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Onset seasons and clinical outcomes in patients with Stanford type A acute aortic dissection: an observational retrospective study

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ABSTRACT

Objectives: To evaluate the association of onset season with clinical outcome in type A acute aortic dissection (AAD).

Design: A single-centre, observational retrospective study.

Setting: The study was conducted in Fuwai Hospital, the National Centre for Cardiovascular Disease, Beijing, China.

Participants: From 2008 to 2010, a set of consecutive patients with type A AAD, confirmed by CT scanning, were enrolled and divided into four groups according to onset season: winter (December, January and February), spring (March, April and May), summer (June, July and August) and autumn (September, October and November). The primary end points were in-hospital death and all-cause mortality during follow-up.

Results: Of the 492 cases in this study, 129 occurred in winter (26.2%), 147 in spring (29.9%), 92 in summer (18.7%), and 124 in autumn (25.2%). After a median follow-up of 20.4 months (IQR 9.7–38.9), the in-hospital mortality in cases occurring in autumn was higher than in the other three seasons (23.4% vs 8.4%, p<0.01). Long-term mortality was comparable among the four seasonal groups (p=0.63). After adjustment for age, gender and other risk factors, onset in autumn was still an independent factor associated with increased risk of in-hospital mortality (HR 2.05; 95% CI 1.15 to 3.64, p=0.02) in addition to surgical treatment. Further analysis showed that the seasonal effect on in-hospital mortality (autumn vs other seasons: 57.4% vs 27.3%, p<0.01) was only significant in patients who did not receive surgical treatment. No seasonal effect on long-term clinical outcomes was found in this cohort.

Conclusions: Onset in autumn may be a factor that increases the risk of in-hospital death from type A AAD, especially in patients who receive conservative treatment. Immediate surgery improves the short-term and long-term outcomes regardless of onset season.

Strengths and limitations of this study

- This is the first study to suggest that patients with type A acute aortic dissection (AAD) with onset in the 'hot-to-cold' transitional season of autumn had the worst short-term outcome.
- This is a large-sample study performed in a single centre with nearly 500 patients with type A AAD with both short- and long-term clinical outcomes.
- The findings in this study might not necessarily be mirrored in other regions because of the different regional and seasonal characteristics and the single-centre setting.
- The potential influence of meteorological factors such as temperature, humidity and air pressure could not be assessed because the relevant data were not available in this study.

INTRODUCTION

Acute aortic dissection (AAD) remains the most common aortic catastrophe, with management and prognosis determined by the location of the affected aortic segment. Stanford type A AAD, which involves the ascending aorta, is most severe and should be treated with urgent surgical intervention.[1] Thus, identification of risk factors affecting prognosis is of great value for risk stratification. Previous studies have shown that cardiovascular conditions such as coronary heart disease,[2–6] stroke,[7 8] supraventricular tachycardia[9] and heart failure[10] are associated with seasonal variations. The incidences of these events show distinct seasonal patterns, with peak admissions during the winter. Also, seasonal frequency variations for aortic dissection (AD) have been recorded and show that the incidence peaks in winter and is lowest in summer.[11–17] However, a few studies have investigated the prognostic value of

onset season in patients with AAD, and they found that seasonal variation in the occurrence of AAD did not influence in-hospital outcomes.[16 18] Moreover, there is a lack of data on the association of onset season with long-term outcomes in patients with type A AAD. Therefore, we hypothesised that there would be a seasonal effect on in-hospital or long-term mortality in patients with type A AAD. This single-centre study enrolled consecutive patients at Fuwai Hospital to analyse the relationship between onset season and clinical outcome of type A AAD.

