Outcomes of Uncomplicated Type B Intramural Hematoma Patients with Type 2 Diabetes Mellitus

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Abstract

Objectives We aimed to summarize the clinical presentation, therapeutic approaches, and outcomes of type B intramural hematoma (IMHB) patients with and without type 2 diabetes mellitus (DM). Methods Patients with uncomplicated IMHBs were included between January 2016 and January 2018 and divided into two groups according to whether they had DM or not. Cox proportional hazard analysis was utilized to investigate the risk factors of aortic-related mortality. Kaplan-Meier survival analysis with the log-rank test was used to estimate the cumulative mortality and aortic-related mortality. Results 149 patients were included and were divided into to two groups (DM group [n=60] and non-DM group [n=89]). Patients in the non-DM group underwent thoracic endovascular aortic repair (TEVAR) treatment more frequently (12% vs 2%, P=0.028) and had a higher reintervention rate during the follow-up (9 in 81 cases, 11% vs 2%, P=0.043). There were significant differences between the two groups regarding the aorta-related mortality rate during the acute phase (9% vs 0%, P=0.042) and the all-cause mortality rate (22% vs 7%, P=0.011). Ulcer-like projection (ULP) development (during the acute phase) (hazard ratio [HR], 1.07; 95% confidence interval [CI], 1.01-1.31, P=0.008), C-reactive protein (CRP) level (HR, 1.92; 95% CI, 1.51-2.49, P<0.001) and MMP-9 level (HR, 16.82; 95% CI, 7.52-28.71, P<0.001) were associated with an elevated risk for aorta-related mortality. Conclusions IMHBs without DM are not benign and have a considerably high aortic-related mortality rate. ULP development (during the acute phase), CRP levels and maximum MMP-9 are associated with an elevated risk for aorta-related mortality.

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Abstract

Objectives

We aimed to summarize the clinical presentation, therapeutic approaches, and outcomes of type B intramural hematoma (IMHB) patients with and without type 2 diabetes mellitus (DM).

Methods

Patients with uncomplicated IMHBs were included between January 2016 and January 2018 and divided into two groups according to whether they had DM or not. Cox proportional hazard analysis was utilized to investigate the risk factors of aortic-related mortality. Kaplan-Meier survival analysis with the log-rank test was used to estimate the cumulative mortality and aortic-related mortality.

Results

149 patients were included and were divided into to two groups (DM group [n=60] and non-DM group [n=89]). Patients in the non-DM group underwent thoracic endovascular aortic repair (TEVAR) treatment more frequently (12% vs 2%, P=0.028) and had a higher reintervention rate during the follow-up (9 in 81 cases, 11% vs 2%, P=0.043). There were significant differences between the two groups regarding the aorta-related mortality rate during the acute phase (9% vs 0%, P=0.042) and the all-cause mortality rate (22% vs 7%, P=0.011). Ulcer-like projection (ULP) development (during the acute phase) (hazard ratio [HR], 1.07; 95% confidence interval [CI], 1.01-1.31, P=0.008), C-reactive protein (CRP) level (HR, 1.92; 95% CI, 1.51-2.49, P<0.001) and MMP-9 level (HR, 16.82; 95% CI, 7.52-28.71, P<0.001) were associated with an elevated risk for aorta-related mortality.

Conclusions

IMHBs without DM are not benign and have a considerably high aortic-related mortality rate. ULP development (during the acute phase), CRP levels and maximum MMP-9 are associated with an elevated risk for aorta-related mortality.

Abbreviations:

CRP: C-reactive protein

ULP: Ulcer-like projection

IMH: Intramural hematoma

IMHB: Type B intramural hematoma

TEVAR: Thoracic endovascular aortic repair

Key words: IMH, Diabetes Mellitus, Mortality, Outcome

Introduction

Although the current treatment strategy (wait-and-watch strategy) for type B intramural hematoma (IMHB) is in line with the management of type B dissections, the long-term outcomes of IMHBs are not as good as those of type B dissections **[1-4]** . Schoenhoff et al.**[5]** reported that 43% of IMHB patients underwent thoracic endovascular aortic repair (TEVAR) during the first two weeks because of the visualization of an entry tear and development of an aneurysm, and 19% of patients received TEVAR after the acute phase and during the first-year**.** Durham and colleagues also reported that the survival rates of type B intramural hematoma patients who underwent interventional treatment was only 76% and only 40% of patients did not require reintervention **[6]** . The cause of this phenomenon is that the evolution of IMHBs is highly unpredictable and can vary from complete resolution to abrupt rupture.

