A Computable Phenotype for HSVAnterior Uveitis: Operationalizing the SUN Classification Criteria

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Purpose

Data models in healthcare have the potential to drastically improve observational research, especially for rare diseases like uveitis. The purpose of this study was to operationalize the Standardization of Uveitis Nomenclature (SUN) classification criteria for herpes simplex virus (HSV) anterior uveitis into the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM). Additionally, we sought to validate and possibly improve our computable OMOP definition by comparing our claims database results with published literature and EHR databases to past manual chart reviews.

Methods

The SUN classification criteria for HSV anterior uveitis were used to construct a computable phenotype, or cohort definition, using the Observational Health Data Sciences and Informatics (OHDSI) ATLAS tool. Concept sets, or lists of concepts or clinical events, were created to represent each specific component of the SUN classification criteria and combined using logic operators to construct a phenotype for HSV anterior uveitis. This phenotype was then applied to multiple databases. We conducted an internal validation by applying the OMOP phenotype to 2 EHR systems and conducting a manual chart review. We also applied the computable phenotype to Optum's Clinformatics® claims database, using OHDSI's phenotype library, for external validation. The effectiveness of each component of the SUN criteria in identifying the patient population was assessed, highlighting the most useful elements and noting those needing improvement.

SUN Classification Criteria for Herpes Simplex Anterior Uveitis	ATLAS
1. Evidence of anterior uveitis	condition occurences of '**OMOPUveitis Anterior uveitis**'
a. anterior chamber cells	condition occurences of '**OMOPUveitis Anterior chamber cell**' measurements of '**OMOPUveitis Anterior chamber cell**'~~, numeric value > 0; with value as concept: ">50 cells", "21-50 cells", "11-20 cells", "5-10 cells", "1+", "2+", "3+", "4+", "present + out of ++++", "present ++ out of ++++", "present +++ out of ++++", "present ++++ out of ++++", "+", "++", "+++", "++++", "trace", "trace", "positive" or "positive"~~ observations of '**OMOPUveitis Anterior chamber cell**'
b. if anterior vitreous cells are present, severity is less than anterior chamber inflammation	condition occurrences of '**OMOPUveitis Anterior vitreous cell**'; having at least 1 condition occurrence of '**OMOPUveitis Other anterior segment inflammation**', at same visit as '**OMOPUveitis Anterior vitreous cell**'
c. no evidence of retinitis	Entry events having at most 0 condition occurrences of '**OMOPUveitis Retinitis exclusion**', starting between 30 days before and 30 days after cohort entry start date; at same visit as cohort entry.
AND	
2. Unilateral uveitis (unless there is a positive aqueous PCR for herpes simplex virus)	Entry events with any of the following criteria: 1. having at most 0 condition occurrences of '**OMOPUveitis Bilateral uveitis**', starting between 30 days before and 30 days after cohort entry start date; at same visit as cohort entry 2. having at least 1 measurement of '**OMOPUveitis HSV AC PCR positive**'
AND	
3. Evidence of herpes simplex infection in the eye	
a. aqueous humor PCR positive for herpes simplex virus OR	having at least 1 specimen of '**OMOPUveitis HSV AC PCR positive**', allow events outside observation period; with any of the following criteria: 1. having at least 1 measurement of '**OMOPUveitis HSV AC PCR positive**', allow events outside observation period 2. having at least 1 observation of '**OMOPUveitis HSV AC PCR positive**', allow events outside observation period
b. sectoral iris atrophy in a patient ≤50 years of age OR	having at least 1 condition occurrence of '**OMOPUveitis HSV iris atrophy**', allow events outside observation period; who are <= 50 years old
c. herpes simplex keratitis	having at least 1 condition occurrence of '**OMOPUveitis HSV keratitis**', allow events outside observation period
Exclusions	
1. Concomitant dermatomal/cutaneous varicella zoster virus (unless aqueous specimen PCR positive for herpes simplex virus)	Entry events with any of the following criteria: 1. having at most 0 condition occurrences of '**OMOPUveitis Dermatomal/cutaneous varicella zoster virus**' 2. having at least 1 observation of '**OMOPUveitis HSV AC PCR positive**' 3. having at least 1 measurement of '**OMOPUveitis HSV AC PCR positive**'
2. Positive serology for syphilis using a treponemal test	Entry events having at most 0 measurements of '**OMOPUveitis Syphilis exclusion**', starting between 30 days before and 30 days after cohort entry start date; at same visit as cohort entry~~; with value as concept: "positive" or "positive"~~
3. Evidence of sarcoidosis (either bilateral hilar adenopathy on chest imaging or tissue biopsy demonstrating non-caseating granulomata)	Entry events with any of the following criteria: 1. having at most 0 condition occurrences of '**OMOPUveitis Sarcoidosis exclusion**', starting between 30 days before and 30 days after cohort entry start date; at same visit as cohort entry 2. having at most 0 observations of '**OMOPUveitis Sarcoidosis exclusion**', starting between 30 days before and 30 days after cohort entry start date; at same visit as cohort entry~~; with value as concept: "present", "present", "positive" or "positive"~~
4. Aqueous specimen PCR positive for cytomegalovirus or varicella zoster virus	Entry events with all of the following criteria: 1. having at most 0 measurements of '**OMOPUveitis CMV AC PCR positive**', starting between 30 days before and 30 days after cohort entry start date; at same visit as cohort entry~~; with value as concept: "positive" or "positive"~~ 2. having at most 0 specimens of '**OMOPUveitis CMV AC PCR positive**', starting between 30 days before and 30 days after cohort entry start date Entry events with all of the following criteria: 1. having at most 0 measurements of '**OMOPUveitis VZV AC PCR positive**', starting between 30 days before and 30 days after cohort entry start date; at same visit as cohort entry~~; with value as concept: "positive" or "positive"~~ having at most 0 specimens of '**OMOPUveitis VZV AC PCR positive**', starting between 30 days before and 30 days after cohort entry start date

