

# Influence of Age on Clinical Presentation, Therapeutic Options, and Outcome in Chinese Patients with Acute Aortic Dissection

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## Summary

It has been shown in previous studies that Chinese patients with acute aortic dissection (AD) were approximately 10 years younger than patients from western countries. However, there is a lack of studies concerning the age-related differences in clinical characteristics and outcomes in Chinese patients with acute AD. A total of 1,061 patients with AD (570 type A and 491 type B AD) were enrolled between 2006 and 2008. The clinical characteristics were compared between the patients in our study and those in the International Registry of Acute Aortic Dissection (IRAD). Compared with patients in the IRAD, those in our study were relatively younger, comprised more males, and had a higher proportion of Marfan syndrome but received fewer surgical interventions. When stratified by 10-year age, younger patients were more likely to have type A AD, familial AD, and Marfan syndrome, whereas older patients tended to comprise more females and type B AD. As age increased, the proportion of surgical intervention gradually decreased regardless of the type of AD. During a median follow-up of 2.2 years, 147 patients died, of whom 94 (63.9%) had type A AD and 53 (36.1%) had type B AD. Long-term mortality increased with increasing age, especially in patients above 70 years old. Furthermore, the recurrence rate of AD was higher in both the young and the older patients. In conclusion, compared with western patients with AD, Chinese patients have distinct characteristics and more attention should be paid to the young and older patients because of their high long-term mortality and recurrence rate.

(Int Heart J 2019; 60: 1373-1380)

**Key words:** Long-term mortality, Recurrence, Marfan syndrome

Acute aortic dissection (AD) is a cardiovascular emergency with a high rate of mortality. Its clinical presentation and outcome in patients with AD vary with age,<sup>1)</sup> gender,<sup>2)</sup> and geography.<sup>3)</sup> It has been shown in several studies that Chinese patients with AD are approximately 10 years younger than patients from western countries.<sup>4-7)</sup> However, the age-related clinical characteristics, treatment strategies, and outcomes in Chinese patients with AD are still not well understood. Accordingly, in our present study, we compared our data with that from the International Registry of Acute Aortic Dissection (IRAD),<sup>8)</sup> which represents the largest cohort of patients with AD from the western world, and evaluated the impact of age on the clinical presentation, therapeutic options, and long-term outcomes in Chinese patients with AD.

## Methods

From January 2006-December 2008, consecutive patients suspicious of having AD admitted to the cardiac emergency center of Fuwai Hospital (National Center for Cardiovascular Diseases in China) were enrolled. Diagnosis of AD was confirmed by aorta angiography using multidetector computed tomographic (CT) scanning. This study was approved by the ethical committee of Fuwai Hospital and all patients provided their written informed consent.

After admission to the hospital, data of baseline characteristics, such as demographics, medical histories, vital signs, and physical findings, were collected. Data of laboratory tests, including white blood cell (WBC) counts; platelet counts; and C-reactive protein, D-dimer, and creatinine values, were obtained. Other recorded data included imaging examinations and in-hospital management,

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This work was supported by the grant (81170286) from the National Natural Science Foundation of China to Dr. Xiaohan Fan.

