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Original Research

Inflammatory Trajectory and Anti-Inflammatory Pharmacotherapy in Frozen Elephant Trunk-Treated Acute Type I Aortic Dissection

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ABSTRACT

Background: Acute DeBakey type I aortic dissection is associated with high morbidity and mortality. Little is known regarding the role of leukocyte trajectory in prognosis.

Methods: We included adult acute DeBakey type I aortic dissection patients with emergency frozen elephant trunk and total arch replacement in 2 cardiovascular centers (2020-2022). We used latent class mixed model to group patients according to their leukocyte patterns from hospital admission to the first 5 days after surgery. We investigated the association of leukocyte trajectory and 30-day and latest follow-up mortality (October 31, 2023), exploratorily analyzing the effects of ulinastatin treatment on outcome.

Results: Of 255 patients included, 3 distinct leukocyte trajectories were identified: 196 in group I (decreasing trajectory), 34 in group II (stable trajectory), and 25 in group III (rising trajectory). Overall, 30-day mortality was 25 (9.8%), ranging from 8.2% (16/196) in group I, 8.8% (3/34) in group II, to 24.0% (6/25) in group III (P for trend = .036). Group III was associated with higher mortality both at 30 days (adjusted hazard ratio, 3.260; 95% CI, 1.071-9.919; $P = .037$) and at the last follow-up (adjusted hazard ratio, 2.840; 95% CI, 1.098-7.345; $P = .031$) compared with group I.

Conclusions: Distinct and clinically relevant groups can be identified by analyzing leukocyte trajectories, and a rising trajectory was associated with higher short-term and midterm mortality.

Introduction

Acute DeBakey type I aortic dissection (AAD) is a major cardiovascular catastrophe, with high mortality and morbidity rates if untreated timely.[1] Total arch replacement and frozen elephant trunk (FET) implantation has become the preferred strategy in treatment of AAD.[2] However, it is well-recognized that systemic inflammation responses run through the initiation, development, diagnosis, and treatment, including thrombogenesis, contrast medium, surgical trauma, circulatory arrest of lower body, hypothermia, mechanical ventilation, and postimplantation syndrome, which significantly was associated with worse outcome.[3–6]

As the most common inflammatory indicator, the leucocyte integrates many parameters that are pertinent to the host response to the dissected aorta, exogenous media, and invasive procedures.[7] Although derangements in the leucocyte are associated with increased mortality in AAD,[8] the impact of individual variations in the leucocyte over time has not been well described. Leucocyte trajectory analysis may contribute to distinguishing unique phenotypic clusters with dissimilar inflammatory processes, to identify patients who may have different outcomes or may benefit from additional anti-inflammatory treatment.

Ulinastatin, also known as human urinary trypsin inhibitor, has multiple pharmacological properties, such as anti-inflammatory and immunomodulatory effects. Currently, it has been widely used for the treatment of acute pancreatitis and septic shock because of its involvement in systemic inflammation and

Abbreviations: AAD, acute DeBakey type I aortic dissection; AvePP, average posterior probability; FET, frozen elephant trunk; HR, hazard ratio; ICU, intensive care unit; LCMM, latent class mixed modeling.

Keywords: inflammatory; latent class extend mixed model; leukocyte trajectory; type I aortic dissection.

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Table 1. Baseline characteristics of the entire cohort and each trajectory group.

