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Letter to the Editor

Improving Recognition of Secondary Hemophagocytic Lymphohistiocytosis (HLH) through a Ferritin-Based Automated Alert: An Interrupted Time Series Analysis

Jack W. Goodall [a,b,*] Thomas G. Nadin,[a,c] Bethan S. Lloyd Jones,[a,b] Otto C. Willan,[a,b] Adam C. Lomas,[b] Athina Tampaki,[b] Thomas C. Darton [a,b] and Rachel S. Tattersall[a,c]

To the Editor:

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening hyperinflammatory syndrome characterized by fever, cytopenias, and hyperferritinemia (1). Primary HLH is caused by genetic mutations and typically presents in infancy, while secondary HLH (sHLH) occurs at all ages and is commonly triggered by infections, hematological malignancies, or rheumatic diseases (1). The rarity and nonspecific clinical presentation of sHLH often results in delayed or missed diagnoses (2).

Cytopenias are a common feature of sHLH, typically leading clinicians to check hematinics, including ferritin, regardless of whether sHLH is suspected. Although a markedly elevated ferritin concentration in a critically unwell patient strongly suggests sHLH, this association remains under-recognized and represents an opportunity to improve recognition.

We aimed to improve sHLH recognition rates in our institution by introducing an automated electronic alert (autoalert), triggered by high ferritin measurements. Values of >6000 μg/L [corresponding to the higher threshold in the HScore, a validated probability tool for HLH (3)] were flagged with a text alert on the sample result. This was supplemented by telephone notifications for levels exceeding 10 000 μg/L. The alert advises clinicians to consider sHLH and links to our institutional guidelines that align with the UK consensus pathway and guidance (4). Ferritin values below this threshold retain a preexisting comment advising clinicians of the typical causes of mild hyperferritinemia (such as liver disease, hemochromatosis, and acute inflammation).

To evaluate the impact of this intervention, we aimed to identify all adults with their first presentation of sHLH at our institution, a large National Health Service teaching hospital group with just over 2000 acute beds, between January 1, 2017, and December 31, 2023, as part of an approved service evaluation. We identified potential cases using International Classification of Diseases (ICD)-10 codes D76.1 ("Hemophagocytic lymphohistiocytosis") or D76.2 ("Hemophagocytic syndrome, infection-associated"), a previously validated approach (5). We additionally reviewed local multidisciplinary team (MDT) referrals and pharmacy records of initiation of anakinra for HLH.

Each potential case underwent a notes review to ensure an accurate and contemporaneous diagnosis was made using clinical phenotyping and HScore biomarker calculation, and that this was their index presentation with sHLH. Cases were only included if their initial presentation was to our hospital to avoid bias from changes in referral patterns for specialist management. A single case of primary HLH was detected in this adult cohort (attributable to X-linked inhibitor of apoptosis protein deficiency) and was not included in this analysis.

Given the temporal clustering and evolving diagnostic criteria for COVID-19–associated hyperinflammation, we excluded these cases a priori to avoid confounding temporal trends. Analyses and visualizations were performed with R v4.4.2 and can be accessed at: https://doi.org/10.6084/m9.figshare.30646703.

We assessed the impact of the autoalert using interrupted time series analysis with Poisson regression, controlling for hospital-wide emergency admissions as an offset. Our analysis showed a significant immediate increase in sHLH diagnoses following implementation (rate ratio: 2.35; 95% CI, 1.04–5.31; $P = 0.046$). No significant baseline ($P = 0.57$) or post-intervention trends ($P = 0.87$) were observed (Fig. 1). Model diagnostics indicated no overdispersion or autocorrelation. Our model estimates that an average of one additional sHLH case per month was identified following the introduction of the autoalert.

