A multi-institutional experience in the aortic and arterial pathology in individuals with genetically confirmed Vascular Ehlers Danlos Syndrome

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Abstract

OBJECTIVE.—Vascular Ehlers-Danlos syndrome (vEDS) is a rare connective tissue disorder due to pathogenic variants in *COL3A1* that lead to impaired type III collagen production. We aim to describe the contemporary multi-institutional experience of aortic and arterial pathology in individuals with vEDS, to evaluate disease patterns, and to refine management recommendations.

METHODS.—This is a cross-sectional retrospective study of individuals with genetically confirmed vEDS between 2000 and 2015 at multiple institutions participating in the Vascular Low Frequency Disease Consortium. Aortic and arterial events including aneurysms, pseudoaneurysms, dissections, fistulae, or ruptures were studied. Demographics, *COL3A1* variants, management, and outcomes data were collected and analyzed. Individuals with and without arterial events were compared.

RESULTS.—Eleven institutions identified 86 individuals with pathogenic variants in *COL3A1* (47.7% male, 86% Caucasian, median age 41 [IQR 31– 49.5] years, 65.1% missense *COL3A1* variants). The median follow up from the time of vEDS diagnosis was 7.5 [IQR 3.5–12] years. A total of 139 aortic/arterial pathologies were diagnosed in 53 (61.6%) individuals (50.9% Male, 88.5% Caucasian, median age 33 [IQR 25–42.3] years. The aortic/arterial events presented as an "emergency" in 52 (37.4%) cases. The most commonly affected arteries were the mesenteric arteries (31.7%), followed by cerebrovascular (16.5%), iliac (16.5%), and renal arteries (12.2%). The most common management was medical management. When undertaken, the predominant endovascular interventions were arterial embolization of medium sized arteries (13.4%), followed by stenting (2.5%). Aortic pathology was noted in 17 (32%) individuals (58.8% male, 94.1% Caucasian, median age 38.5 [IQR 30.8–44.7] years). Most notably, 4 individuals underwent successful abdominal aortic aneurysm (AAA) repair with excellent results on follow up. Individuals with missense mutations, in which glycine was substituted with a large amino acid, had an earlier onset of aortic/arterial pathology (Median age 30 IQR 23.5–37] years) compared to the other pathogenic *COL3A1* variants (Median age 36 [IQR 29.5–44.8] years, P=.065). There were 12 deaths (22.6%) at a median age of 36 [IQR 28–51] years.

CONCLUSIONS.—Most of vEDS arterial manifestations were managed medically in this cohort. When intervention is required for an enlarging aneurysm or rupture, embolization and less frequently stenting, appear to be well tolerated. Open repair of AAA appears to be as well tolerated as those without vEDS; vEDS should not be a deterrent to offering an operation. Future work to elucidate the role of surgical interventions and refine management recommendations in the context of patient centered outcomes is warranted.

Keywords

Vascular Ehlers-Danlos Syndrome; *COL3A1* mutation; Arterial dissection; Arterial aneurysm; Arterial rupture

INTRODUCTION

Vascular Ehlers-Danlos syndrome (vEDS) is a rare syndrome in which type III collagen production is reduced or the collagen produced is defective because of autosomal dominant mutations in *COL3A1*.[1–3] The syndrome, which was previously called Ehlers-Danlos syndrome type IV is one of 13 subtypes of Ehlers-Danlos syndrome.[4] In addition to spontaneous intestinal perforation or rupture of a gravid uterus, the hallmark of the disease is spontaneous arterial dissections, aneurysms, and rupture at a young age.[1,2,5]

Up to 40% of individuals with vEDS experience their first major arterial complication by age 40.[2,6] The classically reported arteries include mesenteric, renal, iliac, femoral and/or the abdominal aorta, followed by the carotid, subclavian, ulnar, popliteal, and tibial arteries.[7] A spontaneous carotid-cavernous fistula (CCF) is pathognomonic of vEDS and estimated to occur in 9.8% of individuals with vEDS.[8]

The predominant challenges to studying vEDS are driven by the rarity of the disease, the heterogeneous presentation of aortic and arterial pathology, the large number of pathogenic variants in *COL3A1* leading to vEDS, lack of robust longitudinal data, and under or misdiagnosis. While we have a basic understanding of the natural history of the disease based on seminal work[2] and a limited understanding of the genotype-phenotype correlation[6,9–11], we do not have a detailed natural history of aortic and arterial aneurysms and dissections in this population. Nor do we have a clear understanding of the risk of complications, once diagnosed and treated.[12] The aim of this study is to describe the contemporary multi-institutional experience of aortic and arterial pathology in individuals with vEDS, to evaluate disease patterns, and refine management recommendations to improve our understanding of genotype-phenotype correlations.

METHODS

The Vascular Low Frequency Disease Consortium

This is a multi-institutional retrospective cross-sectional cohort study of individuals diagnosed with vEDS between January 1, 2000 and December 31, 2015. The 11 institutions were recruited through the Vascular Low Frequency Disease Consortium (University of California-Los Angeles Division of Vascular Surgery).[13] Each participating center obtained its own Institutional Review Board (IRB) approval. The IRBs waived the patient consent

process due to minimal patient risk. Data were collected by each institute's respective investigator(s), deidentified, and then submitted and stored using a password-encrypted database maintained by the University of Washington.

Identification of individuals with vEDS, Inclusion/Exclusion Criteria

Individuals were initially identified with International Classification of Diseases (ICD)-9 -CM code 756.83 or ICD-10-CM code Q79.6 for Ehlers-Danlos syndrome. Confirmatory molecular testing results were then reviewed by a geneticist (PHB) to confirm that the *COL3A1* variant is a pathogenic variant in keeping with the ACMG guidelines.[2,9,10] Individuals were included for analysis only if they had a pathogenic variant in *COL3A1*. The pathogenic *COL3A1* variants were grouped into missense mutations (glycine substations), exon skip and splice site variants, and haploinsufficiency (null mutations). [6,9–11,14–16] The type of amino acid substitution was noted as a large or small amino acid.[6,15]

Demographics, current age, age at diagnosis, family history, clinical diagnostic criteria[17], aortic and arterial pathology, management of aortic and arterial pathology, and outcomes were collected. Family history was defined as a family history of vEDS, aortic or arterial aneurysms and dissections, and/or sudden death. Arterial pathology included aortic and arterial aneurysms, dissections, pseudoaneurysms, fistulae, thrombosis, or ruptures. Arterial pathology was noted as emergent if it was life threatening on presentation. This included aortic or arterial rupture, symptomatic aortic/arterial dissections, and CCF.

