Clinical criteria for COVID-19-associated hyperinflammatory syndrome: a cohort study

Brandon J Webb, Ithan D Peltan, Paul Jensen, Daanish Hoda, Bradley Hunter, Aaron Silver, Nathan Starr, Whitney Buckel, Nancy Grisel, Erika Hummel, Gregory Snow, Dave Morris, Eddie Stenehjem, Rajendu Srivastava, Samuel M Brown

Summary

Background A subset of patients with COVID-19 develops a hyperinflammatory syndrome that has similarities with other hyperinflammatory disorders. However, clinical criteria specifically to define COVID-19-associated hyperinflammatory syndrome (cHIS) have not been established. We aimed to develop and validate diagnostic criteria for cHIS in a cohort of inpatients with COVID-19.

Methods We searched for clinical research articles published between Jan 1, 1990, and Aug 20, 2020, on features and diagnostic criteria for secondary haemophagocytic lymphohistiocytosis, macrophage activation syndrome, macrophage activation-like syndrome of sepsis, cytokine release syndrome, and COVID-19. We compared published clinical data for COVID-19 with clinical features of other hyperinflammatory or cytokine storm syndromes. Based on a framework of conserved clinical characteristics, we developed a six-criterion additive scale for cHIS: fever, macrophage activation (hyperferritinaemia), haematological dysfunction (neutrophil to lymphocyte ratio), hepatic injury (lactate dehydrogenase or asparate aminotransferase), coagulopathy (D-dimer), and cytokinaemia (C-reactive protein, interleukin-6, or triglycerides). We then validated the association of the cHIS scale with in-hospital mortality and need for mechanical ventilation in consecutive patients in the Intermountain Prospective Observational COVID-19 (IPOC) registry who were admitted to hospital with PCR-confirmed COVID-19. We used a multistate model to estimate the temporal implications of cHIS.

Findings We included 299 patients admitted to hospital with COVID-19 between March 13 and May 5, 2020, in analyses. Unadjusted discrimination of the maximum daily cHIS score was 0·81 (95% CI 0·74–0·88) for in-hospital mortality and 0·92 (0·88–0·96) for mechanical ventilation; these results remained significant in multivariable analysis (odds ratio 1·6 [95% CI 1·2–2·1], p=0·0020, for mortality and 4·3 [3·0–6·0], p<0·0001, for mechanical ventilation). 161 (54%) of 299 patients met two or more cHIS criteria during their hospital admission; these patients had higher risk of mortality than patients with a score of less than 2 (24 [15%] of 138 *vs* one [1%] of 161) and for mechanical ventilation (73 [45%] *vs* three [2%]). In the multistate model, using daily cHIS score as a time-dependent variable, the cHIS hazard ratio for worsening from low to moderate oxygen requirement was 1·4 (95% CI 1·2–1·6), from moderate oxygen to high-flow oxygen 2·2 (1·1–4·4), and to mechanical ventilation 4·0 (1·9–8·2).

Interpretation We proposed and validated criteria for hyperinflammation in COVID-19. This hyperinflammatory state, cHIS, is commonly associated with progression to mechanical ventilation and death. External validation is needed. The cHIS scale might be helpful in defining target populations for trials and immunomodulatory therapies.

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Introduction

COVID-19 is a systemic disease with a wide range of clinical manifestations caused by infection with the novel betacoronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] Among other cellular targets, SARS-CoV-2 directly infects macrophages and monocytes via the angiotensin-converting enzyme 2 (ACE2) receptor, resulting in intracellular infection and activation of macrophages.[2] In some patients, this process results in a hyperinflammatory syndrome associated with acute respiratory distress syndrome and end-organ damage.[3,4] Although incompletely characterised, the hyperinflammatory syndrome observed in COVID-19 shares similarities with other hyperinflammatory disorders,[4–6] such as secondary haemophagocytic lymphohistiocytosis,[7–10] macrophage activation syndrome,[11–17] macrophage activation-like syndrome of sepsis,[18] and cytokine release syndrome.[19–24] These disorders, sometimes known as cytokine storm syndromes, share overlapping clinical manifestations and a common pathway of macrophage activation and a self-perpetuating cycle of cytokine production,[7,25] but consensus agreement is lacking with regard to classification and diagnostic criteria. Although a cytokine storm syndrome in COVID-19 has been proposed,[26,27] data suggest that quantitative concentrations of circulating cytokines might be much lower in COVID-19 than in other conditions, including non-COVID-19 acute respiratory distress syndrome.[28]

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Division of Infectious Diseases and Clinical Epidemiology (B J Webb MD, N Grisel MPP, E Stenehjem MD), **Intermountain Healthcare, Intermountain Medical Center, Salt Lake City, UT, USA; Division of Infectious Diseases and Geographic Medicine, Stanford Medicine, Palo Alto, CA, USA** (B J Webb, E Stenehjem); **Pulmonary and Critical Care Medicine, Intermountain Medical Center, Salt Lake City, UT, USA** (I D Peltan MD, S M Brown MD); **Department of Pulmonary and Critical Care Medicine, University of Utah School of Medicine, Salt Lake City, UT, USA** (I D Peltan, S M Brown); **Division of Rheumatology, Intermountain Healthcare, Dixie Regional Medical Center, St George, UT, USA** (P Jensen MD); **Intermountain Acute Leukemia, Blood and Marrow Transplant Program, LDS Hospital, Salt Lake City, UT, USA** (D Hoda MD, B Hunter MD); **Division of Hospital Medicine, Intermountain Healthcare, Intermountain Medical Center, Salt Lake City, UT, USA** (A Silver MD, N Starr DO); **Pharmacy Services, Antimicrobial Stewardship, Intermountain Healthcare, Salt Lake City, UT, USA** (W Buckel PharmD); **Intermountain Healthcare Office of Research, Salt Lake City, UT, USA** (E Hummel BS); **Healthcare Delivery Institute, Intermountain Healthcare, Murray, UT, USA** (G Snow PhD, R Srivastava MD); **Division of Trauma and Critical Care, Intermountain Medical Center, Murray, UT, USA** (D Morris MD); **Office of Patient Experience, Intermountain Healthcare,**