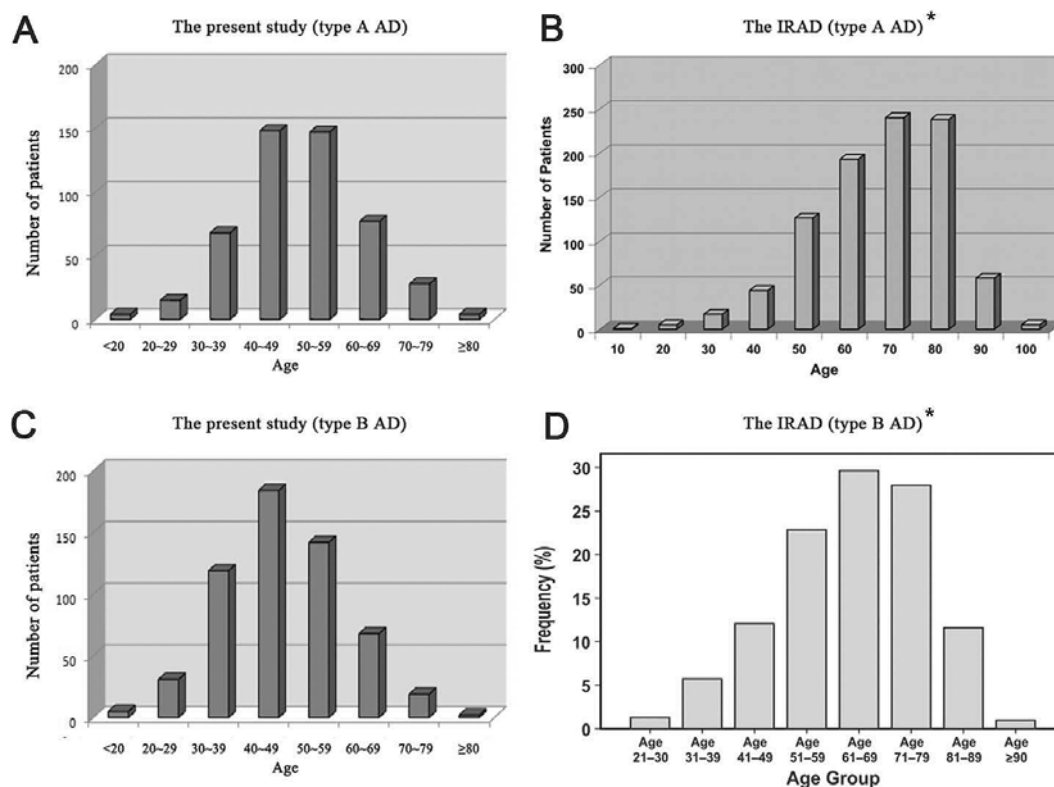
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Received for publication September 5, 2018. Revised and accepted December 3, 2018.

Released in advance online on J-STAGE October 31, 2019.

doi: 10.1536/ihj.18-532

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**Figure 1.** Comparison of frequency in different age groups between the present study and the IRAD. \*Figures are taken from Trimarchi, *et al.*<sup>1)</sup> and Jonker, *et al.*<sup>20)</sup> with permission.

including medical and surgical interventions. The rationale and strategy of the surgical intervention were determined by cardiovascular surgeons. The long-term outcome was defined as all-cause mortality and recurrence during a median follow-up of 2.2 years.

The IRAD is a multicenter registry that includes patients with AD at 30 large referral centers; its rationale and methods have previously been described.<sup>8)</sup> The clinical characteristics and management were compared between our present study and the IRAD.

**Statistical analysis:** Continuous variables are presented as mean  $\pm$  standard deviation or median and the interquartile range according to whether the variable conforms to a normal distribution, and they were then compared using analysis of variance or the Mann-Whitney rank-sum test, as appropriate. Categorical data are presented as numbers and percentages and were compared using the chi-squared or Fisher's exact test. A *P*-value of  $<0.05$  was considered statistically significant. Data were analyzed using SPSS version 19.0 (SPSS Inc., Chicago, Illinois, USA).

## Results

**Comparison of clinical characteristics between the present study and the IRAD:** A total of 1,061 patients with AD (570 type A and 491 type B AD) confirmed by CT imaging were enrolled. Figure 1 shows the frequency in different age groups in the two studies. In the IRAD, the largest frequency distribution in type A AD was in pa-

