Big Data Analytics to Estimate Prevalence of Ehlers-Danlos Syndrome (Vascular Phenotype) and Rate of Rupture Events

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BACKGROUND

Ehlers-Danlos syndromes (EDS) are a heterogeneous group of connective tissue disorders. The most serious subtype of which is the vascular phenotype (EDS-VP).

- EDS includes many clinical subtypes with widely different phenotypes and prognoses.
- EDS-VP is most serious, caused by mutation in *COL3A1* gene, resulting in defective type III collagen protein.
- Defective type III collagen in the walls of arteries and hollow organs leads to tissue fragility and increased susceptibility to rupture.
- EDS-VP has unpredictable course that may lead to premature death from spontaneous arterial or organ ruptures.
- The median age of death for EDS-VP patients is 50 years[1].

Despite the severity of EDS-VP relative to other subtypes of EDS, United States medical coding groups all EDS under a single code. This has limited studying EDS-VP prevalence and outcomes.

- Majority of EDS-VP patients are diagnosed following a major complication (70%) at an average age of 30 years[1].
- There are no good estimates of EDS-VP prevalence[2].
- ~1,500 EDS-VP patients have been identified based biochemical or genetic testing[2]. However, many patients many die before being diagnosed.
- Estimated prevalence is 1:200,000 - 1:50,000, but these numbers lack supportive real-world evidence.

To distinguish EDS-VP from other subtypes of EDS, we developed an inception cohort strategy to identify patients with rupture events using real-world evidence from a large administrative claims database (Figure 1).

- The International Classification of Diseases, Ninth and Tenth Revisions (ICD-9 and ICD-10) as well as the Current Procedural Terminology (CPT) were reviewed to identify diagnosis and procedure codes pertinent to EDS-VP.
- EDS-VP is clinically suspected in patients with any of the major diagnostic criteria[3]: (1) family history of EDS-VP; (2) arterial rupture; (3) spontaneous sigmoid colon perforation; (4) uterine rupture during pregnancy; or (5) carotid-cavernous sinus fistula formation.
- We selected diagnosis, laboratory test, and procedure codes that indicate one of the above major diagnostic criteria.
- Using this approach, we estimate prevalence of EDS-VP in the United States and determine rate of rupture events.

METHODS

Data: This study used the Truven MarketScan® claims database, an administrative database covering over 180 million patients in the United States. Use of medical services is recorded in the database with date of service, provider-type, metropolitan statistical area (MSA) of service, associated diagnoses, and performed procedures. This database is compliant with the Health Insurance Portability and Accountability Act. Because the data are commercially available and deidentified, institutional review board approval was not required. Analyses were conducted in November 2017.

Study design: Administrative claims data, including diagnosis, procedure, and laboratory tests, were evaluated over a three-year identification period from January 1, 2014 to December 31, 2016. Patients were identified as having EDS if they had at least 2 medical claims for an EDS diagnoses, separated by at least 2 months; requiring 2 separate EDS diagnoses helped to minimize misdiagnoses. Patients with suspected EDS-VP were further identified using the inclusion criteria described below. Because hypermobility is common in many subtypes of EDS, but very uncommon in EDS-VP, patients with any claims for hypermobility syndrome were excluded from the EDS-VP group (**Figure 1**).

Inclusion criteria for suspected EDS-VP:

- ≥2 claims for diagnosis of EDS (ICD-9: 756.83, ICD-10: Q79.6) separated by ≥2 months.
- ≥1 claim for diagnosis, laboratory test, or procedure indicating presence of EDS-VP major criteria (**Table 1**).
- No claims for hypermobility syndrome (ICD-9: 728.5, ICD-10: 728.5).

Demographic analysis: The base sample population was defined as all United States patients with administrative claims in the Truven MarketScan® database during the three-year study period. Patients younger than age 18 years at the time of initial EDS diagnosis were classified as pediatric, and those age 18 years and older were classified as adults. All EDS cases and all suspected EDS-VP cases were recorded as total counts and percent of entire base sample population. These data were evaluated separately for adults and children and further stratified by sex and adult age groups.

Prevalence estimates: Prevalence was defined as the number of patients meeting the suspected EDS-VP inclusion criteria per 100,000 patients in the entire sample population over the three years study period. To account for local variations, the prevalence of EDS-VP in each MSA was evaluated separately and an average was calculated to determine a nationwide prevalence. To extrapolate the number of suspected EDS-VP cases in the United States, the calculated prevalence was applied to the 2016 United States Census population estimate. The 2016 adult United States population was estimated to be 326 million. Confidence intervals were calculated assuming a Poisson distribution.