[a]The Florey Institute of Infection and Sheffield NIHR Biomedical Research Centre, Division of Clinical Medicine, School of Medicine and Population Health, The University of Sheffield, Sheffield, United Kingdom; [b]Academic Directorate of Communicable Diseases and Specialised Medicine, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, United Kingdom; [c]Department of Rheumatology, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, United Kingdom.
*Address correspondence to this author at: Department of Clinical Medicine, Hallamshire Hospital, Glossop Rd, Broomhill, Sheffield S10 2JF, United Kingdom. e-mail j.goodall@sheffield.ac.uk.
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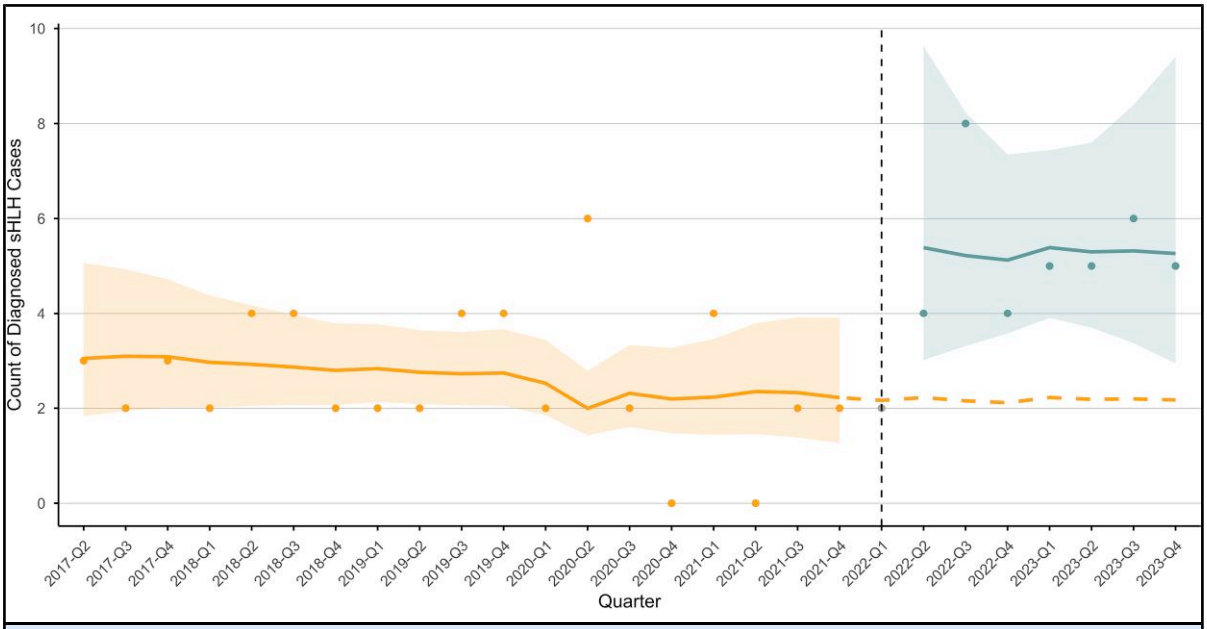

Fig. 1. Number of sHLH diagnoses per quarter at our institution.The vertical dashed line represents the intervention. Data points represent the count of observed sHLH cases. The solid lines denote the fitted model's estimated trend, with the shaded area representing the 95% CI. The dashed line shows the case count the model predicts if the intervention did not occur. Color figure available at https://academic.oup.com/clinchem

Despite excluding cases triggered by COVID-19, the mean number of cases in each quarter of 2020 was 2.75, compared to a mean of 2.5 in the other quarters before the intervention, suggesting that the pandemic did not reduce sHLH triggered by other causes. Sensitivity analyses excluding other respiratory virus-associated cases and restricting to ICD-coded cases yielded consistent effect sizes.

Notably, as our institution co-hosts the national HLH advisory panel, baseline awareness was already high; thus, the observed impact may underestimate potential benefits at centers less familiar with this condition.

This ferritin-based autoalert is designed to prompt consideration of sHLH when extreme hyperferritinemia is detected, encouraging clinicians to calculate a full HScore and consult relevant guidelines, rather than to confirm a diagnosis in isolation. Based on our cohort's ferritin results, we lowered our local autoalert threshold to 3000 μg/L, a level that would have identified all confirmed sHLH cases in this dataset. Future research should explore the optimal threshold, balancing resource use, overdiagnosis, and missed cases and evaluate its performance in other settings. It should also assess whether incorporating additional features such as platelet count and fever could enhance performance.

The management of sHLH is complex, often requiring rapid involvement from multiple specialties, timely initiation of treatment, and intensive care support. Despite these efforts, mortality remains strikingly high [56% mortality at one year (2)]. The first step towards improving outcomes is timely recognition. We propose that widespread implementation of this autoalert could enable earlier identification of affected patients, facilitating prompt investigation of underlying triggers, specialist referral, MDT discussion, and early treatment. Improved recognition may also support recruitment into urgently needed clinical trials, advancing our understanding and management of this high-mortality condition.

Nonstandard Abbreviations: HLH, hemophagocytic lymphohistiocytosis; sHLH, secondary hemophagocytic lymphohistiocytosis; ICD, international classification of diseases; MDT, multidisciplinary team.

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Jack Goodall (Conceptualization-Equal, Data curation-Lead, Formal analysis-Lead, Methodology-Lead, Project administration-Lead, Visualization-Lead, Writing—original draft-Lead, Writing—review & editing-Lead), Thomas Nadin (Conceptualization-Equal, Data curation-Equal, Formal analysis-Equal, Methodology-Equal, Project administration-Equal, Writing—review & editing-Equal), Bethan Lloyd Jones (Data curation-Equal, Methodology-Equal, Writing—review & editing-Equal), Otto Willan (Data curation-Equal, Writing—review & editing-Equal), Adam Lomas (Data curation-Equal, Writing—review & editing-Equal), Athina Tampaki (Data curation-Equal, Writing—review & editing-Equal), Thomas Darton (Conceptualization-Equal, Formal analysis-Equal, Methodology-Equal, Supervision-Equal, Writing—review & editing-Equal), and Rachel Tattersall (Conceptualization-Equal, Formal analysis-Equal, Methodology-Equal, Project administration-Lead, Supervision-Lead, Writing—review & editing-Lead)

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