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# Average Temperature as a Marker of Lymphoma-Associated HLH

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## Abstract

**Peak temperature, and 12-hour mean temperature were analysed in lymphoma patients presenting with a significantly raised serum ferritin. 12 (out of 23) patients were found to have hemophagocytic lymphohistiocytosis (HLH). 12-hour temperature proved a better predictor of HLH than peak temperature in this cohort, which has highlighted the need for further research into this simple clinical parameter.**

**Methods:** This retrospective analysis aimed to assess whether a 12-hour mean temperature (measured around either diagnosis of HLH or peak ferritin value) has value as a quick and simple diagnostic test for HLH in people with lymphoproliferative disease (LPD). Hospital records from 2018 to 2022 were retrospectively screened for patients with LPD and peak ferritin during admission to hospital >3000ng/mL. Patients were grouped as either HLH or non-HLH after consensus discussion at a multi-disciplinary meeting with access to full, detailed patient records and H-scores. **Results:** The total cohort of 23 patients consisted of 12 with HLH and 11 grouped as non-HLH. 12-hour mean temperature at HLH diagnosis was 38.6 °C in the HLH cohort and 37.5 °C measured at the point of peak ferritin measurement in non-HLH groups. It was also positively correlated with HLH status ($P = 0.001$) and showed high retrospective sensitivity and specificity for HLH above 37.7 °C. **Conclusion:** These results demonstrate that a 12-hour mean temperature may add value and diagnostic certainty to the first-line investigations for HLH associated with LPD. The moderately high sensitivity and specificity achieved with this dataset supports the need for further research into whether the test retains validity in larger patient groups.

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**Keywords:** Lymphoma, Haemophagocytic syndrome, Lymphoproliferative disease

## Introduction

Haemophagocytic lymphohistiocytosis (HLH) is a rare and poorly recognized systemic, hyperinflammatory clinical syndrome associated with a high mortality in those affected.[1] In its primary form, HLH is characterized by the presence of genetic abnormalities and typically affects children. Secondary HLH is an altogether more heterogenous condition associated with autoimmune disease, infection and malignancy.[2] The pathophysiology of secondary HLH represents immune dysfunction and dysregulation resulting in a continuous cycle of hyperinflammation causing widespread tissue injury.[3] The clinical and laboratory manifestations of the resultant syndrome most commonly include fever, hyperferritinaemia, cytopaenia, splenomegaly, transaminitis, and hypofibrinoginaemia.[2] Haemophagocytosis can be present on bone marrow aspirate and trephine and soluble CD25 (sCD25) is often elevated representing elevated Interleukin-2.[2] The ability to accurately identify HLH is crucial to outcome. A limitation when using pre-existing HLH scoring systems such as the H-score, or HLH-2004 criteria in HLH associated with lymphoproliferative disease (LPD) is that their validation is not specific to this aetiology.[2,4,5] This is a problem as LPD and HLH share several clinical features which can make the diagnosis of HLH secondary to LPD challenging and is associated with very poor outcomes.[6] The optimized HLH inflammatory (OHI) index was developed to tackle this issue but relies on specialist testing of sCD25 which is not widely available, particularly in under-resourced settings.[5]

This study aims to assess whether a mean 12-hour temperature has value as a quick, simple and easily measurable parameter for the diagnosis of a patient with suspected HLH secondary to LPD.

## Materials and Methods

This study was a single center retrospective study of adult patients with a diagnosis of lymphoma and suspected HLH. All patients had previously been admitted to a single UK Hematology tertiary referral center between 2018 and 2022. Hospital databases were searched for patients admitted to a hematology ward with lymphoma and

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a peak ferritin reading >3000 ng/dL (n = 158 patients). Patients without a diagnosis of lymphoma (n = 129) and duplicates were excluded. This resulted in the identification of 29 patients with a diagnosis of lymphoma. All 29 patients were individually, retrospectively reviewed by the local HLH multidisciplinary advisory group to reach a consensus on their HLH diagnosis. About 6 patients were excluded due to incomplete clinical records, and the remaining 23 patients were split by diagnosis into the groups 'HLH' (n = 12), and 'Non-HLH' (n = 11). The diagnosis of HLH was confirmed with access to full hospital records, radiology and laboratory results. The H-score was calculated for all patients and this was interpreted in the context of the broader clinical picture. No consistent data was available for NK-cell function, genetic testing, or sCD25 and this can be considered a limitation of this study.

