Assessment of Admission COVID-19 Associated Hyperinflammation Syndrome Score in Critically-Ill COVID-19 Patients

Mehmet Yildirim, MD1, Burcin Halacli, MD1, Deniz Yuce, MD2, Yunus Gunegul, MD3, Ebru Ortac Ersoy, MD1, and Arzu Topeli, MD, MSc (Epid.)1

Abstract
Purpose: We aimed to evaluate the relation between admission COVID-19 associated hyperinflammatory syndrome (cHIS) score and intensive care unit (ICU) outcomes.

Materials and Methods: Patients with laboratory confirmed COVID-19 admitted to our ICU between 20th March 2020-15th June 2021 were included. Patients who received immunomodulatory treatment except corticosteroids were excluded. Main outcomes were ICU mortality and invasive mechanical ventilation (IMV) requirement after ICU admission.

Results: Three hundred and seventy patients with a median (IQR) age of 66 (56-77) were analyzed. Median admission cHIS score was 3 (2-4). A cHIS score ≥3 was found to be associated with ICU mortality (sensitivity = 0.63, specificity = 0.50; p < 0.01) and IMV requirement after ICU admission (sensitivity = 0.61, specificity = 0.51; p < 0.01). Patients with an admission cHIS score ≥3 (n = 199) had worse median admission APACHEII, SOFA scores and PaO2/FiO2 ratio than others (n = 171) (p < 0.01). IMV requirement after ICU admission (38.5% vs 26.1%; p = 0.03), ICU (36.2% vs 25.1%; p = 0.02), hospital (39.1% vs 26.9%; p = 0.01) and 28th day (28.1% vs 19.1%; p = 0.04) mortality were higher in patients with admission cHIS score ≥3 than others (p < 0.01). Age <65 years, malignancy and higher admission SOFA score were independent variables associated with admission cHIS score ≥3.

Conclusion: Critically-ill COVID-19 patients with admission cHIS score ≥3 have worse disease severity and outcomes than other patients.

Keywords COVID-19, SARS-CoV-2, hyperinflammation, score, cHIS, intensive care unit

Introduction
Corona virus disease 2019 (COVID-19) which is caused by severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) is a heterogeneous clinical syndrome ranging from asymptomatic illness to ARDS. Although ARDS is the major cause of mortality, hyperinflammation is a serious condition which might lead to secondary hemophagocytic lymphohistiocytosis (HLH), macrophage activation syndrome (MAS) and cytokine release syndrome. SARS-CoV-2 uses the angiotensin-converting enzyme (ACE)-2 receptor in humans for cell entry and attacks immune cells directly. Hyperactivation of macrophages, natural killers and T cells and production of over 100 inflammatory cytokines lead to cytokine storm and hyperinflammation. Compared to patients with mild-moderate COVID-19, higher humoral immune response and higher levels of inflammatory mediators such as Interleukin-6 (IL-6), interferon-γ-inducible protein-10 (IP-10) and monocyte chemoattractant protein-1 (MCP-1) have been found in patients with severe COVID-19. Persistence of hyperinflammation and its degree is also related with higher risk for disease progression and poor outcomes. Immunomodulatory treatments are increasingly used in these situations. However; different results for immunomodulatory treatments have been reported. Various studies have demonstrated that the determination of hyperinflammation and its degree may have a pivotal role in order to predict prognosis and decide on immunomodulatory therapy early in the intensive care unit (ICU).

Despite hyperinflammation is a well-known and important condition in COVID-19, few criteria and scoring systems to detect hyperinflammation have been evaluated. A recent study by Webb et al. proposed to determine specific criteria for COVID-19 associated hyperinflammation syndrome (cHIS). They defined cHIS as; 1. Fever (>38°C), 2. Macrophage activation...
with ferritin $\geq 700\, \mu g/L$, 3. Hematological dysfunction with neutrophil/lymphocyte ratio (NLR) $\geq 10$ or hemoglobin $\leq 9.2\, g/dL$ and platelet count $\leq 110,000$ cells/L, 4. Coagulopathy with D-dimer $\geq 1.5\, \mu g/mL$, 5. Hepatic injury with lactate dehydrogenase (LDH) $\geq 400\, U/L$ or aspartate aminotransferase (AST) $\geq 100\, U/L$ and 6. Cytokinemia with interleukin-6 (IL-6) $\geq 15\, pg/mL$ or triglyceride $\geq 150\, mg/dL$ or C-reactive protein (CRP) $\geq 15\, mg/dL$. Each 6 criteria increase cHIS score one point and the previous admission cHIS scores on ICU mortality and invasive mechanical ventilation (IMV).