	Overall (N = 255)	Group I (n = 196)	Group II (n = 34)	Group III (n = 25)	*P* value
Baseline characteristics					
Age, y	55.0 (45.0-62.0)	55.0 (45.0-62.0)	53.5 (41.5-63.5)	57.0 (47.0-66.0)	.481
Male sex	184 (72.2)	143 (73.0)	30 (88.2)	11 (44.0)	<.001
Height, cm	170.0 (164.5-175.0)	170.0 (165.0-175.0)	170.0 (162.8-174.0)	170.0 (160.0-175.0)	.592
Weight, kg	75.0 (63.5-80.0)	75.0 (65.0-81.0)	70.0 (63.5-77.4)	70.0 (60.0-75.0)	.021
Body surface area, m^2	1.95 (1.85-2.05)	1.96 (1.80-2.07)	1.90 (1.81-1.99)	1.86 (1.71-1.99)	.037
Body mass index, kg/m^2	25.4 (23.3-27.7)	25.7 (23.4-27.7)	24.5 (22.9-26.4)	24.2 (21.6-26.1)	.035
Clinical characteristics					
Time from onset to surgery, h	10 (6-18)	9 (5-18)	10 (5-19)	10 (5-20)	.553
Smoking	43 (16.9)	30 (15.3)	8 (23.5)	5 (20.0)	.451
Alcohol drinking	37 (14.5)	25 (12.8)	7 (20.6)	5 (20.0)	.349
Hypertension	197 (77.3)	153 (78.1)	27 (79.4)	17 (68.0)	.501
Diabetes mellitus	5 (2.0)	2 (1.0)	2 (5.9)	1 (4.0)	.083
Chronic lung disease	12 (4.7)	9 (4.6)	2 (5.9)	1 (4.0)	.933
Coronary heart disease	29 (11.4)	19 (9.7)	6 (17.6)	4 (16.0)	.300
Stroke	6 (2.4)	4 (2.0)	1 (2.9)	1 (4.0)	.422
Any of malperfusion	90 (35.3)	63 (32.1)	14 (41.1)	13 (52.0)	.109
Renal	66 (25.9)	46(23.5)	11 (32.3)	9 (36.0)	
Intestinal	45 (17.6)	29(14.8)	8 (23.6)	8 (32.0)	
Limb	33 (12.9)	23 (11.7)	5 (14.7)	5 (20.0)	
Cerebral	26 (10.2)	18 (9.2)	4 (11.7)	4 (16.0)	
Coronary	36 (14.1)	25 (12.8)	6 (17.6)	5 (20.0)	
Leukocyte count over time, $\times 10^9/L$					
T0	12.3 (9.6-15.2)	12.2 (9.9-14.9)	11.8 (9.1-16.7)	13.4 (8.2-16.4)	.923
T1	11.2 (9.4-13.6)	10.9 (9.1-12.9)	13.5 (10.4-16.6)	12.6 (10.5-15.3)	<.001
T2	11.6 (9.8-14.5)	11.2 (9.5-12.9)	14.7 (11.5-17.4)	16.9 (13.1-19.4)	<.001
T3	11.9 (9.8-14.7)	11.1 (9.4-12.8)	15.3 (13.8-18.1)	20.4 (16.8-23.2)	<.001
T4	10.8 (9.0-13.7)	9.9 (8.4-11.5)	15.2 (14.3-16.2)	18.3 (17.7-20.3)	<.001
T5	10.2 (8.3-12.7)	9.3 (8.0-11.1)	13.8 (12.7-15.7)	18.2 (16.2-22.1)	<.001
Laboratory profiles					
Hemoglobin, g/L	137.0 (124.0-148.0)	137.0 (125.0-148.2)	141.0 (128.2-148.0)	122.0 (116.0-142.0)	.012
Platelet, $\times 10^9/L$	168.0 (132.5-207.0)	167.0 (130.8-199.0)	191.5 (145.8-260.5)	166.0 (129.0-257.0)	.045
Blood urea nitrogen, mmol/L	76.6 (60.4-97.9)	76.5 (59.1-95.4)	80.9 (64.2-122.2)	76.4 (50.5-95.8)	.253
Creatinine, μmol/L	6.8 (5.3-8.4)	6.6 (5.3-8.2)	7.5 (5.5-9.0)	7.1 (5.2-8.9)	.516
eGFR, $mL/min/1.73m^2$	96.2 (71.0-120.7)	98.4 (74.2-121.5)	94.3 (55.8-115.2)	87.0 (57.2-99.3)	.031
Aspartate aminotransferase, u/L	28.4 (23.2-38.0)	28.9 (23.3-40.0)	28.5 (24.5-37.9)	24.8 (18.6-31.8)	.073
Alanine aminotransferase, u/L	29.5 (22.6-42.4)	29.4 (22.7-42.5)	34.9 (26.8-47.0)	23.7 (19.6-30.8)	.012
Albumin, g/L	39.0 (37.7-40.5)	39.0 (37.7-40.6)	39.6 (37.7-40.6)	38.4 (38.0-39.5)	.360
D-dimer, ng/mL	4.8 (2.0-9.9)	4.6 (2.0-9.8)	5.4 (2.1-9.9)	6.5 (1.3-15.6)	.977
Procedural characteristics					
Root procedure					.008
Aortic valve replacement	4 (1.6)	4 (2.0)	0 (0.0)	0 (0.0)	
Bentall	36 (14.1)	27 (13.8)	4 (11.8)	5 (20.0)	
David	11 (4.3)	4 (2.0)	3 (8.8)	4 (16.0)	
CPB time, min	193 (174-232)	186.0 (166.0-222.8)	210.0 (184.5-258.0)	236.5 (192.2-280.8)	.012
Aortic clamp time, min	144 (121-185)	143.0 (120.0-169.0)	148.0 (127.0-202.0)	161.5 (136.2-213.5)	.156
Circulatory arrest time, min	18 (14-26)	19.0 (15.0-24.8)	18.0 (14.5-22.5)	18.5 (15.5-23.5)	.841
CABG	7 (2.7)	3 (1.5)	2 (5.9)	2 (8.0)	.063
Concomitant surgery[a]	6 (2.4)	6 (3.1)	0 (0.0)	0 (0.0)	.784
Packed red cell transfusion (unit)	4.5 (1.8-8.5)	4.0 (1.4, 6.2)	4.8 (1.6, 7.1)	5.3 (2.4, 8.8)	.068
Ulinastatin usage	70 (27.5)	61 (31.1)	4 (11.8)	5 (20.0)	.045
Outcomes					
Mortality at 30 days	25 (9.8)	16 (8.2)	3 (8.8)	6 (24.0)	.042
Mechanical ventilation time, d	2.8 (1.2-6.3)	2.6 (1.2-6.2)	2.2 (0.9-4.2)	4.8 (1.6-7.5)	.123
ICU stay, d	9.0 (6.0-16.0)	9.0 (6.0-15.0)	8.5 (6.0-17.5)	12.0 (7.0-22.0)	.175
Hospital stays, d	21.0 (16.0-30.5)	21.0 (16.0-28.0)	22.5 (14.5-41.8)	26.0 (21.0-36.0)	.141
Follow-up time, mo	25.9 (19.6-37.0)	25.9 (20.0-37.1)	26.1 (20.5-36.0)	26.0 (1.2-36.7)	.760
Mortality at last follow-up	37 (14.5)	24 (12.2)	5 (14.7)	8 (32.0)	.031

Values are n (%) or median (IQR).

CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; eGFR, estimated glomerular filtration rate; ICU, intensive care unit.

[a] Concomitant 1 of the following procedures: mitral or tricuspid valve surgery.

inhibition of proteolytic processes.[9] Understanding of the interaction between ulinastatin and leucocyte trajectory is essential for anti-inflammatory management.

The primary objectives of our study were to identify distinct groups of patients with different leucocyte trajectories and to evaluate the association of leucocyte trajectory with mortality. Secondary objectives were to explore the interactive effect of different trajectories and anti-inflammatory pharmacotherapy (ulinastatin) on outcome.

Methods

Population

From January 2020 through May 2022, adult patients with AAD were included if they underwent emergency total arch repair and FET implantation in the First Affiliated Hospital of Nanjing Medical University (Nanjing) and Beijing Anzhen Hospital of Capital Medical University (Beijing). The diagnosis of AAD was made by aortic computed

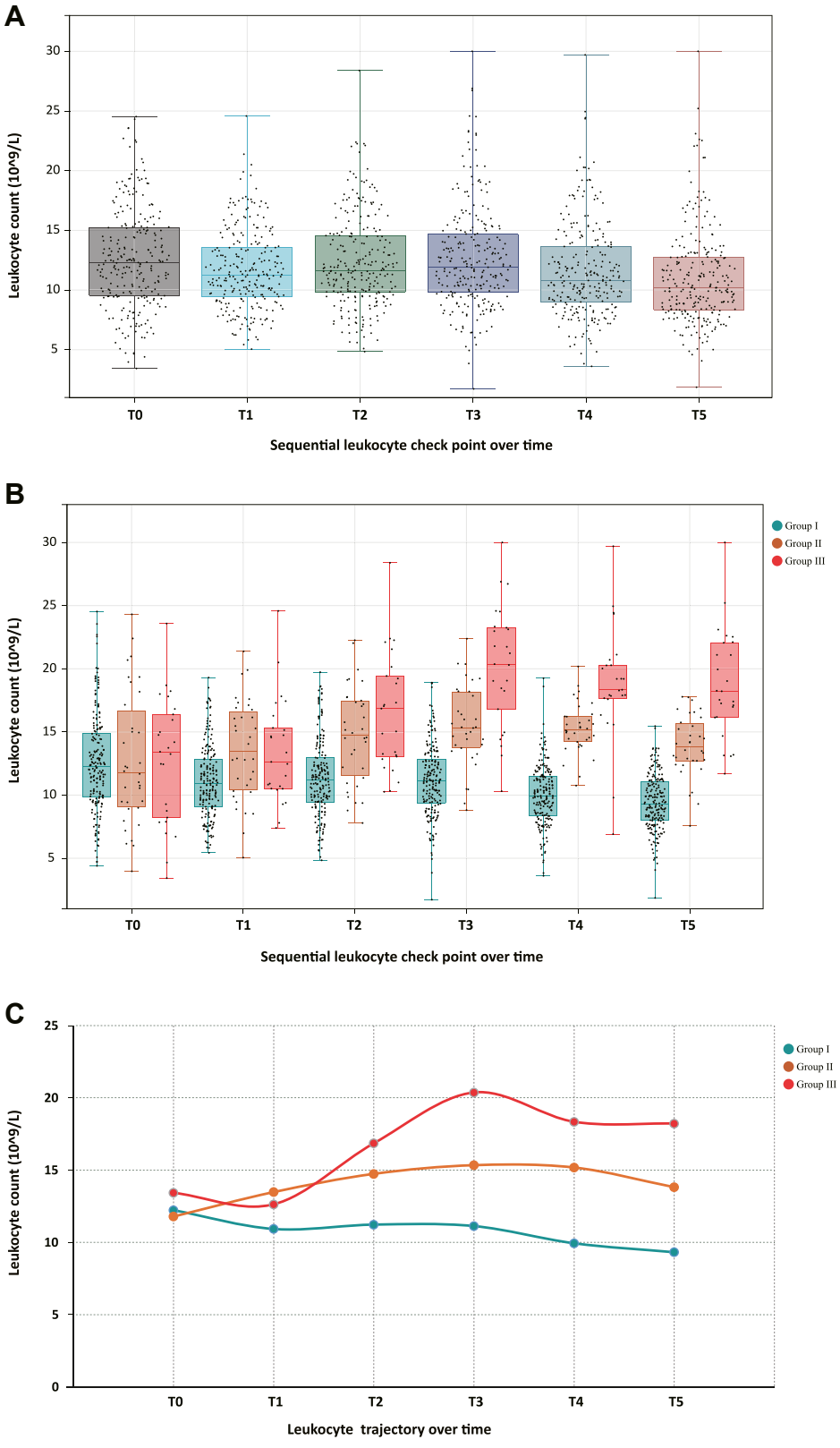


Figure 1.
Trajectory of leukocyte in the 6 sequential time points. (**A**) Overall patients, (**B**) by risk stratification of 3 groups, (**C**) leukocyte trajectory across the sequential time points.

tomography angiography at the initial presentation and the dissection could be classified according to DeBakey.[10] Exclusion criteria included: (1) regional or systemic infection in the last month before surgery, (2) chronic dissection or aneurysm of the aorta, (3) traumatic or iatrogenic aortic dissection, (4) those with only endovascular or medical management, and (5) active malignancy with poor prognosis.

Table 2. Results of Cox proportional hazard model assessing the effect of leukocyte trajectory group on mortality at 30 days and at last follow-up.