Salt Lake City, UT, USA (E Stenehjem)**; and Division of Inpatient Medicine, Department of Pediatrics, University of Utah, Salt Lake City, UT, USA** (R Srivastava)

Correspondence to: Dr Brandon J Webb, Division of Infectious Diseases and Clinical Epidemiology, Intermountain Healthcare, Intermountain Medical Center, Murray, UT 84157, USA
brandon.webb@imail.org

Research in context

Evidence before this study

We evaluated published descriptions and guidelines relating to other hyperinflammatory, or cytokine storm syndromes, specifically focusing on features and diagnostic criteria for secondary haemophagocytic lymphohistiocytosis, macrophage activation syndrome, macrophage activation-like syndrome of sepsis, and cytokine release syndrome. We searched MEDLINE and Embase for English-language clinical research articles published between Jan 1, 1990, and Aug 20, 2020, using combinations of the following search terms: "hyperinflammatory syndrome", "hemophagocytic" or "haemophagocytic lymphohistiocytosis", "macrophage activation", "macrophage activation-like", "cytokine", "cytokine release", and "cytokine storm". We also searched the *medRxiv* preprint server and reference lists for articles published in the same timeframe. We did a similar review of literature, using the same databases, related to COVID-19-associated hyperinflammatory states for English-language clinical research articles published between Jan 1, 2019, and Aug 20, 2020, using the same search terms, as well as "SARS-CoV-2" and "COVID-19". Diagnostic criteria for secondary haemophagocytic lymphohistiocytosis, macrophage activation syndrome, and cytokine release syndrome within specific populations have been proposed. Although consensus definitions and naming conventions are in flux, they share a conserved physiological pathway of unchecked macrophage activation and cytokine production. Six categories of physiological features are common to these hyperinflammatory syndromes: fever, macrophage activation, haematological dysfunction, hepatic inflammation, coagulopathy, and cytokinaemia. The literature suggests that although COVID-19 is also often complicated by a hyperinflammatory syndrome, it is distinct from other hyperinflammatory syndromes, with rare cytopenia and cytokine concentrations that are much lower than described in cytokine release syndrome. Because of these differences, diagnostic criteria for other hyperinflammatory conditions do not apply well to COVID-19. COVID-19-specific criteria have not been described so far and would be important to inform patient selection for clinical trials and immunomodulatory therapy.

Added value of this study

In this cohort study, we describe a rational, physiological framework for characterising the COVID-19-associated hyperinflammatory syndrome (cHIS) using biomarkers that are relevant to COVID-19. We validated these clinical criteria by demonstrating that patients with features of cHIS are at higher risk of progressing to mechanical ventilation or death.

Implications of all the available evidence

The proposed cHIS criteria identify patients with a hyperinflammatory phenotype and further clarify the unique features of COVID-19 in the context of the spectrum of other hyperinflammatory or cytokine storm disorders. These criteria will need to be validated in other COVID-19 populations and can serve as a rational framework for advancing our understanding of the immunology of COVID-19. The cHIS scale appears to have prognostic utility and might be useful for patient selection for clinical trials and immunomodulatory therapy.

Better characterisation of the COVID-19 inflammatory state is urgently needed in the context of emerging treatments. Immunomodulatory therapies, including corticosteroids, cell-signalling inhibitors, and anti-cytokine antibodies have been proposed to attenuate the inflammatory response and prevent organ failure.[29–31] Clinical trials of these therapies in COVID-19 have generally not enriched for evidence of hyperinflammation, which might account for discordant results in trials compared with retrospective evaluation after implementation (NCT04315298 and NCT04317092).[30–32] Although diagnostic criteria exist for haemophagocytic lymphohistiocytosis (both secondary and familial),[8,10] macrophage activation syndrome,[13,15–17] and cytokine release syndrome,[22] these criteria have only been validated in very specific populations. Because both the disease features and the patient population in COVID-19 are distinct, direct application of diagnostic criteria from other hyperinflammatory disorders to COVID-19 is problematic. The lack of clarity contributes to uncertainty about clinical trial target population definitions and clinical indications for immunomodulation. To address this gap, we developed novel diagnostic criteria for the hyperinflammatory syndrome observed in some patients with COVID-19 by comparing published clinical data for this syndrome with that for secondary haemophagocytic lymphohistiocytosis, macrophage activation syndrome, and cytokine release syndrome. We then validated the criteria in a cohort of inpatients with COVID-19.

