

Secondary HLH is uncommon in severe COVID-19

Severe cases of COVID-19, caused by novel coronavirus SARS-CoV-2, have been associated with a hyperinflammatory state.¹ This has been described as a form of secondary haemophagocytic lymphohistiocytosis (sHLH)² that may contribute to increased mortality.³ Screening with the HScore⁴ to identify cases has been recommended to guide immunosuppressive therapy.⁵ In our hospital, a multidisciplinary panel was created to advise on the use of cytokine directed therapies, such as the anti-interleukin-6 receptor antibody tocilizumab, in these patients.⁶

We performed a single-centre, cross-sectional study of 40 COVID-19 patients being treated in intensive care units on

Table 1. Characteristics of patients with COVID-19 infection admitted to intensive care units.

	n (%)
Age (years)	
Mean	57.9
Median	57
Range	33–80
Sex	
Male	26/40 (65)
Female	14/40 (35)
Ethnicity	
Black	16/40 (40)
White	7/40 (17.5)
Asian	4/40 (10)
Latin American	4/40 (10)
Mixed/other/not specified	9/40 (22.5)
Comorbidities	
Diabetes	12/40 (30)
Hypertension	20/40 (50)
Cardiovascular disease	7/40 (17.5)
Respiratory disease	7/40 (17.5)
Renal disease	4/40 (10)
Autoimmune disease	4/40 (10)
Malignancy	3/40 (7.5)
Mental health disorder	5/40 (12.5)
Length of admission (days)	
Mean	28
Median	29.5
Range	2–43
Length of ICU admission (days)	
Mean	15
Median	12.5
Range	1–40
HScore criteria ⁴	

Table 1. (Continued)

	n (%)
Immunosuppression*	3/40 (7.5)
Temperature $\geq 38.4^{\circ}\text{C}$	36/40 (90)
Temperature $>39.4^{\circ}\text{C}$	20/40 (50)
Hepatomegaly or splenomegaly on imaging†	0/15 (0)
Haemoglobin ≤ 92 g/l	39/40 (97.5)
White blood cell count $\leq 5 \times 10^9/\text{l}$	13/40 (32.5)
Platelet count $\leq 110 \times 10^9/\text{l}$	13/40 (32.5)
2 concurrent cytopenias	14/40 (35)
3 concurrent cytopenias	3/40 (7.5)
Ferritin ≥ 2000 $\mu\text{g/l}$	24/40 (60)
Ferritin > 6000 $\mu\text{g/l}$	9/40 (22.5)
Triglycerides ≥ 1.5 mmol/l	32/33 (97.0)
Triglycerides >4 mmol/l	15/33 (45.5)
Fibrinogen ≤ 2.5 g/l	2/40 (5)
AST ≥ 30 IU/l	40/40 (100)
Haemophagocytosis on bone marrow aspirate	0/1 (0)
HScore >169	3/40 (7.5)
Additional HLH 2004 criteria ²	
Haemoglobin <90 g/l	38/40 (95)
Neutrophil count $<1 \times 10^9/\text{l}$	1/40 (2.5)
Platelet count $<100 \times 10^9/\text{l}$	10/40 (25)
≥ 2 concurrent cytopenias	8/40 (20)
Triglycerides ≥ 3 mmol/l	26/33 (78.8)
Fibrinogen <1.5 g/l	0/40 (0)
Ferritin >500 $\mu\text{g/l}$	40/40 (100)
≥ 3 HLH 2004 criteria	19/40 (47.5)
Other markers of inflammation	
CRP >300 mg/l	35/40 (87.5)
CRP >400 mg/l	17/40 (42.5)
CRP >500 mg/l	6/40 (15)
WBC $>30 \times 10^9/\text{l}$	11/40 (27.5)
WBC $>50 \times 10^9/\text{l}$	3/40 (7.5)
Ferritin $>10\,000$ $\mu\text{g/l}$	7/40 (17.5)
Leucoerythroblastic features on blood film‡	10/17 (58.8)
Eosinophils $>0.4 \times 10^9/\text{l}$	25/40 (62.5)

AST, aspartate transaminase; COVID-19, 2019 novel coronavirus disease; CRP, C-reactive protein; HLH, haemophagocytic lymphohistiocytosis; ICU, intensive care unit; IL-1 β , interleukin-1 β ; IL-6, interleukin-6; IL-8, interleukin-8; TNF- α , tumour necrosis factor- α ; WBC, white blood cell count.