METHODS

Patients

From October 2008 to December 2010, consecutive patients with suspected type A AAD who were admitted to the emergency centre of Fuwai Hospital were enrolled. Although the population came from all over the country (figure 1), patients included in this study primarily came from Beijing and nearby areas. The diagnosis of type A AAD was confirmed by multidetector CT scanning. Patients were excluded if the exact date of onset of the illness was unknown or if they had a clear aetiology such as Marfan's syndrome, Loeys-Dietz syndrome, iatrogenic AD secondary to cardiac surgery, thoracic endovascular aortic repair, or a history of operation for AD. All patients with chronic dissections or previous operation were also excluded. In-hospital survival analysis was performed on all patients included in the study, but long-term survival analysis was only performed on discharged patients. This study was approved by the ethics committee of Fuwai Hospital, and written informed consent was obtained from each patient. The study protocol conformed with the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

Data collection

Baseline characteristics data were recorded, including sex, age, duration of pain, and medical history including hypertension, diabetes mellitus, coronary artery disease, smoking status and drinking status. Other recorded clinical characteristics included baseline vital signs at admission (systolic/diastolic blood pressure and heart rate), imaging examinations and hospital management (medical therapy or surgical intervention). The rationale and strategy of the surgical techniques were determined by experienced surgeons in the Department of Cardiovascular Surgery in our hospital. In-hospital outcome data were gathered from medical records. After discharge, follow-up was performed via outpatient clinic visits or by telephone every 3 months.

Season of symptom onset and clinical outcomes

Information on the time of symptom onset was obtained from the history of the present illness in the patient's medical record. For the purpose of seasonal analysis, patients were divided according to their symptom onset into four groups by season: winter (December, January and February), spring (March, April and May), summer (June, July and August) and autumn (September, October and November).[19] The study end points were in-hospital death and long-term all-cause mortality.

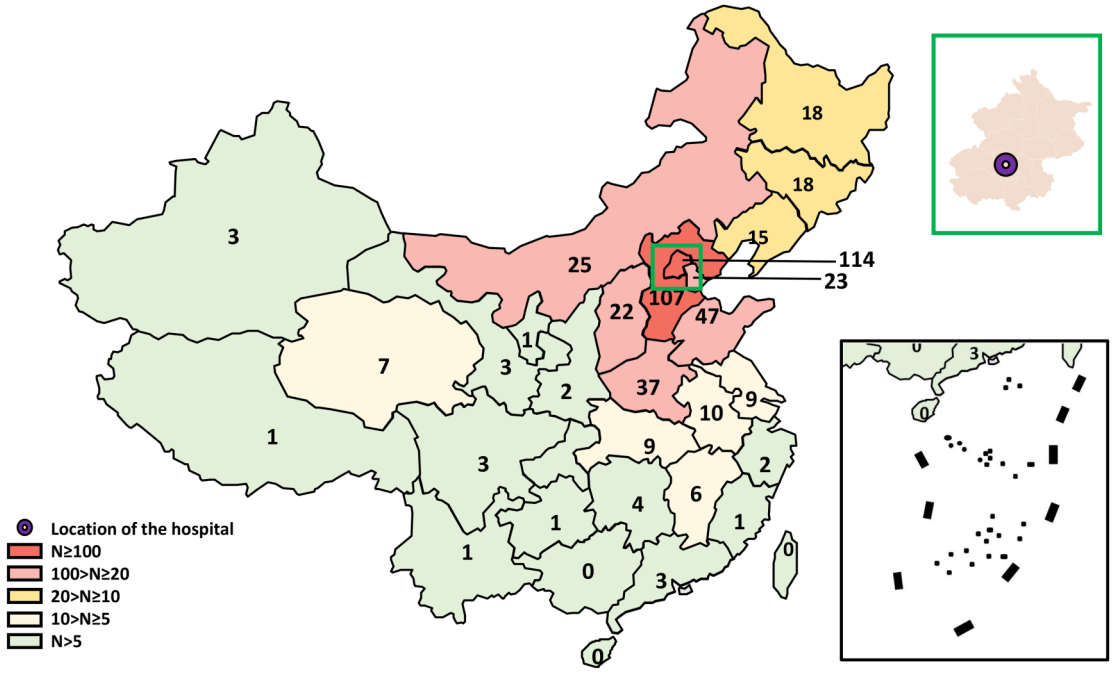

Figure 1 Geographical distribution of the patients enrolled in this study. Numbers represent patient count in the corresponding region.

