EPH25

# Claims-based Algorithms to Identify Persons with Severe Hemophilia A

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## Summary

ICD-10 diagnosis codes for hemophilia A do not differentiate by disease severity.

We developed claims-based algorithms to identify persons with severe hemophilia A among those with hemophilia A.

We conducted a retrospective review of medical records to test algorithm performance.

The algorithm with hemophilia A treatments demonstrated satisfactory performance, increasing confidence in its ability to identify patients with severe hemophilia A in healthcare claims.

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## Background & Objective

- Hemophilia A is an inherited deficiency of clotting Factor VIII that impairs hemostasis and coagulation ability, resulting in excessive musculoskeletal bleeding. It is characterized as severe, moderate, or mild based on level of Factor VIII activity.
- ICD-10 diagnosis codes for hemophilia A do not differentiate by disease severity.
- Compared to less severe patients, those with severe hemophilia A experience differences in disease burden, resource use, and outcomes. Being able to identify patients by disease severity in a large population using healthcare claims data would improve estimates of disease burden and healthcare utilization.
- Particularly when studying rare diseases, use of algorithms that don't accurately identify the population of interest can lead to misclassification bias and incorrect estimation of incidence and health services utilization (Benchimol J Clin Epi 2011).
- **We aimed to develop and test claims-based algorithms to identify persons with severe hemophilia A among those with hemophilia A.**

## Methods

- Conducted a retrospective review of medical records of a purposive sample of 100 male patients with hemophilia A (53 severe, 47 not severe) without von Willebrand disease at 4 geographically dispersed treatment centers in the United States from 01/2020-07/2021.
- Used cognitive interviews with 4 physicians to develop variables that 1) could be used in healthcare claims and 2) could identify patients with severe hemophilia A. Physician verified diagnosis of hemophilia A severity was considered the gold standard.
  - Variables were grouped into distinct concept groups: symptoms of hemophilia A, treatment of symptoms, treatments of hemophilia A, and side-effects of treatments (**Table 1**).
- Tested the variable performance.
  - Calculated sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for each variable.
  - Calculated pairwise correlations for each variable pair within the concept groups.
  - The higher performing variable in pairs with high correlation, defined as |r|≥0.5, remained in the concept group.
- Concept groups were tested individually and in combination to identify algorithms with high sensitivity, specificity, PPV, and NPV. The use of intravenous or intranasal desmopressin (DDAVP) was incorporated in all concept groups testing.
- Patient weight, which is unavailable in healthcare claims, was collected and compared to expected weights based on CDC's weight for age tables.
- To account for the evolving treatment landscape, separate algorithms with or without hemophilia A treatment were identified.

**Table 1. Concept Groups and Variables**

| Concept Group Name | Variables[1] | |
|---|---|---|
| **Symptoms of hemophilia** | • ≥1 non-traumatic intracranial hemorrhage (age ≤60 years[2]) | • ≥2 diagnoses of arthropathy per year (age ≤35 years[2] or any age)<br>• ≥2 diagnoses of hemarthrosis per year |
| **Treatments for symptoms of hemophilia** | • ≥2 joint replacements/fusions (age ≤40 years[2] or any age)<br>• ≥1 joint replacement/fusion (age ≤40 years[2]) | • ≥10 physical therapy visits per year<br>• ≥90-day supply of opioids per 6-month period (age ≤40 years[2])<br>• ≥2 prescriptions for a COX-2 inhibitor per year |
| **Treatments of hemophilia** | • Evidence of prophylaxis – high (at least 50 units of Factor VIII/kg per week for 45 weeks in 1 year)<br>• Evidence of prophylaxis – low (at least 50 units of Factor VIII/kg per week for 22 weeks in 6 months) | • ≥1 prescription for emicizumab<br>• ≥1 central line procedure |
| **Side effects of treatments** | • Evidence of inhibitors (operationalized as ≥1 prescription for a bypassing agent) | |

[1]All variables were originally included for correlation testing. After testing, variables in blue were removed from concept groups.
[2]Age cut offs were determined with clinical input based on when that variable would be more likely to identify severe hemophilia than another condition (e.g., joint replacements due to hemarthrosis rather than advancing age).