Given that subject data was collected locally at each participating institution and then submitted as de-identified data to the consortium, a comparison of all the presentations, COL3A1 variants, and demographics was performed to assure that there were no duplicated cases. Data were analyzed using Microsoft Excel 2007 software (Microsoft, Redmond, WA) and SPSS version 19 for Windows (SPSS, Inc., Chicago, IL). Continuous data are presented as medians and interquartile ranges (IQR).Continuous data were compared using Wilcoxon rank-sum (Mann-Whitney) test. Categorical data were compered by Chi square or Fisher's exact test where appropriate. The comparisons of the onset of the arterial pathology and survival were performed using Kaplan–Meier survival curves with Log-rank test. All statistical tests were two-sided and a P-value < .05 was considered statistically significant.

RESULTS

Eight-six individuals had molecular confirmation of vEDS (47.7% male, 86% Caucasian, median age 41 years, IQR 31– 49.5 years, range 1–88 years). The cohort included 19 (22.1%) individuals who were diagnosed as children (age < 18 years old). The median follow up from the time of vEDS diagnosis was 7.5 (IQR 3.5–12) years.

A total of 139 aortic/arterial pathologies were diagnosed in 53 (61.6%) individuals (50.9% Male, 88.5% Caucasian, median age 33 years, IQR 25–42.3 years). The aortic/arterial events presented as an "emergency" in 52 of (37.4%) cases.

The diagnosis of vEDS was already established in 20 (37.3%) individuals prior to the diagnosis of aortic/arterial pathology. The diagnosis of vEDS was less likely be known in the emergent setting compared to the elective stetting (18.2% vs. 55.2%, P=.007).

There were no differences between men and women in the age of the initial aortic/arterial pathology diagnosis (Median 32 [IQR 23–42] years among men, median 36 [IQR 26.8–43.3 years among women, P=393), or the time of first aortic/ arterial rupture (Median 33 [IQR 15.5–49] years among men, median 39 [IQR 30–46.7] years among women, P=.540). The individuals with aortic/arterial pathology were significantly older than those without (Table 1). In addition, the group without aortic/arterial pathology included 14 children compared to only one child who presented with type B aortic dissection (TBAD) at age 12 years old (had missense mutation, p.Gly244Arg). Those patients with aortic/arterial pathology had more hypertension and deep vein thrombosis. There were no differences in the type of pathogenic *COL3A1* variants or minor clinical diagnostic criteria between those with and without aortic/arterial pathology, with the exception of a lower frequency of hypermobile small joints (32.1% vs. 54.5%, P=.039).

Arterial pathology

The most commonly affected arteries were the mesenteric arteries (31.7%), followed by cerebrovascular and iliac arteries (16.5% each), and renal arteries (12.2%). Arterial pathology included aneurysms (53.8%), dissections (35.3%), rupture (10.1%), pseudoaneurysms (3.4%), thrombosis (2.5%), and CCF (4.2%). Figure 1 shows Kaplan-Meier estimates of cumulative survival free of any arterial pathology. Table 2 summarizes the presentation and management of the arterial pathologies.

- *Carotid cavernous fistulae.* CCF occurred in 4 individuals ((Table 3). Management was predominantly via embolization with satisfactory outcomes (Figure 2). None of the CCFs were associated with mortality.

- *Carotid and vertebral pathology other than CCF.* These patients presented with small aneurysms or dissections. All were managed medically, as detailed in table 2. Most had no complications, with the exception of one patient with a vertebral artery dissection leading to a lateral medullary infarct and death.

- *Mesenteric arteries.* The celiac artery was the most commonly affected mesenteric artery (Figure 3), however, the splenic artery was most frequently affected by rupture (36.4%). Medical management was the most common approach (Table 2) with the exception of cases in which rupture or pseudoaneurysms occurred. These cases were treated most commonly with endovascular embolization, and in one case with stenting (Figure 4), with satisfactory results. There was one mortality in this group (a patient who presented with multiple mesenteric arterial ruptures).

- *Renal arteries.* Renal arteries presented with nearly equal frequency of dissections and aneurysms. Aneurysm sizes were recorded in 4 cases (0.8 cm, 0.8 cm, 1.2 cm, and 3 cm). The predominant approach to treatment was medical management (Table 2), with the exception of two patients requiring intervention:

a 40-year-old male who underwent embolization (no additional detail), and a 29-year-old male (c.1124G>A, p.Gly375Glu) who presented with left renal artery thrombosis that was treated with thrombolysis. This approach was complicated by splenic hemorrhage requiring a splenectomy. He presented 5 months later with aneurysmal degeneration of the renal artery and underwent a successful nephrectomy (6 year follow-up).

- *Iliac arteries.* Twenty-three common, external, and internal iliac arteries had pathology, which was diagnosed as isolated iliac disease in 9 (16.9%), and in association with abdominal aortic aneurysm in 8 (15.1%) individuals (Table 2). Most were managed medically. Stenting was performed in 2 cases (c.3847C>T, p.Gln1283Ter and c.3320G>A, Gly107Glu) for common iliac artery aneurysms, using femoral artery exposure and stent repair, with satisfactory results. Open iliac repair was performed in 3 cases:

  ○ For an iliac artery rupture in a 50-year-old male (c.1295G>A, p.Gly432Asp), which was complicated with post-operative wound dehiscence with development of enterocutaneous fistula

  ○ For an iliac artery dissection with thrombosis treated with an uncomplicated iliofemoral bypass in a 30-year-old male (c.674G>C, p.Gly225Ala). The patient has had 6 years of follow-up post procedure without complication.

  ○ For an iliac artery aneurysm treated with an uncomplicated open bypass in a 41-year-old male (c.2356G>A, p.Gly786Arg). Of note, this individual had a prior open repair for a ruptured abdominal aortic aneurysm repair at age 33. The patient has had 10 years of follow up post procedure without complication.

- *Posterior tibial arteries:* Two patients had posterior tibial artery aneurysms (3.8%); one was managed medically. The other individual was a 19-year-old male with bilateral posterior tibial artery aneurysms (1.5 and 2 cm respectively). Open repair with saphenous vein bypass graft was performed for the larger aneurysm. This procedure was complicated by hematoma due to vein graft disruption, requiring re-operation. Other rare presentations included involvement of the cerebral and coronary arteries as follows:

- *Cerebral arteries.* Only one individual was affected (1.9%). This was a 39-year-old female (Haploinsufficiency/Null mutation) who presented with a left middle cerebral artery dissection. The dissection was managed medically and she is alive at age 43.