Statistical analysis

All statistical analyses were performed using SPSS V.19.0. Continuous variables are presented as mean±SD or median (IQR) according to whether or not they follow Gaussian distribution. Baseline characteristics were compared among the groups using analysis of variance or χ^2 tests. Long-term survival analysis was only performed in discharged patients. In-hospital and long-term mortality among the seasonal groups were compared using χ^2 tests. Kaplan-Meier survival curves for the groups stratified by onset season were constructed and compared using the log-rank test. A Cox proportional hazards regression model was used to assess the role of onset season as a factor affecting AAD survival. A p value of <0.05 was considered significant.

RESULTS

Clinical features of cases of type A AAD occurring in each of the four seasons

After exclusion of cases of type A AAD with incomplete onset time data, a total of 492 were studied, of which 129 occurred in winter (26.2%), 147 in spring (29.9%), 92 in summer (18.7%), and 124 in autumn (25.2%). The average age of all patients was 48.4 years; 398 of the 492 patients (80.9%) were male. The clinical characteristics of patients in the four groups are summarised in table 1.

In general, no significant differences were found in most baseline characteristics among the four seasons. Regarding in-hospital management, treatment with calcium channel blockers and surgical intervention seemed to be significantly less common in patients with type A AAD that occurred in autumn than in patients with type A AAD that occurred in the other seasons (all p<0.05).

Seasonal variation in in-hospital and long-term mortality in type A AAD

During a mean follow-up of 20.4 months (IQR 9.7–38.9), total mortality was 17.3% (85/492) with in-hospital mortality of 12.2% (60/492) and long-term mortality of 5.8% (25/432). The actuarial survival rate at 1 year was 85.8% (422/492). In-hospital mortality in patients with type A AAD that occurred in autumn (23.4%) was the highest, and that in patients with type A AAD that occurred in spring (6.1%) was the lowest (p<0.01). After exclusion of patients who died in hospital, long-term mortality was comparable among the four seasonal groups (p=0.63, detailed in online supplementary table S1). When winter, spring and summer were collectively classified as the non-autumn group, in-hospital mortality was still significantly higher in the autumn group than in the non-autumn group (23.4% vs 8.4%, p<0.01), but long-term mortality did not differ significantly between the autumn and the non-autumn group (4.2% vs 6.2%, p=0.46).

Kaplan-Meier analysis showed that the cumulative in-hospital survival rate was significantly lower in patients with type A AAD occurring in autumn than in patients with type A AAD occurring in the other three seasons (log rank χ^2=24.5, p<0.01). As shown in figure 2A, the survival curves clearly began to separate by the first 2–5 days after admission to the emergency department. Figure 2B shows that the cumulative long-term survival rates were similar among the four seasonal groups in discharged patients (log rank χ^2=0.03, p=0.83).

Seasonal effect on in-hospital death of patients with type A AAD

Table 2 shows the results of Cox regression analysis for predictors of in-hospital death from type A AAD.

