Long-Term Imaging Evolution and Clinical Prognosis Among Patients With Acute Penetrating Aortic Ulcers: A Retrospective Observational Study

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BACKGROUND: Acute penetrating aortic ulcers (PAUs) are reported to dynamically evolve into different clinical outcomes ranging from regression to aortic rupture, but no practice guidelines are available in China.

METHODS AND RESULTS: All 109 patients with acute PAUs were monitored clinically. At 30 days follow-up, 31 patients (28.44%) suffered from aortic-related adverse events, a composite of aortic-related mortality, aortic dissection, or an enlarged ulcer. In addition, 7 (6.42%) patients had clinically related adverse events, including all-cause mortality, cerebral stroke, nonfatal myocardial infarction, acute heart failure alone or acute exacerbation of chronic heart failure, acute renal failure, arrhythmia, and bleeding events. In the present study, the intervention criteria for the Chinese PAU population included a PAU diameter of 12.5 mm and depth of 9.5 mm. The multivariate analysis showed that an ulcer diameter >12.5 mm (hazard ratio [HR], 3.846; 95% CI, 1.561–9.476; \( P = 0.003 \)) and an ulcer depth >9.5 mm (HR, 3.359; 95% CI, 1.505–7.494; \( P = 0.003 \)) were each independent predictors of aortic-related events.

CONCLUSIONS: Patients with acute PAUs were at high risk for aortic-related adverse events and clinically related adverse events within 30 days after onset. Patients with an ulcer diameter >12.5 mm or an ulcer depth >9.5 mm have a higher risk for disease progression, and early intervention may be recommended.

Key Words: acute aortic syndrome ■ aortic-related adverse events ■ endovascular repair ■ penetrating aortic ulcer
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reported for Chinese patients with PAUs is small. Thus, the present study aims to examine the imaging characteristics and clinical prognoses of PAUs and to explore the predictors of aortic-related adverse events in cases of acute PAUs.

End Points and Definitions
The primary end point was 30-day aortic-related adverse events, a composite of aortic-related mortality (death because of aortic rupture and other unexplained sudden death), AD, or an enlarged ulcer (ulcer diameter or ulcer depth). Progression of the observed pathologies was classified as follows: (1) “resolution” referred to a decrease in the size of the ulceration diameter or depth; (2) “worsening” was defined as a deterioration in the aortic conditions, including a significant increase in the diameter or depth of the lesion (according to the computed tomographic angiography, the diameter or depth of the ulcer increased more than 1 mm); (3) “stable” was defined as lesions that did not improved or worsened significantly; (4) rupture was defined as the presence of extraaortic blood confirmed by radiology (after the contrast medium is injected into the vascular cavity, the paraaortic hematoma was formation), surgical examination, or postmortem examination or the finding of an impending rupture during surgery10; and (5) progression to AD was considered when an intimal flap appeared.11

Major secondary end points were clinically related adverse events, including all-cause mortality; cerebral stroke; nonfatal myocardial infarction; acute heart failure alone or acute exacerbation of chronic heart failure; acute renal failure; arrhythmia; or any bleeding as defined by the Bleeding Academic Research Consortium definition (grades 1–5).12 Bleeding was considered medically actionable for Bleeding Academic Research Consortium types 2 through 5 and major for Bleeding Academic Research Consortium types 3 through 5.

Based on symptom onset, acute PAU was <15 days, and chronic PAU was >15 days.7

Imaging Techniques
All patients in the acute phase underwent computed tomography examinations.13 The location, diameter, and depth of the ulcer and maximum hematoma thickening were assessed by computed tomography as reported previously. Computed tomography was performed using a 64-detector Siemens Sensation and intravenous boluses with 80 to 150 mL of nonionic
contrast medium. Imaging data were the average value obtained by radiology technicians through three measurements. The average value of the other hospitals’ imaging data was obtained by the same individual through three measurements.