tients aged 70-80 years, whereas it lied in patients aged 40-60 years in our study. Similarly, in type B AD, patients aged 60-80 years accounted for the largest percentage of the IRAD, whereas patients aged 40-60 years constituted the largest proportion of patients in our study. Table I shows a comparison of the clinical characteristics between the patients in our present study and those in the IRAD. Compared with the IRAD, the patients in our study were nearly 15 years younger than those in the IRAD, both in type A AD and in type B AD. The percentage of male patients in our study (75.3% in type A AD and 85.9% in type B AD) was significantly higher compared to the IRAD (67.5% in type A AD and 65.8% in type B AD). As to the medical histories, the patients in our study had a relatively higher proportion of Marfan syndrome (12.6% versus 4.5%,  $P < 0.001$ ) but had a lower incidence of hypertension, arteriosclerosis, and diabetes mellitus as compared with the IRAD. Moreover, abrupt chest pain was the most common symptom in both studies, but our patients were less likely to present with back pain. In type A AD, the percentage of patients who received surgical interventions was lower compared to the IRAD (70.0% versus 86.4%,  $P < 0.001$ ); however, in type B AD, more surgical interventions (19.1% versus 13.0%,  $P < 0.001$ ) and endovascular management (41.5% versus 23.1%,  $P < 0.001$ ) were adopted in our present study as compared with the IRAD.

**Baseline characteristics associated with age:** Because of the high heterogeneity in clinical symptoms, therapeutic

**Table I.** Comparison of Clinical Characteristics between Patients in Our Present Study and in the IRAD

	Type A AD			Type B AD		
	Our present study (n = 570)	IRAD* (n = 2,952)	P-value	Our present study (n = 491)	IRAD* (n = 1,476)	P-value
Demographics						
Age (years)	46.9 ± 12.0	61.5 ± 14.6	< 0.001	50.6 ± 12.3	63.6 ± 14.1	< 0.001
Male (n, %)	429 (75.3)	1,992 (67.5)	< 0.001	422 (85.9)	972 (65.8)	< 0.001
Patient history (n, %)						
Marfan syndrome	72 (12.6)	122 (4.5)	< 0.001	18 (3.7)	56 (4.0)	0.768
Hypertension	365 (64.0)	2,089 (74.4)	< 0.001	350 (71.3)	1,158 (80.9)	< 0.001
Arteriosclerosis	24 (4.2)	636 (23.8)	< 0.001	21 (4.3)	443 (31.7)	< 0.001
Diabetes mellitus	19 (3.3)	204 (7.7)	< 0.001	23 (4.7)	112 (8.0)	0.015
Presenting symptoms and signs (n, %)						
Chest pain	478 (83.9)	2,509 (85.0)	0.503	393 (80.0)	989 (67.0)	< 0.001
Back pain	65 (11.4)	1,269 (43.0)	< 0.001	57 (11.6)	1,033 (70.0)	< 0.001
Presenting hypertension	209 (36.7)	826 (28.0)	< 0.001	251 (51.1)	974 (66.0)	< 0.001
Pulse deficits on presentation	166 (29.1)	915 (31.0)	0.368	149 (30.3)	280 (19.0)	< 0.001
Abnormal electrocardiography	226 (39.6)	1,889 (64.0)	< 0.001	281 (57.2)	915 (62.0)	0.059
Treatment						
Surgical intervention	399 (70.0)	2,552 (86.4)	< 0.001	94 (19.1)	192 (13.0)	< 0.001
Endovascular management	—	—	—	204 (41.5)	341 (23.1)	< 0.001
Medical therapy	171 (30.0)	329 (11.1)	< 0.001	193 (39.3)	923 (62.5)	< 0.001

AD indicates aortic dissection; and IRAD, International Registry of Acute Aortic Dissection. \*Data were obtained from Pape, *et al.*<sup>9)</sup>

options, and outcomes in patients with AD, we evaluated the clinical characteristics among different age groups. Table II displays the baseline clinical characteristics and medical treatment stratified by 10-year age. As age increased, there was a tendency to have more female patients; type B AD; and hypertensive, atherosclerotic, and diabetic patients. In contrast, younger patients were more likely to have type A AD, familial AD, and Marfan syndrome. Moreover, the older ones were more likely to seek medical care after the onset of symptoms and to be admitted with higher blood pressure. Pericardial effusion and ascending aortic diameter were comparable among the groups, but the WBC and D-dimer levels were significantly higher in older patients compared with the younger ones. In medical management strategies, more patients received antihypertensive agents calcium antagonist, but with less angiotensin-converting enzyme inhibitor/angiotensin receptor blocker as age increased.