	Hazard ratio (95% CI)	*P* value
Mortality at 30 days		
Unadjusted		
Group I	1.0 (reference)	
Group II	1.086 (0.316-3.726)	.896
Group III	3.028 (1.185-7.739)	.021
Adjusted for baseline and clinical factors[a]		
Group I	1.0 (reference)	
Group II	1.481 (0.416-5.279)	.544
Group III	2.920 (1.050-8.124)	.040
Adjusted for baseline, clinical, and procedural factors[b]		
Group I	1.0 (reference)	
Group II	1.202 (0.292-4.946)	.798
Group III	3.260 (1.071-9.919)	.037
Mortality at last follow-up		
Unadjusted		
Group I	1.0 (reference)	
Group II	1.209 (0.461-3.169)	.699
Group III	2.828 (1.270-6.299)	.011
Adjusted for baseline and clinical factors[a]		
Group I	1.0 (reference)	
Group II	1.419 (0.512-3.935)	.501
Group III	2.433 (1.032-5.735)	.042
Adjusted for baseline, clinical, and procedural factors[b]		
Group I	1.0 (reference)	
Group II	1.366 (0.465-4.017)	.571
Group III	2.840 (1.098-7.345)	.031

[a] Adjusted for baseline and clinical factors included age, sex, body mass index, time from onset to surgery, smoking, alcohol drinking, hypertension, diabetes mellitus, chronic lung disease, coronary heart disease, stroke, malperfusion syndrome, hemoglobin, platelet, creatinine, aspartate aminotransferase, alanine aminotransferase, albumin, and D-dimer. [b] Adjusted for baseline, clinical, and procedural factors additionally included aortic root procedure, cardiopulmonary bypass time, circulatory arrest time, concomitant surgery, and packed red cell transfusion.

This study was approved by the institutional review board of the First Affiliated Hospital of Nanjing Medical University (no. 2021-SR-381) and the institutional review board of the Beijing Anzhen Hospital of Capital Medical University (KS2022034). The requirement for informed consent was waived due to the retrospective nature of the study design. This study was conducted in accordance with the Declaration of Helsinki and registered in ClinicalTrials.gov as NCT04398992. Patient selection, data collection, and data analysis were performed in accordance with Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[11]

Measures

Leukocyte count measurements were obtained from Sysmex automated hematology analyzers (Sysmex Canada Inc). Data were collected at 6 continuous time points on each case (T0: hospital admission, T1: intensive care unit [ICU] admission immediately after surgery, T2: first morning after surgery, T3: second morning after surgery, T4: third morning after surgery, and T5: fourth morning after surgery). To allow sufficient elapsed time to generate a leukocyte trajectory and to reduce the potential for survival bias, we limited our analysis to those patients who had an ICU length of stay of at least 4 days and had at least 5 serial measurements to determine the trajectory, with 9 patients who died before day 5 of surgery excluded. Laboratories in the 2 hospitals were certificated via the China National Accreditation Service for Conformity Assessment, which ensures consistency and homogeneity of laboratory results.

Interventions

In brief, circulatory arrest of the lower body was started with selective unilateral antegrade cerebral perfusion at a flow rate of 5.0 mL/kg/min when the cooling temperature reached the target temperature. A stented graft (CRONUS Stent Graft System; MicroPort) was anterogradely inserted into the true lumen of the descending aorta. Then, the stented graft and the descending aorta were anastomosed end-to-end with the 4-branched graft. After resumed perfusion of the lower body, the left common carotid artery was first reconstructed, and then the rewarming began, followed by reconstruction of the left subclavian artery. Then, the proximal ascending aorta was anastomosed with the proximal end of the 4-branched graft. A more detailed procedure for total arch replacement with FET in DeBakey type I AAD is presented in our previous reports.[12–14] In this present study setting, ulinastatin use in the setting of AAD is physician-specific. Ulinastatin (TECHPOOL Biopharma) was used immediately once the patient arrived at the ICU after surgery until ICU discharge according to the institutional protocol (100,000 U once every 8 hours intravenously).[5,15]

Outcomes

The primary outcome was 30-day mortality, defined as any death, regardless of cause, occurring within 30 days after surgery in or out of the hospital, and after 30 days during the same hospitalization subsequent to the operation. Secondary outcomes included the mechanical ventilation duration, ICU length of stay, and hospital length of stay.[16] All alive patients were followed up until October 31, 2023, and 30-day mortality was included in the mortality at the last follow-up.

Statistical analyses

We used latent class extend mixed model to segregate patients according to the trajectory of their total leukocytes based on measurements for the hospital admission before surgery and the first 4 days after surgery to capture the leukocyte trajectory attributable to onset and surgical repair of AAD. We followed a previously described procedure for model building using R latent class mixed modeling (LCMM) package.[17] We started with a 1-group model and increased up to a 5-group model. Trajectories were fitted to third-order polynomials to capture nonlinear patterns over time. The optimal number of trajectories was selected using the standard method of evaluating the Bayesian information criterion, augmented by clinical interpretation and sensibility.[18] Clinical interpretation was based on the final multidisciplinary consensus of our 5A Investigators (details of 5A Investigators are mentioned in Supplementary material) who were cardiovascular surgeons, anesthetists, perfusionists, and critical care physicians, and included an assessment of whether the trajectories were as expected for patients with AAD. Model fit statistics were performed on the final model, by assessing the average posterior probability (AvePP) for each group. The posterior probability is the probability that an individual with a specific pattern belongs to a specific trajectory group and is calculated for each individual in the R LCMM package. The AvePP is calculated by taking the average of the posterior probabilities for each trajectory group. It is recommended that each group should have an AvePP >0.7.[19,20]