Hereby, we aimed to evaluate the predictive accuracy of admission cHIS scores on ICU mortality and invasive mechanical ventilation (IMV).

**Materials and Methods**

The study was approved by the Non-interventional Clinical Researches Ethics Board (reference number: GO 22/277, date: 15th March 2022) of our university and the approval of Turkish Ministry of Health was obtained.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

**Patients’ Selection**

We conducted a retrospective observational study on laboratory confirmed critically-ill COVID-19 patients who were $\geq 18$ years of age. We reviewed the records of COVID-19 patients who had been admitted to our medical ICU between 20th March 2020 and 15th June 2021. All cases of COVID-19 patients had positive results for polymerase chain reaction (PCR) for SARS-CoV-2. Patients who received immunomodulatory therapies (tocilizumab and anakinra) before or after the admission were excluded.

**Data Collection**

Data were collected from electronic medical records and patient charts. Demographic data, comorbidities, Eastern Cooperative Oncology Group (ECOG) Performance Status, Clinical Frailty Scale (CFS) (appropriate permission was obtained), Acute Physiology and Chronic Health Evaluation (APACHE) II score, Sequential Organ Failure Assessment (SOFA) score on admission were recorded. Arterial blood gas analysis, partial pressure of arterial oxygen/fraction of inspired oxygen ratios (PaO2/FiO2) on ICU admission, use of invasive mechanical ventilation (IMV) were noted. The presence of septic shock based on Sepsis-3 definitions and acute kidney injury (AKI) defined by Kidney Disease Improving Global Outcomes criteria on admission were recorded. Secondary bacterial infection and opportunistic infections were defined as positive culture results after 72 h in patients with confirmed viral infection. If available, PCR results for Cytomegalovirus (CMV), Epstein-Barr virus (EBV) and herpes viruses were also checked from the patients’ electronic medical records. To determine admission cHIS score; fever, ferritin, NLR, hemoglobin, platelet, D-dimer, LDH, AST, IL-6, triglyceride and CRP values on admission were noted. cHIS scores were calculated based on the previous study by Webb et al.

**Outcomes**

The main outcomes were ICU mortality and IMV requirement after ICU admission. Presence of IMV requirement after ICU admission was considered as application of IMV after the first 24 h of ICU admission. We also noted 28th day mortality, hospital mortality, ICU and hospital LOS as secondary outcomes.

**Statistical Analysis**

Descriptive statistics were presented using median and interquartile range (25th−75th percentiles−IQR) for continuous variables; frequency and percent for categorical variables and comparisons between independent groups were performed using Mann-Whitney U test and Chi-square test, respectively. The predictive values of prognostic factors for ICU mortality were analyzed using receiver-operator characteristics (ROC) analyses. Cut-off values were determined based on Youden index to maximize sensitivity and specificity. For multivariate analysis, clinically relevant significant variables detected from univariate analysis were further entered into the binary logistic regression analysis to determine independent predictors of admission cHIS score $\geq 3$. A type-I error level of 5% was considered as statistical significance threshold. All analyses were done with SPSS 23 IBM ® statistics program (IBM Inc., Armonk, NY, USA).

**Results**

A total of 397 patients were admitted to our ICU during the study period. After exclusion of 27 patients who received immunomodulatory therapy, 370 patients were analyzed. Ninety-four (25.4%) and 87 (23.5%) patients had an admission cHIS score 2 and 3, respectively (Table 1). Median admission cHIS score was 3 (IQR = 2-4). Based on Youden index an admission cHIS score $\geq 3$ has the best accuracy for ICU mortality (sensitivity = 0.63 and specificity = 0.50; $p < 0.01$) and IMV requirement after ICU admission (sensitivity = 0.61 and specificity = 0.51; $p < 0.01$). At a cut-off value of 2 or higher, admission cHIS score has the best sensitivity for both ICU mortality and IMV requirement (0.90 and 0.87, respectively) (Table 2).