Figure 2 shows the therapeutic strategies in patients with type A and type B AD. As age increased, patients were more likely to receive medical therapy for type A AD. Similarly, surgical and endovascular management were less adopted as age advances, but younger patients tended to receive endovascular interventions compared with surgical management.

**Outcomes associated with age:** During a median follow-up of 2.2 years, 147 patients died, of whom 94 (63.9%) had type A AD and 53 (36.1%) had type B AD. Among these 147 deceased patients, 87 (59.2%) died because of rupture of dissection, 12 (8.2%) died for cardiac reasons, and 48 (32.7%) died for noncardiac reasons. Figure 3 shows the long-term mortality associated with age. The general tendency is that mortality increases with increasing age, especially in patients above 70 years old. However, the recurrence of AD associated with age reveals some differences from mortality (Figure 4). Younger pa-

tients had a relatively higher recurrence rate compared with older ones, especially in those aged 31-40. It is noteworthy that a “U-shaped” relationship was observed between the recurrence of AD and age in patients with type B AD; that is, both younger and older patients had a higher recurrence rate compared to middle-aged patients.

## Discussion

The main findings of the present study are as follows. First, some remarkable differences in the clinical characteristics were observed between the patients in our cohort and those in the IRAD, in which a significantly younger mean age and an inadequate surgical intervention were the main features in our study. Second, the age-associated clinical characteristics were remarkable in Chinese patients with AD. Third, the therapeutic options and outcomes, including long-term mortality and recurrence rate, were associated with the patient's age. Our present study drew an outline of the age-related clinical characteristics in Chinese patients with AD.

Although AD is a cardiovascular emergency with a high potential of mortality, it is not as common as other cardiovascular diseases such as coronary artery disease, hypertension, and heart failure. Therefore, studies with large sample sizes were usually limited. Our center the National Center for Cardiovascular Diseases in China has an opportunity to enroll a large amount of patients around the country, and it also represents the general feature in patients with AD in China. The IRAD is multicenter registry in Europe and North America, which also represents the clinical characteristics in patients with AD in western countries. Because AD is a heterogeneous disease in terms of its clinical presentation and geography, we compared the baseline characteristics in Chinese patients with those in the IRAD. The mean age in the IRAD was 61.5 and