- *Coronary arteries:* There were two cases (3.8%) of coronary artery dissection. One occurred in a 45-year-old woman (c.4360C>T, p.Gln1454Ter) who was initially managed medically but subsequently underwent coronary artery bypass. She has had one-year follow-up without complications. The second case was in a 41-year-old woman (c.2337+2T>C, p.Gly762_Lys779del) who was hospitalized

for a spontaneous perforation of the colon. She developed a left anterior descending coronary artery dissection and subsequent cardiac arrest.

Endovascular Procedures for medium sized arteries

Embolization of medium sized arteries was the predominant endovascular procedure performed (n=16, 13.4%), followed by stenting (n=3, 2.5%) as described previously. Percutaneous access was used in 14 cases for sheath sizes of 4–7 French. Manual pressure post procedure was used in 7 cases (4 in which the vEDS diagnosis was not known at the time); the closure was satisfactory in all 7 cases, with one (14.3%) hematoma reported. A closure device was used in 5 cases: Angio-Seal™ (n=2), StarClose (n=1), Perclose ProGlide (n=1). All were reported to be successful. Open femoral artery exposure and repair was performed in an additional 3 cases, with one complicated by hematoma.

Aortic Pathology

Aortic pathology was identified in 17 (32%) individuals (58.8% male, 94.1% Caucasian, median age 38.5 [IQR 30.8–44.7] years). Hypertension was noted in 52.9% (n=9) and smoking in 29.4% (n=5) of the cases. The most common *COL3A1* variant was a missense mutation with glycine substitution with a large amino acid residue (n=11, 64.7%).

Thoracic aortic pathology was reported in 10 individuals and abdominal aortic pathology was reported in 7 individuals (Table 4). Notably, there were two thoracic endovascular aneurysm repairs (TEVAR) performed for descending thoracic aortic aneurysm ruptures in which the diagnosis of vEDS was unknown at the time. One individual died while the other had a successful repair (Table 4). In one case, an open thoracoabdominal aortic aneurysm (TAAA extent II) was performed successfully in a 19-year-old male with a missense mutation (Table 4).

Among the abdominal aortic aneurysm cases, four individuals underwent successful open abdominal aortic aneurysm (AAA) repair with excellent long-term follow up (3 had ruptured AAA, table 4). In one case, an endovascular aneurysm repair (EVAR) was performed for aortic dissection prior to diagnosing vEDS. This patient had no short-term complications, with one-year follow-up.

Aortic rupture occurred in 7 individuals (41.4%) and was the cause of death in 2 (11.7%) individuals: a ruptured type A aortic dissection and a ruptured TBAD complicated by infectious aortitis.

Mortality

The median follow up after the first arterial event was 5 [IQR 2.5–12] years. There were 12 deaths (22.6%) at a median age of 36 [IQR 28–51] years (58.3% male, 83.3% Caucasian). Table 5 summarizes the characteristics and causes of mortality and figure 5 shows Kaplan-Meier estimates of cumulative survival.

Genotype-phenotype correlation

The molecular confirmation in this cohort was performed by genetic testing, showing a pathogenic variant in *COL3A1* (n=81) or by skin biopsy (N=5). Missense mutations with a substitution of glycine with a large amino acid were the most common type of pathogenic variant (n=44, 51.2%) followed by missense mutations with a substitution of glycine residue with a small amino acid (n=12, 14%). Null mutations occurred in only 7 individuals (8.1%).

While not statistically significant, individuals with missense mutations in which glycine was substituted with a large amino acid had an earlier onset of aortic/arterial pathology (median 30 [IQR 23.5–37] years) compared to the other pathogenic *COL3A1* variants (median 36 [IQR 29.5–44.8] years, P=.065). There were no differences between the variant groups in terms of arterial/aortic pathology or rupture.

DISCUSSION

A substantial challenge to evaluating treatment of arterial/aortic pathology in individuals with vEDS is the rare frequency of the disease (1:50,000), such that few centers have any significant experience.[5,11,12,18] This multi-institutional study is a step in the direction of better understanding the natural history in vEDS and management outcomes.

Several generalizations can be made based on this cohort. Most of the carotid (other than CCF), vertebral, mesenteric, and renal manifestations of the syndrome can be managed medically. When management of arterial manifestations is required due to spontaneous rupture, enlarging aneurysms, or pseudoaneurysms, an endovascular approach, mostly with coil embolization, and less frequently with stenting, appears to be well tolerated and these results are consistent with previous reports.[18,19] Access site management in this series had few complications, including those managed with manual compression and closure devices. This finding is to be interpreted with caution, since we usually recommend open femoral artery exposure and primary repair as previously described[18,20] for access puncture sites in patients with known vEDS diagnosis, as this allows the most control of the artery. While thrombolysis for arterial thrombosis was performed in one case in this series, it was associated with a spontaneous hemorrhagic complication. Given the risk of spontaneous hemorrhage, we do not recommend thrombolysis in individuals with vEDS.

CCF embolization appears to offer satisfactory results. This finding confirms previous reports; a referral to a neuro-interventionalist is recommended in these cases.[21,22] While we did not find a consistent approach for embolization in these cases, the transvenous approach appears to offer a decreased risk of vascular injury.[21,22]

Iliac arteries dissections without thrombosis can be managed medically, while aneurysm repairs are based on association with an AAA. Endovascular stenting of an aneurysmal iliac artery has been reported to be successful.[23]

Several observations can be made in relation to aortic pathology in this cohort. First, aortic disease seems more frequent in thoracic segment than in the abdominal differently that the observed frequency in the general population. Given the small numbers, it is difficult to draw

any additional conclusions from this observation but it is worth noting with plans for further evaluation. Second, an open repair of ruptured AAA appears to be as well tolerated as those without vEDS. Therefore, vEDS should not be a deterrent to offering an operation for a ruptured AAA. We recommend Teflon or felt reinforcements for the anastomoses in all aortic repairs. Third, two TEVARs were reported in this cohort (one associated with death) and one EVAR with a short post-operative follow up duration. These repairs were performed prior to knowing the vEDS diagnosis. There has been a single case report of successful of TEVAR[24] in an individual with vEDS. However, we recommend against the use of TEVAR or EVAR in individuals with vEDS, based on extrapolating from other connective tissues disorders such as Marfan's syndrome. TEVAR and EVAR in this population carry a significant risk of use perforation and erosion at the fixation zones, due to the fragility of the aortic wall, and, with TEVAR, the risk for retrograde aortic dissection.[18,25]

An interesting finding was the observation of a higher frequency of hypertension and deep vein thrombosis in the vEDS patients with arterial pathology. We were not able to ascertain if these diagnoses were pre or post diagnosis of the aortic/arterial pathology. We also did not ascertain if the affected individuals were taking an antihypertensive. Another interesting finding was a significantly higher frequency of small joint hypermobility in the individuals who did not have arterial pathology, but the significance of this finding is unclear.