**Table 1.** Number and proportion of patients by admission cHIS score.

| cHIS score | Total (n = 370) |
|------------|----------------|
| 0          | 17 (4.6%)      |
| 1          | 60 (16.2%)     |
| 2          | 94 (25.4%)     |
| 3          | 87 (23.5%)     |
| 4          | 62 (16.8%)     |
| 5          | 41 (11.1%)     |
| 6          | 9 (2.4%)       |

cHIS: COVID-19 associated hyperinflammatory syndrome
Patients with admission cHIS score <3 versus admission cHIS score ≥3 were compared as seen in Table 3. Patients with admission cHIS score <3 were older than others (p = 0.04). There was no difference in terms of gender and comorbidities between two groups, except for malignancy that was more common in patients with admission cHIS score ≥3 (p < 0.01). While median patient performance scores (ECOG, CFS) were similar in two groups; median disease severity scores (APACHE II and SOFA) were higher in patients with admission cHIS score ≥3 than others (p < 0.01, for both). Median PaO2/FiO2 ratio on admission were lower in admission cHIS score ≥3 group than others (p < 0.01). The frequency of steroid use in cHIS score ≥3 group was 92.5% whereas in cHIS score <3 group 83.6% of the patients received steroid therapy (p < 0.01). Presence of septic shock on admission (p = 0.01), secondary infections (p = 0.02), reactivation of CMV, EBV and/or herpes viruses (p < 0.01) and opportunistic infections (p = 0.02) were more common in those with admission cHIS score ≥3. Thirty eight of the 370 patients were receiving IMV on ICU admission and there were no differences in IMV rates on ICU admission between two groups (p = 0.88). Among the patients who were not receiving IMV on ICU

Table 2. Association Between Admission cHIS Scores and Outcomes.

| cHIS score | ICU mortality | Invasive mechanical ventilation requirement after ICU admission |
|------------|--------------|-------------------------------------------------------------|
|            | Sensitivity | Specificity | Sensitivity | Specificity |
| ≥ 3        | 0.99        | 0.06        | 0.98        | 0.05        |
| ≥ 2        | 0.89        | 0.25        | 0.87        | 0.26        |
| ≥ 1        | 0.63        | 0.50        | 0.61        | 0.51        |
| ≥ 4        | 0.41        | 0.75        | 0.40        | 0.75        |
| ≥ 5        | 0.19        | 0.89        | 0.19        | 0.90        |
| ≥ 6        | 0.07        | 0.99        | 0.06        | 0.99        |

p < 0.01, cHIS: COVID-19 associated hyperinflammatory syndrome, ICU: intensive care unit

Table 3. General Characteristics and Outcomes of Patients.