**Table II.** Comparison of the Baseline Characteristics and Medical Management Stratified by 10 Years

	Age group (years)					P-value
	≤ 30	31~40	41~50	51~60	61~70	> 70
<b>Demographics</b>						
Age (years)	25.5 ± 3.8	36.4 ± 2.7	45.3 ± 2.9	54.9 ± 2.7	65.1 ± 2.7	75.0 ± 3.8
Male (n, %)	58 (86.6)	178 (84.4)	286 (84.6)	216 (77.1)	93 (68.4)	39 (79.6)
<b>Type of AD</b>						
Type A AD	44 (65.7)	137 (64.9)	187 (55.3)	137 (48.9)	66 (48.5)	19 (38.8)
Type B AD	23 (34.3)	74 (35.1)	151 (44.7)	143 (51.1)	70 (51.5)	30 (61.2)
<b>Patient history (n, %)</b>						
Family history of AD	3 (4.5)	5 (2.4)	2 (0.6)	2 (0.7)	0 (0.0)	0 (0.0)
Marfan syndrome	32 (47.8)	36 (17.1)	19 (5.6)	3 (1.1)	1 (0.7)	0 (0.0)
Hypertension	17 (25.4)	100 (47.4)	238 (70.4)	227 (81.1)	109 (80.1)	40 (81.6)
Arteriosclerosis	0 (0.0)	2 (0.9)	10 (3.0)	15 (5.4)	12 (8.8)	9 (18.4)
Diabetes mellitus	0 (0.0)	1 (0.5)	12 (3.6)	14 (5.0)	7 (5.1)	8 (16.3)
Onset-to-admission intervals (hours)	24.0 (5.5-48.0)	14.0 (5.0-30.0)	20.0 (6.0-24.0)	15.0 (5.0-25.0)	10.0 (3.0-20.0)	10.0 (3.0-20.0)
<b>Physical findings</b>						
Systolic blood pressure (mmHg)	124.0 ± 32.1	131.5 ± 34.7	139.2 ± 31.9	134.2 ± 28.8	134.3 ± 34.8	143.6 ± 27.9
Heart rate (bpm)	88.0 (80.0-96.0)	83.0 (75.0-94.0)	80.0 (75.0-90.0)	80.0 (70.0-89.0)	76.0 (69.0-85.0)	72.0 (66.0-80.0)
Hypotension/shock/tamponade (n, %)	6 (9.0)	10 (4.7)	18 (5.3)	13 (4.6)	4 (2.9)	0 (0.0)
<b>Lab examination</b>						
Pericardial effusion (n, %)	14 (20.9)	34 (16.1)	52 (15.4)	43 (15.4)	17 (12.5)	2 (4.1)
Ascending aortic diameter (mm)	45.5 ± 16.2	41.7 ± 12.7	41.1 ± 11.2	40.9 ± 10.5	41.0 ± 10.1	41.3 ± 10.5
White blood cell (× 10 <sup>9</sup> /L)	8.5 (6.6-10.7)	9.2 (7.0-12.2)	9.7 (7.3-13.2)	9.4 (7.1-12.0)	9.1 (7.1-11.4)	8.0 (5.5-10.3)
C reaction protein (mg/L)	32.0 (4.4-83.7)	26.2 (7.0-78.2)	39.8 (6.7-85.3)	30.6 (7.9-83.1)	25.6 (9.4-81.4)	66.6 (11.1-101.7)
D-dimer (μg/mL)	0.6 (0.2-1.4)	2.0 (0.6-4.3)	2.4 (0.7-5.4)	2.6 (0.8-6.1)	3.9 (1.2-6.4)	2.5 (1.1-3.8)
Creatinine (μmol/L)	83.3 (72.7-106.0)	86.3 (72.1-110.1)	89.9 (74.5-112.1)	85.8 (73.1-104.2)	87.9 (73.8-112.5)	86.1 (72.1-101.0)
<b>Treatments (n, %)</b>						
Beta-blockers	50 (74.6)	181 (85.8)	276 (81.7)	234 (83.6)	116 (85.3)	44 (89.8)
Calcium channel blockers	40 (59.7)	138 (65.4)	250 (74.0)	211 (75.4)	102 (75.0)	36 (73.5)
Angiotensin-converting enzyme inhibitors	34 (50.7)	110 (52.1)	169 (50.0)	132 (47.1)	43 (31.6)	17 (34.7)

AD indicates aortic dissection.

63.6 years in type A and type B AD, respectively, and more than 70% of the patients had concomitant hypertension; however, less than 5% had coexisting Marfan syndrome.<sup>9)</sup> In contrast, studies on Chinese patients,<sup>4,7)</sup> including our present study, showed that they were significantly

younger (mean age: 47-51 years) and had fewer age-dependent morbidities such as hypertension, arteriosclerosis, and diabetes but had a higher incidence of Marfan syndrome compared with western patients. It has been demonstrated in previous studies that the prevalence of