The prevalence of diabetes mellitus (DM) in patients requiring cardiac surgery is significantly increasing and achieving tight perioperative glycemic control in DM patients could decrease perioperative morbidity and improve survival **[7]** . Regarding aortic diseases, current studies have demonstrated a negative correlation between DM and the occurrence of aortic diseases **[8-11]** . However, previous studies are contradictory in that patients with DM were found to have poorer outcomes after abdominal aortic aneurysm repair**[12],** whereas mortality and clinical complications in type B aortic dissection patients after TEVAR were significantly reduced in DM patients **[13]** . In our previous study, we had demonstrated that uncomplicated type A IMH patients with DM (receiving the "wait-and-watch strategy" and tight glycemic control) may have lower aorta-related mortality and rates of aorta-related adverse events and reinterventions than the non-DM group **[14]** And whether patients with uncomplicated IMHB (receiving the "wait-and-watch strategy") may benefit from the tight glycemic control remains unclear.

In sum, we hypothesized that in uncomplicated IMHB patients who received the "wait-and-watch strategy" (combined with tight glucose management), patients with DM (compared with patients without DM) would benefit from such a treatment strategy. In this study, we aimed to summarize the clinical presentation, therapeutic approaches, and outcomes of IMHB patients with and without DM.

Methods

Patient Characteristics

Individual informed consent was obtained from each patient, and institutional review board approval was obtained from Xiamen University. Patients with uncomplicated IMHBs were included between January 2016 and January 2018. The definition of "uncomplicated" was based on the status of the syndrome after medical treatment (without signs of aortic rupture on admission and controllable syndrome) and radiographic findings from the computed tomography angiography (CTA) examination on admission (without periaortic hematoma and ulcer-like projection [ULP])**[1][4].** The data from the following were defined as missing: patients who refused further treatment, patients with incomplete imaging data to assess the evolution of IMHB or laboratory test results, and patients lost to follow-up (see details of the CONSORT diagram in **Figure 1**).

Blood Glucose Management

Newly diagnosed type 2 DM patients without standard antidiabetic treatments before the onset of IMHB were identified (diagnostic criteria of type 2 DM included: hemoglobin A1c [HbA1c] [?]6.5%, fasting plasma glucose [?]126 mg/dL, and 2 hour plasma glucose[?]200 mg/dL). The insulin therapy for these patients included the insulin pump with and without long-acting and short-acting subcutaneous insulin to achieve efficient rapid glycemic control during the acute phase (with the help of a physician, **D.J.**). The target blood glucose level included proper blood glucose levels of fasting and premeal states (80-130 mg/dL) and the postprandial state (less than 180 mg/dL) **[7]** . After achieving target glucose control, type 2 DM patients were transitioned to scheduled subcutaneous insulin therapy combined with the admission of oral antidiabetic medication drugs. After TEVAR or open surgery, patients with persistently elevated serum glucose ($>$ 180 mg/dL) received continuous intravenous insulin perfusion to maintain serum glucose $<$ 180 mg/dL during their stay in the intensive care unit and then were transitioned to their preoperative scheduled insulin therapy combined with oral antidiabetic drugs **[7]** .

Treatment Strategy of Intramural Hematoma

Patients with uncomplicated IMHBs received medical therapy to control their pain (intravenous opiate analgesia), heart rate (less than 80 beats per minute), and blood pressure (systolic blood pressure between 100 and 120 mmHg) **[1]** . The acute phase was defined as the first fourteen days from the onset of IMHB, and the disease was considered stable after an uneventful fourteen days (patient was discharged) **[1]** . Electrocardiographic-triggered CTA (GE Healthcare, Milwaukee, WI) was performed at least twice during the acute phase (once on admission and once before discharge) in patient without disease progression and with well-controlled blood pressure, heart rate and pain; in eventful cases (uncontrollable back pain combined with hemodynamic instability), CTA examinations were adjusted accordingly**[1]** . The patients were followed clinically according to standard surveillance protocols **[1]** **[15-17]** . During the follow-up, CTA was also performed at 1, 3, 6, and 12 months and then annually during the extended follow-up. Disease progression was defined as increased pleural effusion, hematoma thickening (thickness [?]10 mm), development of an aortic pseudoaneurysm, aortic dissection or signs of aortic rupture. Under the following situations, the patients would receive TEVAR treatment: during the acute phase, the expansion of the IMH and the development of pseudoaneurysms despite medical therapy, the disruption of intimal tears on CTA examinations with contrast enhancement, and signs of aortic rupture (uncontrollable back pain combined with a precipitous decrease in blood pressure); and during the chronic phase, the development of aortic dissection, the rapid growth of the ULP or aortic diameters ($>$5 mm/year), maximum aorta diameter $>$ 55 mm, or signs of aortic rupture**[1]** . The diameter of the stent graft was based on the diameter of the proximal attachment site with no more than a 10% oversize. At least 1 week of medical therapy (if possible) was employed to provide the initially fragile acute-stage membrane with time to stabilize and become more fibrotic than it was before TEVAR **[15]** . Preoperative or concomitant arch reconstructive methods were also applied, including in situ laser fenestration technology, a sequential debranching procedure and the chimney technique.