The maximum temperature (°C) and 12-hour mean temperature were determined from data reported on continuous observation charts. The 12-hour mean temperature was calculated around the timepoint of peak fever within 7 days from the diagnosis of HLH or the apparent onset of the disease. For patients in the 'Non-HLH' group average temperature was sampled +/- 7d from peak ferritin. It was felt that in those without HLH, +/- 7d from their peak ferritin would provide a comparable point of analysis, correlating with severity of disease. For analysis, a peak temperature reading of 39°C was considered a 'positive' test result. This figure was derived as a middle ground between the >38.5°C threshold suggested in the HLH-2004 criteria and the maximum scoring range of >39.4°C suggested in the H-Score.[4,7] Statistical and graphical analysis of the data included basic descriptive statistics, and a retrospective sensitivity and specificity analysis. A point-biserial Pearson *r* correlation for ferritin / temperature reading versus HLH status was calculated and scatter and box-plots were generated.

## Results

A total of 23 patients were analyzed, 12 (52%) patients were grouped as "HLH" (9 diagnosed at the time and 3 diagnosed in hindsight). About 11 (48%) were considered to have an alternative cause for the raised ferritin and were grouped as 'Non-HLH'. The average age of the patient cohort was 49 years (range 19-74). The male to female ratio was 13:10. There was a slight difference in male to female ratio between HLH and non-HLH groups (8:4 vs. 5:6). The most notable difference in lymphoma sub-type between groups was the 4 patients with T-cell lymphoma in the HLH group versus no T-cell lymphoma in the non-HLH group. This distribution is in keeping with current evidence on malignancy-associated HLH (Supplementary Data Table 1).[8,9] The severity of disease was also different between groups, with the HLH group containing more individuals with recently diagnosed, advanced stage lymphoma. The non-HLH group mainly contained patients who were recently post-chemotherapy or post-SCT (stem cell transplant). Similar proportions of major infection were present in each group, with a marginally higher proportion of opportunistic infection present in the HLH group. The non-HLH group contained 4 patients with infection of unknown source but whom responded well to empirical antibiotic therapy. In the non-HLH group, a raised serum ferritin was attributed to severe infection in 6 (55%) patients, lymphoma in 2 (18%) patients, severe Graft-versus-Host Disease (GvHD) in 1 (9%) patient and in 2 (18%) patients the cause was considered multifactorial and unclear. H-Scores were calculated for HLH and non-HLH groups. The median H-Score for the HLH group was 230 (IQR 245-195), equating to approximately 99% probability of HLH. The non-HLH group had a median H-Score of 174 (IQR 199-116) equating to 59% probability of HLH. The non-HLH group had 6 patients with an H-Score of over 50% with 2 patients scoring >90%.

The most common treatment for HLH, received by 5 patients was methylprednisolone monotherapy. Three patients in the HLH group received methylprednisolone in combination with Anakinra. One patient received dexamethasone, and 3 patients received no therapy due to the diagnosis being made in hindsight.