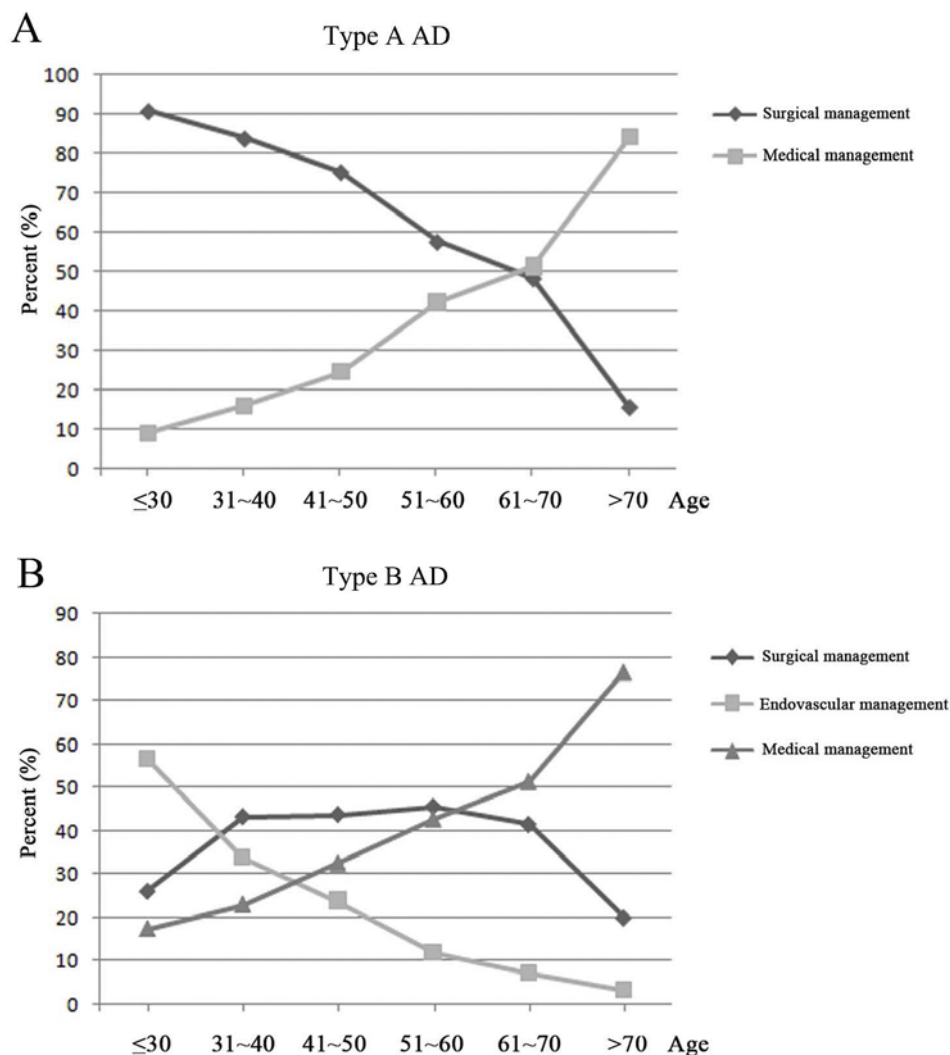


Figure 2. Therapeutic strategies in different age groups in patients with type A and type B AD.

Marfan syndrome in Chinese patients with AD was higher compared to the IRAD,<sup>10-12)</sup> consistent with our results. Whether the incidence of gene mutation associated with Marfan syndrome or AD is higher in Chinese patients than in patients from western countries deserves further study. However, a recent study by Cao, *et al.*<sup>13)</sup> shed some light on this issue, who identified three novel heterozygous mutations in four Chinese patients with suspected Marfan syndrome, which indicated that some mutations associated with Marfan syndrome or AD might be ethnic-specific. Another distinct feature in our study was the relatively higher proportion of male patients. The precise mechanisms are still poorly understood. In Chinese patients, men are considered to be exposed to more risk factors of AD than women, such as hypertension,<sup>14)</sup> smoking,<sup>15)</sup> and Marfan syndrome.<sup>10)</sup> Therefore, improving the awareness and management of controllable risk factors is of great value for the prevention of AD. Moreover, although Chinese patients were relatively younger, the percentage of patients who received surgical treatments was lower than in the IRAD. There are some possible explanations.

Because medical resources are distributed unequally in China, common surgical procedures are performed at local medical institutions and patients at high risk or with complications are sent to our center for further treatment. Therefore, some patients may be too ill to sustain the surgical risk or even die before the surgical intervention. Moreover, because of the imperfect health insurance in China, some patients cannot afford the costly fee, resulting in relatively fewer operation options in patients with type A AD although the guidelines recommend surgical intervention for type A AD. However, in type B AD, most patients had complicated AD, which could not be resolved at the local medical institutions. According to the guidelines recommendation, TEVAR or surgery is recommended in complicated type B AD. Therefore, a relatively higher proportion of patients received surgical or endovascular interventions as compared with the IRAD.

