

Assessment of the Haemophagocytic Lymphohistiocytosis HScore in patients with COVID-19

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Abstract

The clinical manifestation of moderate to severe COVID-19 has parallels to secondary haemophagocytic lymphohistiocytosis (HLH) both clinically and based on molecular inflammatory response. We found no evidence to support the utility of risk stratifying COVID-19 patients using risk scoring methodology designed for HLH.

Keywords: HLH, COVID-19, HScore, cytokine storm

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Introduction

Secondary haemophagocytic lymphohistiocytosis (HLH) is a rare hyperinflammatory syndrome characterized by hypercytokinaemia with multiorgan failure. Recent literature suggests that patients with severe COVID-19 are at risk of developing a severe inflammatory response, known as a cytokine storm [1]. The resulting cytokine profile has been reported as sharing similarities with HLH (including increased MCP1, TNF- α and IL-2). High levels of IL-6 have been associated with a worse outcome in these patients, as have high ferritin concentrations [2, 3].

Viral infections are established as recognized triggers of HLH, and account for about 35% of cases in adults [4]. Diagnosis is through identifying characteristic features, including the presence of laboratory abnormalities (with probability of the condition increasing with number of cytopaenias, raised ferritin, raised transaminases, low fibrinogen and high triglycerides), hepatosplenomegaly and fever $>39^{\circ}\text{C}$. A validated risk calculator known as the HScore [5] is used to identify those patients with a high probability of a diagnosis of HLH. In non-COVID-19 situations, the HScore carries a diagnostic sensitivity of 90%, and specificity of 79% for HLH [6]. This probability is used to drive the decision to initiate immunosuppressive therapy in HLH. Treatment has evolved to include targeted cytokine inhibition, namely IL-1 blockade with anakinra and IL-6 receptor blockade with tocilizumab [2, 7]. Even with appropriate immunosuppressive treatment HLH has a high mortality (up to 80%) [8].

During the current Sars-CoV-2 pandemic, there has been urgency in the development of therapeutic trials investigating potential mechanisms of controlling moderate to severe presentations. This has included anti-viral and immunosuppressive options. Possible detrimental effects of immunosuppression in patients with a new active viral disease include impaired immunity and viral clearance, and increased severity of illness. These concerns have led to caution in using broad immunosuppression in COVID-19, which may be ameliorated by the use of agents targeting specific pathways [2]. Given the parallel in cytokine profile between HLH and COVID-19, it has been

suggested that utilizing the HScore may help identify those patients with the most severe disease, and heightened inflammatory state, who may be more likely to benefit from immunosuppression [7]. One case review has highlighted that ferritin alone is unlikely to help identify those patients with high HScores [9].

Our aim was to establish whether HScore is a useful tool in risk stratifying patients admitted to our central London teaching hospital with COVID-19, given the suggested similarities with HLH, in order to help identify those who may benefit from a similar treatment approach.

Methods

We retrospectively reviewed all 152 SARS-Cov-2 PCR positive (on nasopharyngeal swab) cases admitted to a central London teaching hospital between 16th-25th March 2020 to establish whether they met the criteria for HLH using the HScore. We also compared results for patients that were admitted to the ICU compared to those that were managed on the inpatient ward, and compared those that had died with survivors.

Statistical significance was assessed using Mann-Whitney U test, and Chi-squared test for categorical comparisons.

Results

Of the 152 patients, 105 were male. Median age of admission was 68 (IQR 53-82 years) 31 patients were admitted to the intensive care unit (ICU), and 28 died (seven in the ICU). Ferritin values were available for 106 patients. The median ferritin was 1015 mcg/l (interquartile range (IQR) 529.75-2399.5mcg/l). The median CRP was 98 mg/l (IQR 41-167mg/l). 10 patients developed cytopaenia in two lineages. 18 patients had known underlying immunosuppression prior to admission. 2 patients had documented evidence of organomegaly (one patient with hepatomegaly, and one patient with splenomegaly). In both cases, organomegaly was present prior to the

development of COVID-19. No bone marrow biopsies were collected. The median recorded temperature at the height of illness was 38.4°C (IQR 37.5-38.8°C). The median HScore was 52 (IQR 19-61), with a median percentage risk of HLH of 0.078% (IQR 0.01-0.133%). In terms of those at higher risk of developing HLH, 10 patients had a greater than 5% risk, and six patients had a greater than 10% risk. The highest HScore recorded was 182, with an associated 71% risk of HLH.