Follow-Up
After discharge, all cases were followed up promptly at 1, 6, and 12 months and annually thereafter. The final follow-up date was October 2018. During the follow-up period, patients who experienced recurrent, refractory pain or rupture or whose condition progressed to classical AD were immediately referred for EVAR. For asymptomatic small (diameter <20 mm or depth <10 mm) PAUs, conservative, expectant management was recommended, including strict blood pressure monitoring and vigilant follow-up with imaging techniques annually. If complications or ulcer progression occurred, EVAR treatment or surgical treatment was recommended.

Statistical Analysis
Continuous variables were reported as the mean±SD or median and interquartile range (25th percentile, 75th percentile), and categorical variables were expressed as percentages. A chi-square test or Fisher exact test was used to compare proportions, and an unpaired Student t test, 1-way ANOVA, or Mann–Whitney U test was used to compare means or medians. Survival curves were generated via the Kaplan–Meier method with significant differences assessed for time-to-event data using log-rank tests. The Pearson correlation coefficient was used for bivariate normally distributed data. Multivariable Cox regression models were constructed to identify factors associated with the primary end point. To evaluate whether the diameter or depth of the ulcer could be an effective predictor of the primary end point, a receiver operating characteristic curve analysis was performed. The optimal cutoff level was calculated by the Youden index (sensitivity+specificity−1). A P<0.05 was considered significant. The analyses were performed using SPSS version 22.0 (SPSS, Chicago, IL) (Figure S1).

RESULTS
Study Patients
All 109 patients were diagnosed with acute PAUs by imaging examination. Among the 109 patients, 9 died and 100 survived. Data on patient demographics, risk factors, and outcomes were collected from the 109 patients with acute PAUs (Figure 1). Mean follow-up was 27.11±22.61 months, and median follow-up was 23.13 (11.1, 37.33) months.

Baseline Characteristics and Adverse Events of the Entire Cohort
The baseline characteristics of the entire cohort (109 cases) are shown in Table 1. The average age was 65.21±10.09 years. Of the patients, 87 were men. The incidence of systemic hypertension was 80.73%. More than half of the patients were smokers (71.56%). A total of 33.03% and 9.17% of the patients had hyperlipidemia and diabetes mellitus,
respectively. The baseline imaging data are provided in Table 1. A total of 72 descending thoracic aortas were observed (66.06%). The diameter and depth of the ulcers were 11.31±5.44 and 8.19±4.50 mm, respectively. The maximum ascending and descending aortic diameters were 43.08±4.84 and 30.37±5.62 mm, respectively. We found 33 cases with pleural effusion and 1 case with pericardial effusion. The medication and laboratory examination data are provided in Table 1.

The baseline differences characteristics between with and without aortic-related adverse events are shown in Table S1. Patients without an aortic-related adverse event had PAUs with a smaller diameter (13.27±5.18 mm versus 10.42±5.35 mm; \( P = 0.010 \)) and depth (9.91±5.13 mm versus 7.42±3.99 mm; \( P = 0.007 \)) than those with an aortic-related adverse event. There were no significant differences in sex ratio, systolic and diastolic blood pressure, or laboratory examinations between the 2 groups \( (P>0.05) \) (Table S1).

### Associations Between the Morphological Findings

A total of 109 patients with acute PAUs were reexamined by computed tomographic angiography within 30 days after onset. Among them, 7 (6.42%) patients progressed to typical AD, 23 (21.10%) patients worsened, and 79 (72.48%) patients were stable.

Table 2 shows the associations between the morphological findings and evolution of the PAUs. Patients with stable PAUs had PAUs with a smaller diameter (10.05±5.05 mm versus 14.23±4.71 mm; \( P<0.05 \)) and depth (7.20±3.78 mm versus 10.60±4.94 mm; \( P<0.05 \)) than those with PAUs that had worsened. There were no significant differences in maximum ascending aortic diameter between 3 groups and maximum descending aortic diameters between 2 groups \( (P>0.05) \).

### The End Point Analysis During Follow-Up

At 30 days of follow-up, a total of 31 cases (28.44%) suffered from aortic-related adverse events: 3 patients died from aortic-related causes, 7 patients progressed to AD, and 21 patients experienced ulcer worsening. Until the actual longest follow-up period, 34 patients (31.19%) experienced aortic-related adverse events, 5 patients died from aortic-related causes, 8 patients progressed to AD, and 21 patients experienced ulcer worsening (Table 3).