All 23 patients had a peak ferritin reading over 3000 ng/mL. In the HLH group, median peak ferritin was 6974 ng/mL (IQR 12652-5243 ng/mL) compared with 4549 ng/mL (IQR 5553-3337 ng/mL) in the non-HLH group. The HLH group had greater peak and mean temperatures. The peak temperature in the HLH group was 39.7°C [39.3-40.0] compared with 38.6°C [38.2-39.0] in the non-HLH group. 12-hour average temperature was 38.6°C [38.3-38.0] in the HLH group and 37.5°C [37.1-37.9] in those with alternate diagnosis. Mean temperature recordings per 12-hour temperature was 6.7, with a range of 3-15 readings. Point-biserial (Pearson r) correlation was calculated and showed significant, similar correlation strength for mean and max temperature (0.70 and 0.72) ($P = .001$). Ferritin was insignificantly correlated at 0.103 ($P = .35$). Interpretation of ferritin results must be done cautiously as this cohort only represents patients with ferritin >3000 ng/mL, and the effect of outliers reduces the observed correlation in Figure 1 and 2.

12-hour temperature was assessed for its potential as a diagnostic parameter at a variety of threshold values. In this cohort of patients, a 12-hour temperature cut-off of between ≥37.7°C and ≥37.9°C would have yielded 92% sensitivity and 91% specificity. 100% separation was prevented by 1 apparent outlier in each group (37.5°C in HLH and 39.1°C in Non-HLH). Excluding these 2 results, the 12 hour temperature range in the HLH group was 37.9-39.7°C, and 37.1°C-37.6°C in the non-HLH group.

## Discussion

The identification of HLH in the context of hematological malignancy can be challenging and requires an extensive clinical workup and understanding of the syndrome to achieve an accurate diagnosis.[9] There is a need for more specific criteria or tests which identify the presence of HLH in the context of other diagnoses where the clinical features have significant crossover such as LPD.[5,6] In this cohort of patients, the H-score appeared to have a very high sensitivity for HLH, however, 2 patent's with an H-score >90% were categorized as non-HLH. Abnormal clinical parameters in these patients were more convincingly explained by the presence of active infections, the extent of their lymphoma or the timing of recent intensive chemotherapy. Diagnosing HLH based upon clinical examination and simple laboratory parameters requires experience and a good understanding of the disease. It is therefore important that scoring systems are developed to aid clinicians in the diagnostic process. A recent development in this area is the OHI index, a tool designed for the identification of HLH associated with

**Figure 1** (left): Box & Scatter plot comparing temperature readings and HLH status.

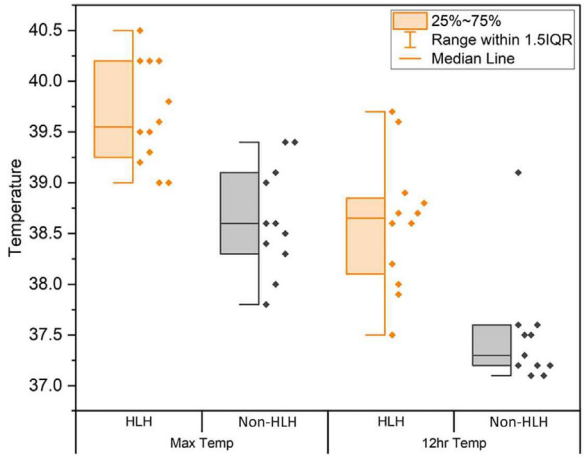
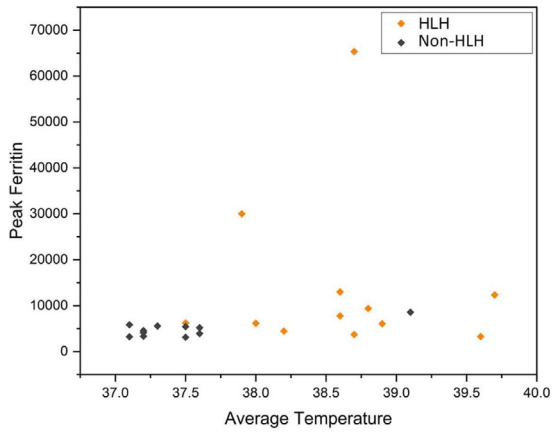