See Online for appendix

Methods

Literature review

In this cohort study, we did a literature review to compare characteristics and pathophysiology of other hyperinflammatory syndromes with that observed in COVID-19. We first searched for publications describing the pathophysiology and features of, and diagnostic criteria for, secondary haemophagocytic lymphohistiocytosis, macrophage activation syndrome, macrophage activation-like syndrome of sepsis, and cytokine release syndrome. We searched MEDLINE and Embase for English-language, clinically oriented articles published between Jan 1, 1990, and Aug 20, 2020, using combinations of the following search terms: "hyperinflammatory syndrome", "hemophagocytic" or "haemophagocytic" "lymphohistiocytosis", "macrophage activation", "macrophage activation-like", "cytokine", "cytokine release", and "cytokine storm" (appendix pp 4–9). We also searched the medRxiv preprint

	Secondary haemophagocytic lymphohistiocytosis[8,10,13,33-37]	Macrophage activation syndrome[11-17,36-40]	Cytokine release syndrome[22-24,41-43]	COVID-19	Values from COVID-19 series that differentiate respiratory failure, ARDS, and death*
Fever (>38·0°C)	Moderate to high†	Moderate to high†	Moderate to high†	Moderate to high†[1,8,10,11,14,15,33,44-47]	>90% have fever
Hepatosplenomegaly	Extremely high†	Moderate to high†	Moderate to high†	ND	Unknown
Encephalopathy	Moderate to high†	Moderate to high†	Extremely high†	Moderate to high†[48-52]	Observed but incidence unknown
Haemoglobin, g/dL	Extremely low‡	Moderate to low‡	Extremely low‡	Mildly low to normal[1,45,53]	12·2 *vs* 13·4
Platelets, 10^9 cells per L	Extremely low‡	Mildly low to normal	Extremely low‡	Mildly low to normal[45,53-58]	143–187 *vs* 173–222
White blood count, 10^9 cells per L	Extremely low‡	Mildly low to normal	Extremely low‡	Mildly low to normal[1,45,53,59]	3·3–11·0 *vs* 4·7–5·3
Absolute lymphocyte count, 10^9 cells per L	Extremely low‡	Mildly low to normal	Extremely low‡	Extremely low‡[1,45,53-58,60]	0·5–0·8 *vs* 1·0–1·4
Neutrophil to lymphocyte ratio	Mildly low to normal	Moderate to high†	ND	Moderate to high†[45,53,54,57,60,61]	5·5–22·0 *vs* 2·8–4·4
Ferritin, ng/mL	Moderate to high†	Extremely high†	Extremely high†	Moderate to high†[53-55,57,58,60,62]	800–1598 *vs* 337–523
Lactate dehydrogenase, U/L	Moderate to high†	Extremely high†	Extremely high†	Moderate to high†[1,45,53,55,58,60,62,63]	400–905 *vs* 221–297
D-dimer, µg/mL	Extremely high†	Moderate to high†	Moderate to high†	Extremely high†[1,45,53-56,60,62,64-66]	0·6–4·0 *vs* 0·3–0·5
Triglycerides, mg/dL	Extremely high†	Extremely high†	Mildly low to normal	Moderate to high†[60]	180 *vs* 120
Fibrinogen, mg/dL	Extremely low‡	Moderate to low‡	Extremely low‡	Extremely high†[53,66]	630 *vs* 450
Aspartate aminotransferase, U/L	Moderate to high†	Moderate to high†	Moderate to high†	Moderate to high†[1,45,53-56,58,62,63]	38–288 *vs* 24–40
Interleukin-6, pg/mL	Extremely high†	Extremely high†	Extremely high†	Moderate to high†[54,55,57,58,60,63,67]	6–72 *vs* 6–13
Soluble interleukin-2 receptor-α (also known as sCD25), pg/mL	Extremely high†	Extremely high†	Extremely high†	Mildly low to normal[57,68]	757 *vs* 663
C-reactive protein§, mg/L	Extremely high†	Moderate to high†	Extremely high†	Extremely high†[53,54,56,58,69]	34–126 *vs* 8–23

ARDS=acute respiratory distress syndrome. ND=no data available. *Range of values reported in published series of patients with COVID-19 that differentiates patients who had severe outcomes (ARDS, critical illness, or death) versus values reported in patients with better outcomes. †Indicates magnitude of increase above the upper limit of normal. ‡ Indicates magnitude of decrease below the lower limit of normal. §Not high-sensitivity C-reactive protein.

Table 1: **Features of hyperinflammatory syndromes and COVID-19**

server and reference lists for articles published in the same timeframe. We then manually reviewed results from electronic searches for relevant articles, using inclusion criteria of clinical descriptions of patient cohorts that described clinical and biochemical features, diagnostic criteria for hyperinflammatory syndromes, or both. Next, we did two additional literature searches, using similar methodology, to search for articles related to COVID-19 using search terms "SARS-CoV-2", and "COVID-19", with a focus on articles that described laboratory and clinical features associated with very severe disease and poor outcomes, including respiratory failure, acute respiratory distress syndrome, or mortality, or described the hyperinflammatory physiology observed in patients with COVID-19 (see appendix pp 4–9 for search terms). For these searches, we restricted the timeframe from Jan 1, 2019, to Aug 20, 2020, and included only English-language articles describing clinical features of human participants. We manually reviewed results from electronic searches for relevance per inclusion criteria listed previously.

cHIS scale

On the basis of the results of our literature review (see appendix pp 1–3 for additional details), we developed a classification framework for defining the unique hyperinflammatory state observed in COVID-19. We first identified a list of core physiological and laboratory features of non-COVID-19 hyperinflammatory syndromes, including those that are generally conserved across published diagnostic criteria for these syndromes. We thus identified the following core features of hyperinflammatory syndromes: fever, hepatosplenomegaly, encephalopathy, haemophagocytosis, macrophage activation, hepatic inflammation, cytopenia and haematological dysfunction, coagulopathy, and elevated concentrations of circulating cytokines.