At 30 days of follow-up, 7 cases suffered from clinically related adverse events: 4 patients died and were classified as all-cause mortality, 1 patient suffered from arrhythmia, and 2 patients suffered from cerebral stroke. Until the actual longest follow-up period, 13 cases suffered from clinically related adverse events, 9

| Characteristic | Demographic and clinical data |
|---------------|-----------------------------|
| Age, y        | 65.21±10.09                 |
| Men           | 87 (79.82)                  |
| BMI, kg/m²    | 24.96±3.31                  |
| Systemic hypertension | 88 (80.73) |
| Smoking       | 78 (71.56)                  |
| Hyperlipidemia| 36 (33.03)                  |
| Diabetes mellitus | 10 (9.17)  |
| Coronary heart disease | 37 (33.94) |
| Imaging       |                            |
| Mean number of penetrating atherosclerotic ulcers | 1.15±0.40 |
| Aortic arch   | 33 (30.28)                  |
| Descending thoracic aorta | 72 (66.06)  |
| Abdominal aorta | 4 (3.67)     |
| Mean ulcer diameter, mm | 11.31±5.44 |
| Mean ulcer depth, mm | 8.19±4.50 |
| Maximum ascending aorta diameter, mm | 43.08±4.84 |
| Maximum descending aorta diameter, mm | 30.37±5.62 |
| Pleural effusion | 33 (30.28)  |
| Pericardial effusion | 1 (0.92)    |
| Medical       |                            |
| Antiplatlet agents | 5 (4.59)     |
| Beta-blockers  | 8 (7.34)                    |
| Calcium antagonists | 35 (32.11) |
| ACE inhibitors | 5 (4.59)                    |
| ARB inhibitors | 16 (14.68)                  |
| Nitrates      | 4 (3.67)                    |
| Statins       | 5 (4.59)                    |
| Systolic BP, mm Hg | 150.07±24.18 |
| Diastolic BP, mm Hg | 85.74±13.24 |
| Heart rate, BPM | 79.01±10.46                |
| Laboratory examinations |
| CKMB, ng/mL   | 11.00 (8.50, 15.50)         |
| TNT exception | 33 (30.28)                  |
| ALT, U/L      | 16.20 (12.00, 23.30)        |
| AST, U/L      | 18.00 (14.54, 24.01)        |
| WBC, 10⁹/L    | 9.97±2.72                   |
| PLT, 10⁹/L    | 206.00 (178.50, 253.00)     |
| HG, g/L       | 133.09±17.43                |
| BUN, mmol/L   | 6.36 (4.97, 9.34)           |
| CR, µmol/L    | 81.10 (68.60, 103.00)       |
| C-reactive protein, mg/dL | 49.30 (19.50, 62.90)     |
| D-dimer, ng/mL| 1.60 (0.80, 2.85)           |

Data are expressed as mean±SD, medians (25th percentiles, 75th percentiles), or number (percentage). ACE indicates angiotensin-converting enzyme; ALT, alanine aminotransferase; ARB, angiotensin receptor blocker; AST, aspartate aminotransferase; BMI, body mass index; BP, blood pressure; BPM, beat per minute; BUN, blood urea nitrogen; CKMB, creatine phosphokinase-myocardial band; CR, creatinine; HG, hemoglobin; PLT, platelet count; TNT, troponin-T; and WBC, white blood cell.
patients died and were classified as all-cause mortality, 1 patient suffered from arrhythmia, and 2 patients suffered from cerebral stroke (Table 3 and Figure 2).