Univariate Cox analysis revealed that onset in autumn was associated with a 3.01-fold increased risk of in-hospital mortality (HR=3.01; 95% CI 1.82 to 5.00, p<0.01) compared with the non-autumn seasons. The other factors associated with in-hospital mortality included admission white blood cell (WBC) count (HR=1.21; 95% CI 1.15 to 1.26, p<0.01), platelet count (HR=0.99; 95% CI 0.98 to 0.99, p<0.01), d-dimer levels (HR=1.01; 95% CI 1.01 to 1.13, p<0.01), serum creatinine levels (HR=1.01; 95% CI 1.00 to 1.01, p<0.01) and surgical intervention (HR=0.01; 95% CI 0.00 to 0.05, p<0.01). After adjustment by multivariate Cox regression for age, sex and other risk factors, onset in autumn was still an independent risk factor associated with in-hospital mortality from type A AAD (HR=2.05; 95% CI 1.15 to 3.64, p=0.02). In-hospital death was still associated with admission WBC count (HR=1.15; 95% CI 1.09 to 1.21, p<0.01), platelet count (HR=0.99; 95% CI 0.99 to 0.99, p=0.01) and surgical intervention (HR=0.01;95% CI 0.00 to 0.06, p<0.01) after multivariate Cox regression analysis.

Seasonal effect on long-term mortality from type A AAD

In discharged patients, univariate Cox analysis did not reveal any association between onset season (autumn or non-autumn) and long-term mortality (table 3). Multivariate Cox analysis confirmed no seasonal effect on long-term death from type A AAD. Surgical treatment was the main factor (HR=0.19; 95% CI 0.08 to 0.45, p<0.01) associated with long-term survival.

Surgical treatment and seasonal effect on clinical outcomes of type A AAD

Because of the significant impact of surgical treatment on both in-hospital and long-term death from type A AAD, patients were subdivided into a surgical intervention group (N=329) and a medical treatment group (N=163). As shown in figure 3, the rates of in-hospital death and long-term mortality were comparable between autumn and non-autumn onset for those who received surgical treatment (rate of in-hospital death, 0.0% vs 0.4%, p=1.00; rate of long-term mortality, 1.4% vs 4.3%, p=0.43). However, for those who received conservative treatment, in-hospital mortality was significantly higher

Table 1 Baseline characteristics of patients with type A AAD onset in different seasons

Characteristic	Winter (N=129)	Spring (N=147)	Summer (N=92)	Autumn (N=124)	p Value
Age, years	48.7±11.8	47.7±11.0	48.6±13.0	48.1±12.2	0.90
Male	103 (78.9)	123 (83.7)	64 (69.6)	108(87.2)	0.01
Hypertension	97 (75.2)	96 (65.3)	68 (73.9)	92(74.2)	0.23
Diabetes mellitus	0 (0.0)	5 (3.4)	9 (9.8)	2 (1.6)	<0.01
Coronary artery disease	6 (4.7)	6 (4.1)	8 (8.7)	3 (2.4)	0.21
Smoker	42 (37.8)	61 (41.5)	33 (35.9)	44 (35.5)	0.79
Alcohol consumption	27(20.9)	36 (24.5)	13 (14.1)	23 (18.5)	0.25
Duration of pain, hours	10.0 (4.0–24.0)	12.0 (5.0–24.0)	20.0 (5.0–24.0)	19 (5.1–24.0)	0.49
SBP, mm Hg	131.8±22.1	136.4±27.4	140.6±26.0	138.2±25.9	0.09
DBP, mm Hg	72.6±19.7	76.2±18.5	79.1±22.3	78.5±18.5	0.06
Heart rate, beats/min	84.7±16.3	85.3±16.5	81.4±14.2	83.0±15.0	0.24
WBC count, $\times 10^9$ cells/L	9.7 (7.1–13.4)	9.9 (7.6–12.5)	9.4 (6.5–13.5)	10.2 (7.9–14.1)	0.48
Platelet count, $\times 10^9$ cells/L	177 (144.0–236.5)	175 (132.0–221.0)	176 (140.0–233.0)	200 (139.0–267.8)	0.16
C-reactive protein, mg/L	8.0 (4.5–55.9)	7.9 (3.91–46.4)	5.8 (3.7–33.0)	5.7 (3.7–46.9)	0.06
d-Dimer, mg/L	3.3 (1.4–5.2)	3.1 (1.3–5.7)	3.8 (1.4–7.9)	4.5 (2.1–9.2)	0.10
Serum creatinine, μmol/L	90.9 (73.2–117.0)	89.0 (74.0–115.0)	86 (75.0–111.0)	92.5 (74.9–127.3)	0.57
Ascending aorta diameter, mm	44.7±10.0	47.0±10.9	44.6±13.4	45.7±11.5	0.30
Treatment					
β-Blocker	99 (76.7)	119 (81.0)	76 (82.6)	96 (77.4)	0.65
CCB	84 (65.1)	114 (77.6)	63 (68.5)	59 (47.6)	<0.01
ACEI	67 (46.7)	72 (48.2)	40 (43.5)	51 (41.1)	0.30
ARB	19 (14.7)	16 (10.9)	11 (12.0)	14 (11.3)	0.78
Surgical intervention	80 (62.0)	108 (73.5)	70 (76.1)	71 (57.3)	0.01