We then reviewed published descriptions of patients with COVID-19 to compare how core physiological features of other hyperinflammatory syndromes are manifest in COVID-19. A more detailed narrative summary of this review is included in the appendix (pp 1–3) and summarised in table 1. We ultimately identified six core categories

***Panel:* Proposed cHIS criteria**

Fever
- Defined as a temperature of more than 38·0°C

Macrophage activation
- Defined as a ferritin concentration of 700 µg/L or more*

Haematological dysfunction
- Defined as a neutrophil to lymphocyte ratio of 10 or more, or both haemoglobin concentration of 9·2 g/dL or less and platelet count of 110 × 10^9 cells per L or less

Coagulopathy
- Defined as a D-dimer concentration of 1·5 µg/mL or more

Hepatic injury
- Defined as a lactate dehydrogenase concentration of 400 U/L or more, or an aspartate aminotransferase concentration of 100 U/L or more

Cytokinaemia
- Defined as an interleukin-6 concentration of 15 pg/mL or more†, or a triglyceride concentration of 150 mg/dL or more‡, or a CRP§ concentration of 15 mg/dL or more¶

cHIS=COVID-19-associated hyperinflammatory syndrome. CRP=C-reactive protein. *Ferritin concentration might be elevated in end-stage renal disease on haemodialysis. †Original validation used a 10 pg/mL threshold; post-hoc analysis suggested that 15 pg/mL has better discrimination for poor outcomes. ‡Triglycerides might be elevated due to concomitant propofol administration. §Not high-sensitivity CRP. ¶CRP was not included in the original validation; post-hoc analysis confirmed use as a third surrogate for cytokinaemia.

of clinical features common to both COVID-19 and non-COVID-19 hyperinflammatory syndromes. We then further adapted this framework to COVID-19 by identifying representative features for each category that are specific to COVID-19. We propose the term COVID-19-associated hyperinflammatory syndrome (cHIS) to describe the condition described by these features. Finally, for each of the six proposed categories, we identified laboratory biomarker thresholds associated with critical illness, acute respiratory distress syndrome, or death in published cohorts of patients with COVID-19. We used these thresholds to develop a six-point, additive clinical scale to assess the presence and severity of cHIS.

Empirical validation

After a-priori development of the cHIS scale, we identified a validation dataset within the Intermountain Prospective Observational COVID-19 (IPOC) registry, which contains demographics, comorbidities, clinical data, and outcomes for all patients with PCR-confirmed COVID-19 admitted to any of 22 hospitals in an integrated health-care system in western USA. We studied all consecutive IPOC patients aged 18 years or older who were admitted to hospital between March 13 and May 5, 2020. Laboratory tests were ordered according to institutional protocols and clinician preference. We assessed all clinical data on each day of admission, and used the last-carried-forward imputation for missing values. We then calculated the maximal cHIS score on each hospital day. To explore crude associations with outcomes, we also determined the maximum daily score attained during the admission. The prespecified primary outcome for analysis was in-hospital mortality, and the key secondary outcome was incidence of mechanical ventilation. Other secondary outcomes included length of hospital stay and intensive care unit (ICU) stay.

This study was approved by the Intermountain Healthcare institutional review board and is aligned with STROBE guidelines for cohort studies.

Statistical analysis

We used descriptive statistics to report clinical and demographic characteristics, laboratory values, and outcomes. For laboratory values, we summarised the maximum or minimum values for each laboratory biomarker, as appropriate. Our prespecified primary analysis was the association of maximum daily cHIS score with in-hospital all-cause mortality using the area under the receiver operating characteristic curve (AUROC). We did a similar analysis for mechanical ventilation. We did prespecified sensitivity analyses to control for the possible effects of other confounding variables on these outcomes by fitting a multivariable logistic regression model for each outcome including cHIS and a prespecified list of potential confounders. For mechanical ventilation, model covariates included age, sex, number of comorbidities, race and ethnicity, and body-mass index. For mortality, we included only cHIS, age, and number of comorbidities due to low event rates. After the primary analysis, we did a cut-point analysis for the cHIS score using the Youden index[70] and the receiver operating characteristic curve, and also used this method to evaluate optimal thresholds for individual biomarkers. In a post-hoc analysis, we recognised that C-reactive protein (CRP) appeared to be a widely available and accurate surrogate marker for cytokinaemia; we therefore included CRP (note that we did not measure high-sensitivity CRP; reported values are in mg/dL) as a third alternative to interleukin (IL)-6 or triglycerides and re-evaluated performance of the score with the inclusion of this variable. Finally, to explore the relative importance of each of the six components of the cHIS scale, we calculated frequency, sensitivity, and specificity for each and described variable importance from random forest modelling.[71]