### Table 2. Relationship Between Penetrating Aortic Ulcer Baseline Morphological Findings and Final Morphological Outcomes

| Morphologic Finding                      | Stable or Regression (n=79) | Worsened (n=23) | Aortic Dissection (n=7) | P Value |
|------------------------------------------|----------------------------|----------------|------------------------|----------|
| Mean ulcer diameter, mm                 | 10.05±5.05                 | 14.23±4.71     | ...                    | 0.001    |
| Mean ulcer depth, mm                    | 7.20±3.78                  | 10.60±5.45     | ...                    | 0.001    |
| Maximum ascending aorta diameter, mm    | 43.32±4.92                 | 42.57±4.94     | 41.97±3.75             | 0.624    |
| Maximum descending aorta diameter, mm   | 30.49±5.09                 | 31.66±6.54     | ...                    | 0.367    |

Data are expressed as mean±SD.

### Table 3. End Points During Follow-Up (n=109)

| Events                              | N   |
|-------------------------------------|-----|
| After 30 days of follow-up          |     |
| Primary end point                   | 31  |
| Aortic-related deaths               | 3   |
| Worsening                           | 21  |
| AD                                  | 7   |
| Secondary end point                 | 7   |
| All-cause mortality                 | 4   |
| Aortic-related deaths               | 3   |
| Non-aortic-related deaths           | 1   |
| Cerebral stroke                     | 2   |
| Hemorrhagic stroke                  | 1   |
| Ischemic stroke                     | 1   |
| Arrhythmia                          | 1   |
| All bleeding                        | 2   |
| BARC 2–5                            | 2   |
| BARC 3–5                            | 2   |

| Long-term follow-up                 |     |
| Total adverse clinical events       | 13  |
| All-cause mortality                 | 9   |
| Aortic-related deaths               | 5   |
| Worsening                           | 21  |
| AD                                  | 8   |
| Cerebral stroke                     | 2   |
| Hemorrhagic stroke                  | 1   |
| Ischemic stroke                     | 1   |
| Arrhythmia                          | 1   |
| All bleeding                        | 5   |
| BARC 2–5                            | 4   |
| BARC 3–5                            | 4   |

Table 2 indicates aortic dissection; and BARC, Bleeding Academic Research Consortium. BARC, bleeding is graded on a scale of 1 to 5, ranging from minor bleeding that is not actionable (type 1) to fatal bleeding (type 5).

#### Predictive Value of the PAU Diameter and Depth for the Prognosis of Chinese Patients

The receiver operating characteristic curve analysis demonstrated that the diameter and depth of the PAU could distinguish patients who met the primary end points from those who did not meet the primary end points, including aortic-related death, AD, and ulcer progression (Figure 3). The optimal cutoff values for the PAU diameter and depth in Chinese patients were 12.5 and 9.5 mm, with areas under the curve of 0.636 and 0.646, respectively. The Kaplan–Meier survival curve analysis showed that patients with an ulcer diameter ≤12.5 mm had a significantly lower aortic-related risk than those with an ulcer diameter >12.5 mm (42.50% [17/40] versus 20.29% [14/69]; P=0.025) (Figure 4). Moreover, patients with an ulcer depth ≤9.5 mm had a significantly lower aortic-related risk than those with an ulcer diameter >9.5 mm (41.86% [18/43] versus 19.70% [13/66]; P=0.016) (Figure 4). Thus, an ulcer diameter >12.5 mm and an ulcer depth >9.5 mm may be risk factors for aortic-related adverse events (primary end points) of acute PAU.

#### Multivariate Predictor Analysis

Linear regression analysis showed that there was a positive correlation between ulcer diameter and ulcer depth (R² linear, 0.467; P<0.001). Bivariate correlation analysis also confirmed that there was a significant positive correlation between ulcer diameter and ulcer depth (Pearson correlation coefficient, 0.683; P<0.001). Because of the significant positive correlation between ulcer diameter and ulcer depth, an ulcer diameter >12.5 mm and ulcer depth >9.5 mm were separately included in multivariate regression analysis. The influencing factors included sex, hypertension, diabetes mellitus, coronary heart disease, and dyslipidemia. The multivariate analysis showed that an ulcer diameter >12.5 mm (hazard ratio [HR], 3.846; 95% CI, 1.561–9.476; P=0.003) and ulcer depth >9.5 mm (HR, 3.359; 95% CI, 1.505–7.494; P=0.003) were independent predictors of aortic-related adverse events (primary end points) (Tables 4 and 5).
Morphological Evolution of Acute PAUs
Typical morphological multidetector computed tomography imaging data obtained during the acute phase of PAU evolution to a dissection are shown in Figure 5. Typical imaging data showing acute PAU stability and enlargement are also shown in Figure 5.