| Total (n = 370) | cHIS score < 3 (n = 171) | cHIS score ≥ 3 (n = 199) | P value |
|----------------|--------------------------|--------------------------|---------|
| Age*           |                          |                          |         |
| Age <65 years old | 66 [56–77]              | 66 [57–76]              | 63 [54–76] | 0.04 |
| Male, n (%)     | 169 (45.7)               | 67 (39.2)               | 102 (51.3) | 0.02 |
| Comorbidities, n (%) |
| Hypertension    | 232 (62.7)              | 106 (62.0)              | 126 (63.3) | 0.50 |
| Cardiac disease | 196 (53.0)              | 101 (59.1)              | 95 (47.7) | 0.06 |
| Diabetes        | 131 (35.4)              | 68 (38.6)               | 63 (31.7) | 0.16 |
| Malignancy      | 129 (34.9)              | 66 (38.6)               | 63 (31.7) | 0.24 |
| Solid organ     | 75 (20.3)               | 23 (13.5)               | 52 (26.1) | <0.01 |
| Hematologic     | 56 (15.1)               | 16 (9.4)                | 40 (20.1) | <0.01 |
| Chronic lung disease | 19 (5.1)                | 7 (4.1)                 | 12 (6.0)  | <0.01 |
| Chronic kidney disease | 64 (17.3)              | 36 (21.1)               | 28 (14.1) | 0.10 |
| ECOG*           | 35 (9.5)                | 19 (11.1)               | 16 (8.0)  | 0.37 |
| CFS*            | 1 (0.02)                | 1 (0.02)                | 0 (0.00)  | 0.30 |
| APACHE II*      | 15 (11 – 19)            | 14 (11 – 17)            | 16 (12 – 21) | <0.01 |
| SOFA on admission* | 4 [2 – 5]              | 3 [2 – 5]              | 4 [3 – 6] | <0.01 |
| PaO2/FiO2 on admission* | 155 [118 – 231]    | 160 [120 – 248]        | 142 [110 – 202] | <0.01 |
| IMV, n (%)      |                          |                          |         |
| During admission | 38 (10.3)               | 18 (10.5)               | 20 (10.0) | 0.88 |
| After admission (n = 332) | 109 (32.8)         | 40 (26.1)               | 69 (38.5) | 0.03 |
| Overall         | 147 (39.7)              | 58 (33.9)               | 89 (44.7) | 0.02 |
| Duration of IMV*, days | 12 [4 – 22]          | 12 [5 – 21]            | 11 [5 – 22] | 0.53 |
| Steroid use, n (%) | 327 (88.4)             | 143 (83.6)              | 184 (92.5) | <0.01 |
| AKI on admission, n (%) | 106 (28.6)             | 47 (27.5)               | 59 (29.6) | 0.51 |
| Septic shock on admission, n (%) | 52 (14.1)             | 16 (9.4)                | 36 (18.1) | 0.01 |
| Secondary bacterial infection, n (%) | 159 (43.0)             | 62 (36.3)               | 97 (48.7) | 0.02 |
| Reactivation of CMV, EBV and/or Herpes viruses | 27 (7.3)             | 6 (3.5)                 | 21 (10.6) | <0.01 |
| Opportunistic infection, n (%) | 84 (22.7)             | 25 (14.6)               | 59 (29.6) | <0.01 |
| ICU mortality, n (%) | 115 (31.1)             | 43 (25.1)               | 72 (36.2) | 0.02 |
| Hospital mortality, n (%) | 124 (33.6)             | 46 (26.9)               | 78 (39.1) | 0.01 |
| 28th day mortality, n (%) | 89 (24.1)             | 33 (19.3)               | 56 (28.1) | 0.04 |
| ICU LOS*, days | 11 [5 – 19]             | 9 [5 – 18]              | 12 [7 – 22] | <0.01 |
| Hospital LOS*, days | 19 [12 – 30]           | 16 [11 – 27]            | 23 [13 – 35] | <0.01 |

*median, [IQR]. Text in bold in p value indicated statistical significance.

cHIS: COVID-19 associated hyperinflammatory syndrome, ECOG: Eastern Cooperative Oncology Group, CFS: clinical frailty scale, APACHE: acute physiology and chronic health evaluation, SOFA: sequential organ failure assessment, PaO2/FiO2: partial pressure of oxygen/Fraction of inspired oxygen ratio, IMV: invasive mechanic ventilation, AKI: acute kidney injury, CMV: cytomegalovirus, EBV: Epstein-Barr virus, ICU: intensive care unit, LOS: length of stay
admission (n = 332), IMV was performed in 109 patients (32.9%) and in those with cHIS score ≥3, frequency of IMV requirement after ICU admission was higher than other patients (38.5% vs 26.1%; p = 0.03). ICU, hospital and 28 days mortality rates (36.2% vs 25.1%; p = 0.02, 39.1% vs 26.9%; p = 0.01, 28.1% vs 19.1%; p = 0.04, respectively) were higher and ICU and hospital LOS were longer (p < 0.01) in patients with admission cHIS score ≥3 than in those with admission cHIS score <3.

Comparison of median laboratory parameters on admission are shown in Supplemental material (Supplemental Table).

