CXCL9 AS A BIOMARKER IN ADULTS WITH MALIGNANCY-ASSOCIATED HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

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Introduction

Secondary HLH is a rare, life-threatening hyperinflammatory syndrome driven by interferon-gamma. In adults, malignancy-associated HLH (mHLH) is the most common form and carries poor survival. CXCL9 is a blood marker of interferon-gamma activity, but its role in diagnosing and predicting outcomes in mHLH is unclear.

Aim

To assess CXCL9 as a diagnostic and prognostic biomarker in adults with malignancy-associated HLH.

Objectives

- **Characterize** adults with malignancy-associated HLH (mHLH) who had CXCL9 testing
- **Compare** CXCL9 levels across different malignancy subtypes (lymphoid vs myeloid)
- **Evaluate** correlations between CXCL9 and other HLH-associated biomarkers (ferritin, sCD25)
- **Identify** CXCL9 thresholds associated with acute in-hospital mortality
- **Assess** the prognostic value of CXCL9 for overall survival in mHLH

Methods

- **Cohort:** Adults with malignancies from a multi-institutional dataset (2021–Aug 2024) of patients hospitalized with hyperinflammatory syndromes (HS) who had CXCL9 testing
- **Exclusions:**
- Therapy-related HS (post-CAR-T or post-transplant)
- History of HLH
- **Data collected:** HLH-related clinical and laboratory variables at the time of first CXCL9 measurement
- **Diagnosis confirmation:** Modified HLH (mHLH) diagnoses verified using **HLH-2004 criteria** and **HScores**

