# IDENTIFICATION AND CHARACTERIZATION OF A RETROSPECTIVE COHORT OF SECONDARY HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (sHLH) PATIENTS IN THE US

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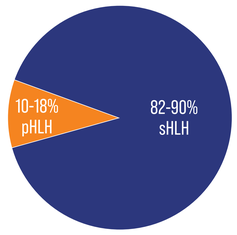
## BACKGROUND

### Hemophagocytic Lymphohistiocytosis (HLH)

- HLH is a life-threatening hyperinflammatory syndrome induced by aberrantly activated myeloid and T cells
  - Primary or familial HLH (pHLH) is a genetic disorder that typically presents in young children[1]
  - Secondary HLH (sHLH), which can occur at any age but is most common in adults, is triggered by infection, autoimmune disease, malignancy, or other/unknown conditions[2]
- HLH is universally fatal without treatment[1,3,4]
  - Treatment with etoposide-based regimens improves outcomes, but survival remains low particularly for malignancy-associated sHLH
  - Currently, there are no approved therapies for sHLH

### HLH Patient Population % of Cases[1,2]




### Limited Data to Support sHLH Diagnosis and Determine sHLH Epidemiology

- Diagnosing sHLH is challenging due to disease rarity, complex diagnostic criteria, and variable presentation
  - Symptoms are often nonspecific and immediately life-threatening
  - HLH-2004 trial established diagnostic criteria for HLH[5]; however, this was developed for primary HLH, and diagnostic cutoff levels for laboratory markers have not been validated in adults[6]
- Studies of the descriptive epidemiology of sHLH are limited and typically identify patients retrospectively through keyword searches and International Classification Disease (ICD) codes, potentially leading to underdiagnosis[2,4,7]
  - sHLH incidence based on patients fulfilling HLH-2004 criteria is estimated to be 1 per 2,000-5,000 adult hospitalizations
- Recently, an Optimized HLH Inflammatory (OHI) index, comprising sCD25 >3,900 U/mL and ferritin >1,000 ng/mL, was identified as having high diagnostic and prognostic value in malignancy-associated sHLH patients[6]
  - The combination of sCD25 and ferritin, two components of the HLH-2004 criteria, was synergistic for both HLH diagnosis and mortality prediction

## OBJECTIVES

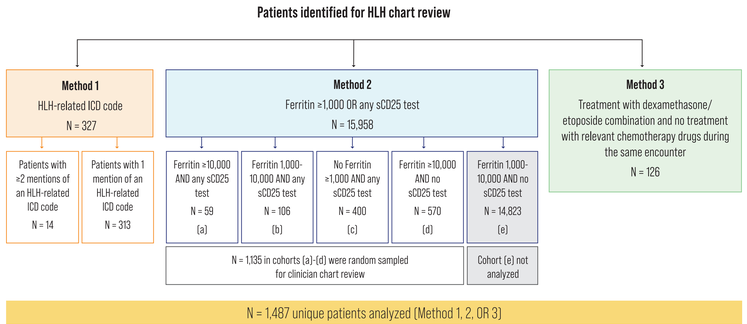
- To compile a historical cohort of sHLH patients at a large US healthcare system to refine the sHLH clinical definition
- This will inform a larger effort to describe sHLH epidemiology and characterize demographic, clinical, and treatment characteristics, survival, and healthcare resource utilization of the cohort, compared with a matched comparison group

## METHODS

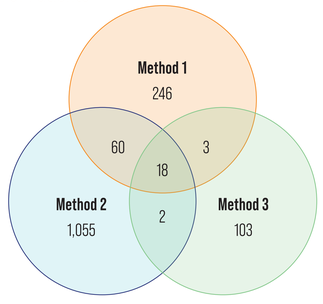
- Queried Electronic Medical Record (EMR) system 2009-May 2022 to identify potential patients; included >800,000 unique inpatient records at 10 hospitals
- Three methods developed for patient identification
  - **Method 1:** Patients with any mention of an HLH-related ICD code (ICD-9 288.4; ICD-10 D76.1, D76.2, D76.3)
  - **Method 2:** Patients with certain ferritin values or sCD25 test, elements of the OHI index[6]
    - Ferritin ≥1,000 ng/mL was used to align with OHI index
    - Ferritin ≥10,000 ng/mL was also considered as it was reported to be 90% sensitive and 96% specific for pHLH[8]
  - **Method 3:** Patients with etoposide and dexamethasone treatment, with filters added to remove patients receiving this treatment as part of a chemotherapy regimen
- A clinician reviewed a random sample of cohorts identified by each method, and HLH/MAS diagnosis was assigned based on expert judgement