Detection of Serum Matrix Metalloproteinase-9

Matrix metalloproteinase-9 (MMP-9) is an important diagnostic biomarker in aortic pathophysiology in which MMP-9 can weaken the aortic media by degrading multiple extracellular components and DM patients have a 2-fold decreased level of MMP-9, which could restrict the degradation of the aortic wall **[16]** . Plasma MMP-9 was measured by using an enzyme-linked immunosorbent assay (ELISA). The MMP-9 level was measured on admission, at day 14 (after the acute phase) and day 90 (after the subacute phase), at 6 and 12 months and then annually during follow-up.

Follow-up and Study Endpoints

All patients were followed for at least three years. The remodeling process was confirmed by the latest CTA scan. The definition of the aortic remodeling process included the stable, resolution and worsening of the hematoma. The primary outcome was aortic-related mortality (confirmed by autopsy or CTA examination), and the secondary outcomes were all-cause mortality and aortic remodeling.

Statistical Analysis

Comparisons between groups were performed by the t -test or Mann-Whitney U test when necessary. Categorical variables are expressed as a frequency and a percentage and were compared with the $\chi 2$ test and Fisher's exact test when appropriate. A Cox proportional hazard analysis was used to calculate the hazard ratios (HRs) and investigate the risk factors of aorta-related mortality. In the multivariate Cox proportional hazard models, the entry and removal criteria were set at P =0.05 and P =0.20. Kaplan-Meier survival analysis with the log-rank test was used to estimate the cumulative mortality and aortic-related mortality in different groups. We used the Kolmogorov–Smirnov test to evaluate the normality of the continuous variables**.** Differences with P values <0.05 were considered statistically significant. IBM SPSS for Windows Version 26.0 (IBM Corp, Armonk, New York) was used for statistical analysis.

Results

Patient Characteristics

Of the patients with intramural hematoma (n=225), one hundred and sixty-six patients were diagnosed with uncomplicated acute IMHBs and included. In total, 149 out of 157 patients completed the follow-up at the end of the study. These patients were classified into two groups (DM group [n=60] and non-DM group [n=89]) according to whether they had DM or not**.** The median follow-up times for each group were as follows: DM group (38.0 months, 95% confidence interval [CI], 36.8-39.1 months) and non-DM group (39.0 months, 95% CI, 36.7-41.2 months). Compared to those without DM, the patients with DM had higher hypertension rate (72% vs 53%, P =0.021) and had lower CRP levels (5.7±1.5 vs 11.3±2.9 mg/dL, P <0.001) and lower white blood cell counts (14.2±1.9 vs 18.3±3.7 10ˆ9/L, P <0.001). The geometric measurements of the aorta indicated that patients the non-DM group had larger ascending aortas (39.9±3.8 vs 37.9±2.5 mm,P <0.001) and descending aortas (37.9±3.5 vs 34.9±2.8 mm, P <0.001) and thicker hematomas (9.5±1.2 vs 7.0±1.3 mm, P <0.001) than those in the DM group. The other demographic characteristics such as concomitant diseases and medical treatment strategy were similar between the two groups (**Table 1**). In the DM group, although the MMP-9 level of DM group reached the highest level (day 14) early than that in the non-DM group (day 90), the MMP-9 levels of DM group were lower than non-DM group at each timepoint (P< 0. 001, **Figure 2A**), and non-DM group had a 2-fold higher level of MMP-9 after the day 90 (**Figure 2A**).

Disease Progression, Treatment and Follow-up

During the acute phase, the occurrence rate of disease progression (20 of 89 cases) was higher in the non-DM group than in the DM group (22% vs 7%, P =0.011), and disease progression occurred obviously earlier than in the non-DM group than in the DM group (6.4±1.3 vs 12.0±1.4 days, P <0.001). Among these twenty cases, the most common sign of disease progression was signs of aortic rupture (eight cases), followed by the development of ULPs (seven cases) and aortic dissection development (two cases) (**Figure 2B**). The occurrence rates of ULPs development (7% vs 0%, P =0.042) and signs of aortic rupture (9% vs 0%, P =0.022) were significantly higher in the non-DM group, while the incidence of other disease progressions signs was similar between the two groups (**Table 2**). Compared to those in the DM group, more patients in the non-DM group received TEVAR treatment during the acute phase (12% vs 2%,P =0.028). The two death cases after TEVAR treatment in the non-DM group include one patient died of retrograde type A aortic dissection and one patient died of aortic rupture (**Figure 2B and Figure 3**).

The aorta-related mortality in patients with IMHB are also summarized in**Table 2** and **Figure 4.** There were significantly differences in the aorta-related death among the DM and non-DM groups during the acute phase (<14 days) (0 vs 8 cases,P =0.042) (**Figure 4A**). The non-DM group also had a higher reintervention rate during follow-up than the DM group (9 in 81 cases, 11% vs 2%, P =0.043). Additionally, the non-DM group had a higher probability of hematoma worsening (22% vs 5%, P =0.004) and a higher rate of aorta-related mortality during the follow-up period (11% vs 2%, P =0.043) than the DM group (**Table 2**).