We did not find sex differences at initial arterial presentation, similar to what has been previously reported.[6] Other studies have shown an increased risk of sudden death related to arterial ruptures in males younger than 20 years.[10] A plausible explanation that unites these disparate findings is the bias toward those who survived to have a diagnosis.

Similar to prior studies, the missense mutations (glycine substitutions) in *COL3A1* were over-represented in this cohort. Missense mutations are the most common type of variant affecting *COL3A1*. The variant results in a substitution of a glycine residue in the Gly-X-Y repeats of the triple helical domain thus disrupting the type III collagen folding. As a consequence a minimal amount of normal collagen (10–15%) is excreted from the cell into the extracellular matrix.[14] Similarly, exon skip and splice site variants create a frameshift that results in exon (s) deletion and production of defective collagen similar to the effect of pathogenic missense variants.[6,16] The biologic explanation is related to the disruptive effect this type of variant has on the type III collagen folding process.[6,10] While, haploinsufficiency/Null mutations lead to the creation of a premature termination codon thus the affected gene is essentially silent resulting in the production of half the amount of normal type III collagen. Thus missense variants cause a more severe phenotype of vEDS, [10] while haploinsufficiency mutations lead to milder phenotype.[6,9–11] In our cohort, individuals with missense mutations in which the substitution of glycine is with a large amino acid appeared to present with aortic/arterial pathology an at earlier age, compared to the other types of variants, including missense mutations with substitution of glycine with a small amino acid. This is plausible as prior work demonstrated increased disruption of the collagen triple helix when Gly is replaced by a large amino acid rather than by a smaller amino acid.[6,15] However, our study was underpowered to detect a statistically significant difference and therefore replication in a larger cohort is warranted.

We recommend a raised index of suspicion at the time of initial presentation of aneurysms and dissections in young individuals especially with a family of aneurysms/dissections and presence of clinical diagnostic features of vEDS. This then should lead to confirmatory genetic testing rather than relying on clinical criteria alone, for vEDS diagnosis given the overlap in clinical features with other forms of Ehlers-Danlos syndrome and other genetically triggered aortopathies.[4,6] Additionally, understanding the type of *COL3A1* variant allows for counseling on the effect of the variant type on an individual.[6,9–11,26] Moreover, individuals with an established diagnosis preoperatively have improved outcomes when undergoing elective surgical repairs or interventions compared to those who require emergency operative repair.[11] Our work and others substantiate that the genetic testing is no longer experimental or investigational and has real consequences to the affected individual, in terms of surveillance, the operative approaches, perioperative care, and pregnancy planning. These consequences are relevant to family members as well.

Once the diagnosis is confirmed, we recommend establishing a multidisciplinary care team locally and at a tertiary care center, to coordinate care including diagnostic testing, surveillance, and surgical repairs.[12] The care team should include a vascular surgeon, a geneticist, and a primary care provider who organizes the variable levels of care needed by the patient. Baseline arterial imaging should be performed during the initial consultation visits. There are no trials delineating the frequency of surveillance imaging, nor did we ascertain the frequency of imaging in this study. In general, we recommend that surveillance imaging be tailored to the symptoms and presentation of each individual.

This study has several limitations. We did not evaluate the role of medical management in mitigating the risk of aortic/arterial pathology, using beta-blockers, losartan, vitamin C, or adjunctive measures during open repairs such as the use of desmopressin (DDAVP).[5,27–29] We were also unable to ascertain if the diagnosis of aneurysms and dissections was incidental, made because of surveillance, or because of symptoms. Additionally, the retrospective nature of this study limits an understanding of the decision-making used in management or the indication for the elective operations beyond what has been presented in the results. Lastly, the imaging for all the individuals in this cohort was not available to review in a standardized manner. Review of imaging is highly relevant to understanding the natural history of vEDS and should be included in future study designs.

Future directions include work within the vEDS Research Collaborative to enroll individuals with genetically confirmed vEDS into a large natural history study.[30] This is necessary to obtain detailed longitudinal data to better characterize the natural history and outcomes to guide future management recommendations.

CONCLUSIONS

Most of the arterial manifestations of vEDS were managed medically in this cohort. When intervention is required due to spontaneous rupture or enlarging aneurysms, embolization (and less frequently stenting) appears to be well tolerated. Open repair AAA was tolerated and as such, the diagnosis of vEDS should not be a deterrent to offering an operation. Future directions include enrolling patients prospectively into the vEDS Research Collaborative to

further ascertain the natural history, elucidate the role of surgical interventions, and to refine management recommendations in the context of patient centered outcomes.

Acknowledgments:

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Highlights

Type of Research:

Cross-sectional retrospective study of the Vascular Low Frequency Disease Consortium

Key Findings: :

In this group of 86 individuals with genetically confirmed vascular Ehlers-Danlos Syndrome (vEDS), with pathogenic COL3A1 variants, most patients were managed medically. For treatment of an enlarging aneurysm or rupture, embolization and stenting were well tolerated. Four patients underwent successful open abdominal aortic aneurysm repair.

Take home message:

Genetic confirmation of pathogenic COL3A1 variants of vEDS is essential for counseling affected individuals on the effect of their variant type and directing care. When intervention is required, embolization and stenting are acceptable options. Open repair of abdominal aortic aneurysms is also well tolerated.