Results

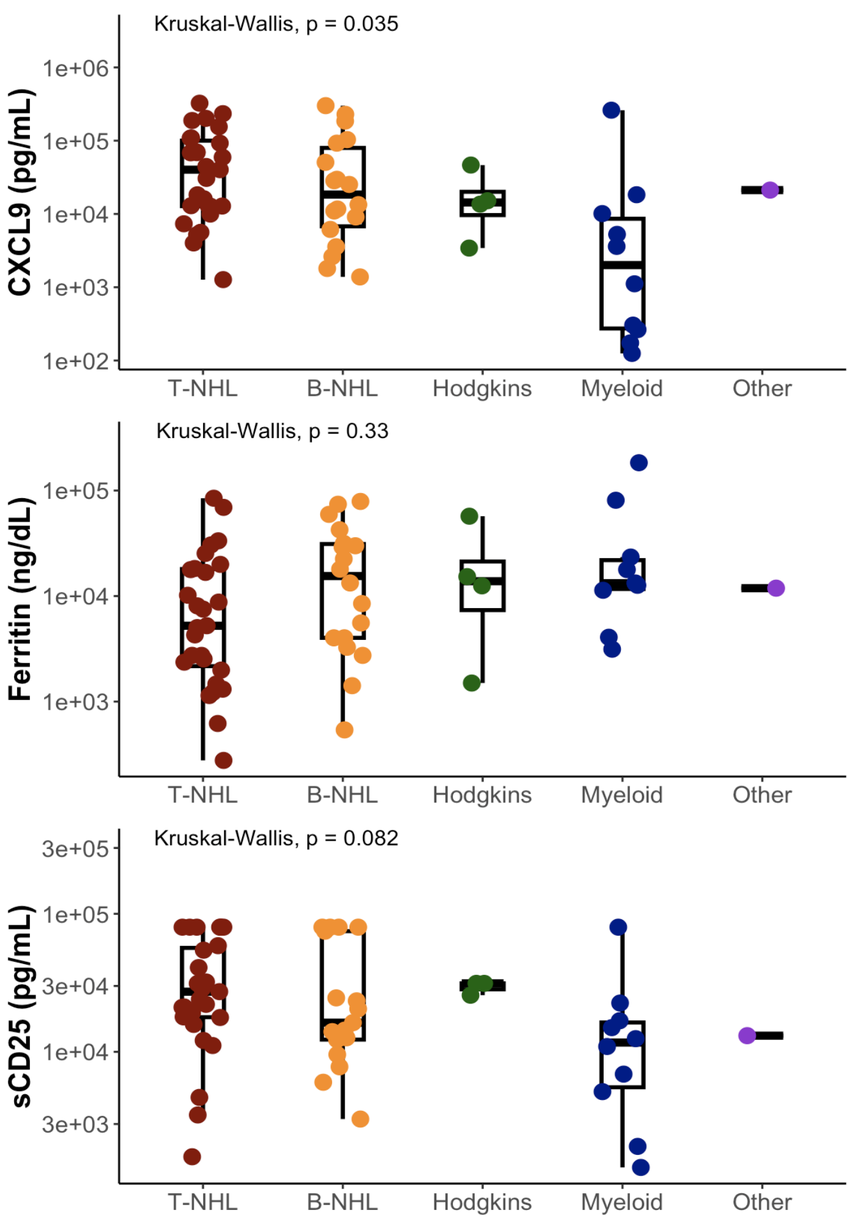


Fig. 1: Barplots comparing key HLH biomarkers across malignancy subgroups. Data presented as medians with interquartile ranges. P-values represent the results of Kruskal-Wallis test.

Results

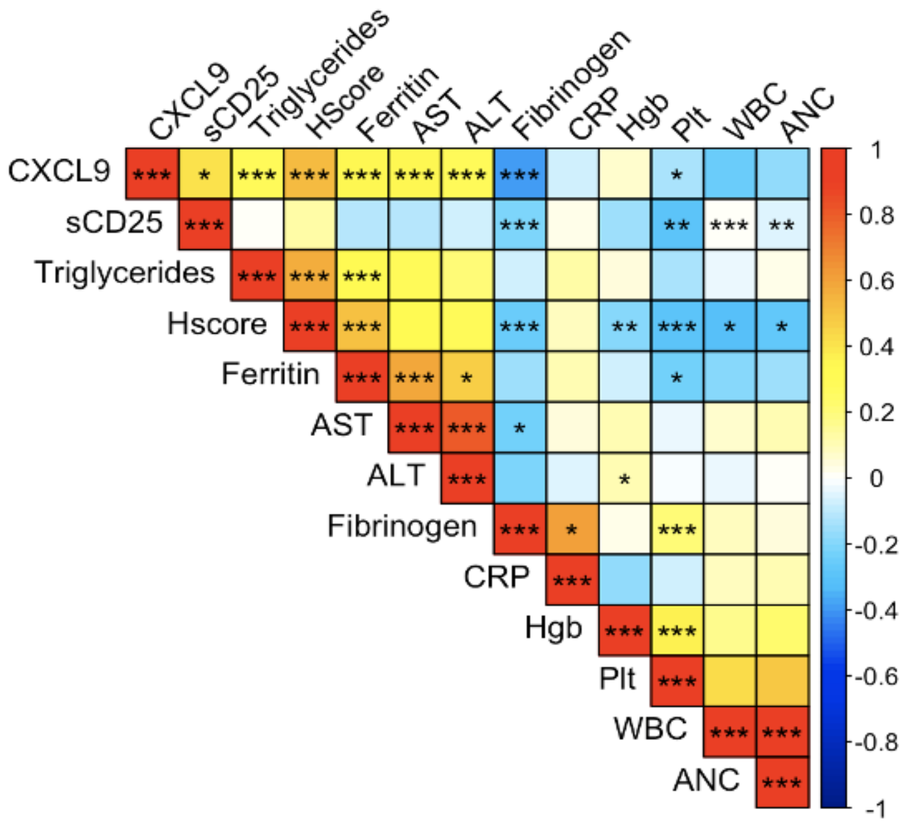


Fig. 2: Multiparameter Spearman correlation matrices including all clinical laboratory values in the malignancy cohort.). The p-values represent results of Spearman's r: ∗ p < 0.05; ∗∗ p < 0. 01; ∗∗∗ p < 0. 001.

