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Relationship between the postoperative lactate dynamic levels, the acute gastrointestinal injury and the prognosis among patients who undergo surgical treatment for acute type A aortic dissection

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ABSTRACT

Introduction: This study aimed to determine the relationship between the postoperative lactate dynamic levels, the postoperative acute gastrointestinal injury (AGI), and the prognosis among the patients who underwent surgical treatment for an acute Stanford type-A aortic dissection (aTAAD).

Methods: A total of 271 aTAAD patients were recruited and monitored. Of the 271 aTAAD patients, 29.2% developed an AGI and were designated as the AGI group (n = 79); the other patients (n = 192) were designated as the non-AGI group. According to the 2-year follow up, the aTAAD patients were also divided into the alive and death subgroups for further analysis.

Results: Binary logistic regression analysis revealed that the postoperative 4-h lactate (P4L) level, time-to-return to the normal blood lactate level (TRNL), postoperative 16-h lactate (P16L) level, and neutrophil granulocyte (NEU) count had a good predictive value for an AGI after aTAAD. The 8-week and 2-year mortality rates were higher in the AGI group than the non-AGI group ($P < 0.05$). Basic data and clinical characteristics were significantly different between the alive and death groups ($P < 0.05$). A higher AGI rate and mortality occurred in the P4L level ≥10.15 mmol/L subgroup, TRNL ≥21-h subgroup, P16L level ≥2.95 mmol/L subgroup, NEU count $\geq 10.9 \times 10^9$/L subgroup, $PaO_2 < 77.7$ mmHg subgroup, WBC count $\geq 9.58 \times 10^9$/L subgroup, and the operative time ≥427 min subgroup than the corresponding comparison subgroups ($P < 0.05$). The postoperative 0-h lactate (P0L) level, TRNL, postoperative 24-h lactate (P24L) level, D-dimer level, fibrinogen degradation products (FDP) level, duration of mechanical ventilation, and length of hospitalization were independent factors influencing the 30-day mortality rate in patients who underwent surgery for an aTAAD ($P < 0.05$). Cox regression multivariate analysis after univariate analysis of all-cause mortality showed the TRNL, postoperative 12-h lactate (P12L) level, P16L level, P24L level, D-dimer level, FDP level, and length of hospitalization were independently associated with the 2-year mortality rate in patients who underwent surgery for an aTAAD ($P < 0.05$).

Conclusion: The postoperative lactate changes and TRNL effectively predicted postoperative AGI and the mortality rate in patients with who underwent surgery for an aTAAD. The TRNL and P24L level were independent risk factors for the 30-day and 2-year mortality rates in patients who underwent surgery for an aTAAD.

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1. Introduction

The incidence of acute Stanford type-A aortic dissection (aTAAD) is increasing year-after-year and has high disability and mortality rates, even after surgical repair [1]. Most postoperative deaths in patients with an aTAAD are due to sepsis or septic shock, and lactic acidosis [1–3]. Hyperlactatemia in patients after an aTAAD surgical repair portends a poor prognosis [3]. Approximately 25% of patients with an aTAAD exhibit poor perfusion [4], especially mesenteric ischemia [5–7] during cardiopulmonary bypass, and reperfusion injury further increase the possibility of an acute gastrointestinal injury (AGI). Early intestinal malperfusion or reperfusion injury after an aTAAD is difficult to assess, and clinical signs usually appear at a later stage, thus delaying the diagnosis and management of patients, which lead to infection and even death [4–8].

Studies have shown that patients with functional impairment of the gastrointestinal tract have a higher incidence of postoperative sepsis or septic shock. Several studies have demonstrated that hyperlactatemia is a sensitive marker of early mesenteric ischemia in the overgrowth of intestinal microflora and becomes an indicator for the assessment of early poor intestinal perfusion [9,10]. Hyperlactatemia is frequently used as a surrogate sign for inadequate cardiac output and may be associated with hyperglycemia [11], increased red blood cell transfusion requirements [12], or decreased lactate elimination [13]. Moreover, hyperlactatemia can be caused by tissue hypoperfusion (type A hyperlactatemia) [14], but can also be caused by normal tissue perfusion (type B hyperlactatemia) [15]. Liver injury, high doses of vasoactive drugs, inadequate rehydration, and postoperative complications may increase lactate production and decrease lactate clearance during and after surgery in patients with an aTAAD [16–20]. After diagnosis with superior mesenteric artery blockage, increased lactic acid levels have been reported in fewer than one-half of the patients (12 of 27) [19]. Numerous studies have only focused on the lactate level at a single point in time [17–21]; no studies on the dynamic changes and recovery of lactate and intestinal damage and management have been published.

In this study, we explored the relationship of the postoperative dynamic lactate changes, the AGI and the prognosis among the patients who underwent surgical repair of an aTTAAD. In addition, we focused on the postoperative risk factors for mortality in these patients.

2. Materials and methods

2.1. General data

This study was approved by the Clinical Research Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University (ethics number: XJTU1AF2020LSK-078). All patients signed written informed consent before surgery. All data were analyzed using a blinded method.

Patients with an aTAAD who were hospitalized for surgical treatment in Cardiovascular Surgery Department of our hospital from January 2019 to June 2020 were screened and followed. The follow-up evaluations were discontinued by June 2022. Eligible patients were diagnosed with a Stanford type A entrapment by computed tomography angiography (CTA). The inclusion criteria were as follows: aTAAD patients (Stanford A) within 2 weeks of symptom onset who were treated surgically within 24 h of admission. The patients (age range, 18–75 years; mean age, 57 $\pm$ 6 years) were divided into a Non-AGI group and a AGI group based on whether the AGI occurred within 24 h after surgery. Comprehensive assessment of gastrointestinal tract function were completed to define whether AGI occurred based on the following findings: 1) clinical manifestations of gastrointestinal tract function impairment such as diarrhea, abdominal distension, vomiting, constipation, reduced bowel sounds, gastric retention, gastrointestinal bleeding, 2) abdominal pressure detection; 3) fecal smears; 4) intestinal ultrasound (intestinal tube wall thickness, intestinal diameter, stratification, peristalsis, and ultrasonic score); and food tolerance. If the patient was manifested as any of the clinical manifestations of gastrointestinal tract function impairment, and confirmed by abdominal pressure detection, fecal smears and intestinal ultrasound, the patient was diagnosed of AGI [22].

The following were the criteria for exclusion before aTAAD surgery: (1) congenital heart disease; (2) medically-induced aortic dissection; (3) traumatic aortic dissection; (4) severe valvular disease; (5) history of cardiogenic shock or pericardial tamponade; (6) severe organ dysfunction, such as liver or kidney failure; (7) malignancy; (8) suspected subclinical myocardial involvement (e.g., a history of chronic inflammation or acute infection); (9) history of gastrointestinal, hepatic, and renal diseases, malignancy, and metabolic or immunologic diseases; (10) patients in who an AGI diagnosis was not established or imperfect clinical data, or patients who were lost to follow-up; and (11) AGI present prior to surgery.