We recognised a priori that measurement of the association between cHIS and mechanical ventilation and mortality is not synonymous with prediction of these outcomes, which requires accounting for temporal sequence and competing risks. We were also aware of the risk of immortal time bias with the main analysis. We therefore did a prespecified secondary analysis to evaluate the impact of cHIS on clinical deterioration over time. Given the dynamic clinical progression of COVID-19 over time, we did not restrict to cHIS scores in the first 24–48 h of hospital admission. We used a Markov multistate model,[72]

specified with six clinical transition states representing the highest degree of respiratory failure experienced on any given calendar day: use of supplemental oxygen at 0–3 L/min via nasal canula; use of oxygen at 4–6 L/min; use of oxygen at more than 6 L/min via a face mask, or a non-rebreather or nasal moustache delivery device; use of high-flow nasal canula or non-invasive positive pressure ventilation; mechanical ventilation or extracorporeal membrane oxygenation; and in-hospital death. In this model, daily cHIS scale values were included as a time-dependent ordinal variable with levels of 0, 1, and 2 or more (simplified from all scale values to avoid non-convergence of the model). No confounders were included in this model. The hazard ratio (HR; and 95% CI) of cHIS for each transition state was estimated. Statistical analyses were done with SPSS (version 25.0) and R (version 4.0.2).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We compare features of well described hyperinflammatory conditions with those described in the unique hyperinflammatory syndrome of COVID-19 in table 1 and in the appendix (pp 1–3). The cHIS appears to share a core pathophysiological feature of prominent macrophage activation with other hyperinflammatory syndromes; however, other features observed in COVID-19 are distinct from classic cytokine storm syndromes, including a scarcity of cytopenias and lower quantitative concentrations of circulating inflammatory cytokines than in other comparable diseases.[2–4,28–29]

Six physiological categories of features were included in the proposed cHIS classification system: fever, macrophage activation, haematological dysfunction, hepatic inflammation, coagulopathy, and cytokinaemia. Using prespecified thresholds for laboratory biomarkers within each category, a six-criterion, additive clinical scale for cHIS (panel) was thus specified a priori, before any empirical validation was performed.

We identified 299 patients admitted to hospital between March 13 and May 5, 2020, with COVID-19, accounting for 2535 inpatient days. Table 2 presents the distribution of baseline characteristics for the cohort. Data were complete for fever, haematological dysfunction, and hepatic inflammation. 184 (62%) patients had documented ferritin concentrations, 158 (53%) had D-dimer values, and 298 had data for at least one marker of cytokinaemia (either IL-6, triglycerides, or CRP). Median age was 56 years (IQR 43–68); 132 (44%) patients were female, and patients had median 2 (1–4) comorbidities. The number of combined inpatient days by maximum oxygen requirement were as follows: 1213 (48%) of 2535 for 0–3 L/min,

	Total (n=299)	cHIS score 0–1 (n=138)	cHIS score ≥2 (n=161)
Age, years	56·0 (43·0–68·0)	53·5 (39·0–66·0)	68·0 (59·0–46·5)
Sex			
Female	132 (44%)	75 (54%)	57 (35%)
Male	167 (56%)	63 (46%)	104 (65%)
Race			
American Indian or Alaskan Native	21 (7%)	8 (6%)	13 (8%)
Asian	4 (1%)	2 (1%)	2 (1%)
Black or African American	6 (2%)	3 (2%)	3 (2%)
Native Hawaiian or Pacific Islander	21 (7%)	5 (4%)	16 (10%)
White	209 (70%)	99 (72%)	110 (68%)
Not specified or multiple	38 (13%)	21 (15%)	17 (11%)
Hispanic or Latino ethnicity	106 (35%)	46 (33%)	60 (37%)
Hispanic-Latino ethnicity or non-white race	173 (58%)	73 (53%)	100 (62%)
Body-mass index, kg/m²	31·7 (26·0–37·1)	31·1 (25·7–36·9)	31·8 (26·5–37·3)
Comorbidities	2 (1–4)	1 (1–3)	3 (2–4)
Diabetes	105 (35%)	36 (26%)	69 (43%)
Hypertension	163 (55%)	66 (48%)	97 (60%)
Coronary artery disease	23 (8%)	9 (7%)	14 (9%)
Arrhythmia	97 (32%)	31 (22%)	66 (41%)
Chronic pulmonary disease	78 (26%)	33 (24%)	45 (28%)
Chronic kidney disease	49 (16%)	21 (15%)	28 (17%)
Congestive heart failure	31 (10%)	9 (7%)	22 (14%)
Chronic liver disease	41 (14%)	15 (11%)	26 (16%)
Active malignancy	7 (2%)	2 (1%)	5 (3%)
Obesity	131 (44%)	54 (39%)	77 (48%)
Immunosuppressed	8 (3%)	2 (1%)	6 (4%)
Cerebrovascular disease	25 (8%)	9 (7%)	16 (10%)
Chronic neurological disease	56 (19%)	23 (17%)	33 (20%)
Outcomes			
Length of hospital stay, days	5·2 (2·7–10·1)	3·1 (2·0–5·4)	9·2 (5·1–16·6)
Intensive care unit stay	135 (45%)	24 (17%)	111 (69%)
Mechanical ventilation	76 (25%)	3 (2%)	73 (45%)
In-hospital all-cause mortality	25 (8%)	1 (1%)	24 (15%)
Laboratory assessments*			
Haemoglobin, g/dL	12·2 (10·5–13·6)	12·7 (11·5–14·0)	11·6 (10·0–13·2)
Platelet count, 10^9 cells per L	172 (133–222)	195 (152–245)	152 (114–203)
White blood cell count, 10^9 cells per L	5·1 (3·9–6·5)	5·1 (4·0–6·6)	5·0 (3·7–6·3)
Absolute lymphocyte count, 10^9 cells per L	0·8 (0·5–1·1)	1·0 (0·7–1·4)	0·6 (0·3–0·9)
Neutrophil to lymphocyte ratio	6·3 (3·8–13·0)	4·6 (2·6–6·6)	10·3 (5·6–21·8)
Ferritin, ng/mL	378 (209–1412; n=184)	298 (100–453; n=53)	754 (272–1864; n=131)
C-reactive protein†, mg/dL	3·9 (4·8–23·6; n=206)	0·6 (1·3–11·0; n=68)	17·5 (8·6–27·7; n=138)
Blood urea nitrogen, mg/dL	18 (12–32)	13 (10–20)	25 (15–45)
Creatinine, mg/dL	1·0 (0·8–1·3)	0·9 (0·7–1·2)	1·1 (0·8–1·4)
Aspartate aminotransferase, U/L	55 (36–94)	42 (29–55)	77 (49–147)
Total bilirubin, mg/dL	0·6 (0·5–0·8)	0·5 (0·4–0·8)	0·7 (0·5–0·9)
Lactate dehydrogenase, U/L	369 (228–555; n=170)	257 (171–346; n=50)	446 (272–626; n=120)