*Immunosuppression defined as HIV positive or receiving longterm immunosuppressive therapy (i.e., glucocorticoids, cyclosporine, azathioprine).

†Imaging defined as either ultrasound or computed tomography scans.

‡Leucoerythroblastic features include the presence of both granulocyte and erythroid precursors in the peripheral blood.

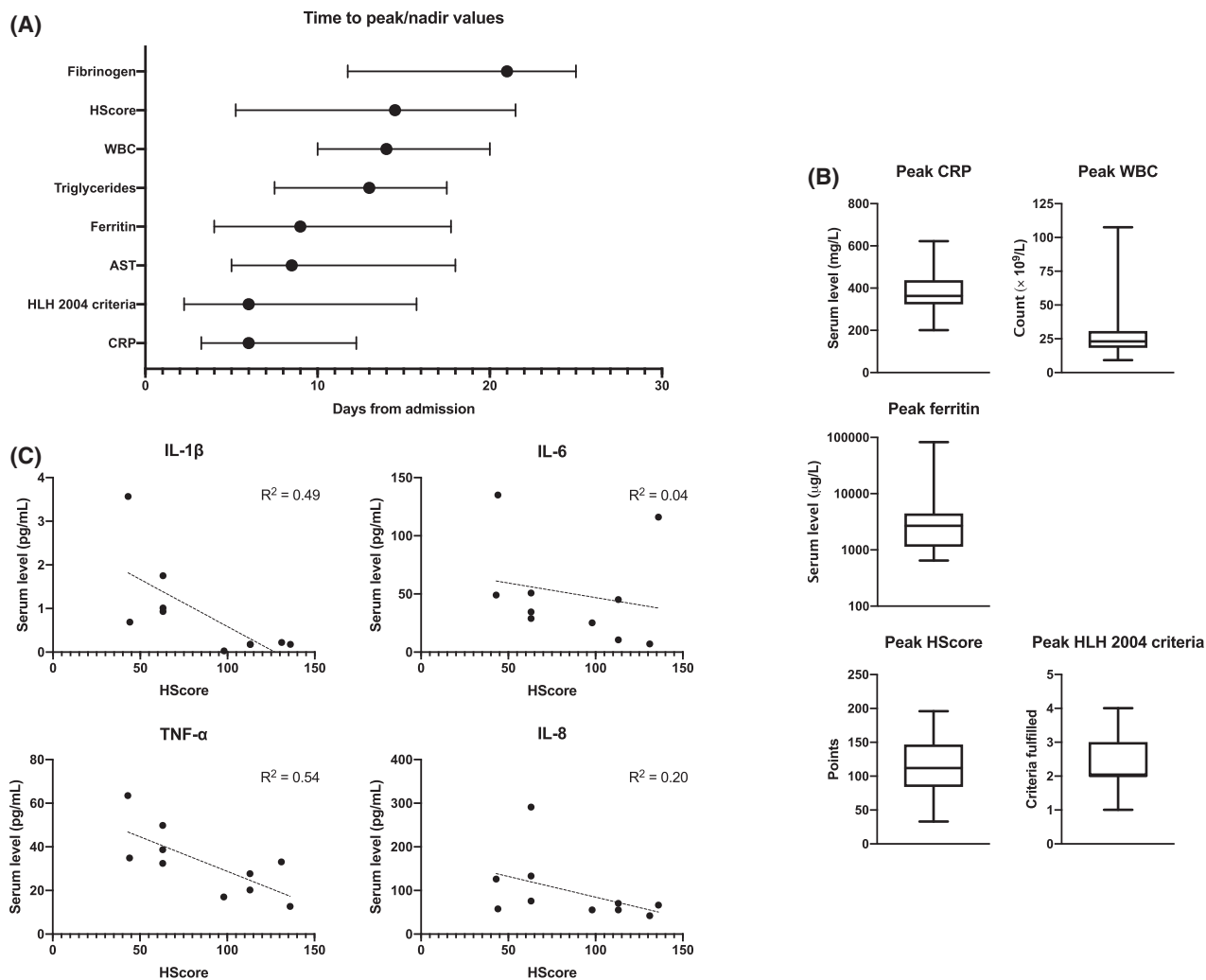


Fig 1. Measures of inflammation in patients with COVID-19 infection admitted to intensive care units. (A) Median time to nadir fibrinogen level and peak HScore⁴, WBC, triglycerides, ferritin, AST, HLH 2004 criteria² and CRP values, measured in days from admission to hospital. Bars = 25th and 75th percentiles. (B) Median peak values of CRP, WBC, ferritin, HScore and HLH 2004 criteria. Box = 25th and 75th percentiles; bars = minimum and maximum values. (C) Serum levels of IL-1β, IL-6, TNF-α and IL-8 as a function of HScore in ten patients (patient treated with tocilizumab prior to cytokine levels excluded from analysis). Dotted line = line of best fit determined by linear regression; associated R² value in top right of each graph.

May 1, 2020, who had tested positive for SARS-CoV-2 by polymerase chain reaction. We calculated the HScore on each day of admission using the most recent results for each variable contributing to the score.^{4,7} All but two patients had positive SARS-CoV-2 results from samples taken within 2 days of admission. Patient characteristics are listed in Table 1.

Despite evidence of hyperinflammation in this cohort, with high fevers, peak serum C-reactive protein (CRP) levels of >300 mg/l in 35 patients (87.5%) and peak serum ferritin >10 000 µg/l in seven (17.5%), only three (7.5%) achieved an HScore >169: the cutoff used to identify sHLH at a sensitivity of 93% and specificity of 86%.⁴

The low number of patients with HScore >169 was consistent with the absence of certain cardinal features of sHLH.

Neither hepatomegaly nor splenomegaly was identified in any of the patients assessed by ultrasound or computed tomography imaging (*n* = 15). Fibrinogen levels of ≤2.5 g/l were seen in only two patients (5%). Anaemia was frequently observed, seen in 95% of the cohort, with haemoglobin falling to ≤92 g/l at a median of 8 days after admission. Neutropenia was rare, with only one patient having a neutrophil count of <1 × 10⁹/l. Conversely, we found that these patients tended to have high white blood cell counts (WBC), reaching >20 × 10⁹/l in 25 patients (62.5%), and elevated fibrinogen levels were seen in 38 (95%). Ferritin levels reached >500 µg/l in all patients, but were >6000 µg/l in only nine (22.5%). Peak values of HScore parameters, HLH 2004 criteria and other inflammatory markers are shown in Table 1. The time at which peak/nadir values of HScore