We also found some age-related distinct characteristics in Chinese patients with AD. As the age increased, the percentage of females gradually increased, consistent with the results from the IRAD.<sup>2)</sup> Moreover, as the age in-

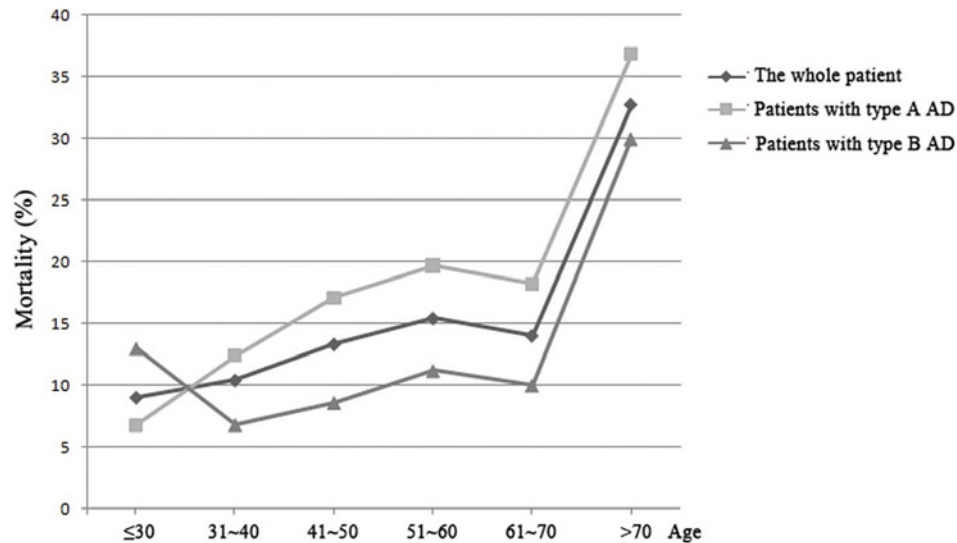


Figure 3. Long-term mortality in different age groups.

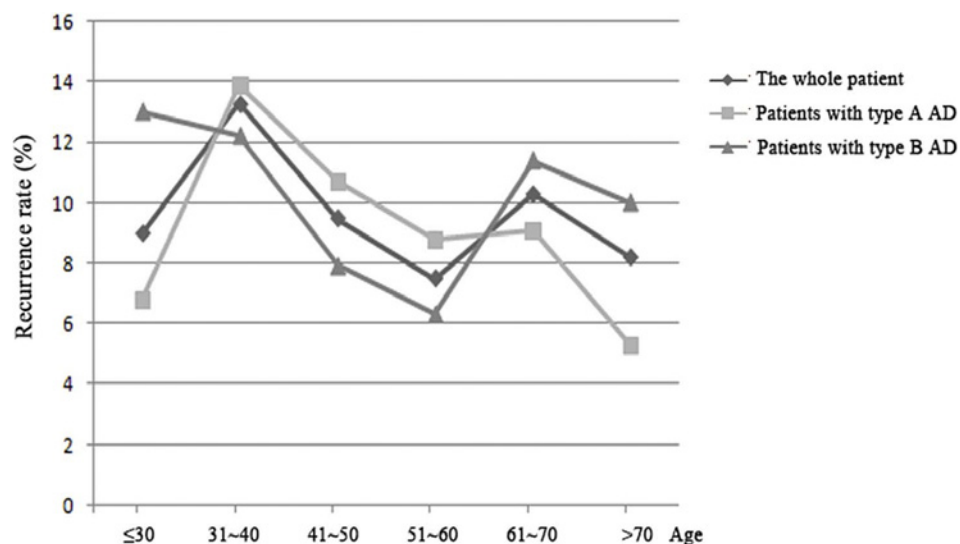


Figure 4. Recurrence rate in different age groups.

creased, the percentage of type A AD gradually decreased, whereas that of type B AD gradually increased. Accordingly, familial AD and Marfan syndrome are more common in the youth, whereas age-dependent cardiovascular morbidities, such as hypertension, arteriosclerosis, and diabetes mellitus, are more prevalent in older ones, suggesting that AD that occurs in the younger patients is more likely to be associated with heredity,<sup>11)</sup> whereas AD in older patients is more associated with aortic lesions related to age-dependent morbidities.<sup>16)</sup> Furthermore, older patients tend to seek medical care after the onset of symptoms earlier than the younger ones, possibly because of the weak tolerance after AD occurrence and the relatively better consciousness of seeking medical care in the case of physical disorders.