TOC Summary:

In this multi institutional retrospective study of 86 individuals with genetically confirmed vascular Ehlers-Danlos Syndrome, with pathogenic COL3A1 variants, most patients were managed medically. When intervention was required for an enlarging aneurysm or rupture, embolization and stenting were well tolerated. Four patients underwent successful open abdominal aortic aneurysm repair.
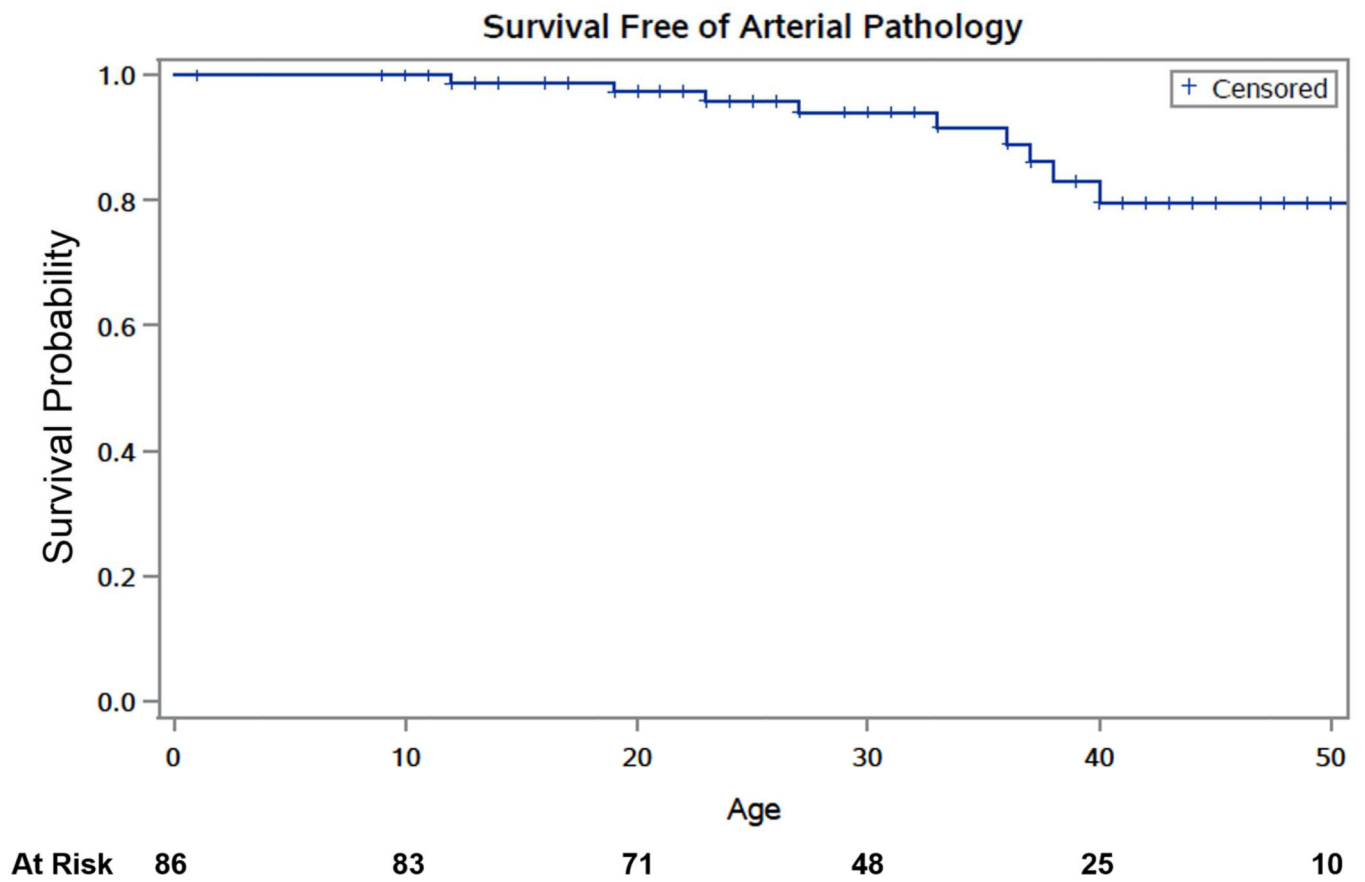
Figure 1.
Kaplan-Meier estimates of cumulative survival free of any arterial pathology in a cohort of individuals with vascular Ehlers-Danlos syndrome.

Figure 2.
The angiographic findings of a carotid cavernous fistula in a 41-year-old woman with vascular Ehlers-Danlos syndrome due to a splice site mutation (c.2337+2T>C/p.Gly762_Lys779del) presenting with sudden onset ipsilateral retro-orbital pain, blurry vision, and tinnitus. (A) Pre-embolization. (B) Post coil embolization.
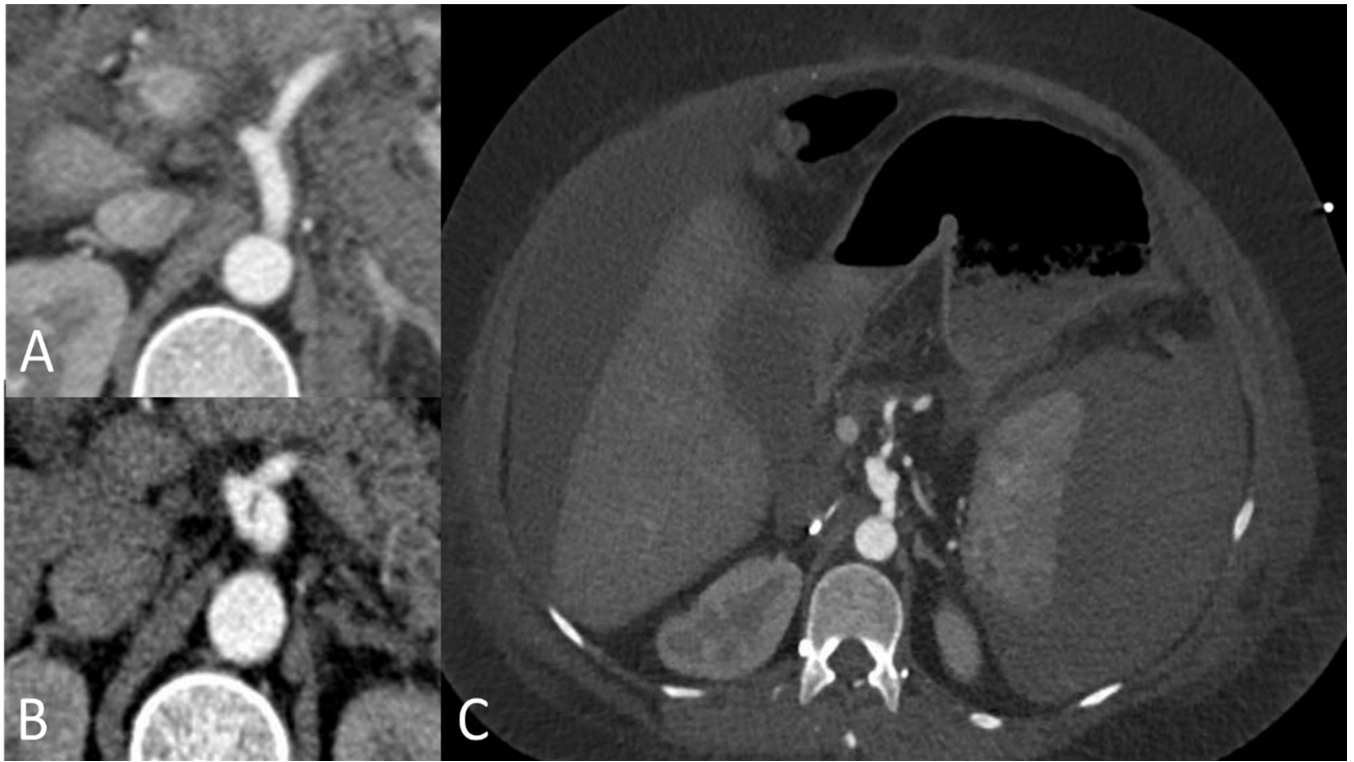
Figure 3.
Celiac artery dissection in 36 year old woman with vascular Ehlers-Danlos syndrome due to a splice site mutation (c.2337+2T>C/p.Gly762_Lys779del) managed medically. **A**. axial CT imaging obtained one month prior to the dissection when she presented with a spontaneous hemoperitoneum managed medically. **B**. Axial CT imaging demonstrating focal dissection and mild enlargement of the celiac artery. This remained unchanged on follow up imaging over the next 5 years. **C**. Axial imaging demonstrating a large spontaneous subcapsular splenic hematoma and hemoperitoneum. This occurred following a complicated hospitalization for perforated sigmoid diverticulitis requiring sigmoid resection, transverse colostomy and Hartmann's pouch.