We summarized the baseline characteristics of the entire cohort and compared baseline characteristics across the identified trajectory groups using the Kruskal–Wallis or χ^2 test. Summary statistics are presented as mean with SD or median with IQR for continuous variables, and frequency and percent for categorical variables. To investigate the association of trajectories on mortality, we constructed a multivariable Cox proportional hazard model with hazard ratio (HR) and 95% CI adjusted for variables known or thought to be associated

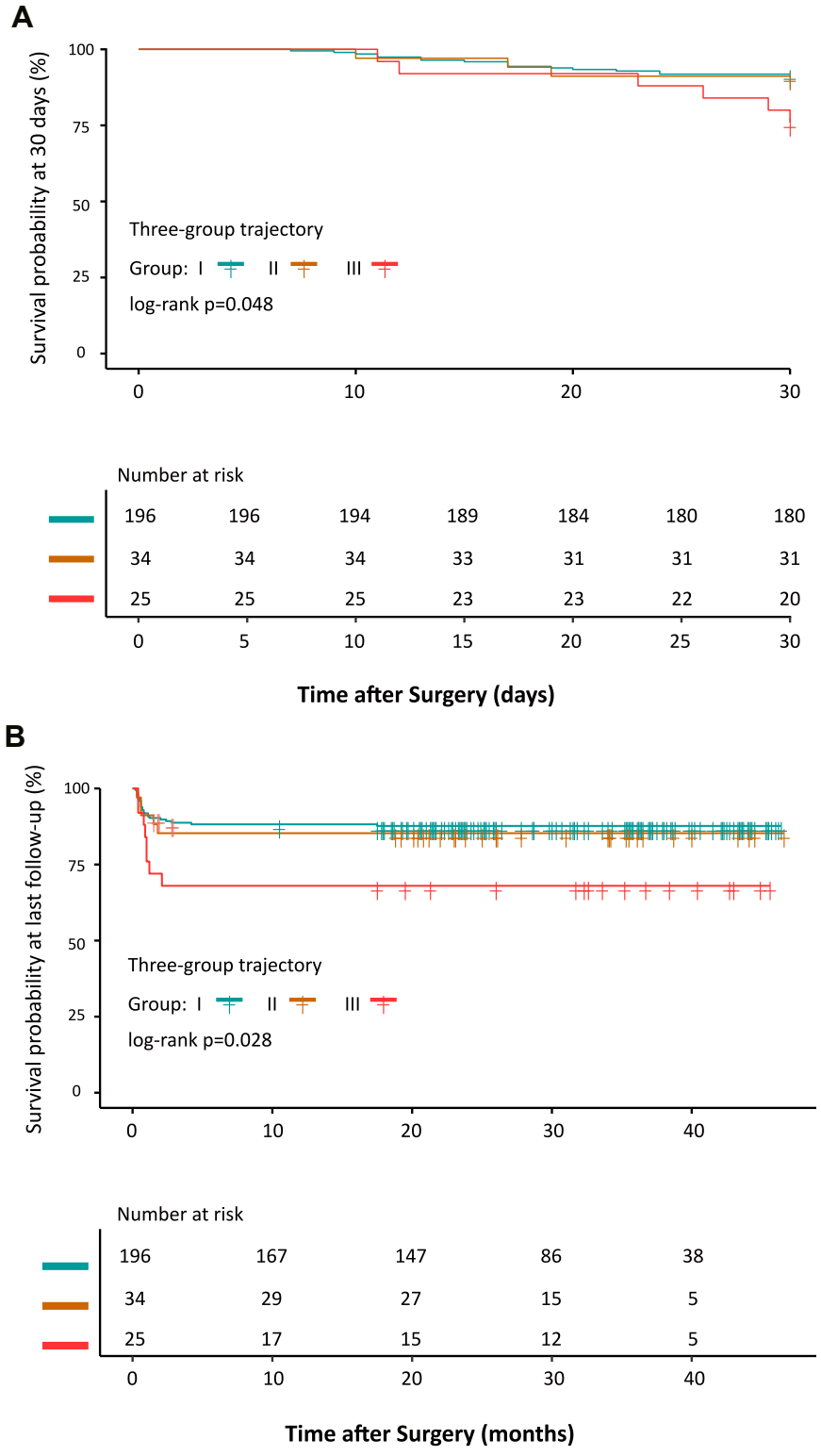


Figure 2.
Kaplan-Meier curve among different leukocyte trajectory groups. (**A**) Kaplan-Meier curve at 30 days after surgery. (**B**) Kaplan-Meier curve at the last follow-up.

with mortality: age, sex, body mass index, time from onset to surgery, smoking, alcohol drinking, hypertension, diabetes mellitus, chronic lung disease, coronary heart disease, stroke, malperfusion syndrome, hemoglobin, platelet, creatinine, aspartate aminotransferase, alanine aminotransferase, albumin, D-dimer, aortic root procedure, cardiopulmonary bypass time, circulatory arrest time, concomitant surgery, and packed red cell transfusion. We performed tests for linear trends by regarding each trajectory group as a continuous scale in the models.[21] We did an exploratory analysis to investigate the potential effect of postoperative ulinastatin use across subgroups using the

Table 3. Mortality at 30 days and at last follow-up of leukocyte trajectory group by ulinastatin use.