2.2. Surgical method

The procedure was performed under hypothermia and general anesthesia with CBP, and the temperature was 26–28 °C. All the patients with a type A AAD were treated with surgery within 1 day of admission. Circulatory arrest was established when the nasopharyngeal temperature reached 25–28 °C. Selective cerebral perfusion was started through the right axillary and left common carotid arteries followed by opening the ascending aorta and transverse arch. The primary intimal tear in the proximal descending aorta was sealed using a stented elephant trunk, and the distal aorta was transected circumferentially close to the proximal margin of the origin of the left subclavian artery to avoid recurrent laryngeal nerve injury. The frozen elephant trunk was then inserted into the true lumen of the descending thoracic aorta in a bound, compressed state. The proximal edge of the residual aorta was trimmed to match the proximal end of the stent graft. The anastomosis between the 4-branched prosthetic graft and the distal aorta containing the intraluminal-stented graft was carried out using the "open" aortic technique. After the anastomosis was completed, blood perfusion of

the lower body was initiated via the limb of the 4-branched prosthetic graft. One limb of the prosthetic graft was then anastomosed to the left common carotid artery in an end-to-end fashion. After the anastomosis was completed, selective cerebral perfusion was discontinued. Then, CBP was gradually resumed to normal flow and rewarming was started. The innominate and left subclavian arteries were anastomosed to the respective limbs of the 4-branched prosthetic graft in an end-to-end style. The proximal segment of the left subclavian artery was oversewn with a continuous suture. A shunt from the outer wall of the aorta to the right atrium was performed with residual aortic wall and pericardium after opening circulation.

2.3. Laboratory indicators studied

All patients were monitored preoperatively while fasting, and postoperatively at 0, 4, 8, 12, 16, 20, and 24 h for lactate levels, the time-to-return to the normal blood lactate (TRNL) level, white blood cell (WBC) count, neutrophil (NEU) count, Pro-BNP, and C-reactive protein (CRP) level using a fully automated hematology analyzer (Mindray, model: BC6800Plus; Shenzhen Myriad Biomedical Electronic Co., Ltd., Shenzhen, China). The aspartate transferase, alanine aminotransferase, total bilirubin, direct bilirubin, indirect bilirubin, total cholesterol, urea, creatinine, and uric acid levels, and myocardial enzyme profiles were measured on a fully automated biochemistry analyzer (model 008AS; Hitachi, city, Japan). D-dimer and fibrin degradation products (FDP) were measured on a hemagglutination analyzer-3 (model CS5100; Sysmex, city, Japan). When the patient's temperature and inflammation indicators were elevated postoperatively, and the diagnosis of lung infection, blood flow infection, urinary system infection caused by pathogens, which were detected in sputum or respiratory lavage, urine, and blood cultures (partly by NGS), this was defined as infection.

3. Statistical methods

All data were analyzed using SPSS 26.0 statistical software. The mean ± standard deviation (x ± s) was used for normally distributed measures and an independent samples *t*-test was used for comparison between groups. Data that did not conform to a normal distribution are expressed as the median (interquartile spacing), i.e., Q (Q1, Q3), and the rank-sum test was used for comparison between groups. Count data are expressed as rates or composition ratios, and the $\chi 2$ test was used for comparison between groups. The receiver operating characteristic (ROC) curve was used to determine the predictive value affecting the occurrence of gastrointestinal functional impairment after surgery. Binary logistic regression analysis was used for risk factor analysis. The K-M survival curve was used for survival analysis. The log-rank test was used for differences between the two groups. The threshold for univariate statistical analysis for variables to be included in the multivariable logistic regression were as follows: dynamic lactate level ($\geq$3 mmol/L = 1, <3 mmol/L = 0); and TRNL level $\geq$21 h = 1, TRNL level <21 h = 0. Other binary variables were ordered variables. A two-tailed $P < 0.05$ was considered statistically significant.

4. Results

4.1. Comparison of basic data and clinical characteristics between the AGI and non-AGI groups

Two hundred seventy-nine aTAAD patients who met the inclusion criteria were enrolled in the current study. Eight patients were

Table 1
Comparison of clinical parameters between the AGI and non-AGI groups.

Indicators	Non-AGI group (n = 192)	AGI group (n = 79)	*P*
Age, y	52 (44–58)	54 (45–62)	0.184
Male, n (%)	140 (73)	56 (71)	0.734
Smoking history, n (%)	113 (59)	41 (52)	0.293
BMI (kg/m^2)	25.45 (22.49–27.72)	26.37 (24.22–29.95)	0.022*
Pro-BNP (ng/L)	619 (238–1230)	783 (242–1780)	0.203
LVEF (%)	60 (55–63)	60 (55–64)	0.416
D-dimer (mg/L)	7.33 (2.70–17.10)	13.41 (4.81–28.30)	0.001*
FDP (mg/L)	23.21 (8.56–48.95)	41.09 (16.49–97.43)	0.000*
WBC ($\times 10^9$/L)	10.27 (8.00–13.15)	12.94 (10.32–16.56)	0.000*
NEU ($\times 10^9$/L)	9.12 ± 3.70	11.52 ± 4.79	0.000*
Preoperative PaO_2 (mmHg)	76.5 (67.8–87.5)	71.7 (63.3–77.9)	0.002*
Operative time (min)	360 (290–420)	390 (330–475)	0.003*
Extracorporeal circulation time (min)	143 (122–162)	149 (130–167)	0.047*
Aortic cross-clamp time (min)	76 (65–89)	77 (68–99)	0.190
Duration of mechanical ventilation (d)	2 (1–3)	8 (4–18)	0.000*
ICU length of stay (d)	5 (3–7)	13 (9–30)	0.000*
Length of hospitalization (d)	17 (13–20)	23 (18–40)	0.000*
Infection, n (%)	12 (6)	74 (94)	0.000*

Footnotes: Non-AGI: non-acute gastrointestinal injury; AGI: acute gastrointestinal injury; BMI: body mass index; Pro-BNP: N-terminal pro-brain natriuretic peptide; LVEF: left ventricular ejection fraction; FDP: fibrinogen degradation products; WBC: white blood cells; NEU: neutrophil granulocytes; PaO_2: partial pressure of oxygen; ICU: intensive care unit.
*$P < 0.05$.

lost to follow-up lost during the 2-year period, thus 271 patients were included and analyzed (196 males and 75 females). There were 79 patients in the AGI group and 192 patients in the non-AGI group. The mean follow-up time was 117 ± 67 weeks.