DISCUSSION
To our knowledge, the present study is the largest retrospective analysis to observe acute PAUs in the Chinese population. In addition, we evaluated the clinical features, evolution in imaging, clinical outcomes, and multivariate predictors of acute PAUs. There were several main findings. First, within 30 days after onset, the incidences of aortic-related adverse events and clinically related adverse events in acute PAUs were 28.44% and 6.42%, respectively. Clinically related adverse events mainly occurred 30 days after onset, accounting for 53.85% of the total number of clinically related adverse events, which suggested that close medical surveillance during the first month might contribute a good prognosis. Second, the receiver operating characteristic curves for predicting the primary end points were plotted, and the first cutoff values for the Chinese patients were 12.5 mm for ulcer diameter and 9.5 mm for ulcer depth. Third, an ulcer diameter >12.5 mm and ulcer depth >9.5 mm were independent risk factors for aortic-related adverse events (primary end points), which increased the incidence of events by 3.8 times and 3.3 times, respectively. Fourth, the Kaplan–Meier survival curve analysis showed that patients with an ulcer diameter ≤12.5 mm had a significantly lower aortic-related risk than those with an ulcer diameter >12.5 mm (P=0.025); patients with an ulcer depth ≤9.5 mm had a significantly lower aortic-related risk than those with an ulcer depth >9.5 mm (P=0.016). Finally, we
analyzed the first evidence of PAU morphological evolution in the Chinese population, including stability, progression, and classical AD. The findings of and evidence from this study may be conducive to providing a reference for the treatment of PAUs in the Chinese population. Moreover, these findings may have a large influence on intervention standards and the primary prevention of PAUs in Chinese patients.

In the present study, within 30 days, the incidences of aortic-related adverse events in and aortic-related deaths of patients with acute PAUs were 28.44% and 6.42%, respectively. In addition, the incidence of long-term aortic-related adverse events was 31.19%. Botta et al\textsuperscript{16} reported that the 30-day mortality rate of 18 patients with PAUs was 11.1%. An average-3-year follow-up study\textsuperscript{17} reported the incidence of aortic-related adverse events (including PAU enlargement and progression to AD) to be 30.00% for 20 patients who received imaging follow-up. Furthermore, Tittle et al\textsuperscript{11} reported that the incidence of aortic-related adverse events (including PAU enlargement and progression to AD) was 77.33% for 15 patients who received imaging follow-up. The incidence of aortic-related adverse events was similar to that in the study by Botta et al, but significantly lower than that in the study by Tittle et al. In our center, all patients were under medical guidance after diagnosis, which may contribute to reducing the incidence of aortic-related adverse events. To our knowledge, there were no computed tomography images of acute PAU evolution. The present study showed 3 types of clinical progression of PAU, which enriched the imaging data for PAU treatment.

The present study provides the first intervention criteria in a Chinese population, namely, a cutoff value of 12.5 mm for the ulcer diameter or 9.5 mm for the ulcer depth. In the 2014 European Society of Cardiology AD guidelines,\textsuperscript{7} early intervention treatment may be recommended for patients with asymptomatic PAUs with diameters >20 mm or depths >10 mm. The differences between the present study and the Western guidelines suggest that race, bodily form, and habits may influence treatment strategies for PAUs.\textsuperscript{18} Notably, the ulcer diameter is significantly smaller in this study than that in the European guidelines, but the ulcer depth is slightly smaller in this study than that in the European guidelines. The authors made a bold guess that the tolerance of Chinese people in terms of the ulcer depth was similar to that of European people but that the tolerance of Chinese people in terms of the ulcer diameter was poor. Thus, further verification is needed with a study