Values are mean±SD, n (%) or median (IQR).
AAD, acute aortic dissection; ACEI, ACE inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; DBP, diastolic blood pressure; SBP, systolic blood pressure; WBC, white blood cell.

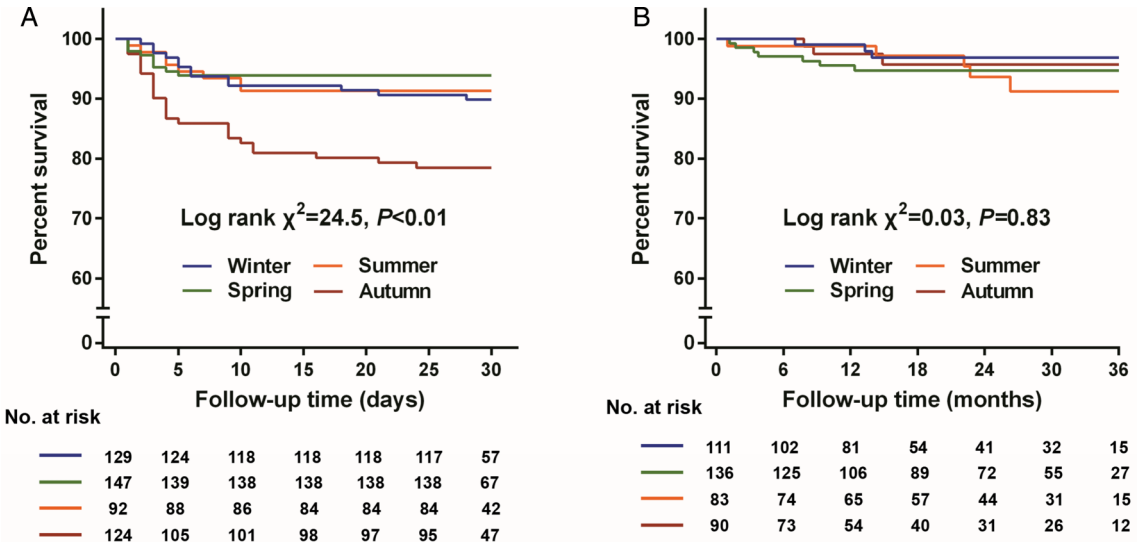

Figure 2 Survival curves according to onset season (winter, spring, summer and autumn). (A) Kaplan-Meier curves for in-hospital survival according to onset season (in all patients); (B) Kaplan-Meier curves for long-term survival according to onset season (in discharged patients).