	No ulinastatin	Ulinastatin use	Risk differences	*P* value
Group I				
Mortality at 30 days	11 (8.1%)	5 (8.2%)	0.002 (–0.301 to 0.304)	.991
Mortality at last follow-up	17 (12.6%)	7 (11.5%)	0.034 (–0.268 to 0.337)	.825
Group II				
Mortality at 30 days	3 (10.0%)	0 (0%)	0.471 (–0.578 to 1.521)	.508
Mortality at last follow-up	5 (16.7%)	0 (0%)	0.632 (–0.422 to 1.687)	.377
Group III				
Mortality at 30 days	6 (30.0%)	0 (0.0%)	0.926 (–0.087 to 1.939)	.160
Mortality at last follow-up	8 (40.0%)	0 (0.0%)	1.155 (0.124 to 2.186)	.086
Overall				
Mortality at 30 days	20 (10.8%)	5 (7.1%)	0.129 (–0.147 to 0.404)	.379
Mortality at last follow-up	30 (16.2%)	7 (10.0%)	0.185 (–0.091 to 0.460)	.208

Wald statistics for cross-product terms of trend variables and subgroup membership.[22] All statistical analyses were performed using STATA software version 13.0 (StataCorp). *P* values <.05 were considered statistically significant.

Results

Patients characteristics

A total of 255 patients were included finally, with 184 (72.2%) males, the median (IQR) age of 55 (45-62) years, the median (IQR) time from onset to emergency surgery of 10 (6-18) hours and 70 (27.5%) patients received ulinastatin. Of 255 patients, 4 (1.6%) cases underwent aortic valve replacement, 36 (14.2%) cases underwent the Bentall procedure, and 11 (4.3%) cases underwent the David procedure. The median (IQR) time of cardiopulmonary bypass, aortic clamp, and hypothermic circulatory arrest was 193 (174-232) minutes, 144 (121-185) minutes, and 18 (14-26) minutes, respectively. Baseline, clinical, and procedural characteristics are listed in Table 1. The median follow-up time was 25 (IQR, 19-37) months among AAD patients alive.

Three-group trajectory model

Analysis of latent class mixed model showed that the 3-group trajectory model provided the best fit, which well represented distinct leucocyte patterns for AAD patients (Figure 1), with the lowest Bayesian information criterion value and adequate clinical sensibility (Supplemental Tables S1 and S2; Supplemental Figures S1 and S2). The ratio between the predicted (probability of group membership) and the actual group membership for each group ranged from 0.47 to 1.0. All AvePP for each group were greater than 0.7, which ranged from 0.72 (group II) to 0.90 (group I). Thus, the model diagnostics support the correct group assignment for the 3-group model.

Of the patients, 196 (76.8%) were assigned to group I (decreasing trajectory), in which the leucocyte count was slightly higher than normal at the start and gradually decreased over time; 34 (13.3%) patients were in group II (stable trajectory), in which the leucocyte count was slightly higher than normal at the start and subsequently flat over time; 25 (9.8%) patients were in group III (rising trajectory), in which the leucocyte count was moderately high at the start and continued to rise over time. Patients in group III had oldest age (median, 57 [IQR, 47-66] years), lowest body surface area (1.86 [1.71-1.99] m^2), body mass index (24.22 [21.60-26.12] kg/m^2), hemoglobin level (122 [116-142] g/L), platelet count (166 [129-257] $\times$ 10^9/L) and estimated glomerular filtration rate (87.0 [57.2-99.3] mL/min/1.732 m^2), whereas they had highest percentage of aortic root replacement (9/25 [36.0%]) than did those in group II and III. There were no differences regarding clinical risk factors, or biochemical profiles among the 3 groups (Table 1).

The effect of trajectory group and outcomes

For the entire cohort, 30-day mortality was 25 (9.8%), including circulatory failure in 7, neurologic dysfunction in 2, ventricular arrhythmia in 3, infection in 3, respiratory failure in 4, renal failure in 2, hepatic failure in 1, and gastrointestinal hemorrhage in 3. Thirty-day mortality was 8.2% (16/196) in group I, 8.8% (3/34) in group II, to 24.0% (6/25) in group III (P for trend = 0.036). At the time of the last follow-up, unadjusted mortality was 14.5% (37/255), ranging from 12.2% (24/196) in group I, 14.7% (5/34) in group II, to 32.0% (8/25) in group III (P for trend = 0.018). Besides, the median (IQR) ICU length of stay, mechanical ventilation length of duration, and hospital length of stay was 9 (6-16) days, 2.8 (1.2-6.3) days, and 21 (16-31) days, respectively (Table 1).