**Figure 2** (right): Scatter plot showing 12-hour mean temperature plotted against peak ferritin.




hematological malignancy.[5] The use of sCD25 >3900 U/mL and ferritin >1000 ng/mL was validated in a cohort of 225 patients at identifying HLH and predicting those with the highest mortality.[5] These results are promising for more accurate HLH diagnosis in patients with LPD, however, the availability and varied turnaround time of sCD25 testing in the UK means that, at present, its use is limited. Therefore, simple and easily measurable clinical parameters which improve diagnostics in HLH associated with hematological malignancy are desirable. Temperature is a parameter that can be measured by the majority of clinical staff, and monitoring is considered routine for hospital inpatients. This makes temperature a valuable marker of HLH as clinicians need not request additional tests to assess its level and trends. With increasing use of electronic patient records it is also feasible that simple temperature algorithms could be devised to automatically flag temperature profiles in at risk patients e.g. those with LPD. Whilst the presence of fever is considered critical to the clinical syndrome that is HLH, the grade of fever was not studied specifically in the early diagnostic criteria.[2,4,10] The Hscore did differentiate between grades of fever but did not comment in detail on fever duration.[7] Whilst there is a lack of large prospective studies assessing duration of fever in HLH, results from multiple recent single-center studies report prolonged fever as a key finding in their patients with the condition.[11–13] The results from this small study address this gap in the literature, by demonstrating 12-hour mean temperature could be a relatively specific feature of HLH related fever in patients with LPD. Exact temperature values with clinical significance require further research to clarify, however, this dataset would suggest values over 37.7 may have diagnostic

utility. This study is limited by its retrospective nature and single-center design, and this must be considered when generalizing the results to prospective patient care. Due to the complex presentation of HLH, no test is recommended in isolation to diagnose the condition.

Ferritin is a clinical marker of HLH that has been extensively studied. The time of peak ferritin was used in this study as the reference point from which to collect average temperature readings for the non-HLH group. The lack of a definitive timepoint for comparison is a limitation when comparing those with and without HLH. It was therefore felt that peak ferritin provided a consistent marker of high disease severity in the non-HLH group. It is worth noting that lower ferritin readings are generally considered more sensitive for HLH, as described by the OHI study and HLH-2004 criteria.[4,5,7] Selecting a higher ferritin reading for this studies data-collection (3000 ng/mL) was a methodological necessity that unfortunately limits the ability to draw conclusions about ferritin readings and HLH status. That being said, the median ferritin of 6974 ng/mL for the HLH group is in-line with levels specific for HLH reported in the literature.[4,5,7,9]

## Conclusion

These results demonstrate that a 12-hour mean temperature may add value and diagnostic certainty to the first-line investigations for HLH associated with LPD. The moderately high sensitivity and specificity achieved with this dataset supports the need for further research into whether the test retains validity in larger patient groups. Further analysis must also be conducted to determine the most optimal timeframe and threshold value for mean temperature readings, as well as analyzing whether it can predict the HLH before the condition reaches peak severity.

### *Clinical Practice Points*

- We know that HLH presents a challenging diagnosis in hematology patients; often requiring the use of scoring systems and specialist laboratory investigations.
- Existing literature documents the association of raised temperature with the syndrome of HLH, and major clinical scores utilize a peak temperature reading.
- This dataset adds to the existing understanding of fever and HLH, by suggesting that an average temperature reading may have greater specificity for the condition than peak readings.
- If further validated in larger studies, this may allow for more accurate HLH scoring systems to be developed. Greater understanding of simple parameters will also assist in the prediction of hemophagocytic syndrome by AI systems that may be integrated into future clinical practice.

## Disclosure

There are no conflicts of funding or interest that are relevant to this research.

## CRediT authorship contribution statement

**Cameron Clark:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Jack Goddard:** Writing – review & editing. **Rachel Tattersall:** Writing – review & editing, Supervision, Methodology. **Nick Morley:** Writing – review & editing, Supervision, Methodology, Conceptualization.