Figure 1. Computable Phenotype

Results

In our EHR manual chart review of the US Veterans Affairs Corporate Data Warehouse EHR database, 5,404 patients with HSV anterior uveitis were identified. A random validation sample of 27 patients was collected. 70% of patients in this validation sample were correctly identified, while the remaining 30% were incorrectly included for having HSV Keratitis but not uveitis, VZV Keratouveitis, or VZV Keratitis. In a similar review of USC Roski Eye Institute's EHR data, 38 patients with HSV anterior uveitis were identified. In a random validation sample of 10 patients, 90% were correctly identified for HSV anterior uveitis.

In our external validation review with Optum's Clinformatics claims database, 399,914 patients met the criteria to enter the cohort of HSV anterior uveitis. Of this entry cohort, 10,858 (2.7%) patients remained by meeting all the inclusion and exclusion criteria of the SUN definition. We found this consistent with the findings in "Incidence, prevalence, and risk factors of infections

uveitis and scleritis in the United States: A claims-based analysis" by Zhang et al. in 2020. This project took a sample of the same Optum claims database by including patients with index uveitis diagnoses based on ICD-9 codes. 2.4% or 442 out of 18,23 patients who initially met entry criteria were identified to have HSV Anterior Uveitis, providing external validation for our OMOP phenotype.

The most discriminatory inclusion criterion was found to be evidence of HSV infection in the eye. The criterion of evidence of herpes simplex infection in the eye was encapsulated by three concept sets: a. Positive PCR for herpes simplex on aqueous specimen, b. Sectoral iris atrophy in a patient ≤50 years of age, and c. Herpes simplex keratitis. A history of HSV Keratitis was found to be the most common. In contrast, almost no patients were found to have been included in the cohort because of a positive PCR assay or sectoral iris atrophy. Additionally, among our final cohort, Iridocyclitis and Acute and Subacute Irodcyclitis concepts were found to have the highest incidence rates among the 10,858 patients initially included in our entry cohort

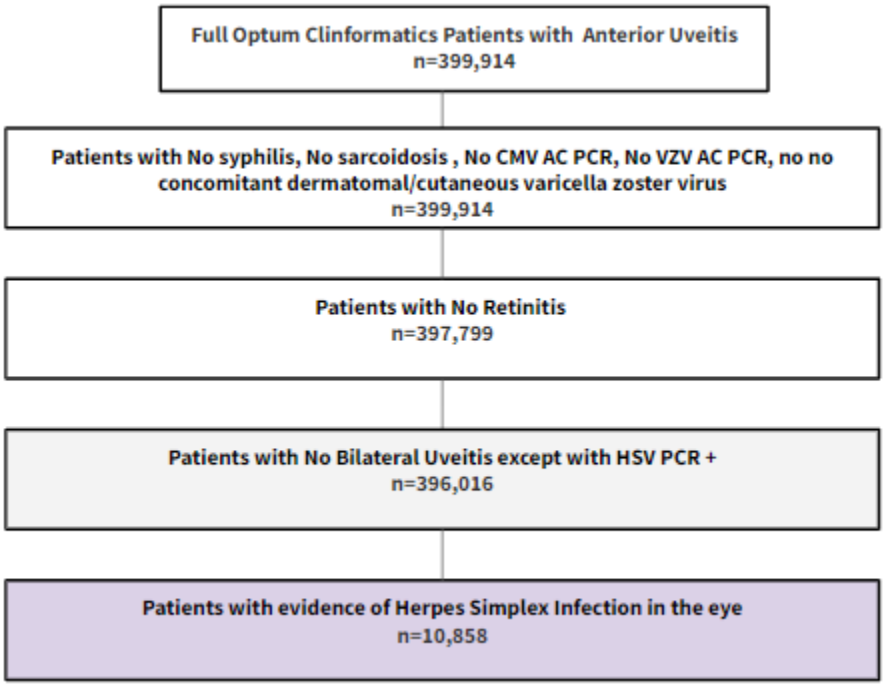

Figure 2. Cohort Attrition Diagram

Conclusion

Our findings show that Iridocyclitis and Acute and Subacute Iridocyclitis conditions were the standard concepts that were most prevalent in identifying uveitis patients. HSV keratitis conditions were the most significant component of the SUN criteria in identifying patients specifically with HSV infection in the eye. Furthermore, these findings were validated by EHR chart review data and existing claims data literature for HSV anterior uveitis, indicating the possible utility of operationalizing other nonstandardized uveitides into the OMOP CDM in the future. The absence of certain clinical data points in administrative claims databases, like PCR results and sectoral iris atrophy, highlights areas where data collection and recording practices may need enhancement to fully utilize the SUN criteria in observation research.

References

Zhang, Y., Amin, S., Lung, K. I., Seabury, S., Rao, N., & Toy, B. C. (2020). Incidence, prevalence, and risk factors of infectious uveitis and scleritis in the United States: A claims-based analysis. *PLOS ONE*, *15*(8). https://doi.org/10.1371/journal.pone.0237995