The baseline data demonstrate (Table 1) that the following postoperative measures were significantly higher in the AGI group than the non-AGI group (all $P < 0.01$): BMI; D-dimer level; FDP level; WBC count; NEU count; preoperative PaO_2; operative time; extracorporeal circulation time; length of ICU stay and hospital stay; duration of mechanical ventilation; and infection rate. The preoperative partial pressure of oxygen (PaO_2) was significantly lower in the AGI group than the non-AGI group ($P < 0.05$).

Table 2 shows that the lactate levels 0, 4, 8, 12, 16, and 20 h postoperatively, the TRNL level, maximum lactate level, and 30-day, 8-week, 3-month, 1-year, and 2-year mortality rates were significantly higher in the AGI group than the non-AGI group (all $P < 0.05$).

4.2. Postoperative AGI risk factors in patients with an aTAAD

Statistically significant postoperative AGI risk factors based on univariate analysis were as follows: dynamic lactate level (≥3 mmol/L = 1, <3 mmol/L = 0); and TRNL level (TRNL ≥21 h = 1, TRNL <21 h = 0). The above independent variables were introduced into the binary logistics regression analysis with AGI as the dependent variable. The results suggested that the postoperative 4-h lactate level [P4L] (OR = 4.467, 95% CI, 1.986–10.048; $p < 0.001$), TRNL level (OR = 2.124, 95% CI, 1.024–4.405; $p < 0.05$), preoperative PaO_2 (OR = 1.029, 95% CI, 1.006–1.052; $p < 0.05$), and WBC count (OR = 1.274, 95% CI, 1.106–1.466; $p < 0.05$) were independently correlated with postoperative AGI in patients with an aTAAD ($P < 0.05$, Table 3).

4.3. Comparison of ROC analysis of different indicators to predict the occurrence of AGI after aTAAD surgery

ROC analysis of the patients with an aTAAD revealed that the P4L level (AUC = 0.756), TRNL level (AUC = 0.763), P16L level (AUC = 0.705), and NEU count (AUC = 0.738) had good predictive value for an AGI. The thresholds for predicting an AGI were as follows: P4L level, 10.15 mmol/L; P16L level, 2.95 mmol/L; NEU count, 10.9×10^9/L; and TRNL level, 21 h (Fig. 1, Table 4).

The follow-up results showed that the 8-week (32% vs. 15%) and 2-year mortality rates (47% vs. 16%) were higher in the AGI group than the non-AGI group ($P < 0.05$; Fig. 2A and B).

4.4. Subgroup analysis of different indicators to predict the occurrence of AGI after aTAAD surgery

Take P4L level, TRNL level, P16L level, NEU count, preoperative PaO_2, WBC, and operative time as indicators, and divide the patients into subgroups.

Higher AGI (46% vs. 8%; Fig. 3A) and mortality rates (37% vs. 10%; Fig. 3B) occurred in the P4L level ≥10.15 mmol/L subgroup (n = 151) than the P4L level <10.15 mmol/L subgroup (n = 120; both $P < 0.05$). Analysis of the TRNL level subgroups showed higher AGI (47% vs. 10%; Fig. 3C) and mortality rates (39% vs. 10%; Fig. 3D) in the TRNL level ≥21 h subgroup (n = 141) than the TRNL level <21 h subgroup (n = 130; both $P < 0.05$). Analysis of the P16L level subgroups showed higher AGI (43% vs. 14%; Fig. 3E) and mortality rates (36% vs. 14%; Fig. 3F) in the P16L level ≥2.95 mmol/L subgroup (n = 139) than the P16L level <2.95 mmol/L subgroup (n = 132; both $P < 0.05$). Analysis of the NEU count subgroups showed higher AGI (49% vs. 16%; Fig. 3G) and mortality rates (32% vs. 21%; Fig. 3H) in the NEU count ≥10.9×10^9/L subgroup (n = 107) than the NEU count <10.9×10^9/L subgroup (n = 164; both $P < 0.05$).

Analysis of the preoperative PaO_2 subgroups showed lower AGI (20% vs. 35%; Fig. 4A) and mortality rates (22% vs. 27%; Fig. 4B) in the $PaO_2 \geq 77.7$ subgroup (n = 106) than the PaO_2 <77.7 subgroup (n = 165; both $P < 0.05$). Analysis of the WBC count subgroups

Table 2
Comparison of lactate changes and mortality rates between the AGI and non-AGI groups in patients with aTAAD surgeries.

Indicators	Non-AGI group (n = 192)	AGI group (n = 79)	*P*
Preoperative lactate (mmol/L)	1.4 (1.1–2.0)	1.5 (1.2–2.0)	0.220
Postoperative 0-h lactate (mmol/L)	10.7 ± 5.1	13.3 ± 4.9	0.000*
P4L (mmol/L)	9.1 (6.3–13.2)	13.9 (11.0–17.0)	0.000*
Postoperative 8-h lactate (mmol/L)	6.3 (4.2–9.7)	9.9 (7.3–12.6)	0.000*
Postoperative 12-h lactate (mmol/L)	3.9 (2.2–6.3)	6.4 (3.8–10.1)	0.000*
Postoperative 16-h lactate (mmol/L)	2.6 (1.5–4.1)	3.8 (2.5–6.7)	0.000*
Postoperative 20-h lactate (mmol/L)	2.1 (1.3–3.1)	2.8 (1.9–4.8)	0.001*
Postoperative 24-h lactate (mmol/L)	1.6 (1.2–2.5)	1.9 (1.3–3.1)	0.064
Maximal lactate steady state (mmol/L)	11.7 ± 5.0	15.2 ± 4.3	0.000*
TRNL (h)	20 (16–28)	24 (20–28)	0.000*
30-day mortality rate, n (%)	29 29 (15)	25 25 (32)	0.002*
8-week mortality rate, n (%)	• 29 (15)	2525 (32)	0.002*
• 3-month mortality rate, n (%)	29 29 (15)	3535 (44)	0.000*
1-year mortality rate, n (%)	30 (16)	35 (44)	0.000*
2-year mortality rate, n (%)	31 (16)	37 (47)	0.000*

Footnotes: Non-AGI: non-acute gastrointestinal injury; AGI: acute gastrointestinal injury; P4L: postoperative 4-h lactate; TRNL: time-to-return to normal blood lactate level.
*$P < 0.05$.

Table 3
Logistic regression analysis of relative factors for AGI in patients with an aTAAD surgery.