After logistic regression analyses; age <65 years, presence of malignancy and admission SOFA score were found to be independent variables which is associated with admission cHIS score ≥3 when adjusted for APACHE II score and presence of septic shock on ICU admission (Table 4).

Association of individual admission cHIS criteria and ICU mortality revealed that hematological dysfunction (sensitivity = 0.64 and specificity = 0.55, AUROC = 0.60, 95%CI = 0.54–0.66; p < 0.01) has the best accuracy for sensitivity and macrophage activation (sensitivity = 0.43 and specificity = 0.72, AUC = 0.57, 95%CI = 0.51–0.64, p = 0.03) for specificity. To predict IMV requirement after ICU admission, best sensitivity was 0.70 for fever (AUROC = 0.59, 95%CI = 0.53–0.65; p = 0.01) and specificity was 0.70 for coagulopathy (AUROC = 0.61, 95%CI = 0.54–0.67; p < 0.01) (Table 5).

### Table 4. Multivariate Analysis for Determining Independent Variables Associated with Admission cHIS Score ≥3.

| Parameters                      | Odds Ratio (95% Confidence Interval) | P value |
|---------------------------------|--------------------------------------|---------|
| Age <65 years old               | 2.09 (1.30–3.36)                     | <0.01   |
| Malignancy                      | 2.32 (1.26–4.24)                     | <0.01   |
| Admission SOFA score            | 1.15 (1.01–1.30)                     | 0.04    |
| APACHE II score                 | 1.02 (0.97–1.08)                     | 0.43    |
| Septic shock on admission       | 0.95 (0.45–2.01)                     | 0.89    |

R² = 0.92, Hosmer and Lemeshow Test: 0.68
Text in bold in p value indicated statistical significance.

cHIS: COVID-19 associated hyperinflammatory syndrome, APACHE: acute physiology and chronic health evaluation.

### Table 5. Association Between Outcomes and Admission cHIS Score Components.

|                | ICU mortality                                                                 |
|----------------|-------------------------------------------------------------------------------|
|                | Sensitivity | Specificity | AUROC | 95% CI | P value |
| Fever (n = 224, 60.4%) | 0.64        | 0.41        | 0.53   | 0.47–0.60 | 0.40 |
| Macrophage activation (n = 121, 32.7%) | 0.43        | 0.72        | 0.57   | 0.51–0.64 | 0.03 |
| Haematological dysfunction (n = 188, 50.8%) | 0.64        | 0.55        | 0.60   | 0.54–0.66 | <0.01 |
| Coagulopathy (n = 141, 38.1%) | 0.59        | 0.71        | 0.65   | 0.59–0.71 | <0.01 |
| Hepatic inflammation (n = 178, 48.1%) | 0.49        | 0.52        | 0.50   | 0.44–0.57 | 0.90 |
| Cytokinaemia (n = 165, 44.6%) | 0.41        | 0.54        | 0.47   | 0.41–0.54 | 0.41 |
|                | Sensitivity | Specificity | AUROC | 95% CI | P value |
|                | 0.70        | 0.46        | 0.59   | 0.53–0.65 | 0.01 |
|                | 0.35        | 0.69        | 0.52   | 0.45–0.58 | 0.60 |
|                | 0.61        | 0.55        | 0.58   | 0.52–0.64 | 0.02 |
|                | 0.51        | 0.70        | 0.61   | 0.54–0.67 | <0.01 |
|                | 0.50        | 0.52        | 0.51   | 0.45–0.57 | 0.79 |
|                | 0.45        | 0.54        | 0.50   | 0.43–0.56 | 0.90 |

Text in bold in p value indicated statistical significance.

ICU: intensive care unit, cHIS: COVID-19 associated hyperinflammatory syndrome, AUROC: area under the receiver operating curve, CI: confidence interval

### Discussion

This study showed that a threshold of 3 or greater admission cHIS score may be used as a prognostic tool in critically-ill COVID-19 patients to predict mortality. To the best of our knowledge, this is the first study which have examined relationship between ICU admission cHIS score and mortality.

