American Journal of Hematology

WILEY

CORRESPONDENCE

Ferritin, C-Reactive Protein, and Soluble CD25 Distinguish TAFRO From HLH

Steven Rowe[1] | Mariam Goubran[2] | Mateo Sarmiento Bustamante[3] | Saishravan Shyamsundar[3] | Bridget Austin[3] | Kathleen McNicholas[1] | Marley Blommers[4] | Junyan Shi[5] | Lisa K. Peterson[6] | Lusia Sepiashvili[7] | Andre Mattman[8] | Joshua D. Brandstadter[3,9] | David C. Fajgenbaum[3] | Luke Y. C. Chen[2,10,11]

[1]Discipline of Medicine, Memorial University of Newfoundland, St. John's, Newfoundland, Canada | [2]Division of Hematology, University of British Columbia, Vancouver, British Columbia, Canada | [3]Center for Cytokine Storm Treatment & Laboratory, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA | [4]Faculty of Medicine, Dalhousie University, Halifax, Nova Scotia, Canada | [5]Department of Pathology and Laboratory Medicine, Vancouver General Hospital and University of British Columbia, Vancouver, British Columbia, Canada | [6]Department of Pathology, University of Utah, Salt Lake City, Utah, ARUP Institute for Clinical and Experimental Pathology, Salt Lake City, Utah, USA | [7]Department of Paediatric Laboratory Medicine, Hospital for Sick Children, Toronto, Ontario, Canada | [8]Department of Pathology and Laboratory Medicine, St. Paul's Hospital, Vancouver, British Columbia, Canada | [9]Division of Hematology-Oncology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA | [10]Division of Hematology, Dalhousie University, Halifax, Nova Scotia, Canada | [11]Coastal Program for Rare Inflammatory Diseases, Dalhousie University, Halifax, Nova Scotia, Canada

Correspondence: Luke Y. C. Chen (lchen2@bccancer.bc.ca)

Received: 4 August 2025 | **Revised:** 3 September 2025 | **Accepted:** 13 September 2025

Funding: L.Y.C.C.'s research is supported by a philanthropic gift from the Hsu & Taylor Family through the VGH & UBC Hospital Foundation and Nova Scotia Health. D.F.'s research is supported by the National Heart, Lung, and Blood Institute (R01HL141408), United States Food and Drug Administration (R01FD007632), Castleman Disease Collaborative Network, Recordati Rare Diseases, and the Colton Center for Autoimmunity at the University of Pennsylvania.

Keywords: Castleman disease | CRP | ferritin | hemophagocytic lymphohistiocytosis | soluble CD25 | TAFRO

To the Editor,

Hemophagocytic lymphohistiocytosis (HLH) and the thrombocytopenia, anasarca, fever, reticulin myelofibrosis, and organomegaly subtype of idiopathic multicentric Castleman disease (iMCD-TAFRO) are both rare cytokine storm syndromes with substantial clinical and laboratory overlap. Both present with fever, organomegaly, and thrombocytopenia and can also include mild lymphadenopathy and tissue hemophagocytosis [1, 2]. First-line treatment in iMCD-TAFRO is interleukin (IL)-6 inhibition, whereas HLH is commonly treated with etoposide-based therapy, corticosteroids, and specific cytokine inhibition such as JAK inhibitors and interferon-gamma inhibitors.

The serum inflammatory markers ferritin, C-reactive protein (CRP), and soluble CD25 (sCD25) are all elevated in cytokine storm syndromes including HLH, Still's disease, and COVID-19 cytokine storm, and the pattern of elevation can help distinguish between these conditions [3, 4]. Serum ferritin is secreted from macrophages via a non-classical lysosomal pathway [5], CRP is produced by hepatocytes in response to IL-6, IL-1, and tumor necrosis factor (TNF), and sCD25 is a marker of T-cell activation [6]. Ferritin $>500\,\mu g/L$ and sCD25 $>2400\,U/mL$ are thresholds used in the HLH-2004 diagnostic criteria, and while inflammatory markers are known to be elevated in iMCD-TAFRO, very little literature exists on the degree of elevation typically expected and how this may differ from overlapping conditions [7–9]. The purpose of this study is to examine whether CRP, ferritin, and sCD25 can help differentiate HLH from iMCD-TAFRO.