Indicators	B	SE	Wald	*P*	OR	95% confidence interval	
						Lower limit	Upper limit
Postoperative 0-h lactate (mmol/L)	0.537	0.871	0.380	0.538	1.710	0.310	9.422
P4L (mmol/L)	1.470	0.414	12.589	0.000*	4.351	1.931	9.803
Postoperative 8-h lactate (mmol/L)	0.065	0.231	0.079	0.779	1.067	0.679	1.678
Postoperative 12-h lactate (mmol/L)	−0.356	0.495	0.517	0.472	0.701	0.266	1.849
Postoperative 16-h lactate (mmol/L)	−1.183	0.474	6.237	0.013*	0.306	0.121	0.775
Postoperative 20-h lactate (mmol/L)	−0.333	0.380	0.766	0.382	0.717	0.340	1.511
Maximal lactate steady state (mmol/L)	−1.488	1.281	1.348	0.246	0.226	0.018	2.783
TRNL	0.781	0.382	4.190	0.041*	2.184	1.034	4.615
BMI (kg/m^2)	−0.075	0.040	3.494	0.062	0.928	0.858	1.004
D-dimer (mg/L)	−0.028	0.025	1.256	0.262	0.973	0.926	1.021
FDP (mg/L)	0.004	0.006	0.391	0.532	1.004	0.991	1.017
Preoperative PaO_2 (mmHg)	0.029	0.011	6.310	0.012*	1.029	1.006	1.052
WBC ($\times 10^9$/L)	0.241	0.072	11.366	0.001*	1.273	1.106	1.465
NEU ($\times 10^9$/L)	−0.413	0.077	28.454	0.000*	0.662	0.568	.770
Operative time (min)	−0.003	0.001	4.573	0.032	0.997	0.995	1.000
Extracorporeal circulation time (min)	−0.001	0.004	0.044	0.833	0.999	0.991	1.007

Footnotes: P4L: postoperative 4-h lactate; TRNL: time-to-return to normal blood lactate level BMI: body mass index; FDP: fibrinogen degradation products; WBC: white blood cells; NEU: neutrophil granulocytes; PaO_2: partial pressure of oxygen.
Some indicators that did not have a significant impact ($P > 0.05$) are not shown in this table.
*$P < 0.05$.

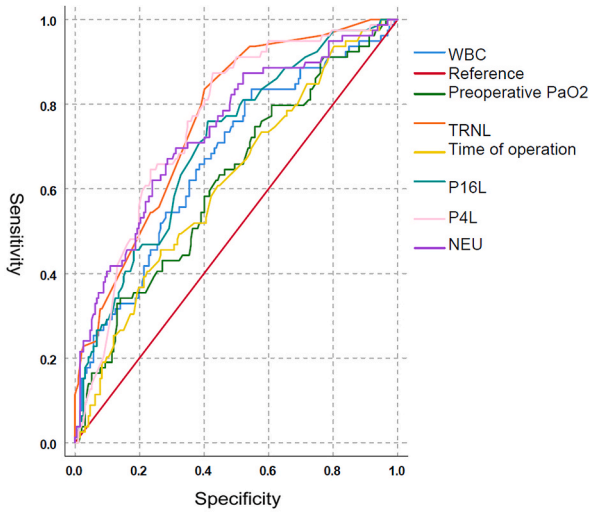

Fig. 1. ROC analysis of different indicators on the occurrence of AGI after surgery in patients with an aTAAD.

showed lower AGI (13% vs. 39%; Fig. 4C) and mortality rates (18% vs. 29%; Fig. 4D) in the WBC count $<9.58 \times 10^9$/L subgroup (n = 101) than the WBC $\geq 9.58 \times 10^9$/L subgroup (n = 170; both $P < 0.05$). Analysis of the operative time subgroups showed lower AGI (24% vs. 43%; Fig. 4E) and mortality rates (20% vs. 41%; Fig. 4F) in the operative time <427 min subgroup (n = 199) than the operative time ≥427 min subgroup (n = 72; both $P < 0.05$).

4.5. Comparison of clinical characteristics and lactate level changes between the alive and death groups

The results suggest (Table 5) that the age, Pro-BNP level, LVEF, D-dimer level, FDP level, NEU count, operative time, extracorporeal circulation time, aortic cross-clamp time, duration of mechanical ventilation, length of ICU stay and hospital stay, infection rate, and AGI rate were significantly different in the death group than the alive group (all $P < 0.05$).

The lactate levels at 0, 4, 8, 12, 16, and 20 h, the TRNL level, maximum lactate level, and AGI rate were also significantly higher in the death group than the alive group (all $P < 0.05$; Table 6).

Table 4
ROC analysis of different indicators for the occurrence of AGI in patients with aTAAD after surgery.

Indicators	AUC	Threshold	SE	95% CI	Sensitivity (%)	Specificity (%)	*P*
P4L (mmol/L)	0.756	>10.15	0.031	0.695–0.816	87.3	57.3	0.000*
TRNL (h)	0.763	>21	0.034	0.704–0.822	83.5	59.9	0.000*
WBC ($\times 10^9$/L)	0.671	>9.58	0.037	0.600–0.743	83.5	45.3	0.000*
Preoperative PaO_2 (mmHg)	0.618	<77.7	0.036	0.544–0.691	74.7	44.3	0.002*
Postoperative 16-h lactate (mmol/L)	0.705	>2.95	0.034	0.638–0.771	75.9	58.9	0.000*
Operative time (min)	0.615	>427	0.030	0.543–0.688	39.2	78.6	0.000*
NEU ($\times 10^9$/L)	0.738	>10.9	0.037	0.671–0.804	67.1	71.4	0.000*

Indicators	Actual sensitivity (%)	Actual specificity (%)	Positive predictive value	Negative predictive value	Youden index
P4L (mmol/L)	45.7	91.7	87.3	57.3	0.374
TRNL (h)	46.8	90.0	83.5	60.9	0.368
WBC ($\times 10^9$/L)	38.8	87.1	83.5	45.8	0.259
Preoperative PaO_2 (mmHg)	35.2	80.2	73.4	44.3	0.154
Postoperative 16-h lactate (mmol/L)	43.2	85.6	75.9	58.9	0.288
Operative time (min)	43.1	75.9	63.2	57.3	0.190
NEU ($\times 10^9$/L)	48.6	83.5	48.6	71.4	0.321

Footnotes: P4L: postoperative 4-h lactate; TRNL: time-to-return to normal blood lactate level BMI: body mass index; FDP: fibrinogen degradation products; WBC: white blood cells; NEU: neutrophil granulocytes; PaO_2: partial pressure of oxygen.
*P < 0.05.