(Table 2 continues on next page)

	Total (n=299)	cHIS score 0–1 (n=138)	cHIS score ≥2 (n=161)
(Continued from previous page)			
D-dimer, µg/mL	1·3 (0·7–2·3; n=158)	0·6 (0·4–0·9; n=43)	1·6 (0·9–2·7; n=115)
Interleukin-6, pg/mL	22·5 (8–65; n=72)	5 (5–6·5; n=5)	24 (9–74; n=67)
Prothrombin time, s	14·2 (13·5–15·9; n=92)	13·7 (13·1–14·3; n=17)	14·4 (13·6–16·3; n=75)
Triglycerides, mg/dL	146 (83–374; n=55)	115 (57–268; n=6)	175 (86–396; n=49)
Fibrinogen, mg/dL	528 (77–730; n=30)	75 (53–81; n=3)	579 (77–734; n=27)
Procalcitonin, ng/mL	0·4 (0·18–0·77; n=173)	0·4 (0·2–0·6; n=68)	0·4 (0·2–0·9; n=105)

Data are median (IQR) or n (%) unless otherwise stated. cHIS=COVID-19-associated hyperinflammatory syndrome.
*Laboratory values represent the minimum or maximum value during the admission, as appropriate.
†Not high-sensitivity C-reactive protein.

Table 2: **Clinical and laboratory characteristics of patients with COVID-19, stratified by peak cHIS score during the hospital stay**

	Patients (n=299)
cHIS score 0	40 (13%)
cHIS score 1	98 (33%)
cHIS score 2	62 (21%)
cHIS score 3	38 (13%)
cHIS score 4	27 (9%)
cHIS score 5	21 (7%)
cHIS score 6	13 (4%)

cHIS=COVID-19-associated hyperinflammatory syndrome.

Table 3: **Proportions of patients by highest single-day cHIS score achieved during their admission**

228 (9%) for 4–6 L/min, 48 (2%) for more than 6 L/min but not high-flow nasal canula or non-invasive positive pressure ventilation, 157 (6%) for high-flow nasal canula or non-invasive positive pressure ventilation, and 857 (34%) for mechanical ventilation. The median daily cHIS score was 2 (IQR 1–3). At some point during their stay, 161 (54%) patients achieved a daily cHIS score of 2 or higher. The proportions of patients by highest single-day cHIS score achieved during their admission are reported in table 3.

Discrimination of the maximum daily cHIS score during the hospital admission by AUROC was 0·81 (95% CI 0·74–0·88) for in-hospital mortality and 0·92 (0·88–0·96) for mechanical ventilation. A score of less than 2 versus 2 or more distinguished patients along multiple clinical endpoints: median length of hospital stay of 3·1 days (IQR 2·0–5·4) versus 9·2 days (5·1–16·6); 24 (17%) of 138 patients versus 111 (69%) of 161 patients requiring ICU care; three (2%) versus 73 (45%) patients requiring mechanical ventilation; and one (1%) versus 24 (15%) deaths in hospital (table 2). In a sensitivity analysis, bivariate regression for cHIS and mechanical ventilation showed an odds ratio (OR) of 4·1 (95% CI 3·0–5·7, p<0·0001). In a multivariable regression model, the OR was 0·99 (95% CI 0·96–1·01) adjusting for age, 0·67 (0·29–1·5) adjusting for male sex, 1·1 (0·48–2·5) adjusting for Hispanic ethnicity or non-white race, and 1·3 (1·1–1·5) adjusting for total comorbidities. The cHIS scale was highly associated with mechanical ventilation (OR 4·3 [95% CI 3·0–6·0], p<0·0001). In bivariate regression for in-hospital mortality, the OR was 1·9 (95% CI 1·5–2·5, p<0·0001). In the multivariable logistic regression model, the OR was 1·05 (95% CI 1·0–1·08) adjusting for age and 1·3 (1·0–1·5) adjusting for comorbidities. The cHIS scale remained associated with mortality (OR 1·6 [95% CI 1·2–2·1], p=0·0020).