We identified patients with secondary HLH (sHLH) treated at Vancouver General Hospital from January 2000 to January 2025 (UBC Clinical Research Ethics Board approval H25-00959) and iMCD-TAFRO patients from the University of Pennsylvania Advancing Castleman Care with an Electronic Longitudinal

Steven Rowe and Mariam Goubran contributed equally to this manuscript.

Registry (ACCELERATE) (Institutional Review Board protocol approval: 824758). ACCELERATE is the largest global registry of Castleman patients where all enrolled patients' diagnoses are independently confirmed by a panel of expert clinicians and pathologists. Triggers for secondary HLH in our cohort included hematological malignancy (48%), infections (21%), autoimmune disease (11%), and idiopathic (21%). Ferritin, CRP, and sCD25 values were collected from the time of diagnosis and the most abnormal values within 10 days of diagnosis. Mean and median values were identified and compared using box plots and the Mann–Whitney *U* test for non-parametric data. Statistics were performed using the R Statistics program. Receiver operator characteristic (ROC) curves were performed using the Youden index to identify optimal cut-off points for ferritin, CRP, and sCD25 in distinguishing between iMCD-TAFRO and HLH. Grid search analysis was used as a secondary means of determining optimal cut-off points.

Measurement of sCD25 was done by chemiluminescent immunoassay and reported in U/mL for 37 (35 HLH, 2 iMCD-TAFRO) patients. The sCD25 was measured by ELISA in 22 patients (all iMCD-TAFRO), which is reported in pg/mL. Historically, there has been no known conversion factor between these methods [8]. However, in parallel with the present study, the investigators (J.S., L.K.P., L.S., A.M., L.Y.C.C.) conducted a quality improvement study to determine conversion factors from ELISA (pg/mL) to U/mL and applied these to the study dataset. Conversion factors between various CD25 assays can be found in the Supporting Information of this work.

We identified 56 patients with sHLH and 73 patients with the TAFRO subtype of iMCD. Details of the sHLH cohort have been reported previously [4]. sCD25 was available for 27/73 iMCD-TAFRO patients and 39/56 HLH patients. Baseline characteristics of participants are described in Table 1.

We found that CRP, ferritin, and sCD25 distinguish sHLH from iMCD-TAFRO with high sensitivity and specificity (Figure 1). The median CRP for sHLH was 69 mg/L (IQR 32–110) versus 190 mg/L (IQR 90–299, p value <0.001) for iMCD-TAFRO. Median ferritin for sHLH was 16,722 μg/L (IQR 6350–40,000) versus 571 μg/L (IQR 345–1116, p value <0.001) for iMCD-TAFRO. Median sCD25 in sHLH was 5837 U/mL (IQR 3379–13,272) versus 1065 U/mL (IQR 667–1556, p value <0.001) for iMCD-TAFRO.

TABLE 1 | Baseline characteristics and laboratory values of patients with HLH and iMCD-TAFRO.

Characteristic	sHLH ($n=56$)	iMCD-TAFRO ($n=73$)
Age mean (years, range)	46 (3–63)	33 (2–74)
Sex (% female)	48%	37%
Fever (temperature ≥ 38.0°C)	57%	86%
Fluid accumulation/anasarca	No data	100%
Lymphadenopathy	No data	100%
Splenomegaly	28%	88%
Hepatomegaly	11%	23%
Thrombocytopenia ($<150\times10^9$/L)	96%	100%
Hemophagocytosis on bone marrow biopsy	85% (33/39)	55% (6/11)
Laboratory values (reference range), median, and interquartile range		
Creatinine (0.61–1.28 mg/dL)	0.68 (0.45–0.96)	2.0 (1.5–3.54)
Hemoglobin (12–15 g/dL)	8.5 (7.7–9.4)	68 (6.5–8.0)
Platelets ($150–400\times10^9$/L)	54 (29–94)	29 (15–57)
WBC ($4–11\times10^9$/L)	4 (1–9)	4.3 (2.8–6.5)
CRP (< 5 mg/L)	69 (32–110)	190 mg/L (90–299)
Ferritin (20–300 μg/L)	16,722 (6350–40,000)	571 (345–1116)
sCD25 (< 852 U/mL)	5837 (3379–13 272)	1065 (667–1556)
D-Dimer (< 500 μg/L)	7000 (2749–12 146)	No data
AST (< 35 U/L)	215 (72–531)	57 (36–107)
ALP (< 147 U/L)	No data	270 (151–459)
LDH (< 240 U/L)	1283 (540–3216)	No data
Triglycerides (< 1.70 mmol/L)	3 (2–4)	No data
Fibrinogen (2.30–4.40 g/L)	2 (1–4)	No data