The Cox regression analysis revealed that ULP development (during the acute phase) (HR, 1.07; 95% CI, 1.01-1.31, P=0.008), CRP level (HR, 1.92; 95% CI, 1.51-2.49, P<0.001) and MMP-9 level (HR, 16.82; 95% CI, 7.52-28.71, P<0.001) were associated with an elevated risk for aorta-related mortality (**Table 3**). The Kaplan-Meier survival analysis revealed a significant increase in the aortic-related mortality rate of the DM

group compared with that of the non-DM group (P =0.0023, **Figure 4B**).

Discussion

Intramural hematoma is part of the spectrum of acute aortic syndromes (5–25%) and is more common in the descending thoracic aorta (type B, 60–70%) than in the ascending aorta [**1-3**] . IMH without malperfusion syndrome are always regarded as a benign disease, and the "wait and watch strategy" (initial medical treatment plus necessary thoracic endovascular aortic repair treatment) is the first recommendation for these patients [**1-3**][**17**]**.** Many potential risk factors of IMHB have also been summarized, including a maximum aortic diameter larger than 45 mm, increased pleural effusion, hematoma thickening larger than 10 mm, ULP development, and elevated C-reactive protein (CRP) levels [**1**]**.** Overall, patients with IMHB have a more favorable long-term prognosis than patients with aortic dissection and an in-hospital mortality risk lower than 10% during the acute phase [**1**]**.** The mortality rate after TEVAR during the acute phase in our study was (**Table 2** , 18% in the non-DM group) obviously lower than that in the report from Schoenhoff et al. (the mortality rate of TEVAR within and after the first two weeks was 25% and 29%, respectively) and was higher than that of type B aortic dissection patients who underwent TEVAR treatment (0% to 18%, and median 6%) [**5**] . Falconi et al. [**18**] reported that of 27 patients with type B IMH managed conservatively and followed for a mean of 33 months, 47% underwent regression, 14% remained stable, and 39% progressed to aortic dissection or enlargement. Motoyoshi et al. [**18**] reported that of 26 patients managed medically, 6 patients (23%) had spontaneous regression and 7 patients (27%) required a surgical procedure. Although the non-DM group in our study had a higher reintervention rate than the DM group during the follow-up [11% vs 2%, P =0.044], the reinvention rate was obviously lower than previous studies (60% [**6**] , 39%[**18**] , 27% [**19**]).

One possible explanation for this higher mortality rate after receiving TEVAR treatment was the larger aorta diameters and thicker hematoma thickness in the non-DM group. Bischoff et al. [**20**]indicated that patients with larger ascending aorta diameters had a worse clinical outcome than those with smaller aortas. Ye et al. also recommended that patients with aortic diameters larger than 45 mm and hematoma thicknesses thicker than 10 mm should be included in the "complicated" group, and that a more aggressive TEVAR treatment was required in these patients to prevent a fatal evolution of the IMHB[**21**] . In addition, the geometry of the aorta can be influenced by TEVAR, which could result in a poor outcome, especially in those with ascending aortas larger than 40 mm (who are more likely to suffer from retrograde type A aortic dissection after TEVAR)[**22**] . In the non-DM group, one patient died of retrograde type A aortic dissection after TEVAR during the acute phase. All the two patients who died after TEVAR in the non-DM group all had ascending aorta larger than 40 mm (**Supplement 1**). Perhaps, an ascending aorta larger than 40 mm is another potential evolution predictor of IMHB.

The other possible explanation for this higher mortality rate was the improper timing of TEVAR and the stent graft size. The current timing of TEVAR for uncomplicated IMHBs is in line with that for the uncomplicated type B aortic dissections (patients with expansion of the IMH despite medical therapy, and the disruption of the intimal tear on CTA scans with contrast enhancement) [**1**][**4**] . However, the disease progression of IMHB is highly unpredictable, and the current guidelines were based on good outcomes of TEVAR for type B aortic dissections[**23**][**24**] and on some small sample studies for IMHBs[**1**][**4**][**25**][**26**] . In other large sample studies, up to 62% of IMHB patients required TEVAR treatment (43% underwent TEVAR during the first two weeks and 19% after acute phase and during the first year), and the mortality rate within and after the first two weeks were 25% and 29%, respectively [**5**] . In our study, all 12 patients with uncontrollable symptoms (especially refractory pain) underwent TEVAR. All the two patients who finally died of aorta-related complications still complained of refractory pain after TEVAR (**Supplement 1**). Juvonen et al. [**27**] reported that patients with uncharacteristic or atypical pain have a higher risk of rupture over time than those without pain. Medical management of such patients is unwarranted unless their life expectancy and quality of life were markedly impaired [**28**] . A more aggressive TEVAR procedure (while the symptoms are still controllable) would likely have better outcomes (acute phase mortality: 0%, Bischoff et al.[**20**] , 0%, Ye et al. [**21**]), and this more aggressive strategy is likely to prevent the progression of IMHBs and