In the multistate model, using the daily score as a time-dependent variable, the HR for cHIS for transitioning from receiving 0–3 L/min to receiving 4–6 L/min was 1·4 (95% CI 1·2–1·6), the HR for transitioning from receiving 0–3 L/min to mechanical ventilation was 4·0 (95% CI 1·9–8·2), and the HR for transitioning from receiving 4–6 L/min to high-flow nasal canula or non-invasive positive pressure ventilation was 2·2 (95% CI 1·1–4·4). The multistate model indicates that on any given day, a patient with a score of 1 has a four times greater hazard than a patient with a score of 0 of progressing from 0–3 L/min to mechanical ventilation later during the hospital admission, and, similarly, a patient with a score of 2 or more on any given day has a four times greater hazard of future deterioration to ventilation than a patient with a score of 1. The multistate model transitions for mortality had very broad confidence intervals given the small number of deaths.

Results of a post-hoc sensitivity analysis to evaluate the frequency and association of individual cHIS criteria with clinical outcomes are shown in table 4. At a threshold of 2 or greater, the scale had excellent sensitivity for both mechanical ventilation and mortality. Coagulopathy, hyperferritinaemia, haematological dysfunction, and cytokinaemia were most specifically associated with mechanical ventilation, whereas coagulopathy was most associated with mortality. Variable importance plots for individual components of the cHIS scale suggested that for mechanical ventilation, cytokinaemia and haematological dysfunction were the most important variables (appendix p 10). For mortality, haematological dysfunction and hepatic inflammation were the most important variables (appendix p 11). Optimal cutoff-point analyses largely corroborated laboratory thresholds identified a priori from the COVID-19 literature (appendix pp 12–14), with the exception of IL-6, which might be more predictive at cutoff points in the 15–20 pg/mL range, and D-dimer, for which a modestly lower threshold of 1 µg/mL seemed to be relevant. Post-hoc sensitivity analysis in which a CRP concentration of 15 µg/dL or mg/dL or more was included as a third alternative for cytokinaemia, in addition to IL-6 and triglycerides, showed that the cHIS scale performed equally well with this addition (discrimination for

	Patients (n=299)	Mechanical ventilation			Mortality		
		Sensitivity (95% CI)	Specificity (95% CI)	AUROC (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	AUROC (95% CI)
Fever	231 (77%)	0·93 (0·85–0·98)	0·28 (0·23–0·35)	0·61 (0·54–0·68)	0·88 (0·68–0·97)	0·24 (0·19–0·29)	0·56 (0·45–0·67)
Hyperferritinaemia	73 (24%)	0·57 (0·45–0·68)	0·87 (0·81–0·91)	0·72 (0·64–0·79)	0·56 (0·35–0·75)	0·78 (0·73–0·83)	0·67 (0·55–0·79)
Haematological dysfunction	98 (33%)	0·76 (0·65–0·85)	0·82 (0·76–0·87)	0·79 (0·73–0·86)	0·84 (0·63–0·95)	0·72 (0·66–0·77)	0·78 (0·69–0·87)
Hepatic inflammation	100 (33%)	0·64 (0·53–0·75)	0·77 (0·71–0·82)	0·71 (0·64–0·78)	0·72 (0·50–0·87)	0·70 (0·64–0·75)	0·71 (0·60–0·82)
Coagulopathy	65 (22%)	0·50 (0·38–0·62)	0·88 (0·83–0·92)	0·69 (0·61–0·77)	0·44 (0·25–0·65)	0·80 (0·75–0·85)	0·62 (0·50–0·75)
Cytokinaemia	105 (35%)	0·82 (0·71–0·89)	0·81 (0·75–0·86)	0·81 (0·75–0·87)	0·76 (0·54–0·90)	0·68 (0·63–0·74)	0·72 (0·62–0·83)
cHIS score ≥2	161 (54%)	0·95 (0·88–0·99)	0·59 (0·52–0·65)	0·92 (0·88–0·96)	0·96 (0·78–1·00)	0·49 (0·43–0·55)	0·81 (0·74–0·88)
cHIS score ≥3	99 (33%)	0·87 (0·77–0·93)	0·81 (0·75–0·86)	0·92 (0·88–0·96)	0·80 (0·59–0·92)	0·68 (0·62–0·73)	0·81 (0·74–0·88)
cHIS score ≥4	61 (20%)	0·71 (0·59–0·81)	0·92 (0·87–0·95)	0·92 (0·88–0·96)	0·64 (0·42–0·81)	0·80 (0·74–0·84)	0·81 (0·74–0·88)

AUROC=area under the receiver operating characteristic curve. cHIS=COVID-19-associated hyperinflammatory syndrome.

Table 4: **Association with outcomes by individual cHIS components**

mortality 0·81 [95% CI 0·74–0·88] without CRP *vs* 0·81 [0·74–0·88] with CRP).