parameters and other inflammatory markers were reached is shown in Fig 1A. Fig 1B shows the distribution of the peak values of selected markers, HScore and HLH 2004 criteria.² As of May 15, 2020, 28 patients (70%) remained on intensive care, nine (22.5%) had been stepped down to medical wards and three (7.5%) had died. The median (range) peak HScores for each group were 114 (52–196), 98 (33–150) and 98 (83–147), respectively.


One patient achieved a peak HScore of 196, associated with fever, ferritin 56 362 µg/l, WBC 107.6 × 10⁹/l and CRP 400.2 mg/l, and was the only patient treated with tocilizumab (single dose of 8 mg/kg), which was followed by a rapid drop in ferritin, CRP and resolution of fever. He subsequently developed secondary bacterial pneumonia.


Serum cytokine levels (interleukin-1β, interleukin-6, tumour necrosis factor-α and interleukin-8) were measured in 11 patients. Surprisingly, comparison of HScore and cytokine levels (Fig 1C) indicated a non-significant trend towards a negative association. The only patient with very high IL-6 levels (4336 pg/ml) was the patient who was treated with tocilizumab, and this was consistent with the known cytokine rise following IL-6 receptor blockade.

We observed an unexpected phenomenon of leucoerythroblastic (LE) features on peripheral blood film⁸ (immature granulocyte precursors and nucleated red cells—normally restricted to the bone marrow) in association with high WBC. These features occurred at a median of 14 days from admission and were delayed in comparison to peak CRP and ferritin (Fig 1A). Of 17 patients for whom blood films were available, 10 (58.8%) showed LE features.

Leucoerythroblastic reaction associated with COVID-19 has recently been identified in a single case report, but our data indicate that this may be much more common, suggesting that severe COVID-19 can have profound effects on the bone marrow.

Our experience indicates that HScore has limited application in severe COVID-19 and that the hyperinflammatory state lacks a number of the key features of sHLH.⁹ Thus, it may not be appropriate to use HScore to guide use of immunomodulatory therapy.

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