Surgical intervention is the firstly recommended strategy for type A AD according to the current guidelines for

AD.<sup>17)</sup> However, owing to the increased risks of thoracic aortic surgery in elderly patients, physicians may less frequently offer surgical treatment to elderly patients. The IRAD study also showed that as the age increased, the percentage of surgical treatments decreased.<sup>9)</sup> Our present study also demonstrated similar findings regardless of the type of AD. Although advanced age is not a reason to refuse surgery, institutions or individual physicians may approach this issue differently. The decision of whether or not to offer surgical intervention to an elderly patient should be based on individual patient characteristics and the expertise of the medical institutions. It is worth noting that although the patients in our study were enrolled between 2006 and 2008 and the guidelines for the management of AD had been updated during the past 10 years,<sup>17)</sup> the general principles for the management of type A and type B are recommended coincidentally by the guide-

lines.<sup>17,18)</sup> Therefore, we believe that although our registry reflected the data of 10 years ago, the conclusion was still useful for understanding the status of Chinese patients with AD.

Long-term mortality increased as the age increased. Patients above 70 years of age had a significantly higher rate of mortality as compared with those below 70 years of age. It has been shown in previous studies that older age, especially above 70 years, is independently associated with an increased risk of poor prognosis,<sup>16,19-21)</sup> consistent with our findings. In addition to the age-related decrease in physical activity and functional fitness as well as the increase in comorbidities such as atherosclerosis that may adversely affect the outcomes, advanced age was associated with less administration of surgery, which might adversely affect the outcomes in patients with type A AD. Although surgical intervention is not necessary in type B AD without complications, age-related comorbidities such as atherosclerosis, hypertension, and diabetes also adversely affect the prognosis. Recurrence is an important issue in patients with AD; in the IRAD, 5.3% had recurrent AD.<sup>22)</sup> In our present study, the percentage of AD recurrence was higher than in the IRAD, especially in the younger and older patients. There are some possible interpretations for this. First, as mentioned above, the prevalence of genetic diseases such as Marfan syndrome is more common in young Chinese patients with AD compared with western patients, and the IRAD study demonstrated that Marfan syndrome independently predicts recurrent AD.<sup>22)</sup> Therefore, the high prevalence of inherited connective tissue diseases may partly contribute to the relatively higher AD recurrence in young Chinese patients. Second, the older patients were less likely to receive surgical interventions regardless of the type of AD, and the vascular lesion was not removed, which may increase the risk of AD recurrence. In addition, the older patients often had more comorbidities, such as atherosclerosis and hypertension, associated with AD occurrence, and these risk factors were usually not well controlled, which also increased the risk of AD recurrence in the older patients. The higher recurrence in the older patients also in part interpreted the high long-term mortality, which suggested that both younger and older patients are predisposed to poor prognosis and clinicians should give them more care.

There are some limitations in our study. First, this was a single-center observational study. Because the medical resources are distributed unevenly in different areas in China, the clinical characteristics may vary among different regions. Second, the decision-making of surgical intervention was based on multiple factors, including the indication of AD lesion, age, comorbidities, physical fitness status, patient's preference, and also the economic status. Therefore, the choice of patients for surgical intervention may not strictly obey the current guideline recommendation. Third, no detailed operative data, including operative procedures and perfusion techniques, were available. In addition, the percentage of patients aged 70 or more was relatively low in our present study, and the characteristics of these patients may have been biased. Finally, the medications during the long-term follow-up were not collected, which may affect the long-term outcomes.

## Conclusion

The mean age of Chinese patients with AD was significantly lower compared to the IRAD; however, surgical intervention was inadequate in patients with type A AD. More attention should be paid to the young and older patients because of their high long-term mortality and recurrence rate.

## Disclosure

**Conflicts of interest:** None.

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