Rate of rupture events and interventions: To determine the rate of rupture events in the suspected EDS-VP patient population, we evaluated diagnosis and procedure claims related to arterial or solid organ rupture events over the same three-year period. We limited evaluation to a subgroup of suspected EDS-VP patients with ≥1 year of claims history preceding the first EDS diagnosis. By ensuring at least 1 year of prior claims history, we could confirm that each claim for a rupture event indicated the initial claim for the event and did not reflect claims for follow up encounters for remote rupture events. Claims were grouped into one of seven different categories of rupture events, based on literature reports of the most common events in EDS-VP populations (**Table 2**). Total patient counts for each rupture category were reported. Counts were limited to one rupture events per category for each patient per year to prevent duplicate counting for follow up encounters. Finally, we calculated the percentage of each rupture event that was intervened upon, either by surgical or endovascular procedure.

Figure 1. Study Design and Inclusion Criteria for Suspected EDS-VP Patients.

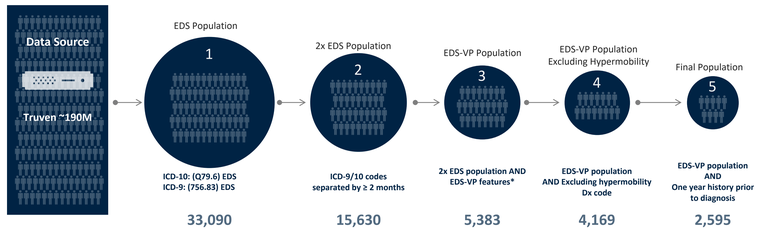

Figure 2. Geographic Distribution of EDS-VP Patients.

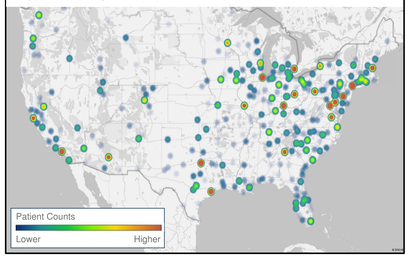

Figure 3. EDS-VP Patients with Events in Multiple Years.

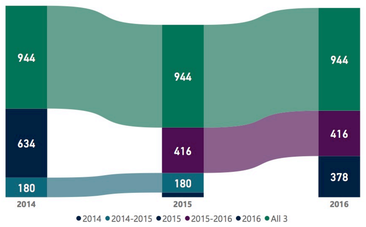

Figure 4. Rate of EDS-VP Rupture Events.

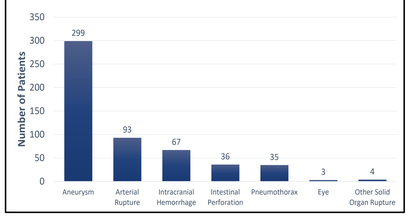

Figure 5. Rate of Interventions for EDS-VP Ruptures.

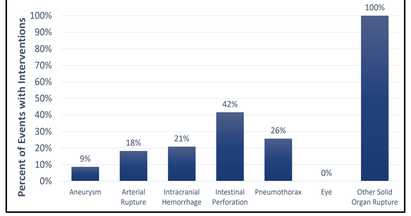

Table 1. Claims Used to Identify EDS-VP Patients

Diagnosis Codes	Aneurysm and/or dissection:
	Carotid artery
	Cerebral artery
	Iliac artery
	Splenic artery
	Thoracic aorta
	Vertebral artery
	Carotid-cavernous fistula
	Hemorrhagic stroke (age <40 y)
	Intestinal rupture
	Uterine rupture
Laboratory Tests	*COL3A1* genetic testing
Procedure Codes	Surgical or endovascular repair:
	Carotid artery
	Carotid-cavernous fistula
	Iliac artery
	Splenic artery
	Thoracic aorta
	Vertebral artery
	Angiography
	Blood transfusion

Table 2. Claims Used to Identify EDS-VP Rupture Events

Event Category	Included Diagnoses	Excluded Diagnoses
Aneurysm	Aneurysms of large- or medium-sized arteries	Abdominal aorta
Arterial rupture	Rupture/dissection of large- or medium-sized arteries	Abdominal aorta
	Heart wall rupture	Coronary artery
	Chordae tendineae rupture	
	Mitral valve prolapse	
	Carotid-cavernous sinus fistula	
Intracranial hemorrhage	Intraparenchymal hemorrhage	Ischemic stroke
	Subdural hemorrhage	Embolic stroke
	Subarachnoid hemorrhage	
	Stroke (age <45 years)	
Intestinal perforation	Bowel wall rupture	Gastrointestinal hemorrhage
		Perforated ulcers
Pneumothorax	Pneumothorax	Pulmonary hemorrhage
Eye	Globe rupture	Microvascular disease
Other solid organ rupture	Bladder wall rupture	
	Spleen rupture	
	Kidney rupture	