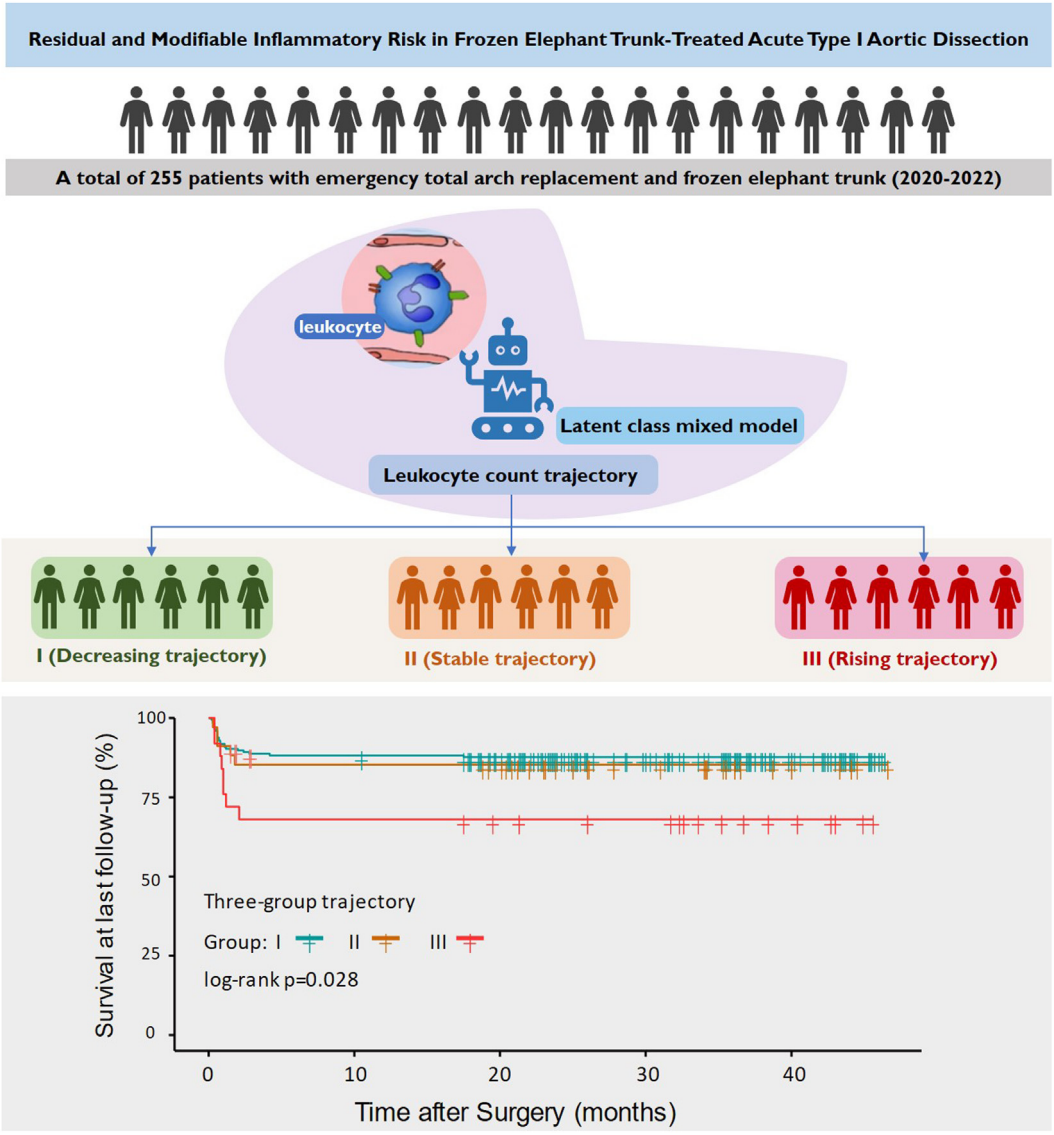
Group III was associated with a high risk of mortality at 30 days (crude HR, 3.028; 95% CI, 1.185-7.739; *P* = .021) and at the last follow-up (crude HR, 2.828; 95% CI, 1.270-6.29; *P* = .010) compared with group I. After adjusting for baseline, clinical, and procedural variables known to be associated with mortality, a multivariable Cox proportional hazard model showed that group III remained independently associated with an increased mortality at 30 days and at the last follow-up compared with group I (Table 2). Kaplan-Meier survival curves illustrate differences in mortality among the 3 trajectory groups (Figure 2).

Exploratory analysis

Overall, a trend existed for decreased mortality when ulinastatin was used (5/70 [7.1%] vs 20/185 [10.8%], *P* = .379 at 30 days; 7/70 [10.0%] vs 30/185 [16.3%], *P* = .208 at last follow-up) despite no statistical differences (Table 3). By analysis of trajectory group and treatment effect, a trend also existed for decreased mortality when ulinastatin was used in both group II (0/4 [0%] vs 3/30 [10.0%], *P* = .508 at 30 days; 0/4 [0%] vs 5/30 [16.7%], *P* = .377 at last follow-up) and group III (0/5 [0%] vs 6/20 [30.0%], *P* = .160 at 30 days; 0/5 [0%] vs 8/20 [40.0%], *P* = 0.086 at last follow-up) despite no statistical differences (Table 3). However, neither difference nor trend existed in group I patients when ulinastatin was used (5/61 [8.2%] vs 11/135 [8.1%], *P* = .991 at 30 days; 7/61 [11.5%] vs 17/135 [12.6%], *P* = .825 at the last follow-up). In addition, there was no significant interaction among the 3 groups in terms of mortality at 30 days (P for interaction = 0.207) and mortality at the time of last follow-up (P for interaction = 0.113). Alluvial plot showed the distribution of 3 trajectory groups across ulinastatin use and mortality at 30 days and at the last follow-up (Supplemental Figure S3).

Discussion

In this historical cohort study of patients with AAD, we used group-based trajectory analysis to segregate patients into 3 distinct and clinically relevant leukocyte trajectories: group I (decreasing trajectory), II (stable trajectory), and III (rising trajectory), with different initial values and unique evolutionary patterns over time (Central Illustration). Group



Central Illustration.
Rising leukocyte trajectory as a residual inflammatory risk factor was significantly associated with higher short-term and midterm mortality than decreasing trajectory following aortic dissection surgery.