## RESULTS

### Patient Identification Algorithm




### Overlap in the Identification of Patients

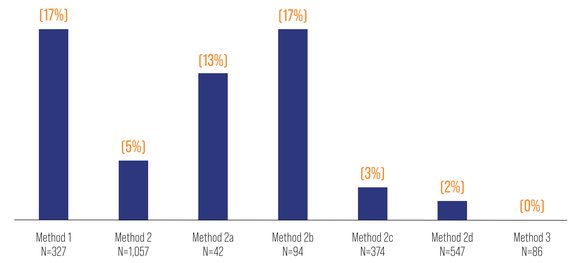



### Chart Review of Initial Random Sample

| Method | Description | Total patients identified in EMR (N) | Number of unique patients for chart review (N)* | Random sample for chart review (N) | N (%) with HLH/MAS diagnosis |
|---|---|---|---|---|---|
| 1 | ICD codes | 327 | 327 | 65† | 11/65 (17%) |
| 2 | Ferritin ≥1,000 OR sCD25 test, cohort (e) removed | 1,135 | 1,057 | 118 | 6/118 (5%) |
| 2a | Ferritin ≥10,000 AND any sCD25 | 59 | 42 | 8‡ | 1/8 (13%) |
| 2b | Ferritin 1,000-10,000 AND any sCD25 | 106 | 94 | 18‡ | 3/18 (17%) |
| 2c | No ferritin ≥1,000 AND any sCD25 test | 400 | 374 | 37‡ | 1/37 (3%) |
| 2d | Ferritin <10,000 AND no sCD25 test | 570 | 547 | 55‡ | 1/55 (2%) |
| 3 | Treatment | 126 | 86 | 17† | 0/17 (0%) |
| Any method | 1 OR 2 OR 3 | 1,487 unique patients | - | 200 | 17 (9%) |

*Patients with an ICD code were removed from cohorts identified with Methods 2 and 3 to create a unique patient population for random sampling. Patients identified with Method 2 were also removed from Method 3 before random sampling.
†20% random sample.
‡10% random sample.

### Percent Diagnosed With HLH/MAS in Random Sample




### Discussion

- Our patient identification algorithm identified cohorts that were, on average, approximately 40-55 years of age in a random sample; the confirmed HLH/MAS cases in our sample were largely adult-onset cases
  - This is consistent with the higher incidence of sHLH observed in the literature[2,9,10]
  - sHLH vs pHLH diagnoses and triggering events will be confirmed in a future publication
- Using a random-sample chart review, ferritin levels or sCD25 testing (Method 2) captured additional HLH/MAS patients that were not identified by ICD codes alone (Method 1)
  - 17% of patients identified with Method 1 (N=327, ICD codes for HLH) had a confirmed HLH/MAS diagnosis
  - 5% of patients identified with Method 2 (N=1,135, ferritin levels or sCD25 testing) had a confirmed HLH/MAS diagnosis
  - If we extrapolate the random-sampled HLH/MAS diagnosis ratios to the full cohorts, Method 2 has the potential to identify an additional 95% (or almost double) the number of identified HLH/MAS patients vs ICD codes alone, since the cohort for Method 2 is much larger
  - Interestingly, a subset of Method 2 with sCD25 >3,900 U/mL had a HLH diagnosis ratio of 18%, supporting OHI criteria

## CONCLUSIONS

- Since HLH is a rare, heterogenous, and complex disease to diagnose and treat, HLH-related ICD codes may not accurately and sufficiently capture the spectrum of HLH patients
- Our expanded algorithm using ferritin and sCD25 values captured a substantial number of patients with this life-threatening disease that would otherwise not have been captured with ICD codes
- A refined algorithm improves our ability to identify patients with this rare and complex disease; the algorithm could prove helpful in understanding the potential underestimation of the incidence of HLH due to the inconsistent use of ICD codes
- These results will continue to be evaluated and confirmed through 1) chart review of the full sample (each chart reviewed by two clinicians) and 2) the addition of another healthcare site with >450 patients identified with an HLH-related ICD code

Note: The abstract for this study has been updated based on new findings that are included in the poster.

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