Table 3. Patient Counts of EDS and EDS-VP Cases

Variable	No. (%) Sample Size	EDS Cases	EDS-VP Cases
Adult patients, age ≥18 y	145 million	11,494	3,521
Male	68 million (46.9%)	1,916 (16.7%)	631 (17.9%)
Female	77 million (53.1%)	9,578 (83.3%)	2,890 (82.1%)
Pediatric patients, age <18 y	51 million	4,136	643
Male	26 million (51.3%)	1,641 (39.7%)	270 (42%)
Female	25 million (48.7%)	2,495 (60.3%)	373 (58%)
Age category	196 million	15,630	4,164
<18	51 million (25.9%)	4,136 (26.5%)	643 (15.4%)
18-34	54 million (27.6%)	5,586 (35.7%)	1,386 (33.3%)
35-44	27 million (13.8%)	2,578 (16.5%)	824 (19.8%)
45-54	27 million (13.6%)	1,770 (11.3%)	628 (15.1%)
55-64	24 million (12.3%)	1,214 (7.8%)	503 (12.1%)
≥65	13 million (6.8%)	346 (2.2%)	180 (4.3%)

RESULTS

Demographic analysis: Summarized in **Table 3**. Male to female ratio was near equal in base sample population. Compared to base sample population, EDS-VP patients were younger with a mean age of 36 ± 17 years and 34% of the patients between the ages of 18 and 34 years. For both EDS and EDS-VP, there were more female than male cases. Suspected EDS-VP patients were concentrated in more populated areas with New York City, Chicago, and Dallas being the top three MSAs (**Figure 2**). After controlling for general population density, the highest relative density of EDS-VP patients were located in Iowa metropolitan areas (**Data not shown**).

Prevalence estimates: We identified 4,169 suspected EDS-VP cases. After stratifying by the number of cases in each MSA, controlling for differences in population density, we calculated an average nationwide EDS-VP prevalence of 2.2 per 100,000 (95% CI, 2.1-2.3). Based on these prevalence estimates, if we were to apply our estimates to the United States population, 7,087 cases of EDS-VP would be estimated for the United States over the time period of 2014-2016 (95% CI, 6,845-7,329).

Rate of rupture events and interventions: 2,595 suspected EDS-VP patients were evaluated. 11% had at least one rupture event at an average rate of 1.2 events per year. 33% had multiple rupture events and several of the events affected more than one arterial site or organ system. **Figure 3** illustrates the distribution of patients who had more than one rupture events in different years of the study. Of the total 537 rupture events, 299 (56%) involved an arterial aneurysm, 93 (17%) arterial rupture, 67 (12%) intracranial hemorrhage, 36 (7%) intestinal perforation, 35 (7%) pneumothorax, 3 (<1%) eye rupture, and 4 (<1%) other solid organ ruptures (**Figure 4**). The percentage of each event category requiring surgical or endovascular intervention were 9% of events involving arterial aneurysm, 18% of arterial rupture, 21% of intracranial hemorrhage, 42% of intestinal perforation, 26% of pneumothorax, 0% of eye, and 100% of other solid organ ruptures (**Figure 5**).

LIMITATIONS

- Reliance on administrative data, without confirmatory biochemical or genetic testing, limits certainty of EDS-VP diagnosis in our study population.
- Medical codes lack granularity to capture unique characteristics of EDS-VP, lowering sensitivity and specificity of our approach.
- Although we employed a broad range of ICD and CPT codes to capture rupture events, it is possible that capture was sub-optimal and not all rupture events and interventions were captured accurately.
- Truven sample population may differ demographically from the Unites States population with a higher proportion of employer sponsored commercially insured patients, limiting generalizability of our approach.

CONCLUSIONS

- This study assessed the prevalence and clinical burden of EDS-VP in the United States.
- Using big data claims analyses and EDS-VP-associated event criteria, we identified a presumed EDS-VP population based on phenotypic presentation.
- Our EDS-VP prevalence estimates are slightly higher than those reported for genotypically-confirmed cases of *COL3A1* mutation carriers. Therefore, we may be capturing some additional phenotypically similar subtypes of EDS or those due to mutations other than *COL3A1*.
- Demographics of our population were similar to prior reports.
- The rate of arterial and organ ruptures along with percentage of these events requiring invasive interventions reflects a high clinical burden for these patients.
- Coupled with previously published estimates that 25% of EDS-VP patients experience a major complication by age 20 years and 80% by 40 years, it is imperative that comprehensive efforts are geared towards early detection and diagnosis.
- Future studies using electronic medical records, genetic analysis, and specialty lab data should be leveraged to confirm and advance these findings.

REFERENCES

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3. Malfait F, *et al.* Am J Med Genet C Semin Med Genet, 175, 8-26, (2017).

DISCLOSURES

TG, MK, and TA, are employed by HVH Patient Precision Analytics, which received funding for this research from Acer Therapeutics. JP is a consultant for HVH Patient Precision Analytics. CS is an employees of Acer Therapeutics.

Presented at NORD Rare Diseases and Orphan Products Breakthrough Summit | Washington, D.C. | October 15-16, 2018