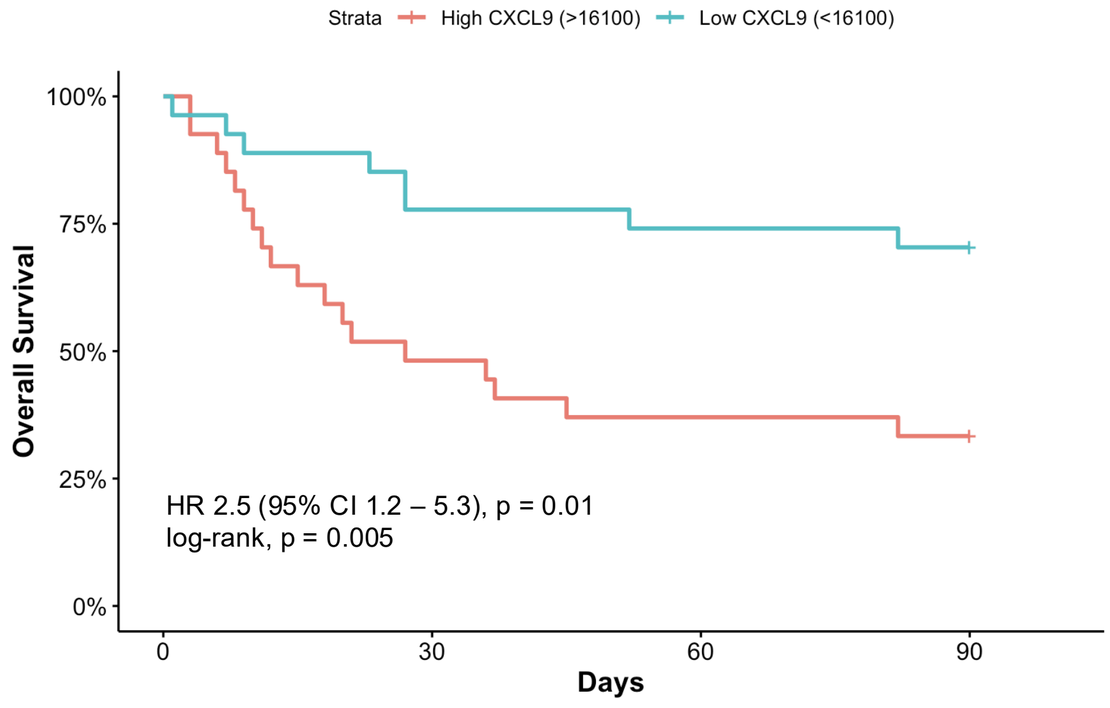


Fig. 3: Patients with CXCL9 ≥16,100 pg/mL demonstrated inferior OS with a median of 36 (IQR, 11–185) days vs 157 (IQR, 48–190, P=0.005) days. This threshold remained significant on multivariate analysis (HR 2.5, P=0.01).

Summary

- CXCL9 was elevated in adults with malignancy-associated HLH, particularly in lymphoma cases.
- Correlated more strongly with HLH biomarkers than ferritin or sCD25.
- Independently predicted in-hospital mortality and overall survival.
- Threshold ≥16,100 pg/mL identified high-risk patients.
- Highlights CXCL9 as a powerful tool for diagnosis and risk stratification.

Discussion

CXCL9 is a strong diagnostic and prognostic biomarker in malignancy-associated HLH, especially in lymphoma cases. Hematologic malignancies are the most common triggers, so thorough evaluation for underlying cancer is essential, even during HLH-directed therapy. Combined with traditional markers like ferritin, sCD25, and cytokine profiles, CXCL9 improves early recognition, risk stratification, and identification of high-risk patients who might be missed by conventional criteria.

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