result in a better prognosis than medical treatment plus necessary TEVAR (for patients with uncontrollable symptoms and fatal evolution). Further studies are necessary to evaluate whether uncomplicated IMHBs without diabetes mellitus could benefit from more aggressive TEVAR treatment while the symptoms are still controllable. In addition, in our study, the diameter of the stent graft was oversized by less than 10% which was smaller than those in the study of Schoenhoff et al. (10% to 15%).**[5].** However, both in our study and in the study of Schoenhoff et al. **[5]** , the mortalities rates were higher than those after TEVAR for type B aortic dissection**[4][29]** . For aortic dissections, there is a general agreement in the current guidelines that the oversizing factor should not exceed 5% **[29]** . Is it necessary to utilize less oversizing (not exceeding 5% **[29]**) for stent grafts like the recommendations for aortic dissection for patients with IMHB?

In addition, ULP development during the acute phase and the CRP level was associated with an elevated risk for aorta-related mortality. Moral et al. **[30]** reported that 10% of the patients with uncomplicated IMHBs suffered from the development of an ULP during the acute phase; among these patients, the disease progression rate was as high as to 91%, and 36% of them died of aortic-related complications. Kitai et al. reported that 71% of the patients with IMHBs had an ULP during the acute phase, and 76% of them showed progression (enlargement or progression to aortic aneurysm) that required further treatment**[31]** . The potential risk factors of ULP development are large aortic diameters and hematoma thicknesses, which are also the non-DM patients of IMHBs **[30].** In addition, in the clinical work, a higher CRP level may be indirect evidence that could represent the degree of the inflammatory reaction and pathophysiological changes in the aortic wall under such unstable hemodynamic conditions; a sustained high CRP level has significant prognostic value in IMHB patients **[32].**

Newly diagnosed type 2 DM patients with IMHB probably benefit from antidiabetic treatments and tight glycemic control may influence the evolution of IMHB. The potentially protective value of DM has been well described **[8-11],** and the possible explanations included the increasing matrix of the aortic wall (suppression of plasmin and decreased levels/activity of MMP-9), and decreased aortic mural macrophage infiltration and neovascularization **[16]** . MMP-9 is involved in tissue degradation and remodeling in aortic dissection and is significantly increased in aortic dissection patients, and a higher level of MMP-9 can weaken the aortic media by degrading multiple extracellular components; DM patients have a 2-fold decreased level of MMP-9, which may restrict the degradation of the aortic wall**[16].** Unlike the effect of hyperglycemia on immune cell activity in type 2 DM, the impact of insulin deficiency in type 2 DM on macrophage activity has not been wildly studied. Tessaro et al. demonstrated that the administration of exogenous insulin in diabetes may enhance the immune activity of macrophage **[33]** and the insulin treatment may diminish this protective effect of hyperglycemia that prevent the aortic aneurysm development process (under laboratory conditions) **[34].** For these reasons, it seems that the administration of insulin is probably a risk factor of disease progression in type 2 DM patient with IMHB. In our study, after receiving tight glycemic control recommended by guidelines**[7],** the DM group had an MMP-9 level that was dramatically increased (reached the highest value) during the acute phase and the MMP-9 level of DM group reached the highest level early than that in the non-DM group. But, the MMP-9 levels of DM group were lower than non-DM group at each timepoint ($P< 0.001$, **Figure 2A**) and non-DM group had a 2-fold higher level of MMP-9 after the day 90 than DM group, which probably indicated the potentially protective effect of hyperglycemia probably not decreased after the administration of insulin which probably could explain the significantly lower aorta-related mortality in the DM group during the follow-up period. Until now, the mechanism of the protective effect of hyperglycemia, administration of insulin and other antidiabetics treatment in aortic diseases are still unclear and require further studies.

There are several limitations to this study. First, in this study, the majority of patients received only two CTA examinations during the acute phase (once on admission and once before discharge), and the diagnosis of ULP could be influenced by the preciseness of CTA images. Closer monitoring for the development of an ULP is necessary in further studies. Second, in future studies, we should enroll more patients with different medical treatment strategies, which may provide more meaningful insight into the influence of these strategies on IMHBs.

Summary

Our study suggests that type B intramural hematomas without diabetes mellitus are not benign diseases and have a considerably high aortic-related mortality rates both in the acute phase and during long-term follow-up. Furthermore, ulcer-like projection development (during the acute phase), C-reactive protein level and maximum matrix metalloproteinase-9 are associated with an increased risk of aorta-related mortality.

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Figure 1 CONSORT Diagram of Patient Selection

The CONSORT diagram of the patient selection process is illustrated in this figure. The definition of an intramural hematoma (IMH) is the absence of an intimal dissection or false lumen flow with the presence of a circular or crescent-shaped hematoma larger than 5 mm in the aortic wall. Eligible uncomplicated type B IMH patients who refused further medical treatments and those without complete imaging records, laboratory test results and follow-up data were considered as missing data We used the method of complete-case analysis in which we discarded these missing data with incomplete information.