III was independently associated with a significantly increased risk of mortality both at 30 days and at the last follow-up than group I. A decreased trend existed for mortality when ulinastatin was used in group II and III patients despite no significant statistical differences, suggesting the possibility of heterogeneity in anti-inflammatory pharmacotherapeutics of AAD.

Recognition is now solid that AAD is a highly heterogeneous inflammatory syndrome, and inflammation underlies both the pathogenesis and prognosis in patients with AAD. Recent evidence from the Chinese population showed that the elevated admission leukocyte count was significantly associated with in-hospital mortality as well as short-term clinical events, which has important clinical implications for risk-stratifying patients with AAD.[23] Another observation based on secondary analysis of data from the MIMIC-III database also showed that higher than normal leukocytes on admission may predict postdischarge mortality in patients with AAD.[24] However, a major limitation of the 2 studies was a lack of further exploration of the role of perioperative leukocyte trajectory over time in outcomes and treatment decisions. In other areas, a recent study evaluating the leukocyte trajectory of hospitalized patients with septic shock showed 7 subphenotypes of sepsis,[19] and demonstrated that a rising leukocyte trajectory was associated with higher mortality, which suggests there are subphenotypes of septic shock that are based on leukocyte trajectory, highlighting the heterogeneity of septic shock. Therefore, the trajectory of leukocytes over time may serve as a potential indicator for clinicians, signaling patients at higher risk of experiencing adverse outcomes. These data hold the potential for informing real-time decisions at an individual patient level. Conversely, unique leukocyte trajectories can provide a valuable understanding of the variations in traits or genetic composition that exemplify the biological diversity of the host in instances of AAD.

It is suggested that leukocyte count is a marker of inflammation and immune system health. There is evidence that leukocyte count is not fixed over time and there is heterogeneity in leukocyte trajectory that is associated with morbidity and mortality. Given LCMM is a method that can identify unobserved heterogeneity in longitudinal data and attempts to classify individuals into groups based on a linear model of repeated measurements.[25] By use of this method to repeat leukocyte count measures of patients with AAD from 2 cardiovascular centers, we revealed 3 leukocyte trajectory phenotypes and found a significant association between trajectory class membership and shorter and midterm mortality. In

addition, we advanced these phenotypes to anti-inflammatory pharmacotherapeutics (ulinastatin) and found that a trend existed for mortality when ulinastatin was used in patients with a significant residual inflammatory risk despite no significant statistical differences, which highlights the importance and necessity of identification and refining of trajectory information for data interpretation, facilitating interaction of trajectory phenotypes and precise therapies, and informing future priorities for individualized anti-inflammatory decisions of AAD patients in clinical practice.[26,27] Besides, it is suggested that preoperative anemia was associated with poor outcomes after cardiac surgery.[28] As a result, intraoperative packed red cell transfusion would contribute to the systemic inflammatory responses both by activation of inflammation and coagulation and by directly changing plasma concentrations of inflammatory mediators.[29] Therefore, databases that include high-quality clinical, laboratory, and therapeutic data, and possibly biomarkers and genetic information will be required to comprehensively understand which factors contribute to leukocyte trajectory group assignment.

Strength and limitation

A strength of this study was the use of LCMM, which allows exploration of variability according to unique phenotypic groupings instead of population summary estimates. To allow the data to show different trajectories, we did not prespecify groups but allowed the data to guide the results through an algorithmic classification procedure. To minimize selection bias, we included all consecutive patients with AAD who underwent emergency total arch replacement and FET implantation. We chose to analyze the total leukocyte count for familiarity among treating clinicians and generalizability to knowledge users. There are inevitable limitations to our study. First, our analysis was limited by the small numbers of patients in some of the leukocyte trajectory groups, so we could not draw firm conclusions from certain groups with low absolute numbers, which may result in insufficient power to detect differences between groups. Second, because of the historical nature of this study, the influence of unmeasured confounders cannot be excluded. Finally, it is unknown if a single variable trajectory is the best model to take forward to understand the biological differences among the groups; perhaps a multiple trajectory model including both platelet and leukocyte count plus other physiologic and laboratory variables such as temperature, creatinine, and/or bilirubin, or genomic information would give more instructive and predictive trajectories.

Conclusions

In patients with AAD, distinct and clinically relevant groups can be identified by analyzing leukocyte trajectories. Rising leukocyte trajectories are associated with increased mortality. A trend existed for mortality when ulinastatin was used in patients with a residual inflammatory risk despite no significant statistical differences. Further studies are required to understand the clinical characteristics and prognosis associated with distinct leukocyte trajectories and whether there is any specific population that clearly benefits from anti-inflammatory pharmacotherapy for this residual but modifiable risk factor.

Declaration of competing interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethics statement and patient consent

This study was approved by the institutional review board of the First Affiliated Hospital of Nanjing Medical University (no. 2021-SR-381) and the institutional review board of the Beijing Anzhen Hospital of Capital Medical University (KS2022034). The requirement for informed consent was waived due to the retrospective nature of the study design. This study was conducted in accordance with the Declaration of Helsinki and registered in ClinicalTrials.gov: NCT04398992.

Supplementary material

To access the supplementary material accompanying this article, visit the online version of the Journal of the Society for Cardiovascular Angiography & Interventions at 10.1016/j.jscai.2024.101935.

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