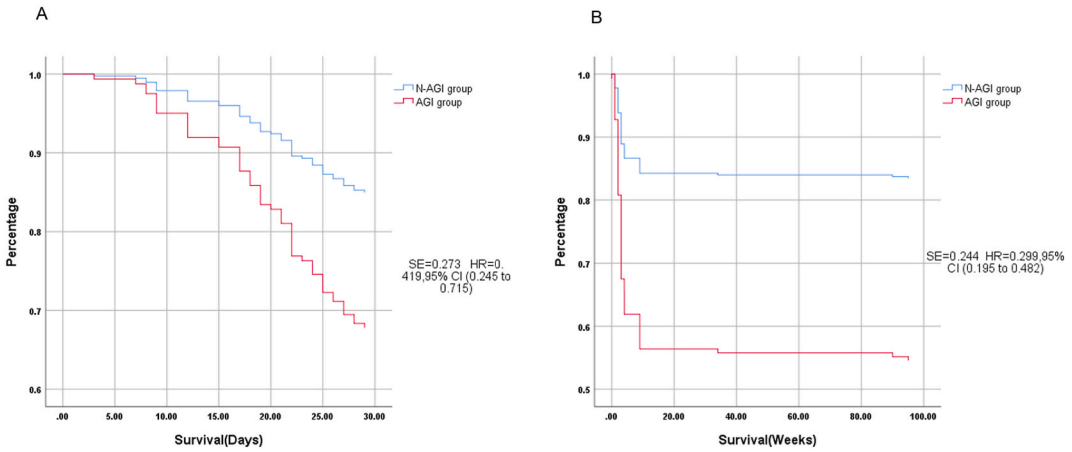

Fig. 2. A. Survival rate of the AGI group was significantly lower than the non-AGI group at 8 weeks postoperatively (P < 0.05); B. Survival rate of the AGI group was significantly lower than the non-AGI group 2 years postoperatively (P < 0.05).

4.6. 30-Day mortality risk factors in patients with an aTAAD after surgery

Thirty-day mortality risk factors in patients with an aTAAD after surgery with statistically significant differences based on univariate analysis were assigned the following values: death = 1; alive = 0; AGI = 1; non-AGI = 0; infection = 1; and non-Infection = 0. The preceding independent variables were introduced into the binary logistics regression analysis with the occurrence of death as the dependent variable. The results suggested that the postoperative 0-h lactate (P0L) level (OR = 1.806; 95% CI, 1.179–2.766; p < 0.05), TRNL level (OR = 1.149; 95% CI, 1.016–1.301; p < 0.05), postoperative 24-h lactate (P24L) level (OR = 2.074; 95% CI, 1.126–3.820; p < 0.05), D-dimer level (OR = 1.166; 95% CI, 1.042–1.306; p < 0.05), FDP (OR = 0.959; 95% CI, 0.929–0.989; p < 0.05), duration of mechanical ventilation (OR = 1.386; 95% CI, 1.166–1.648; p < 0.05), and length of hospitalization (OR = 0.630; 95% CI, 0.512–0.774; p < 0.05) were independent factors influencing the 30-day mortality rate in patients with an aTAAD (P < 0.05; Table 7).

4.7. Comparison of COX analysis of different indicators to predict the occurrence of 2-year mortality after aTAAD surgery

Cox regression multivariate analysis after univariate analysis of all-cause mortality showed that the TRNL level (HR = 1.039; 95% CI, 1.002–1.078; p < 0.05), postoperative 12-h lactate (P12L) level (HR = 1.201; 95% CI, 0.874–1.171; p < 0.05), postoperative 16-h lactate (P16L) level (HR = 0.800; 95% CI, 0.679–0.941; p < 0.05), P24L level (HR = 1.120; 95% CI, 1.029–1.219; p < 0.05), D-dimer level (HR = 1.034; 95% CI, 1.013–1.055; p < 0.05), FDP level (HR = 0.994; 95% CI, 0.988–1.000; p < 0.05), and length of