Figure 2

A) Levels of Plasma Matrix Metalloproteinase-9 in the Two Groups

Plasma matrix metalloproteinase-9 (MMP-9) was measured by using enzyme-linked immunosorbent assay technique, designed by R&D Systems (Minneapolis, MN, USA), according to the manufacturer's instructions and protocols. The levels of MMP-9 were measured at day 14 (after the acute phase), at day 90 (after the subacute phase), at 6 and 12 months and then annually during the follow-up. In the DM group, although the MMP-9 level of DM group reached the highest level (day 14) early than that in the non-DM group (day 90), the MMP-9 levels of DM group were lower than non-DM group at each timepoint ($P< 0.\ 001$,**Figure 2A**), and non-DM group had a 2-fold higher level of MMP-9 after the day 90

B) Clinical Outcomes of Uncomplicated Type B Intramural Hematomas

Sudden death occurred in six patients in the non-DM group (three patients with signs of aortic rupture, one patient with aortic pseudoaneurysm and one patient with retrograde type A aortic dissection) and two patients died after receiving the thoracic endovascular aortic repair (TEVAR) including one case of aortic rupture and one case of retrograde type A aortic dissection. Only two patients underwent conservative treatment because their symptoms were still controllable, while the other eleven patients with uncontrollable symptoms underwent TEVAR (one case of signs of aortic rupture, one case of aortic pseudoaneurysm, two cases of aortic dissection and seven cases of ulcer-like projection development). In the DM group, only one patient of the four with disease progressions received TEVAR (one case of aortic dissection) and other three patients with controllable symptoms received conservative treatment

Figure 3 Evolutions of Type B Intramural Hematomas in non-DM Group

A)This patient with diabetes mellitus (DM) suffered from the hematoma thickening.

B) This patient with ulcer-like projection (ULP) development received emergency thoracic endovascular aortic repair (TEVAR).

C) This patient with increased pleural effusion.

D) This patient with an ULP and increased pleural effusion underwent TEVAR because of aortic rupture signs, and died of a retrograde type A aortic dissection.

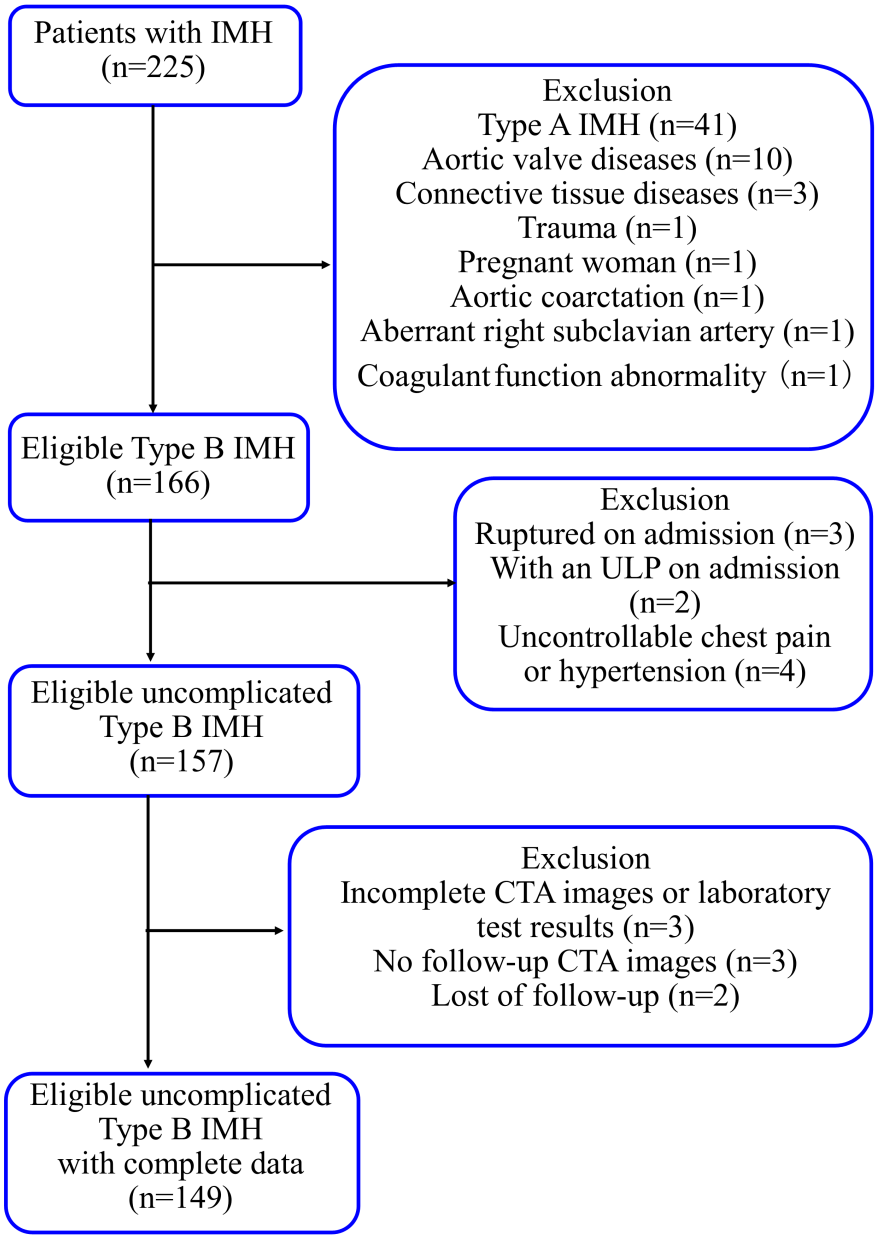
E) The rapid growth of an ULP that became an aneurysm during follow-up.