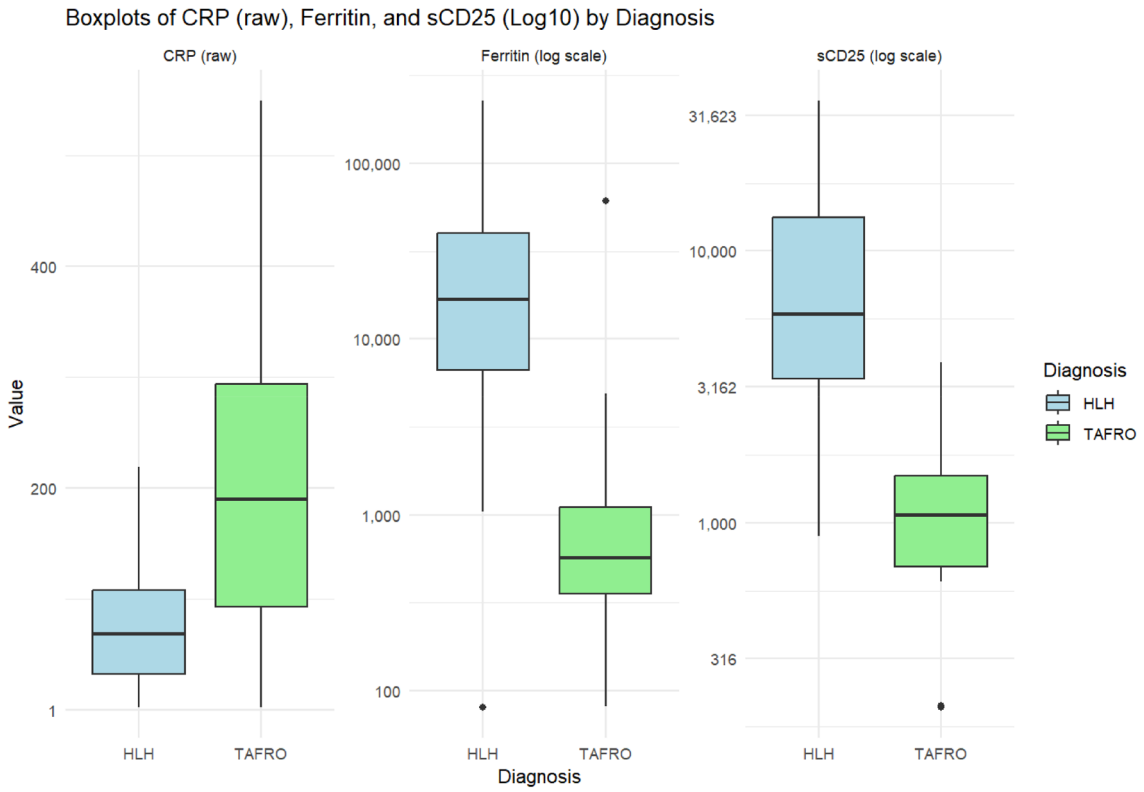

FIGURE 1 | CRP, Ferritin (log10 scale), and sCD25 (log10 scale) in HLH versus iMCD-TAFRO. The median CRP for HLH was 69 mg/L (IQR 32–110) versus 190 mg/L (IQR: 90–299, p value < 0.001) for TAFRO. Median ferritin for HLH was 16,722 μg/L (IQR 6350–40,000) versus 571 μg/L (IQR 345–1116, p value < 0.001) for iMCD-TAFRO. Median sCD25 in sHLH was 5837 U/mL (IQR 3379–13,272) versus 1065 U/mL (IQR 667–1556, p value < 0.001) for iMCD-TAFRO.

ROC curves demonstrate the ability of these blood-based tests to distinguish sHLH from iMCD-TAFRO (Figure 2). The optimal cut-off for CRP was 128.6 mg/L with a sensitivity of 67.2% and specificity of 83.9%, with an area under the curve (AUC) of 0.75. The optimal cutoff for ferritin was 1854 μg/L with a sensitivity of 91.9% and specificity of 94.5%, with an AUC of 0.94. The optimal cutoff for sCD25 was 3184 U/mL with a sensitivity of 96.3% and specificity of 75.6%, and an AUC of 0.93. The combined cut-off of CRP > 128.6 mg/L, ferritin < 1854 μg/L, and sCD25 < 3184 U/mL had a sensitivity of 100% and specificity of 52% and an AUC of 0.99. Using a grid search analysis, the combined optimal cutoffs identified were CRP > 80 mg/L, ferritin < 4900 μg/L, and sCD25 < 3900 U/mL with a sensitivity of 97.3% and specificity of 72.0% for iMCD-TAFRO over sHLH. CRP is higher and ferritin and sCD25 are lower in iMCD-TAFRO than in sHLH.