### Table 4. Multivariate Predictor Analysis of Adverse Aortic-Related Events in Patients With Penetrating Aortic Ulcer

|                        | HR  | 95% CI      | P Value |
|------------------------|-----|-------------|---------|
| Ulcer diameter >12.5 mm| 3.846 | 1.561–9.476 | 0.003   |
| Male                   | 0.779 | 0.303–2.003 | 0.604   |
| Hypertension           | 1.087 | 0.429–2.749 | 0.861   |
| Diabetes mellitus      | 1.226 | 0.402–3.740 | 0.720   |
| Coronary heart disease | 0.580 | 0.258–1.304 | 0.188   |
| Dyslipidemia           | 0.409 | 0.160–1.042 | 0.061   |

HR indicates hazard ratio.

### Table 5. Multivariate Predictor Analysis of Adverse Aortic-Related Events in Patients With Penetrating Aortic Ulcer

|                        | HR  | 95% CI      | P Value |
|------------------------|-----|-------------|---------|
| Ulcer depth >9.5 mm    | 3.359 | 1.505–7.494 | 0.003   |
| Male                   | 0.941 | 0.372–2.379 | 0.898   |
| Hypertension           | 0.945 | 0.378–2.362 | 0.904   |
| Diabetes mellitus      | 1.866 | 0.612–5.693 | 0.273   |
| Coronary heart disease | 0.525 | 0.231–1.196 | 0.125   |
| Dyslipidemia           | 0.535 | 0.230–1.242 | 0.146   |

HR indicates hazard ratio.
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with a larger sample size. Moreover, an ulcer diameter >12.5 mm and an ulcer depth >9.5 mm were independent risk factors for aortic-related adverse events within 30 days. Nevertheless, in the study by Janosi et al.,9 a PAU depth >15 mm was an independent predictor of mortality. Moreover, in the Chinese population, an ulcer diameter >12.5 mm predicted a poor prognosis. The reasons may be as follows: (1) the present study enrolled patients acute PAUs; (2) the included patients in the present study were mainly from the Chinese population, in contrast to the study by Janosi et al; and (3) there were differences in the primary end points between the 2 studies, namely, the present study included aortic-related deaths and PAU deterioration. Combining the findings of the aforementioned 2 studies may produce significant influences on the prognostic evaluations of patients with PAUs. The intervention criteria of the present study may greatly contribute to improving treatment strategies for PAUs in the Chinese population.

In 1986, PAU was first characterized by Stanson et al.19 A PAU is formed by atheromatous plaque disruption in the internal elastic lamina. Previous studies have shown that hypertension, hyperlipidemia, and severe atherosclerosis are risk factors for PAUs.7,20–22 In a study by Cho et al.,23 92.38% and 45.71% of the patients had hypertension and coronary artery disease, respectively. Botta et al.16 reported that the incidence of hypertension was 84.2%. In a study by Chou et al.,17 the incidences of hypertension, dyslipidemia, and coronary artery diseases were 86.11%, 55.56%, and 33.33%, respectively. Consistently, the results from the present study showed that the incidences of systemic hypertension, dyslipidemia, and coronary artery diseases were 80.73%, 33.03%, and 33.94%, respectively. Based on this analysis, for patients with acute PAUs with hypertension and coronary heart disease, we suggest that monitoring blood pressure and the levels of blood lipids and providing accurate medication guidance and health education may reduce the incidence of aortic-related adverse events.

In the present study, early intervention treatment may be recommended for patients with acute PAUs with diameters >12.5 mm or depths >9.5 mm. Conversely, for patients with acute PAUs, controlling blood pressure and blood lipid levels while undergoing regular imaging reexaminations in accordance with the follow-up time is suggested. To date, the treatment

Figure 5. Typical morphological multidetector computed tomography imaging data.