Figure 4.
Angiogram showing a proper hepatic artery pseudoaneurysm in a 49 year old man with vascular Ehlers-Danlos syndrome due to a haploinsufficiency mutation (A). The pseudoaneurysm was excluded with 5-mm x 2.5-cm Viabahn stent (B and C)
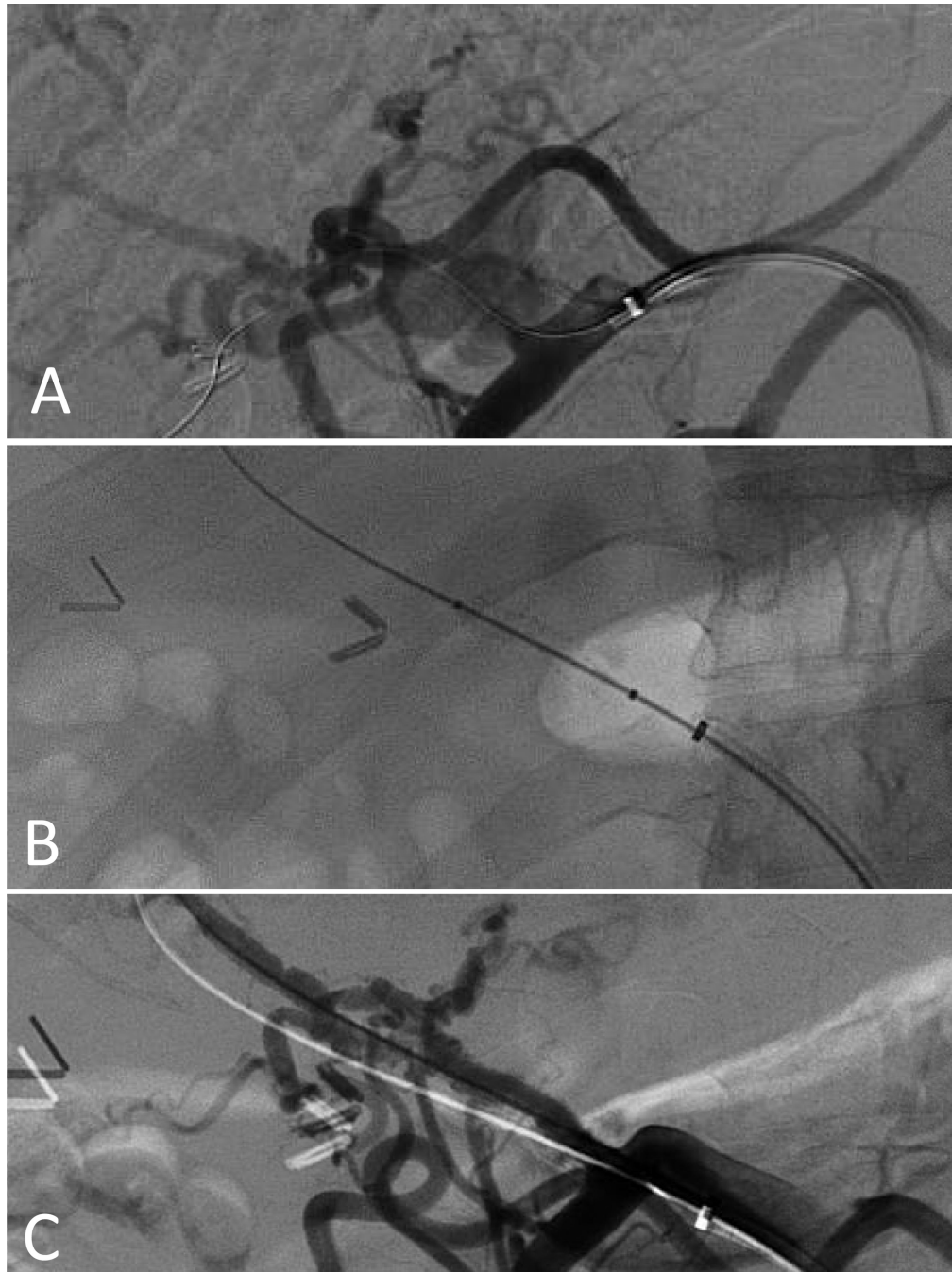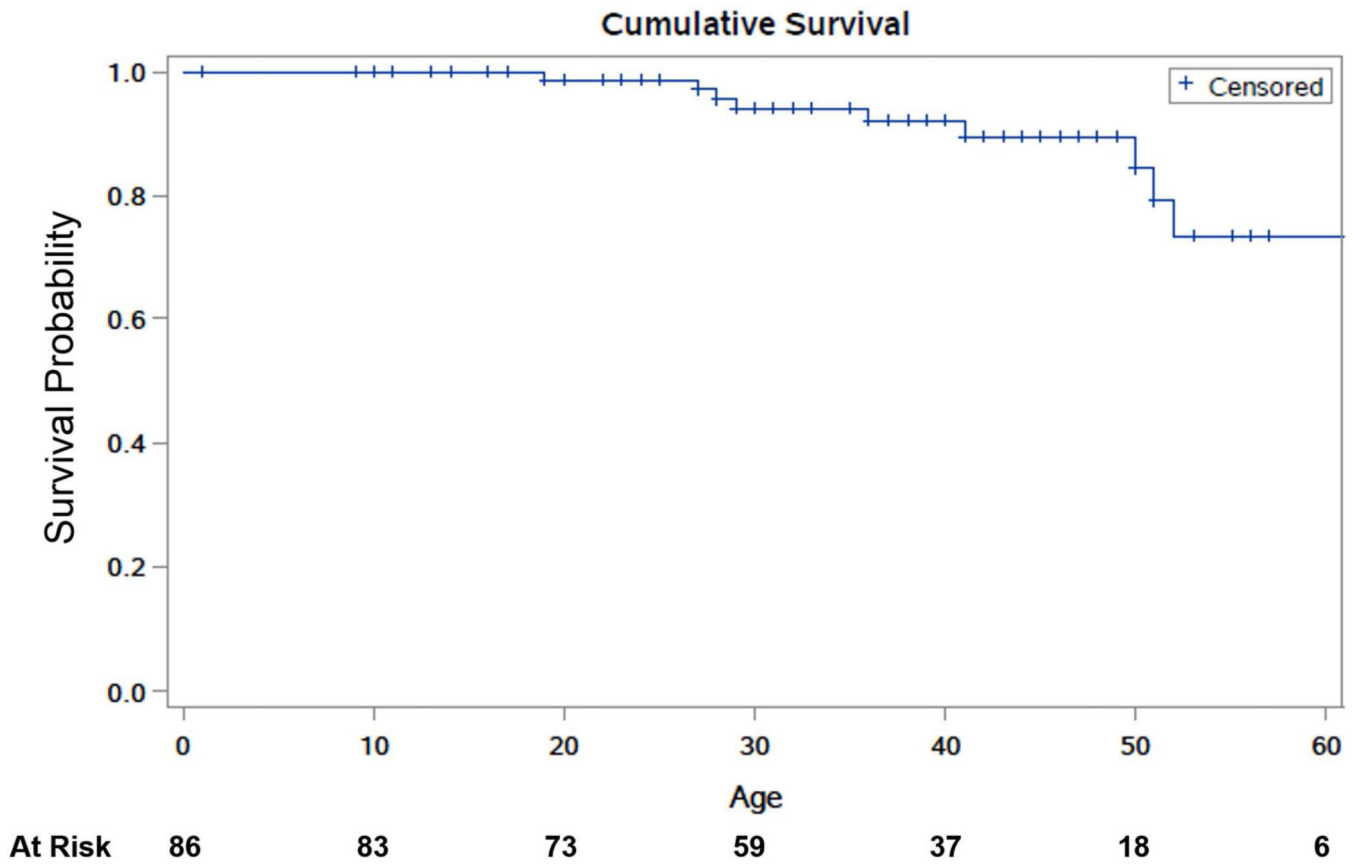
Figure 5.
Kaplan-Meier estimates of cumulative survival in individuals with vascular Ehlers-Danlos syndrome