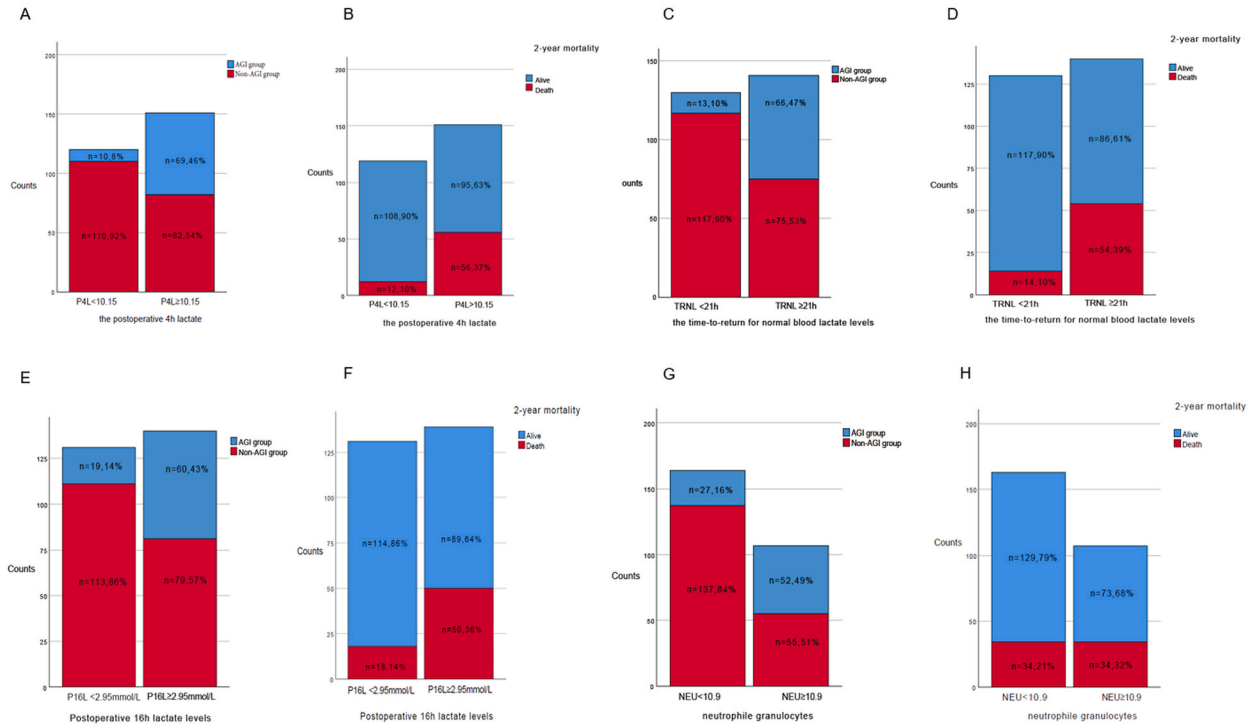

Fig. 3. Significant differences were found on the subgroups in consideration of AGI and mortality rates ($P < 0.05$). A. AGI rate of P4L level ≥10.15 mmol/L subgroup (n = 151) vs. P4L level <10.15 mmol/L subgroup (n = 120); B. 2-year mortality rate of P4L level ≥10.15 mmol/L subgroup (n = 151) vs. P4L level <10.15 mmol/L subgroup (n = 120); C. AGI rate of TRNL level ≥21 h subgroup (n = 141) vs. TRNL level <21 h subgroup (n = 130); D. 2-year mortality rate of TRNL level ≥21 h subgroup (n = 141) vs. TRNL level <21 h subgroup (n = 130); E. AGI rate of P16L level ≥2.95 mmol/L subgroup (n = 139) vs. P16L level <2.95 mmol/L subgroup (n = 132); F. 2-year mortality rate of P16L level ≥2.95 mmol/L subgroup (n = 139) vs. P16L level <2.95 mmol/L subgroup (n = 132); G. AGI rate of NEU count ≥10.9×10^9/L subgroup (n = 107) vs. NEU count <10.9×10^9/L subgroup (n = 164); H. 2-year mortality rate of NEU count ≥10.9×10^9/L subgroup (n = 107) vs. NEU count <10.9×10^9/L subgroup (n = 164).

hospitalization (HR = 0.957; 95% CI, 0.927–0.987; $p < 0.05$) were independently associated with the 2-year mortality rate in patients with an aTAAD ($P < 0.05$; Table 8).

5. Discussion

Postoperative gastrointestinal dysfunction in patients with an aTAAD is one of the main complications of primary disease and extracorporeal cardiac surgery [23,24]. If aTAAD patients have low cardiac output or circulatory instability after surgery, the use of high doses of catecholamines, and thus gastrointestinal vasoconstriction and reduced perfusion, together with the use of intra- and post-operative sedative and analgesic drugs, inhibit peristaltic and emptying functions of the gastrointestinal tract [25,26], causing flora disorders, the proliferation of harmful flora, and the reduction of beneficial flora, eventually leading to infection and poor nutrient absorption in patients and increasing the risk of postoperative mortality in patients [27–29].

It has been demonstrated that early hypoperfusion in patients with an aTAAD is not diagnosed in time, resulting in reduced tissue and organ oxygenation and metabolism, leading to multi-organ dysfunction and increased mortality [30,31]. As an intermediate metabolite of glycolysis in the body during tissue ischemia and hypoxia, lactate can effectively assess the perfusion of tissues and organs as well as reflect the oxygen metabolism of the body. Although patients with an aTAAD improve their postoperative ischemic-hypoxic status through aggressive surgical treatment, preoperative ischemia and hypoxia may have caused organ perfusion injury or caused organ ischemia and hypoxia and reperfusion injury again after surgical stress, extracorporeal circulation, or aortic block. The lactate level in the blood correlates with the immediate level of inflammation [32,33], thus dynamic lactate changes and recovery time are particularly important in clinical practice. During cardiopulmonary bypass, blood lactate levels ≥5 mmoL/l are linked to a greater in-hospital mortality rate and postoperative problems [34]. Therefore, lactate concentration is a possible biomarker in heart surgery patients.

The relationship between lactate levels and gastrointestinal malperfusion remains largely uncertain, and there is little research at home and abroad on when lactate is best measured for determining the severity of organ malperfusion, and whether rapid lactate recovery is predictive of gastrointestinal damage in patients. Huang [35] concluded in animal experiments that the plasma lactate level and early lactate clearance rate are objective and accurate guidelines for determining the treatment effect, severity of disease, and prognosis of dogs with gastrointestinal critical illness, and can be used as indicators for assessing the condition and prognosis of dogs