Table 2 Predictors of in-hospital mortality by univariate and multivariate Cox analysis

	Univariate			Multivariate		
Variable	**HR**	**95% CI**	**p Value**	**HR**	**95% CI**	**p Value**
Age, per year (continuous)	0.99	0.97 to 1.01	0.36	0.98	0.96 to 1.02	0.11
Gender, male vs female	1.34	0.66 to 2.72	0.42	1.15	0.55 to 2.39	0.72
Autumn, vs other seasons	3.01	1.82 to 5.00	<0.01	2.05	1.15 to 3.64	0.02
Autumn vs winter	2.35	1.24 to 4.44	0.01	–	–	–
Autumn vs spring	4.10	1.94 to 8.67	<0.01	–	–	–
Autumn vs summer	2.92	1.34 to 6.40	<0.01	–	–	–
Pericardial effusion	1.34	0.76 to 2.35	0.31	–	–	–
WBC count, per 1×10^9 cells/L (continuous)	1.21	1.15 to 1.26	<0.01	1.15	1.09 to 1.21	<0.01
Platelet count, per 1×10^9 cells/L (continuous)	0.99	0.98 to 0.99	<0.01	0.99	0.99 to 0.99	0.01
d-Dimer, per 1 mg/L (continuous)	1.01	1.01 to 1.13	<0.01	1.02	0.97 to 1.07	0.42
C-reactive protein, per 1 mg/L (continuous)	1.00	1.00 to 1.01	0.06	–	–	–
Serum creatinine, per 1 μmol/L (continuous	1.01	1.00 to 1.01	<0.01	1.00	0.99 to 1.00	0.86
Ascending aorta diameter, per 1 mm (continuous)	1.01	0.98 to 1.03	0.54	–	–	–
Surgical intervention	0.01	0.00 to 0.05	<0.01	0.01	0.00 to 0.06	<0.01

WBC, white blood cell.

in patients whose onset was autumn than in those whose onset was non-autumn (57.4% vs 27.3%, p<0.01), while no differences were observed in long-term mortality between autumn and non-autumn onset in patients who were discharged (12.5% vs 12.5%, p=1.00).

DISCUSSION

This retrospective clinical study analysed the association of onset season for type A AAD with short- and long-term clinical outcomes. Our results show that patients with onset in autumn had higher in-hospital mortality than those with onset in other seasons. Long-term mortality did not differ among patients with onset in the four different seasons. After adjustment by multivariate Cox analysis, the seasonal effect of onset in autumn on in-hospital death in patients with acute type A AAD was still significant. Our study also confirmed that surgical intervention was an independent protective factor that could significantly reduce both in-hospital and long-term death.

Previous studies suggested a possible seasonal effect on the onset of AAD by reporting a high incidence of AAD in winter and a low incidence of AAD in summer. Although Mehta *et al*[11] reported a seasonal pattern characterised by a winter onset peak only for type B but not for type A AAD by analysing International Registry of Aortic Dissection (IRAD) data, their further analysis of patients with AD (without classification) showed that the winter categorisation was independent of climatic zone.[15] A meta-analysis of 60 567 patients with acute aortic rupture and dissection (AARD) also found a

Table 3 Predictors of long-term mortality by univariate and multivariate Cox analysis in patients who were discharged

	Univariate			Multivariate		
Variable	HR	95% CI	p Value	HR	95% CI	p Value
Age, per year (continuous)	1.01	0.97 to 1.04	0.77	0.99	0.97 to 1.03	0.97
Gender, male vs female	0.67	0.27 to 1.69	0.40	0.74	0.29 to 1.91	0.54
Autumn, vs other seasons	0.75	0.26 to 2.21	0.61	0.66	0.22 to 1.97	0.46
Autumn vs winter	0.96	0.26 to 3.62	0.96	–	–	–
Autumn vs spring	0.59	0.18 to 1.89	0.37	–	–	–
Autumn vs summer	0.83	0.22 to 3.10	0.78	–	–	–
Pericardial effusion	1.90	0.83 to 4.36	0.13	–	–	–
WBC count, per 1×10^9 cells/L (continuous)	0.94	0.84 to 1.06	0.32	0.94	0.83 to 1.06	0.28
Platelet count, per 1×10^9 cells/L (continuous)	1.04	0.99 to 1.01	0.06	1.00	0.99 to 1.01	0.11
d-Dimer, per 1 mg/L (continuous)	1.03	0.96 to 1.11	0.37	–	–	–
C-reactive protein, per 1 mg/L (continuous)	1.00	0.99 to 1.01	0.88	–	–	–
Serum creatinine, per 1 μmol/L (continuous)	1.00	0.98 to 1.01	0.66	–	–	–
Ascending aorta diameter, per 1 mm (continuous)	0.99	0.96 to 1.03	0.59	–	–	–
Surgical intervention	0.20	0.09 to 0.44	<0.01	0.19	0.08 to 0.45	<0.01