Figure 4 Kaplan–Meier Survival Analysis Results

A) There were significantly differences in the aorta-related death among the diabetes mellitus (DM) and non-DM groups during the acute phase (<14 days) (0 vs 8 cases, P=0.042).

B) The Kaplan-Meier survival analysis revealed a significant increase in the aortic-related mortality rate of the DM group compared with that of the non-DM group (P=0.0023)

Supplement 1Aorta-related Death Cases During the Acute Phase



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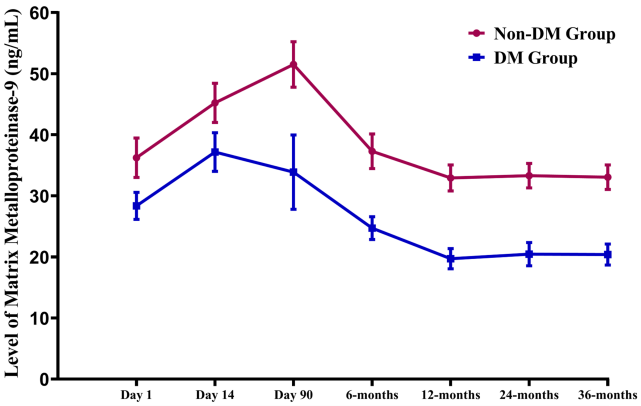