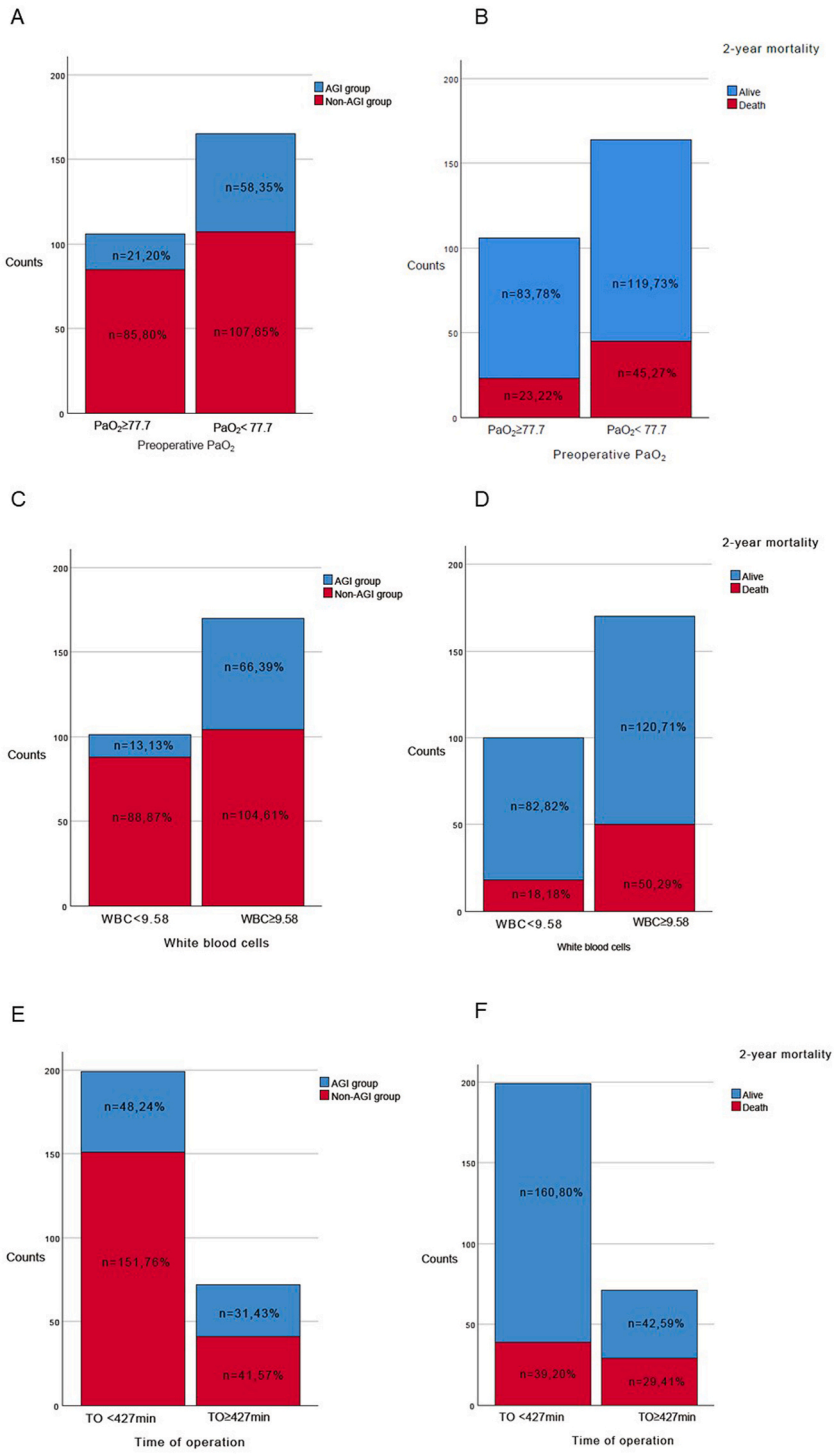

Fig. 4. Significant differences were found on the subgroups in consideration of AGI and mortality rates ($P < 0.05$). A. AGI rate of $PaO_2 \geq 77.7$ subgroup ($n = 106$) vs. $PaO_2 < 77.7$ subgroup ($n = 165$); B. 2-year mortality rate of $PaO_2 \geq 77.7$ subgroup ($n = 106$) vs. $PaO_2 < 77.7$ subgroup ($n = 165$); C. AGI rate of WBC count $< 9.58 \times 10^9$/L subgroup ($n = 101$) vs. WBC $\geq 9.58 \times 10^9$/L subgroup ($n = 170$); D. 2-year mortality rate of WBC count $< 9.58 \times 10^9$/L subgroup ($n = 101$) vs. WBC $\geq 9.58 \times 10^9$/L subgroup ($n = 170$); E. AGI rate of operative time <427 min subgroup ($n = 199$) vs. operative time ≥427 min subgroup ($n = 72$); F. 2-year mortality rate of operative time <427 min subgroup ($n = 199$) vs. operative time ≥427 min subgroup ($n = 72$).

Table 5
Comparison of clinical parameters between the death groups and alive groups.

Indicators	Alive group (n = 203)	Death group (n = 68)	*P*
Age, y	52 (43–57)	57 (48–65)	0.001*
Male, n (%)	150 (74)	46 (68)	0.319
Smoking history, n (%)	116 (57)	38 (56)	0.856
BMI (kg/m^2)	25.51 (22.49–28.34)	26.47 (23.72–28.16)	0.183
Pro-BNP (ng/L)	556 (224–1210)	1049 (392–1803)	0.002*
LVEF (%)	60 (55–65)	58 (53–61)	0.006*
D-dimer (mg/L)	7.00 (2.62–17.08)	20.80 (10.86–33.00)	0.000*
FDP (mg/L)	21.70 (7.12–48.48)	56.98 (26.11–106.10)	0.000*
WBC ($\times 10^9$/L)	10.68 (8.23–14.67)	11.35 (9.32–14.02	0.524
NEU ($\times 10^9$/L)	9.87 ± 4.27	11.31 ± 4.56	0.019*
Preoperative PaO_2 (mmHg)	76.1 (67.5–85.5)	71.7 (63.5–78.0)	0.059
Operative time (min)	360 (300–420)	413 (290–484)	0.011*
Extracorporeal circulation time (min)	143 (123–159)	150 (135–175)	0.009*
Aortic cross-clamp time (min)	75 (65–90)	77 (71–99)	0.032*
Duration of mechanical ventilation (d)	2 (1–4)	6 (3–11)	0.000*
ICU length of stay (d)	6 (4–9)	9 (4–18)	0.001*
Length of hospitalization (d)	18 (16–22)	15 (6–22)	0.000*
Infection, n (%)	23 (11)	63 (93)	0.000*

Footnotes: Non-AGI: non-acute gastrointestinal injury; AGI: acute gastrointestinal injury; BMI: body mass index; Pro-BNP: N-terminal pro-brain natriuretic peptide; LVEF: left ventricular ejection fraction; FDP: fibrinogen degradation products; WBC: white blood cells; NEU: neutrophil granulocytes; PaO_2: partial pressure of oxygen; ICU: intensive care unit.
Some indicators that did not have a significant impact ($P > 0.05$) are not shown in this table.
*$P < 0.05$.

Table 6
Comparison of lactate levels and AGI rate between the death groups and alive groups.

Indicators	Alive group (n = 203)	Death group (n = 68)	*P*
Preoperative lactate (mmol/L)	1.5 (1.1–2.0)	1.5 (1.1–1.9)	0.610
Postoperative 0-h lactate (mmol/L)	10.6 ± 4.7	14.2 ± 5.4	0.000*
P4L (mmol/L)	9.8 (6.4–13.6)	14.8 (11.2–18.0)	0.000*
Postoperative 8-h lactate (mmol/L)	6.5 (4.3–10.0)	9.3 (6.7–13.0)	0.000*
Postoperative 12-h lactate (mmol/L)	3.8 (2.3–6.6)	6.7 (4.2–10.4)	0.000*
Postoperative 16-h lactate (mmol/L)	2.6 (1.6–4.3)	3.9 (2.8–6.6)	0.000*
Postoperative 20-h lactate (mmol/L)	2.1 (1.2–3.1)	2.8 (2.1–4.6)	0.001*
Postoperative 24-h lactate (mmol/L)	1.5 (1.2–2.5)	2.7 (1.6–6.3)	0.064
Maximal lactate steady state (mmol/L)	11.8 ± 4.8	15.7 ± 4.8	0.000*
TRNL (h)	11 (7–14)	15 (10–18)	0.000*
AGI, n (%)	37 (18)	42 (62)	0.000*

Footnotes: AGI: acute gastrointestinal injury; P4L: postoperative 4-h lactate; TRNL: time-to-return to normal blood lactate level.
*$P < 0.05$.

Table 7
Logistic regression analysis of relative factors for 30-day mortality.

Indicators	B	SE	Wald	*P*	OR	95% confidence interval	
						Lower limit	Upper limit
Postoperative 0-h lactate (mmol/L)	0.591	0.218	7.380	0.007*	1.806	1.179	2.766
TRNL (h)	0.139	0.063	4.872	0.027*	1.149	1.016	1.301
Postoperative 24-h lactate (mmol/L)	0.729	0.312	5.479	0.019*	2.074	1.126	3.820
D-dimer (mg/L)	0.154	0.058	7.118	0.008*	1.166	1.042	1.306
FDP (mg/L)	−0.042	0.016	6.991	0.008*	0.959	0.929	0.989
Duration of mechanical ventilation (d)	0.326	0.088	13.667	0.000*	1.386	1.166	1.648
Length of hospitalization (d)	−0.463	0.105	19.345	0.000*	0.630	0.512	0.774

Footnotes: TRNL: time-to-return to normal blood lactate level; FDP: fibrinogen degradation products.
Some indicators that did not have a significant impact ($P > 0.05$) are not shown in this table.
*$P < 0.05$.