WBC, white blood cell.

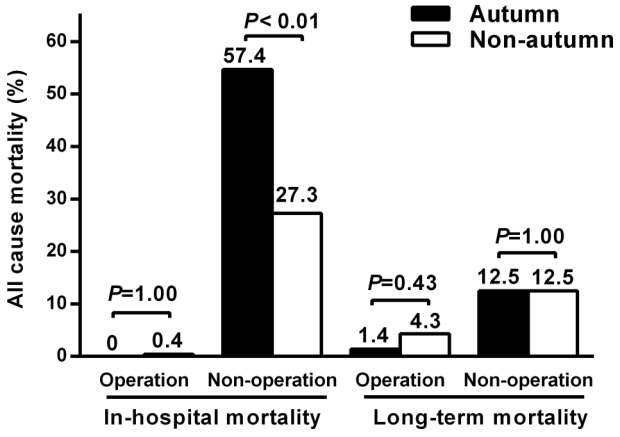

Figure 3 Comparison of all-cause mortality stratified by whether the patient had an operation and whether onset was in autumn.

winter increase in AARD incidence.[13] In addition, a study that included 89 365 cases of AAD in the USA demonstrated that the incidence of AAD was highest in January and lowest in July.[16] An Italian study that included 4615 patients with AAD also showed the highest incidence in January and the lowest incidence in August.[20] The reason for this seasonal pattern is not fully clear. The cold weather in winter can lead to increased sympathetic activity (vasoconstriction, vascular spasm and increased blood pressure). The haemorheological changes in winter (increased blood viscosity and altered coagulation and fibrinolytic systems) may also make the aorta vulnerable to high blood pressure.[17]

It has been noticed that non-accidental mortality increased sharply in the transitional season in the general population. Kalkstein[21] found evidence of a two-step increase in mortality during transition from hot to cold seasons in Minneapolis and Detroit in the USA. Mortality begins to increase steadily in early September, flattens out from mid-October through mid-November, and then increases rapidly until the first week of January. A similar finding for mortality distribution in transitional seasons in Russia was reported,[22] and the increase in mortality was greater going from hot to cold (autumn) than from cold to hot (spring). In the north of China, which has distinct seasonal patterns characterised by transition from very hot wet summers to extremely cold dry winters during a short period in the first month of autumn, it is observed that large day-to-day temperature changes and diurnal temperature variation can increase the risk of cardiac mortality.[23 24] A rapid decrease in temperature is associated with a reduction in lung function[25] and elevated resting metabolism during acute cold stress.[26 27] In the area in which this study was carried out, temperatures in autumn change dramatically, which may exacerbate the imbalance of homoeostasis in patients with severe disease such as hypertension. However, with the increasing industrialisation and urbanisation of northern China, most people are living in relatively stable warm conditions in the winter. Moreover, the universal use of air conditioning has made a relatively comfortable cool environment for people in summer. However, the transitional season effect on the body has been mainly overlooked. Previous studies investigated the prognostic value of the onset season in patients with AAD, but they did not find any effect of seasonality on the outcome and in-hospital clinical events.[16 18] This may be due to the differences in demographic and geographic characteristics between China and the West. Other studies have shown that excess morbidity and mortality in winter are associated with stroke and myocardial infarction.[28 29] Cardiovascular death has been found to occur less frequently in the summer months.[30] The seasonal effect on cardiovascular death indicates that the season of onset of cardiovascular

disease might be an overlooked factor associated with clinical outcomes.