HLH and iMCD-TAFRO often mimic each other, and distinguishing between them is crucial for optimizing management. In this study, we examined simple, widely available inflammatory markers and demonstrated that CRP is higher in iMCD-TAFRO than HLH, while ferritin and sCD25 are much higher in HLH than iMCD-TAFRO. The grid search optimal cutoffs for distinguishing iMCD-TAFRO were CRP > 80 mg/L, ferritin < 4900 μg/L, and sCD25 < 3900 U/mL. These findings have important practical implications. Clinical findings can help clinicians distinguish between different cytokine storm syndromes. For example, fluid accumulation or anasarca is an obligate feature in iMCD-TAFRO, common in severe Still's disease, and not commonly seen in HLH. Combining clinical findings with ferritin, CRP, and sCD25 can help clinicians accurately treat HLH and iMCD-TAFRO.

Accurate and rapid diagnosis of cytokine storm syndromes is crucial yet cognitively challenging. Current guidelines often recommend diagnostic tests that are available only in highly specialized centers, have long turnaround times, or are not clinically validated tests. For example, while measurement of inflammatory cytokines and cytokine receptors is recommended for Castleman disease [10] and functional assessment of lymphocyte cytotoxicity in HLH [11], very few centers can conduct these tests or interpret them within a meaningful timeframe.

Among the biomarkers we examined, sCD25 is a "send out" test at some institutions. This biomarker is well studied in cytokine storm syndromes, and interestingly, the cutoff of > 3900 U/mL to distinguish HLH from iMCD-TAFRO is also the cutoff for diagnosing malignancy-associated HLH in the optimized hyperinflammatory index (OHI) [12] and for distinguishing HLH from Still's disease [3]. Although current iMCD diagnostic guidelines indicate that sCD25 is elevated in iMCD-TAFRO [10], this elevation is quite modest compared to HLH. The marked elevation of sCD25 in HLH relative to iMCD-TAFRO and Still's disease underscores the central role of T-cell activation in the pathophysiology of HLH.

This study provides an important diagnostic tool to help clinicians diagnose cytokine storm syndromes. Ferritin, CRP,