Table 8
Univariate and multivariate predictor analyses of all-cause deaths.

Variables	Univariate Analysis			Multivariate Analysis		
	HR	95%CI	P Value	HR	95%CI	P Value
AGI，n(%)	2.920	1.803–4.729	0.000*			
Infection, n (%)	2.715	1.679–4.391	0.000*			
Postoperative 0-h lactate (mmol/L)	1.102	1.055–1.151	0.000*	1.137	0.974–1.327	0.103
TRNL (h)	1.042	1.027–1.058	0.000*	1.039	1.002–1.078	0.040*
Maximal lactate steady state (mmol/L)	1.127	1.078–1.179	0.000*	0.902	0.707–1.151	0.408
P4L (mmol/L)	1.124	1.076–1.174	0.000*	1.012	0.874–1.171	0.873
Postoperative 8-h lactate (mmol/L)	1.113	1.064–1.165	0.000*	0.994	0.869–1.137	0.933
Postoperative 12-h lactate (mmol/L)	1.111	1.061–1.163	0.000*	1.201	1.012–1.425	0.036*
Postoperative 16-h lactate (mmol/L)	1.060	1.009–1.113	0.021*	0.800	0.679–0.941	0.007*
Postoperative 20-h lactate (mmol/L)	1.028	1.003–1.053	0.027*	0.988	0.939–1.041	0.659
Postoperative 24-h lactate (mmol/L)	1.165	1.107–1.227	0.000*	1.120	1.029–1.219	0.009*
Age, y	1.041	1.017–1.066	0.001*	0.990	0.961–1.020	0.530
D-dimer (mg/L)	1.025	1.015–1.034	0.000*	1.034	1.013–1.055	0.001*
FDP (mg/L)	1.006	1.004–1.009	0.000*	0.994	0.988–1.000	0.056
Operative time (min)	1.002	1.000–1.003	0.013*	1.000	0.999–1.002	0.645
Aortic cross-clamp time (min)	1.009	1.001–1.018	0.024*	0.997	0.977–1.018	0.778
Extracorporeal circulation time (min)	1.007	1.001–1.012	0.019*	1.002	0.989–1.015	0.782
Duration of mechanical ventilation (d)	1.019	1.006–1.032	0.003*	1.038	0.999–1.079	0.057
Length of hospitalization (d)	0.970	0.947–0.994	0.014*	0.957	0.927–0.987	0.005*
NEU($\times 10^9$/L)	1.059	1.009–1.112	0.021*	1.041	0.966–1.122	0.293

Footnotes: AGI: acute gastrointestinal injury; FDP: fibrinogen degradation products; NEU: neutrophil granulocytes; P4L: postoperative 4-h lactate; TRNL: time-to-return to normal blood lactate level.
Some indicators that did not have a significant impact ($P > 0.05$) are not shown in this table.
*$P < 0.05$.

with gastrointestinal critical illness.

In the current study, the BMI, lactate levels at 0, 4, 8, 10, 12, 16, and 20 h, the TRNL level, maximal lactate steady state, mortality rate, and infection rate were significantly higher in the AGI group than the Non-AGI group. The 8-week and 2-year mortality rates were higher in the AGI group than the non-AGI group. The P0L level, TRNL level, P24L level were independent factors influencing the 30-day mortality rate in patients with an aTAAD. Cox regression multivariate analysis after univariate analysis of all-cause mortality showed that the TRNL, P12L level, P16L level, P24L level, were independently associated with the 2-year mortality rate in patients with an aTAAD surgery. These results demonstrated that the postoperative lactate levels are highly related to the occurrence of AGI and the mortality rate in patients who treated aTAAD with surgeries.

The TRNL level was shown to be a better predictor of postoperative AGI in patients with an aTAAD than a single lactate level. The NEU count and BMI are also influential factors for AGI in an aTAAD, which is consistent with previous studies [17,20], but the predictive value is not as good as the TRNL level, thus it can be considered that the time required for lactate recovery to normal levels was the best predictor of gastrointestinal impairment and long-term prognosis after an aTAAD. To enhance prognosis, closer monitoring is recommended to ensure proper tissue perfusion [34].

In the current study it was shown that the operative time, P16L level, and NEU count were protective factors for an AGI. The operative time was long, and some patients completed the operation. Due to hemostasis, the time of admission to the ICU was delayed, and the postoperative lactic acid level detection time was delayed, so the time required for lactic acid to return to normal and the dynamic level of lactic acid may be reduced [36]. In this way, the operative time was a protective factor of AGI. The second was the NEU count, which was retained from preoperative patients. When the level of the NEU count was very high, an HA-380 adsorption column or pharmacological interventions will be tandem during extracorporeal circulation during the operation, and drug intervention will reduce the probability of postoperative gastrointestinal dysfunction, which leads to the conclusion that the NEU count was the protective factor for AGI in the analysis [37–39]. Due to the different length of operation among patients, the dynamic lactic acid retention time was also different, which led to the fact that the P16L level obtained in the analysis was a protective factor for AGI. Therefore, in future studies, independent cohort studies will be conducted on these three indicators again to explore their relationship with postoperative AGI.

This research was limited by the small sample in a single center and the lack of lactic acid levels 24 h postoperatively. Lactic acid detection was performed at an interval of 4 h within 24 h after surgery, and the detection time after 24 h was irregular and not recorded, which neglected the impact of sustained lactic acid level or delayed lactic acid elevation in the patients. Further multicenter studies with longer monitoring of lactic acid level within 24 h, 48 h, 72 h, or 7 days are needed to illustrate the clinical significance of dynamic lactate levels and recovery for the early assessment of gastrointestinal function for the patients who undergo surgeries for aTAAD.

6. Conclusion

Overall, AGI occurs at a high rate, and is closely related with the 8-week and 2-year mortality rates among the patients who undergo

surgeries for aTAAD. The postoperative lactate changes and TRNL level effectively predicted postoperative gastrointestinal function and mortality rate in patients with an aTAAD. The TRNL and P24L levels were independent risk factors for the 30-day and 2-year mortality rates in patients with an aTAAD.

Author contribution statement

Xue Wang conceived and designed the experiments, performed the experiments, analyzed, and interpreted the data, and wrote the paper. Chao Deng, Fengwei Guo and Xiantong Cao performed the experiments, analyzed and interpreted the data, and wrote the paper. Yang Yan conceived and designed the experiments, contributed reagents, materials, analysis tools or data, and wrote the paper. All authors approved the final draft of manuscript for submission and publication.

Data availability statement

Data will be made available on request.

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Ethical statement

This study was approved by the Clinical Research Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University (ethics number: XJTU1AF2020LSK-078). This study was proceeded in compliance with all relevant ethical regulations. All patients signed written informed consent before surgery.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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