A, C, and E. During the acute phase, a computed tomographic angiography scan demonstrates the presence of a penetrating aortic ulcer and a periaortic hematoma. B. The ulcer is enlarged. D. Computed tomographic angiography scan shows that the ulcer is stable and that the periaortic hematoma has almost completely disappeared. F. Computed tomographic angiography scan reveals a typical dissection.
strategy for PAUs are ambiguous in the European and American guidelines, which do not have a criterion for interventional therapy. In the 2014 ESC guidelines, medical treatment is recommended for all type B PAUs (Ⅰ C), and repetitive imaging is indicated for uncomplicated type B PAU (Ⅰ C). EVAR (Ⅱ a C) or surgery (Ⅱ b C) may be considered for complicated type B PAUs. In the 2010 ACCF guidelines, EVAR is recommended for symptomatic PAU (Ⅱ b C). Thus, the findings of and evidence from the present study may provide a reference for the diagnosis, treatment and long-term prognosis of acute PAU in the Chinese population.

**Limitations**

The present study was a retrospective observational study with inherent shortcomings. Because most of the patients with acute PAUs were asymptomatic during long-term follow-up, patient compliance was poor, which may have led to an underestimation of the incidence of aortic-related adverse events in acute PAUs. Most of the patients in the present study had thoracic PAUs, so we have not studied whether the location of ulcer affects the prognosis. In a future study, we will expand the sample size to specifically explore the effect of ulcer location on prognosis. The cutoff value in the present study needs to be validated in large samples. Therefore, a large-scale, randomized control trial is required.

**CONCLUSIONS**

In the context of acute PAU, patients with aortic-related adverse events and clinically related adverse events are at high risk within 30 days after onset. Patients with an ulcer diameter >12.5 mm or an ulcer depth >9.5 mm have a higher risk for disease progression, and early intervention may be recommended.

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**Supplementary Materials**

Table S1

Figure S1

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Table 1. The baseline differences characteristics between with and without aortic-related adverse event in the study population (n=109).

| Characteristic                        | With aortic-related adverse event (n=34) | Without aortic-related adverse event (n=75) | P value |
|---------------------------------------|-----------------------------------------|--------------------------------------------|---------|
| Demographic and clinical data         |                                         |                                            |         |
| Age, y                                | 63.50±9.64                              | 65.99±10.25                                | 0.235   |
| Men, n (%)                            | 28 (82.35)                              | 59 (78.67)                                 | 0.657   |
| BMI                                   | 25.03±3.66                              | 24.93±3.16                                 | 0.883   |
| Systemic hypertension, n (%)          | 28 (82.35)                              | 60 (80.00)                                 | 0.773   |
| Smoking, n (%)                        | 28 (82.35)                              | 50 (67.57)                                 | 0.111   |
| Hyperlipidemia, n (%)                 | 13 (38.24)                              | 23 (30.67)                                 | 0.436   |
| Diabetes, n (%)                       | 5 (14.71)                               | 5 (6.67)                                   | 0.280   |
| Coronary heart disease, n (%)         | 10 (29.41)                               | 27 (36.00)                                 | 0.501   |
| Imaging                               |                                         |                                            |         |
| Mean number of penetrating atherosclerotic ulcers | 1.06±0.34                               | 1.19±0.43                                  | 0.099   |
| Aortic arch, n (%)                    | 8 (23.53)                               | 25 (33.33)                                 | 0.302   |
| Descending thoracic aorta, n (%)      | 25 (73.53)                               | 47 (62.67)                                 | 0.267   |
| Abdominal aorta, n (%)                | 1 (2.94)                                | 3 (4.00)                                   | 1.000   |
| Mean ulcer diameter, mm               | 13.27±5.18                              | 10.42±5.35                                 | 0.010   |
| Mean ulcer depth, mm                  | 9.91±5.13                               | 7.42±3.99                                  | 0.007   |
| Maximum ascending aorta               | 42.42±4.71                              | 43.37±4.90                                 | 0.345   |
**diameter, mm**

| Maximum descending aorta | Mean | SD | p-value |
|--------------------------|------|----|---------|
| 3.05±7.09                | 3.09±4.87 | 0.859 |

**Pleural effusion, n (%)**

|        | Mean | SD | p-value |
|--------|------|----|---------|
| 11 (32.35) | 22 (29.33) | 0.751 |

**Pericardial effusion, n (%)**

|        | Mean | SD | p-value |
|--------|------|----|---------|
| 0 (0.00) | 1 (1.33) | 1.000 |