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## Supplementary Data Table 1

**Data table displaying extended information on the disease status of included cases.**

| Patient ID | HLH Status | H-Score | Average Temperature | Malignancy | Disease Notes | | Concomitant Disease |
|---|---|---|---|---|---|---|---|
| H1 | HLH | >99% (242) | 37.5 | TCL | Active disease - Stage 3 | Minor - | Fungal throat infection |
| H2 | HLH | >99% (252) | 38.6 | NLPHL | Active disease - Stage 3 | Major - | Urinary infection + Adenovirus + Fungal throat |
| H3 | HLH | 97% (223) | 38.2 | WM | Active disease - Unusual population of T cells | Minor - | Fungal throat infection |
| H4 | HLH | 99% (277) | 38.0 | TCL | Active disease - Stage 4 | Major - | Adenovirus + EBV reactivation |
| H5 | HLH | 99% (237) | 39.7 | TCL | Post intensive chemotherapy | Major - | E.Coli line infection |
| H6 | HLH | 60% (177) | 38.7 | HL | Active disease - Stage 4 | Major - | EBV reactivation |
| H7 | HLH | >99% (248) | 38.9 | TCL | Deceased before staging | - | |
| H8 | HLH | 75% (187) | 37.9 | DLBCL | Active disease - Stage 4 | Major - | E.Coli bacteraemia + EBV reactivation + Urinary infection |
| H9 | HLH | 50% (165) | 39.6 | FL | Queried high-grade transformation | Major - | Suspected pneumonia |
| H10 | HLH | 99% (237) | 38.6 | Burkitt's | Post intensive chemotherapy | Minor - | HHV6 Reactivation |
| H11 | HLH | 94% (218) | 38.7 | MCL | Relapsed MCL post allogeneic transplant | Major - | Enterococcus Pneumonia |
| H12 | HLH | 90% (203) | 38.8 | CHL | Active disease - Stage 4 | - | |
| N1 | non-HLH | 75% (183) | 37.2 | BCL | Remission | Major - | Suspected infection responsive to antibiotics |
| N2 | non-HLH | 59% (174) | 37.3 | CHL | Post-Allo. Remission | Major - | Fungal groin infection + Rhinovirus |
| N3 | non-HLH | 65% (178) | 37.6 | Burkitt's | Remission | Major - | Suspected infection responsive to antibiotics |
| N4 | non-HLH | 4% (116) | 37.1 | FL | Relapsed disease | - | |
| N5 | non-HLH | 18% (144) | 37.2 | FL | Queried relapse post-allo | Major - | Lung GVHD / Pneumonia |
| N6 | non-HLH | 2% (106) | 37.5 | DLBCL | Post-chemotherapy | Major - | Suspected infection responsive to antibiotics |
| N7 | non-HLH | 14% (139) | 37.1 | CHL | Remission | Major - | Line infection + PCP Pneumonia |
| N8 | non-HLH | 98% (238) | 39.1 | FL | High-grade transformation | Major - | Pneumonia |
| N9 | non-HLH | 2% (106) | 37.2 | Burkitt's | Post-chemotherapy | Major - | Wound infection |
| N10 | non-HLH | 87% (199) | 37.5 | MCL | Post-auto | Major - | Suspected infection responsive to antibiotics |
| N11 | non-HLH | 97% (226) | 37.6 | CHL | Post-allo | Major - | Severe GVHD + Multiple infections. |

*Legend:* TCL = T-cell lymphoma, NLPHL = Nodular lymphocyte predominant Hodgkin's Lymphoma, WM = Waldenstrom's Macroglobulinaemia, CHL = Classical Hodgkin's lymphoma, DLBCL = Diffuse large B-cell lymphoma, FL = Follicular lymphoma, Auto = Autologous stem-cell transplant, Allo = Allogeneic stem-cell transplant, EBV = Epstein-Barr virus, PCP = Pneumocystis Jirovecii, GVHD = Graft versus host disease, HHV6 = Human Herpesvirus 6.