital mortality was 11.4%. This was consistent with study by Masuda and colleagues (10.6% in 2014) (6), and was lower than those from other investigators (3,5,7-10). This may reflect continuous improvement in surgical technique and peri-operative management. However, race and referral-based facility may also explain the relatively low mortality. We found that APACHE II score could be a useful tool to predict in-hospital mortality. AST >80 μ/L and XCT >120 min were also independent predictors.

APACHE II score is a severity of disease classification system based on 12 physiologic measurements, age and previous health status (11). It is a well validated score

system that is widely used in ICU setting. Due to its limitation, it may not be appropriate for all disease types. Giamarellos-Bourboulis *et al.* discussed that if comparing patients at a wide range of age with various baseline condition (e.g., septic patients), APACHE II score may not be sufficient to estimate death risk (12). There was no previous study investigating whether APACHE II score is suitable for predicting TAAD mortality. In current study, the mortality rate increased significantly as the score increased. In our cohort, most patients were healthy non-elderly adults with few comorbidities. APACHE II score provided a good prediction for TAAD in-hospital mortality. We also calculated the area under the receiver operating characteristics curve (AUROC) for APACHE II score (*Figure S1*). The AUROC was 0.9172 ($P < 0.0001$), which also proved that APACHE II score is an excellent model to predict TAAD in-hospital death. APACHE II score could quantify severity and help physicians to have a general idea

about patients' situation at admission. The score system may also be used in future TAAD studies to identify high risk patients. We originally planned to decompose the score system to analyze each variable, but we were only able to collect age, temperature, heart rate, Cr level, WBC counts and MAP data. We analyzed the available variables and found that only Cr level greater than 200 $\mu\text{mol/L}$ was related to TAAD in-hospital mortality in univariate analysis, but all of them were not significant in adjusted model. This might indicate that the other variables in the score system (AaDO₂ or PaO₂, pH arterial, respiratory rate, serum sodium, serum potassium, Glasgow coma scale) could have a greater weight in predicting TAAD in-hospital mortality. The prognostic implication of APACHE II score in TAAD patient will need to be further confirmed in future studies.

Among other pre-operative biomarkers, AST >80 μL was an independent predictor besides APACHE II score. One study found that elevated AST levels was significant in univariate analysis but marginally insignificant in multivariable analysis (OR =3.204; 95% CI, 0.986–10.409, P=0.0527) (13). A high AST level may result from organ injury (liver, heart, muscle, etc.) and/or inflammatory response to acute stress. Abnormal baseline AST may also indicate pre-existing liver disease, or organ ischemia during TAAD. Another research showed that TAAD patients' AST level also tended to increase after surgery (14). Because gastrointestinal complications (15), kidney injury (16), myocardial ischemia are frequently present during or after TAAD surgeries, patients with abnormal pre-operative AST level at baseline might have a greater organ injury or inflammatory response during and after surgery, which may be associated with higher mortality. This result may also suggest that liver protection and anti-inflammatory treatment should be further investigated in patients treated surgically.

TAAD surgeries are technically challenging and require extra-corporal cardiopulmonary bypass. We found that patients whose XCT more than 2 hours had over 4 times higher risk of in-hospital mortality. It is not new that long XCT is related to patients' death in general heart surgeries, but such data are lacking in TAAD surgeries. Nissinen *et al.* found that XCT >150 min was associated with a high risk of 30-day mortality (OR =1.21/30 min, 95% CI, 1.01–1.52) independently of the complexity of surgery (17). Doenst *et al.* also found that XCT was an independent predictor of mortality for patients with LVEF >40% regardless of surgery complexity (OR =1.014 per min of XCL, 95% CI, 1.01–1.02) (18). Regarding TAAD, Goda

et al. found that TAAD nonsurvivors had much longer XCT than survivors (206±96 *vs.* 161±58 min) (13). Some researchers had also found that long CPBT was related to mortality (19–21). In our study, CPBT was a significant risk factor in univariate analysis, but not significant after adjusted for APACHE II score and AST (230–260 *vs.* <230 min, HR =2.193, 95% CI: 0.654–7.353, P=0.2034; >260 *vs.* <230 min, HR=3.127, 95% CI, 0.997–9.812, P=0.0507). XCT remained significant in adjusted models. XCT and CPBT were highly correlated in our data (correlation coefficients =0.74332, P<0.0001), and XCT length is the determinant factor of CPBT length. We believe that they are similar important predictors, but XCT might have slightly better predicting value. A prolonged XCT indicates technical challenge and/or complications during surgery, which might affect patient outcome, such as longer ICU stay (22) and TAAD postoperative renal impairment and renal failure (23). These factors might then affect patients' in-hospital mortality. Therefore, improving intra-operative management and shorten XCT is an important way to improve in-hospital mortality.

This study had several limitations. First, this was a single center study and the sample size was relatively small. Less than 5% of the patient population were older than 65, which limits generalizability in elderly patients. Second, while prolong CPBT time itself increases mortality, surgery complexity and intraoperative issues might be confounding factors. Third, over-fitting might be a problem when we used Apache II score in disease with low event counts. Since we lacked the data of some important indexes (AaDO₂ or PaO₂, pH arterial, respiratory rate, serum sodium, serum potassium, Glasgow coma scale), we were not able to decompose APACHE II score system. We also could not collect the data of the five principle factors discovered by IRAD. Further research with more comprehensive data will be needed to better identify predictors to TAAD in-hospital mortality.

Conclusions

APACHE II score >25, AST >80 μL and XCT >120 min are independent risk factors of surgical treated TAAD patients' in-hospital mortality. Improving peri-operative managements are important to improve patients' outcome.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

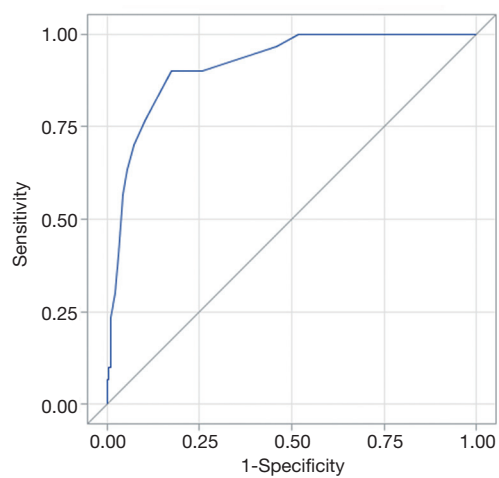
Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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ROC curve for APACHE II score
area under the Curve =0.9172

Figure S1 Receiver operating characteristics curve for APACHE II score in predicting TAAD in-hospital death. TAAD, type A aortic dissection.