## Limitations

- Included a small and purposive sample of patients, which may not be representative of the general population and may have artificially decreased algorithm performance.
- Clinic medical records are incomplete. Hospitalizations, procedures, and home bleeding episodes may not have been thoroughly documented.
- Assumed that the data abstracted from medical records is represented in healthcare claims but did not validate algorithms in the full healthcare claims records of the included study patients.

## Results Study Sample

- Mean age of the sample was 27.7 years and was similar among patients with mild/moderate and severe disease (**Table 2**).
- Average weight for both groups was similar, both when using weights reported in medical charts (mild/moderate 70.9kg; severe 67.3kg) and expected weights based on age (mild/moderate 65.5kg; severe 68.8kg).
- Mean follow up was approximately 2.5 years (899 days).

**Table 2. Study Sample**

| | All Patients | Mild/Moderate Hemophilia A | Severe Hemophilia A |
|---|---|---|---|
| Number of patients, % | 100 | 47 (47%) | 53 (53%) |
| Mean age in years at last clinic visit (SD) | 27.7 (19.6) | 28.2 (21.3) | 27.3 (18.1) |
| Mean weight in kg reported in medical charts (SD) | 69.0 (27.6) | 70.9 (30.8) | 67.3 (24.5) |
| Mean weight in kg expected based on age (SD) | 67.3 (25.0) | 65.5 (26.1) | 68.8 (24.1) |
| Mean study period (follow-up), days (SD) [median] | 899 (174.1) [824.0] | 926 (172.5) [879.0] | 876 (173.8) [811.0] |

SD=Standard deviation

## Results Algorithm Performance

- In the pairwise correlation analysis, a total of 4 variables were removed (**Table 1**, variables in blue).
- The candidate algorithm with hemophilia A treatments included: FVIII prophylaxis (≥50 units of FVIII/kg/week for 45 weeks/year) OR emicizumab use OR central venous catheter placement/removal
  - Resulted in 92.5% sensitivity, 66.0% specificity, 75.4% PPV, and 88.6% NPV (**Table 3**).
- The candidate algorithm without hemophilia A treatments included: symptoms of hemophilia A (non-traumatic intracranial hemorrhage OR arthropathy OR hemarthrosis) OR treatments for symptoms (≥2 joint replacements OR ≥10 physical therapy visits OR ≥90-day opioid supply OR ≥2 COX-2 inhibitor prescriptions)
  - Resulted in 52.8% sensitivity, 70.2% specificity, 66.7% PPV, and 56.9% NPV (**Table 3**).

**Table 3. High-Performing Concept Groups**

| Concept Groups | Sensitivity | PPV | Specificity | NPV |
|---|---|---|---|---|
| **With hemophilia A treatment**<br>Treatments of hemophilia and no DDAVP[1] | 92.5% | 75.4% | 66.0% | 88.6% |
| **Without hemophilia A treatment**<br>Symptoms of hemophilia OR treatments for symptoms, and no DDAVP[2] | 52.8% | 66.7% | 70.2% | 56.9% |

DDAVP=Intravenous or intranasal desmopressin, PPV=positive predictive value, NPV=negative predictive value
[1]Included FVIII prophylaxis (≥50 units of FVIII/kg/week for 45 weeks/year) OR emicizumab use OR central venous catheter placement/removal.
[2]Included symptoms of hemophilia (non-traumatic intracranial hemorrhage OR arthropathy OR hemarthrosis) OR treatments for symptoms (≥2 joint replacements OR ≥10 physical therapy visits OR ≥90-day opioid supply OR ≥2 COX-2 inhibitor prescriptions).

## Conclusions

- We developed evidence-based algorithms informed by clinicians and tested the performance of these algorithms in medical records. Using this methodology helps the algorithms resonate clinically to future users, such as clinicians, researchers, and payers.
- The algorithm with hemophilia A treatments demonstrated satisfactory sensitivity and specificity, increasing confidence in its ability to identify patients with severe hemophilia A in healthcare claims, with expected weight potentially being a suitable proxy for use in healthcare claims. We expect algorithm performance to be better in a real-world random sample of patients (compared to our purposive study sample).
- This algorithm will help improve estimates of disease burden and healthcare utilization of patients with severe hemophilia A by allowing researchers to use healthcare claims datasets to identify these patients.
- Future research should focus on developing a satisfactory algorithm without hemophilia A treatments as the treatment landscape continues to evolve.

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### References

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