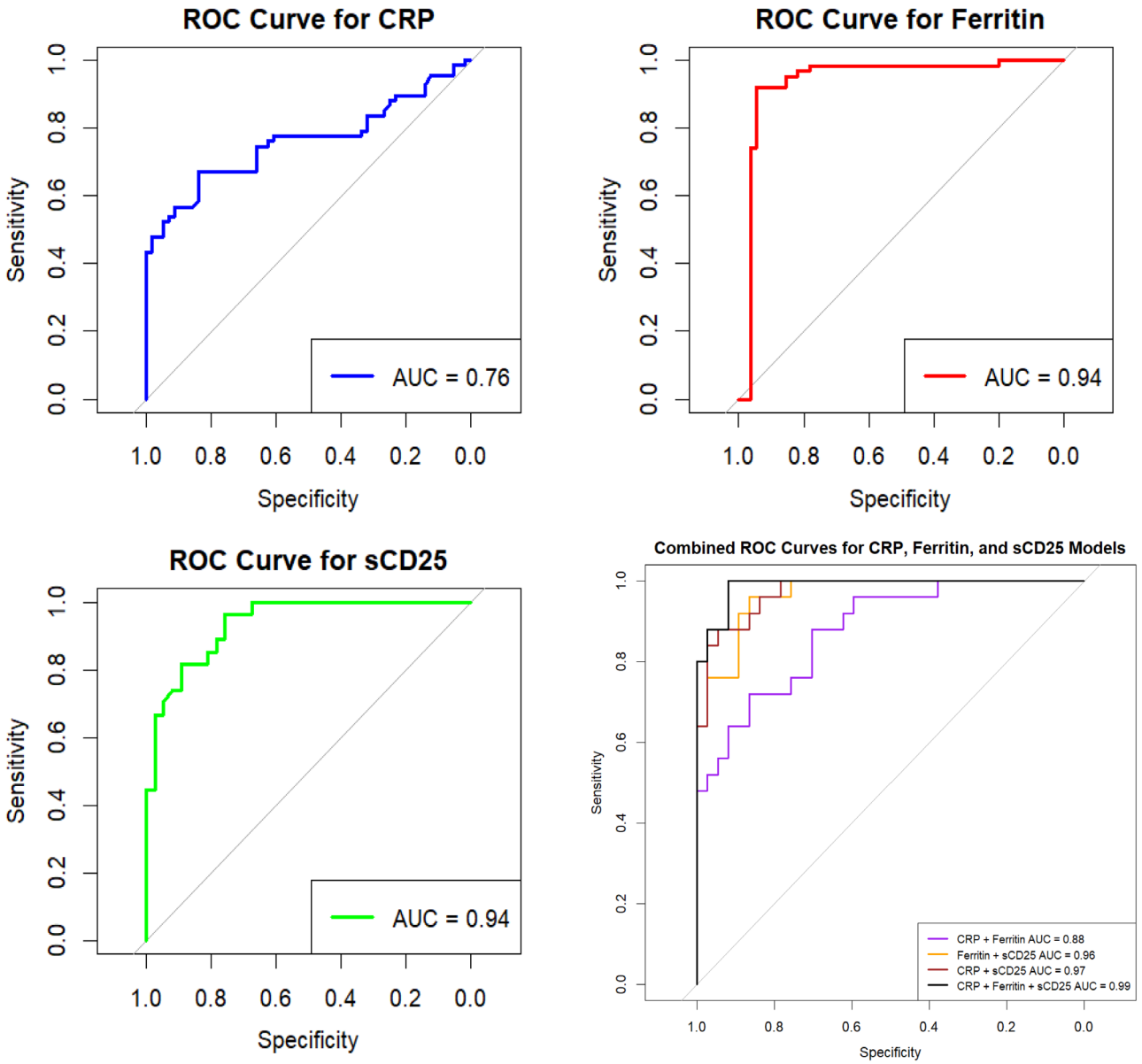

FIGURE 2 | ROC curves for CRP, sCD25, ferritin, and combinations of these values. The optimal cut off for CRP was 128.6 mg/L with a sensitivity of 67.2% and specificity of 83.9%, with area under the curve (AUC) 0.75. The optimal cutoff for ferritin was 1854 μg/L with a sensitivity of 91.9% and specificity of 94.5%, with AUC 0.94. The optimal cutoff for sCD25 was 3184 U/mL with sensitivity of 96.3% and specificity of 75.6%, and AUC 0.93. The AUC improves to 0.99 when combining all three parameters.

and sCD25 have utility as individual biomarkers to distinguish HLH from iMCD-TAFRO and are even better when used in combination. One limitation of the study is the heterogeneity of assays used to measure sCD25, as evidenced by analytical variations across different immunoassay platforms and inconsistencies in reporting units (U/mL vs. pg/mL). To enable cross-assay comparisons, we arbitrarily designated the Siemens Immulite assay as the reference and applied various approaches to estimate conversion factors, including internal comparison studies, testing laboratory claimed data, and personal communications. Another limitation is the relatively small subset of iMCD-TAFRO ($n = 27$) and HLH patients ($n = 39$) with available sCD25 levels, representing only a portion of the full iMCD-TAFRO ($n = 73$) and HLH ($n = 56$) cohorts, which reduces the reliability of the sCD25 findings compared to our CRP and ferritin analyses. Likewise, the timing of presentation and sampling of blood-based biomarkers relative to the natural history of the disease could affect the levels of these tests. An important caveat is that even when a cytokine storm syndrome is accurately diagnosed, patients may still need to undergo biopsy of lymph nodes, bone marrow, or other tissues to obtain a histological diagnosis of Castleman disease, lymphoma, or other conditions.

HLH and iMCD-TAFRO are rare cytokine storm syndromes that are similar and can be challenging to distinguish. Our study demonstrates significant differences in the biochemical profiles of iMCD-TAFRO and HLH, which can be used to differentiate them with strong statistical predictive value. Future research should be aimed at the discovery of disease-specific serum markers to screen for and confirm cytokine storm syndromes such as HLH and iMCD-TAFRO.