We found no correlation between increasing age and HScore. There was also no correlation between ferritin concentration and age.

Those patients admitted to ICU demonstrated a significantly higher ferritin (median 2399mcg/l vs 854mcg/l for non-ICU, $p < 0.001$ using Mann-Whitney U test) and HScore (median risk 0.67% vs 0.03% for non-ICU, $p < 0.00001$) compared with non-ICU patients. There was no significant difference in the distribution of immunosuppressed patients in those that were admitted to ICU compared to those with ward-based care ($p = 0.67$). There were no significant differences in ferritin or HScore between all survivors and non-survivors.

Discussion

From our results, we have found no evidence to support the utility of the HScore in risk stratification in COVID-19. Although patients admitted to ICU did have a significantly higher HScore, the overall percentage risk was very low (median HLH risk 0.078%), and did not approach the diagnostic threshold for HLH in the vast majority. Whilst our results do not contradict the notion that hyperinflammation may contribute to poor outcomes in COVID-19, it is important not to assume the same inflammatory processes underlie HLH and COVID-19 without sufficient evidence. Our data suggest that decisions about treatment cannot be directly borrowed from HLH scoring.

The role of immunosuppression in the therapeutic arsenal against COVID-19 is currently unclear and will rely on pooled prospective data and careful assessment of patient characteristics and point in disease course. Case series do suggest that there is potential benefit in COVID-19 from similar

treatment approaches to HLH. In light of a recent clinical trial, dexamethasone is now approved for all hospitalized patients in the United Kingdom requiring oxygen therapy [10]. Anakinra has shown to have benefit in the intravenous form in both moderate and severe patients [11], especially given its safety in concomitant bacterial infections [12]. The effectiveness of tocilizumab is being assessed in a randomised placebo-controlled trial in patients with severe pneumonitis (COVACTA <https://clinicaltrials.gov/ct2/show/NCT04320615>). We did not find that the HScore reliably discriminated between those requiring ICU, nor those at risk of death. So far, immunosuppressive therapy trials in COVID-19 have been directed at those with severe disease. Therefore, if the HScore cannot reliably discriminate those likely to die, or who will require higher level care, it is unlikely to be useful to identify those who will benefit from this treatment approach.

The current pandemic of Sars-CoV-2 has highlighted the life-threatening effects of severe hyperinflammation. Although parallels can be drawn from other disease processes, our results emphasise that the current risk assessment tool for HLH, the HScore, does not identify those patients with COVID-19 most at risk of requiring higher levels of care, or at risk of deterioration and death. Therefore this tool does not have a place in the assessment of patients with SARS-Cov-2.

Potential Conflicts of Interest

H.L. reports grants and personal fees from SOBI and Novartis, outside the submitted work. All other authors have no potential conflicts of interest.

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Table 1: Table showing the median and interquartile ranges of the parameters of the HScore and calculated HScore in a cohort of 152 patients with confirmed COVID-19. Final column shows the weighted contribution of the parameters to H-score as described by Fardet et al[5]

| | Median | Interquartile range | Weighted criteria for HScore |
|------------------|--------------------------|--------------------------|--|
| Haemoglobin | 125 g/l | 138.5-106.25 | Cytopenia; 0 (one cell lineage), 24 (two cell lineages), 34 (three cell lineages) |
| White cell count | 6.49 x10 ⁹ /l | 9.265-5.1175 | |
| Neutrophils | 5.21 x10 ⁹ /l | 3.54-7.7 | |
| Lymphocytes | 0.87 x10 ⁹ /l | 0.87 x10 ⁹ /l | |
| Platelets | 210 x10 ⁹ /l | 270.25-154.25 | |
| Fibrinogen | 5.9 g/l | 4.8-6.4 | 0 (>2.5) or 30 (≤2.5) |
| Ferritin | 1015 µg/L | 529.75-2399.5 | 0 (<2000), 35 (2000-6000), or 50(>6000) |
| Triglycerides | 1.7mmol/l | 1.3-2.7 | 0 (<1.5), 44(1.5-4), or 64(>4) |
| AST | 54 U/ml | 35.75-78 | 0 (<30) or 19 (≥30) |
| Fever | 38.4°C | 37.5-38.8°C | 0 (<38.4), 33 (38.4-39.4), 49 (>39.4) |
| HScore | 52 | 19-61 | |