**Medical**

|                        | Mean | SD | p-value |
|------------------------|------|----|---------|
| Antiplatelet agents, n (%) | 2 (5.88) | 3 (4.00) | 0.646 |
| Beta-blockers, n (%)    | 3 (8.82) | 5 (6.67) | 0.703 |
| Calcium antagonists, n (%) | 10 (29.41) | 25 (33.33) | 0.685 |
| ACE inhibitors, n (%)   | 0 (0.00) | 5 (6.67) | 0.322 |
| ARB inhibitors, n (%)   | 5 (14.71) | 11 (14.67) | 1.000 |
| Nitrates, n (%)         | 1 (2.94) | 3 (4.00) | 1.000 |
| Statins, n (%)          | 1 (2.94) | 4 (5.33) | 1.000 |

**Systolic BP, mmHg**

|        | Mean | SD | p-value |
|--------|------|----|---------|
| 151.03±30.55 | 149.64±20.90 | 0.783 |

**Diastolic BP, mmHg**

|        | Mean | SD | p-value |
|--------|------|----|---------|
| 86.38±14.61 | 85.45±12.66 | 0.736 |

**Heart rate, BPM**

|        | Mean | SD | p-value |
|--------|------|----|---------|
| 77.29±9.57 | 79.79±10.81 | 0.251 |

**Laboratory examinations**

|                      | Mean | SD     | p-value |
|----------------------|------|--------|---------|
| CKMB, ng/ml          | 11.00 (8.75, 14.00) | 12.00 (8.00, 16.00) | 0.593 |
| TNT exception, n (%) | 9 (26.47) | 24 (32.00) | 0.560 |
| ALT, U/L             | 18.40 (12.93, 27.18) | 15.63 (11.60, 22.00) | 0.100 |
| AST, U/L             | 19.58 (15.86, 24.01) | 17.84 (14.31, 24.39) | 0.482 |
| WBC, 10^9/L          | 10.67±3.43 | 9.66±2.29 | 0.121 |
| Test                        | Mean ± SD    | Median (25th percentile, 75th percentile) | p-value |
|-----------------------------|--------------|-----------------------------------------|---------|
| PLT, 10^9/L                | 237.68±135.32 | 219.31±73.24                           | 0.461   |
| HG, g/L                    | 134.35±15.18 | 132.52±18.42                           | 0.613   |
| BUN, mmol/L                | 6.54 (4.99, 9.59) | 6.33 (4.96, 9.05)                      | 0.537   |
| CR, μmol/L                 | 78.80 (70.25, 101.30) | 84.44 (68.20, 103.00)                | 0.736   |
| C-reactive protein, mg/dL  | 54.02 (26.83, 88.33) | 44.60 (15.90, 55.87)                | 0.067   |
| D-dimer, ng/ml             | 1.33 (0.68, 3.18) | 1.61 (0.80, 2.74)                     | 0.971   |

BMI, Body Mass Index; ACE, Angiotensin-converting Enzyme; ARB, Angiotensin Receptor Blocker; BP, Blood Pressure; CKMB, Creatine Phosphokinase-myocardial Band; TNT, Troponin-T; BNP, Brain Natriuretic Peptide; ALT, Alanine Aminotransferase; AST, Aspartate aminotransferase; WBC, White Blood Cell; PLT, Platelet Count; HG, Hemoglobin; CR, Creatinine. Data are expressed as mean±SD, medians (25th percentiles, 75th percentiles), or number (percentage).
Figure S1. Statistical analysis protocol.

1. Descriptive analysis: Baseline characteristics
2. An unpaired Student’s t-test or one-way ANOVA: the associations between the morphological findings and evolution of the PAUs
3. Descriptive analysis and log-rank tests: the endpoint analysis during follow-up
4. ROC curve analysis: to determine a cutoff value
5. The log-rank tests: to verify whether the cutoff value was valuable
6. Pearson correlation analysis: the correlation between ulcer diameter and ulcer depth
7. The multivariate COX regression models: to identify factors associated with the primary endpoint