Author Contributions

Steven Rowe drafted, edited the manuscript, and analyzed the data. Mariam Goubran analyzed the data, created graphs, and helped draft the manuscript. Bridget Austin, Mateo Sarmiento Bustamante, Saishravan Shyamsundar, Kathleen McNicholas, and Marley Blommers acquired and organized the data. Andre Mattman, Junyan Shi, Lisa K. Peterson, and Lusia Sepiashvili worked on conversion factors for soluble CD25 values. Joshua D. Brandstadter and David C. Fajgenbaum provided data through the CDCN and edited the manuscript. Luke Y.C. Chen conceptualized and supervised the project.

Acknowledgments

Luke Y. C. Chen's research is supported by a philanthropic gift from the Hsu & Taylor Family through the VGH & UBC Hospital Foundation and Nova Scotia Health. David Fajgenbaum's research is supported by the Clinton Foundation and the Chen Zuckerberg Initiative. The authors thank the patients and families of all participants.

Ethics Statement

Ethics approval was granted by the University of Pennsylvania and University of British Columbia ethics boards.

Conflicts of Interest

L.Y.C.C. has received speaker's fees from Recordati Rare Diseases and from Amgen.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

1. M. Goubran and L. Chen, "Hemophagocytic Lymphohistiocytosis and Other Cytokine Storm Syndromes in Adults," *Canadian Hematology Today* 4, no. 1 (2025): 37–46.

2. L. Y. C. Chen, L. Zhang, and D. C. Fajgenbaum, "Expert Perspective: Diagnosis and Treatment of Castleman Disease," Arthritis and Rheumatology, ahead of print, June 5, (2025), https://doi.org/10.1002/art.43269.

3. M. Beckett, C. Spaner, M. Goubran, et al., "CRP and sCD25 Help Distinguish Between Adult-Onset Still's Disease and HLH," *European Journal of Haematology* 113, no. 5 (2024): 576–583.

4. M. Goubran, C. Spaner, S. Stukas, et al., "The Role of C-Reactive Protein and Ferritin in the Diagnosis of HLH, Adult-Onset Still's Disease, and COVID-19 Cytokine Storm," *Scientific Reports* 14, no. 1 (2024): 31306.

5. L. A. Cohen, L. Gutierrez, A. Weiss, et al., "Serum Ferritin is Derived Primarily From Macrophages Through a Nonclassical Secretory Pathway," *Blood* 116, no. 9 (2010): 1574–1584.

6. A. Hayden, M. Lin, S. Park, et al., "Soluble Interleukin-2 Receptor is a Sensitive Diagnostic Test in Adult HLH," *Blood Advances* 1, no. 26 (2017): 2529–2534.

7. Y. Nishimura, D. C. Fajgenbaum, S. K. Pierson, et al., "Validated International Definition of the Thrombocytopenia, Anasarca, Fever, Reticulin Fibrosis, Renal Insufficiency, and Organomegaly Clinical Subtype (TAFRO) of Idiopathic Multicentric Castleman Disease," *American Journal of Hematology* 96, no. 10 (2021): 1241–1252.

8. L. Y. C. Chen, M. Goubran, and C. Spaner, "Hemophagocytic Lymphohistiocytosis," *New England Journal of Medicine* 392, no. 15 (2025): 1557–1558.

9. J. I. Henter, A. C. Horne, M. Aricó, et al., "HLH-2004: Diagnostic and Therapeutic Guidelines for Hemophagocytic Lymphohistiocytosis," *Pediatric Blood and Cancer* 48, no. 2 (2007): 124–131.

10. D. C. Fajgenbaum, T. S. Uldrick, A. Bagg, et al., "International, Evidence-Based Consensus Diagnostic Criteria for HHV-8–Negative/Idiopathic Multicentric Castleman Disease," *Blood* 129, no. 12 (2017): 1646–1657.

11. P. La Rosée, A. Horne, M. Hines, et al., "Recommendations for the Management of Hemophagocytic Lymphohistiocytosis in Adults," *Blood* 133, no. 23 (2019): 2465–2477.

12. A. Zoref-Lorenz, J. Murakami, L. Hofstetter, et al., "An Improved Index for Diagnosis and Mortality Prediction in Malignancy-Associated Hemophagocytic Lymphohistiocytosis," *Blood* 139, no. 7 (2022): 1098–1110.

Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Data S1:** ajh70081-sup-0001-Supinfo.docx.