Discussion

Although clinicians and investigators have generally agreed that serious COVID-19 is associated with dysregulated inflammation—with an emphasis early in the pandemic on a cytokine storm—the nature of this inflammation is poorly understood. Notably, it has now been observed that median circulating concentrations of inflammatory cytokines reported in COVID-19 are an order of magnitude lower than in other hyperinflammatory syndromes, including non-COVID-19 acute respiratory distress syndrome.[28] Similarly, early suggestions that COVID-19 induces secondary haemophagocytic lymphohistiocytosis[27] have now also been revised given the distinct lack of cytopenias, hepatosplenomegaly, fibrinogen consumption, or markedly elevated soluble IL-2 receptor-α (also known as sCD25) in COVID-19. However, an evolving understanding of the immunopathology of COVID-19 suggests that uncontrolled macrophage and monocyte activation due to a dysfunctional interferon response to SARS-CoV-2 infection has a key role in subsequent inflammatory response and organ injury.[2,4,29,73,74] Other mechanisms, including genetic polymorphisms related to the inflammatory response might also play a part.[75] In recognition of the general similarities and still distinctive manifestations of COVID-19 hyperinflammation compared with other hyperinflammatory disorders, we have proposed and validated a clinical classification scale for the cHIS.

The strength of the proposed cHIS scale derives from a rational framework for characterising this disease in the context of previously described hyperinflammatory disorders,[8,10,15] relevance to reports of the prognostic implications of individual biomarkers in cohorts of patients with COVID-19, and associations in a multicentre validation cohort—robust to multiple sensitivity analyses—between an elevated score and clinical outcomes, and the fact that the score is based on clinically available laboratory biomarkers. In addition, by modelling cHIS as a time-dependent variable in a multistate model, our data suggest that the more cHIS features a patient has on any given day, the higher the likelihood of future clinical deterioration.

The primary implication of our findings is for the definition of target populations for clinical trials and identification of candidates for clinical use of immunomodulating therapies.

In non-COVID-19 acute respiratory distress syndrome, a strategy for stratifying patients on the basis of hypo-inflammatory versus hyperinflammatory phenotypes has been proposed as a means of focusing immunomodulating therapies on patients who are more likely to benefit.[76] Applying a similar approach to COVID-19 could clarify which subgroups of patients might benefit from corticosteroids, selective cytokine antagonists, or macrophage-targeted cell-signalling modifiers, and when in their course of disease benefit is most likely to be realised. For example, recent work suggests differential efficacy of corticosteroids depending on the presence of inflammation.[77,78] It is also conceivable that discrepant results with IL-6 inhibition in highly selected real-world observational cohorts[30,32] and recent clinical trials (NCT04315298 and NCT04317092) might in fact be related to trial enrolment of immunologically undifferentiated target populations. Heterogeneity of treatment effect analyses of trials with undifferentiated patients with COVID-19 and larger prospective cohorts with intentional sampling of additional inflammatory markers are important next steps. We recommend that trials and clinical protocols for immunomodulatory therapies include attention to the presence of actual markers of inflammation.

This study should be interpreted in the context of important limitations. Although the diagnostic criteria were selected a priori based on existing literature and without reference to patient data in the multihospital cohort in which the criteria were independently validated, the relatively modest sample size and low observed mortality might limit generalisability to other populations

in which patient demographics, clinical characteristics, and management might differ. Our study also has the drawbacks characteristic of its retrospective design, including potential threats to data accuracy, missing data, and indication and temporal biases. We have attempted to address these through imputation and multistate modeling, but independent, external, and preferably prospective validation is needed to confirm these observations.

The cHIS scale appears to reflect COVID-19-specific patterns of inflammation. It was adapted from related hyperinflammatory syndromes and independently validated by linkage to outcomes. The proposed cHIS criteria therefore exhibit construct, content, and face validity. These criteria might have prognostic value and usefulness in identifying patients for research trials and clinical uses of anti-inflammatory therapies. Additional validation in large external cohorts, including trial populations, is urgently indicated.

Contributors

BJW, IDP, PJ, DH, BH, AS, NS, WB, EH, DM, RS, and SMB contributed to the study concept. BJW, IDP, SMB, and GS were involved in the study design. BJW, IDP, PJ, WB, DH, BH, and SMB contributed to the literature review. BJW, NG, and GS collected data. BJW, GS, and SMB did the statistical analysis. BJW, IDP, PJ, DH, BH, AS, NS, WB, EH, DM, ES, RS, and SMB were involved in interpretation of results. All authors were involved in manuscript preparation and critical review of the manuscript.

Declaration of interests

IDP reports salary support through a grant from the US National Institutes of Health (NIH). RS reports effort supported by US federal grants through the Agency for Healthcare Research and Quality, NIH, and the Patient-Centered Outcomes Research Institute, as well as institutional support (Intermountain Healthcare) in his equity as founding member of the I-PASS Patient Safety Institute. RS also reports monetary awards, honorariums, and travel reimbursement from multiple academic and professional organisations for talks about paediatric hospitalist research networks and quality of care. SMB reports salary support from the NIH, US Centers for Disease Control, and the US Department of Defense; he also reports receiving support for chairing a data and safety monitoring board for a respiratory failure trial sponsored by Hamilton, effort paid to Intermountain for steering committee work for Faron Pharmaceuticals and Sedana Pharmaceuticals for ARDS work, support from Janssen for Influenza research, and royalties for books on religion and ethics from Oxford University Press/Brigham Young University. BH reports personal fees from Kite Pharma outside the submitted work. BJW reports partial salary support from a US federal grant from the Agency for Healthcare Research and Quality. At the time of submission, Intermountain Healthcare has participated in COVID-19 trials sponsored by: AbbVie, Genentech, Gilead, Regeneron, Roche, and the NIH ACTIV and PETAL clinical trials networks; several authors (BJW, IDP, DH, BH, and SMB) were site investigators on these trials but received no direct or indirect remuneration for their effort. All other authors declare no competing interests.

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