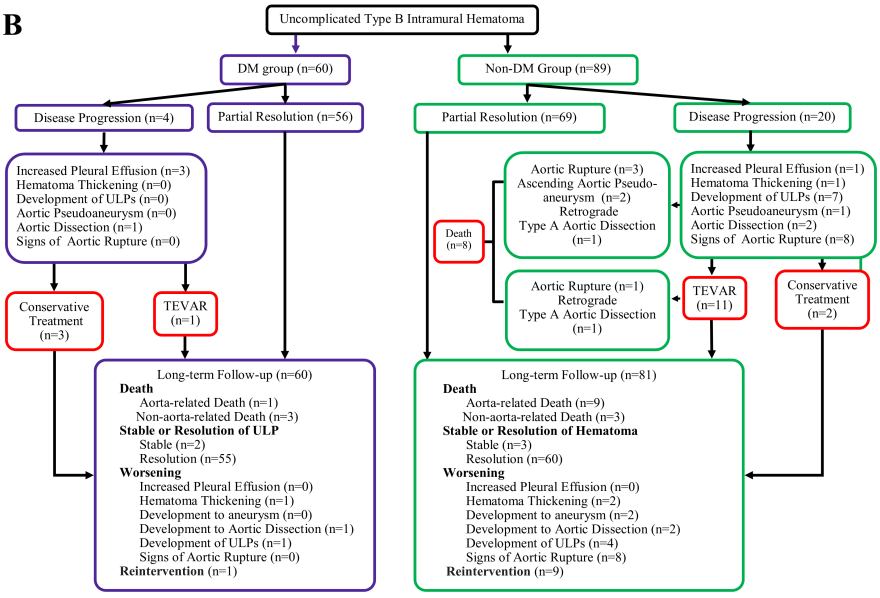
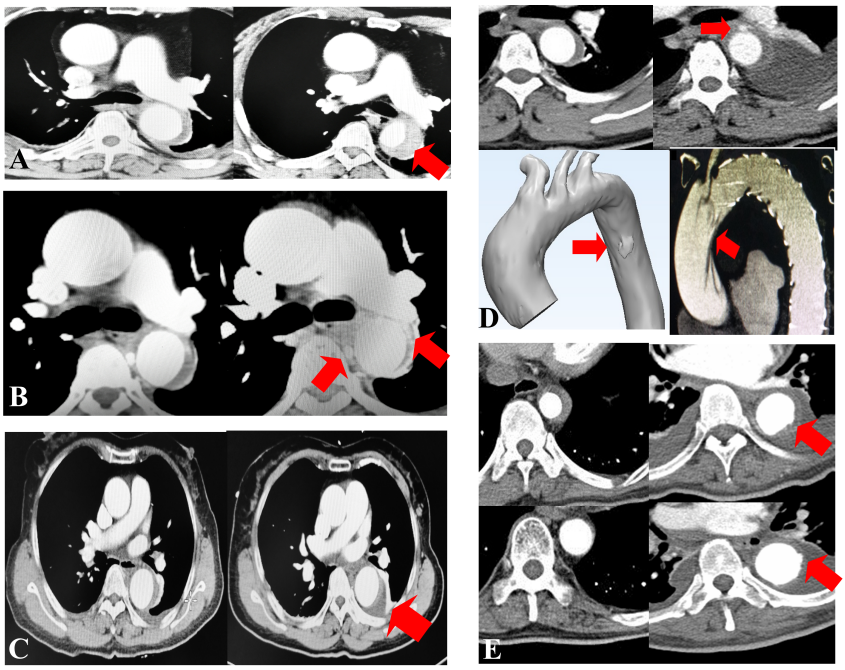
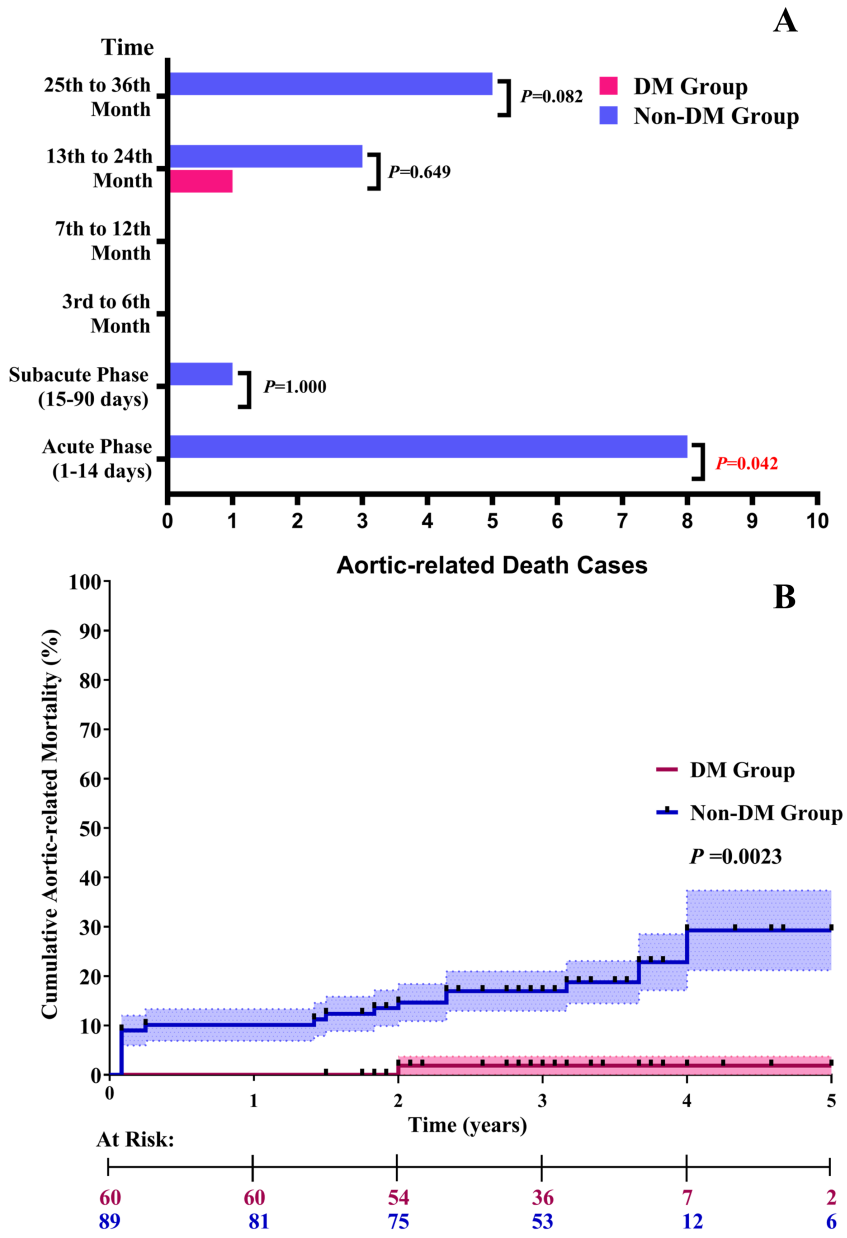


	DM Group	Non-DM Group	*P* value
MMP-9 (ng/mL)			
Day 1	28.4±2.2	35.2±3.2	<0.001
Day 14	37.2±3.1	44.2±3.2	<0.001
Day 90	33.9±6.0	50.5±3.7	<0.001
6-months	24.7±1.8	36.3±2.8	<0.001
12-months	19.7±1.6	32.9±2.1	<0.001
24-months	20.5±1.9	33.3±2.0	<0.001
36-months	20.4±1.7	33.0±2.0	<0.001

B







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