Table 1.

A comparison of individuals with vascular Ehlers-Danlos syndrome with and without a diagnosis of aortic/arterial pathology

N (%), Median [IQR]	Aortic/Arterial pathology (n=53)	No aortic/arterial pathology (n=33)	P
Current Age	41 [31–49.5]	25 [15–41.5]	<.001
Age range	19–79	1–88	-
Age at diagnosis	32 [23–43.3]	18 [10–31]	<.001
Male	27 (50.9)	14 (42.4)	0.442
Caucasian	47 (88.7)	27 (81.8)	0.491
BMI	24.6 [21.6–27.4]	22.9 [17.1–25.3]	0.068
Hypertension	17 (32.1)	2 (6.1)	0.005
Deep vein thrombosis	12 (22.6)	1 (3)	0.014
Intestinal perforation	9 (17)	5 (15.2)	0.823
Spontaneous PTX/HTX	7 (13.2)	5 (15.2)	0.800
Current or past smoker	12 (22.6)	5 (15.2)	0.396
Family history of VEDS	24 (45.3)	18 (54.5)	0.403
Follow up post vEDS diagnosis	7.5 [3.5–12]	5 [1–11]	0.152
Died	13 (24.5)	0	0.002
Age at death	39 [27.8–51.3]	-	-

Table 2.

Presentation and management of arterial pathology in patients with vascular Ehlers-Danlos syndrome by artery involved. The % given is the percentage of all arterial pathology

Arteries N (%)	% Male	Median Age (IQR)	Known vEDS diagnosis	Missense mutation	Dissection	Aneurysm, Pseudoaneurysm	Rupture	Medical Management	Endovascular Embolization	Endovascular Stenting	Open Repair
Carotid N=17 (12.2)	5 (41.7)	27 (24–36)	4 (33.3)	8 (66.7)	6 (50)	5 (41.7), 1 (8.3)	0	100%	0	0	0
Vertebral N=6 (4.3)	2 (33.3)	27.5 (22–32.5)	3 (50)	5 (83.3)	4 (66.6)	1 (16.7)	0	100%	0	0	0
Celiac N=14 (10.5)	6 (40)	44 (33–50)	12 (80)	11 (73.3)	7 (46.7)	7 (46.7), 2 (13.3)	2 (13.3)	13 (86.7)	1 (6.7) *	0	1 (6.7)
Gastric N=3 (2.2)	0	37 (36–37)	2 (66.7)	2 (66.7)	1 (33.3)	0	0	3 (100)	0	0	0
Phrenic N=1 (0.7)	0	58	1 (100)	1 (100)	0	1 (100)	0	1 (100)	0	0	0
Splenic N=11 (7.9)	3 (27.3)	44 (31–51)	6 (54.5)	6 (54.5)	2 (18.2)	8 (72.7)	4 (36.4)	4 (36.4)	6 (54.5)	0	1 (9.4)
Hepatic N=8 (5.8)	5 (62.5)	47 (38.5–50.5)	5 (62.5)	4 (50)	0	7 (87.5), 1 (12.5)	1 12.5	5 (62.5)	2 (25)	1 (12.5) (Figure 3)	0
Superior mesenteric N=6 (4.3)	1 (16.7)	45.5 (39–54.4)	5 (83.3)	3 (50)	2 (33.3)	2 (33.3)	1 (16.7)	5 (83.3)	1 (16.7) *	0	0
Renal N=17 (12.2)	12 (70.6)	37 (30.5–41)	9 (52.9)	13 (76.5)	7 (41.2)	8 (47.1), 1 (5.9)	0	14 (82.4)	1 (5.9)	0	2 (11.8)
Iliac N=23 (16.5)	18 (78.3)	41 (30–48)	12 (52.2)	19 (82.6)	7 (30.4)	16 (69.6)	1 (4.3)	17 (73.9)	1 (4.2)	2 (8.7)	3 (13)
Femoral N=2 (1.4)	1 (50)	27,33	0	2 (100)	1	1	0	1	0	0	1
Popliteal N=1 (0.7)	0	26	0	1 (100)	0	1	0	1 (100)	0	0	0
Posterior Tibial N=3 (2.2)**	2 (100)	19,32	1 (50)	1 (50)	0	3	0	2	0	0	1