The pathological basis for most AD is a mediolytic (dissolution of components of the medial layer) or dysplastic (abnormal proliferation of smooth muscle cells leading to a thickened arterial wall) artery, resulting in relative vulnerability of the blood vessels.[31] Laplace's law has traditionally been used to describe the arterial deformation and rupture; it states that the circumferential wall tension is a linear function of the aortic radius and the pressure gradient across the aortic wall, which is dependent on both the intraluminal blood pressure and the extraluminal tissue pressure.[17] The weakened aortic wall tends to rupture when the pressure gradient changes dramatically and the mechanical stress acting on the wall exceeds the strength of the wall tissue.[32]

Seasonality is mainly influenced by climate changes including temperature, atmospheric pressure (AP), humidity and other meteorological variables. There is much evidence that seasonal meteorological variables influence blood pressure in both hypertensive and normotensive individuals,[33–35] and decreased outdoor temperature is in some way accompanied by increased intravascular systolic pressure.[36] Changes in AP may increase transmural arterial stress by transiently lowering tissue pressure with respect to blood pressure, creating a net expansive force.[37] The alteration in AP could also affect the partial pressure of oxygen and carbon dioxide in the circulation[38] and thus activate chemoreceptors and baroreceptors leading to elevated sympathetic stimulation. Some studies have confirmed that the fluctuation in AP might increase the risk of rupture in abdominal aortic aneurysm.[12 37] In autumn, it becomes cold and wet due to frequent rain precipitation, with aggregate fluctuations in AP.[39] The decrease in temperature and change in AP may cause sympathetic activity to increase, resulting in vasoconstriction, increased blood pressure and vasospasm, and increasing or sharp fluctuations in systolic blood pressure may lead to increased risk of dissection rupture. These might be the reasons for the poor outcomes of patients with onset in autumn. In addition to the autumn months (September, October and November), this study found a high in-hospital mortality associated with onset in February, which also has fluctuating weather patterns. There is a traditional Chinese saying 'warming spring and freezing fall', which means people should keep warm in spring and wear less clothing in autumn to preadapt and minimise the effects of environmental change on the body. Alternating seasons and sudden changes in both temperature and AP can cause patients' conditions to deteriorate during treatment, but more studies are needed to further clarify the relationships between AD, seasonal changes and treatment (especially drug therapy). It is widely accepted that surgery can significantly improve the outcome of type A AAD, and the in-hospital death rate of patients who have received surgery is lower than that of patients who have received conservative therapy. Our analysis also indicated that the short-term prognosis of patients undergoing surgery was not affected by onset season. In addition, this study suggests that conservative treatment could increase the risk of in-hospital death for patients with onset in autumn, and more aggressive treatment should be administered.

There are some limitations in this study. First, our data did not include temperature, humidity, AP and other specific climate data, which may have provided a more thorough explanation for the seasonal effect. The second limitation is our single-centre study design: our findings might not necessarily be mirrored in other countries with more temperate climates.

CONCLUSION

Seasonal patterns may exist in prognosis of type A AAD. Onset in autumn may be a factor that increases the risk of in-hospital death from type A AAD, especially in patients who receive conservative treatment. Urgent surgery improves the short-term and long-term outcomes regardless of onset season.

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Contributors ZC, XF and YY participated in the study design. ZC and BH performed the data analysis. HL, ZZ, ZL, SZ and RH helped with patient data collection and follow-up. The first draft of the manuscript was written by ZC and XF. All authors interpreted the results, revised the report, commented on the manuscript and approved the final version.

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Competing interests None declared.

Patient consent Obtained.

Ethics approval Study protocols were approved by the appropriate institutional review boards of Fuwai Hospital and complied with the Declaration of Helsinki.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

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