*
Same individual, death due to multiple mesenteric arterial ruptures

**
One individual had bilateral posterior tibial arteries aneurysms

Table 3.

Presentation and management of carotid cavernous fistulae in patients with vascular Ehlers-Danlos syndrome

Age/Sex	*COL3A1* variant	Presentation	Management, access site	Length of stay (days), disposition
49F	c.2131G>A, p. Gly544Ser (missense)	Rupture	Embolization, Percutaneous, 5 Fr, manual pressure closure	7, Home, Alive at 63 14 years follow up
51M	IVS8+5 G>A (Exon skip)	N/A	Embolization, Percutaneous, 5 Fr, manual pressure closure	3, Home, alive at 70
41F	c.2337+2T>C, p.Gly762_Lys779del (splice site)	Ipsilateral retro-orbital pain, blurry vision, and tinnitus	Embolization, Percutaneous, 6 Fr, closure with angioseal (Figure 3)	4, Home. Less than 1 year follow up. Died from unrelated complications
42F	Pathogenic	Bilateral	Non-operative	N/A

Table 4.

Presentation and management of aortic pathology in 17 individuals with vascular Ehlers-Danlos syndrome.

Age/Sex	COL3A1 variant*	Location /type	Management	Known vEDS diagnosis	Outcomes
		Thoracic Aorta (N=10)			
33M	c.601G>C, p.Gly201Arg	Thoracic aneurysm	Medical	Yes	Died at age 51 due to stroke
44F	c.970G>A, p.GlyS24Ser	ATA aneurysm	Medical	Yes	Alive at age 48
37F	c. 764G>A,p.Gly255 Glu	Ruptured type A aortic dissection	Medical	Yes	Cause of death
79M	c.SS20G>A, p.Gly1107Glu	Arch PAU	Medical	Yes	-
40F	c.2222G>A, p.Gly574Asp	DTAA	Medical	Yes	Diameter 4.2 cm. Alive at age 41
53M	c.S966delG, p.Lys1S2SArgfs*64 (null)	TBAD/rupture	Medical	Yes	Cause of death, Ruptured due to aortitis
40M	c.926G>A, p.Gly142Glu	TBAD, mild ATA dilation	Medical	No	Alive at age 49
12M	c.547G>C, p.Gly18SArg	DTAA rupture	TEVAR	No	Discharged home after 2 days. Died at age 27 from multi-organ failure
27F	c.1024G>A, p.GlyS42Arg	DTAA rupture	TEVAR	No	Cause of death
19M	c.12S1G>C, p.Gly244Arg	TBAD	Open Repair	Yes	Extent II TAAA repair at age 21. Discharged home after 10 days. Alive at age 29
		Abdominal Aorta (N=7)			
33F	c.996+2G>A, p.Gly318_Pro332del (splice site)	Infrarenal abdominal aortic dissection	Medical	No	Aortic diameter 1.9 cm. Alive at age 34
30F	c.1330G>A, p.Gly444Arg	Abdominal aortic dissection	Medical	Yes	-
45M	Pathogenic	AAA/ Dissection	EVAR	No	Alive at age 46
27M	c.2113G>A, p.Gly705Arg	AAA/Dissection	Open Repair	No	Discharged home after 8 days. alive at age 31
33M	c.2356G>A, p.Gly786Arg	Ruptured AAA	Open Repair	No	Takeback for a ruptured gallbladder. Alive at age 51
43F	Pathogenic	Ruptured AAA	Open Repair	No	Discharged to rehab after 24 days, wound complicated by infection. Alive at age 48
48M	c.3847C>T, p.Gln1283Ter	Ruptured AAA	Open Repair	Yes	Take back right limb ischemia. Discharged home after 7 days. Alive at age 56

AAA: Abdominal Aortic Aneurysm. ATA: Ascending Thoracic Aorta. DTAA: Descending Thoracic Aortic Aneurysm. EVAR: Endovascular Aneurysm Repair. PAU: Penetrating aortic ulcer. TBAD: type B aortic dissection. TEVAR: Thoracic Endovascular Aneurysm Repair.

*
All are missense mutations unless specifically noted.

Table 5.

Age and causes of death among 12 individuals with vascular Ehlers-Danlos syndrome along with the age of diagnosis, pneumothorax, colon perforation, first arterial pathology and rupture

| Age/Sex | Col3A1 Variant | Age | | | | | Cause of Death |
		Diagnosis	Pneumo thorax	Colon Perforation	Arterial pathology	Arterial Rupture	
19M	Pathogenic	19			19	19	Myocardial infarction with associated ventricular rupture
27F	c.1024G>A, p.Gly342Arg	17	23		27	27	Hemothorax
28F	c.2069G>T, p.Gly690Val	23			23	26	Lateral medullary infarct due to vertebral artery dissection
29M	c.547G>C, p.Gly183Arg	12			12	12	Multiple organ failure
36F	c.764G>A, p.Gly255Glu	36			36	36	Ruptured type A aortic dissection
41F	c.2337+2T>C,	24		36	36	41	Cardiac arrest due to left anterior
50F	IVS34+2T>C, p.Gly762_Lys779del Pathogenic	32	33	46	38	46	descending coronary artery dissection multiple visceral arteries ruptures
51M	c.601G>C, p.Gly201Arg	29	25		33		Stroke
53M	c.3966delG, p.Lys1323Argfs*64	43			36	53	ruptured type B aortic dissection due to Infectious aortitis
28M	c.2445+2dupT, IVS37+2dupT, p.Gly798 Pro815del	24	22		22		unknown
52M	1295G>A, p.Gly432Asp	51			40	50	unknown
70M	IVS8+5 G>A, p.Gly195_Ser212del	58		50	51		unknown