In COVID-19 patients, after 7–8 days of initiation of symptoms, the sudden clinical deterioration characterized by severe respiratory failure occurs due to a particular IL-6 mediated immune dysregulation. At this stage patients develop chest infiltrates, ground glass opacities on imaging with lymphocytopenia and increased acute phase reactants suggesting reactivation of immune system. A subset of these patients experienced systemic hyperinflammation response mediated by activation of complicated immune pathways that lead to ARDS, AKI, heart failure, hemodynamic insufficiency, coagulopathies and secondary infections. In critically-ill COVID-19 patients hyperinflammatory markers are higher than in those who do not need intensive care.

Both innate and adaptive immunity can be activated by SARS-CoV-2 and immune dysregulation may lead to local and systemic damage with lymphocytopenia, reduction in the frequency of CD4⁺, CD8⁺ T cells, B cells and natural killer cells. Also, immune dysregulation causes the inhibition of T cell recirculation by the cytokines such as interferon-1 (IFN-1) and tumor-necrosis factor-α (TNF-α). Aging causes several alterations in the physiology of many organs. Impaired immune response related with aging is called immunosenescence. Immunosenescence is associated with progressive disability in triggering humoral and cellular response.
against infections. Therefore, aged people are at greater risk for developing severe illness in the course of influenza or COVID-19. 34,35 Age associated weaker IFN-1, natural killer cells, T cells and B cells activation and their decrease in SARS-CoV-2 infection could be responsible for poor inflammatory response and increased risk of morbidity and mortality. 36 Supporting these evidences, in our study, younger age (<65 years) was associated with high cHIS score. Malignancy is another factor which is independently associated with high cHIS score. In previous articles, excess mortality has been observed in critically-ill COVID-19 patients with cancer.37,38 Cancer associated systemic inflammatory response is characterized by elevated inflammatory biomarkers such as CRP, TNF-α, ferritin, NLR.39 In patients with malignancy, cancer associated systemic inflammatory response may contribute to hyperinflammation in the course of COVID-19. Similar to our findings, in a recent multicenter study analyzing 1071 cancer patients, inflammatory indices (NLR; Prognostic Nutritional Index, modified Glasgow Prognostic Score) worsened at COVID-19 diagnosis and the degree of systemic inflammation was associated with higher mortality and shorter median survival rates.40 Although the main mechanism underlying high mortality in cancer patients is not still fully understood, susceptibility to hyperinflammation in cancer patients during COVID-19 course may contribute to poor prognosis.

Reactivation of multiple viruses are common in critically-ill patients with or without preexisting immunodeficiency and are associated with poor prognosis. During the course of sepsis, reactivation of CMV, EBV and herpes viruses may cause secondary HLH which is thought a hyperinflammatory condition in critically-ill patients.41 Higher incidence of EBV, CMV and herpes viruses have been also reported in critically-ill COVID-19 patients. Simonnet et al 42 analysed 34 critically-ill COVID-19 patients who underwent testing for CMV, EBV and herpes viruses and reported that 85% of patients developed CMV, EBV and/or herpes viruses viremia. Due to the fact that hyperinflammatory state is also common and a well-described risk factor for poor prognosis in critically-ill COVID-19 patients, some studies have focused on relationship between reactivation of viruses and hyperinflammation.43,44 In a case series, levels of EBV viremia correlated with IL-6 levels in critically-ill COVID-19 patients while there was no correlation in non-COVID-19 ICU patients.43 Similar to these findings, we found higher viral reactivation rates in patients with higher inflammation. However; due to the retrospective design, all of our patients were not undergone testing for CMV, EBV and herpes viruses which may underestimate incidence of reactivation of viruses.

Corticosteroids are associated with reduced inflammation in patients with COVID-19 related ARDS.45 In our unit, we have used steroid therapy in COVID-19 patients with respiratory failure if there is not a contraindication. Despite the frequent use of steroid in admission cHIS score ≥3 group, poor prognosis was encountered at the same time. Randomized controlled trials have revealed that corticosteroids improved survival and other clinical outcomes especially in hospitalized COVID-19 patients with systemic inflammation and respiratory failure that requires oxygen therapy or IMV.46,47 However; patient responses to corticosteroid vary and many factors may influence the efficacy of corticosteroid therapy during COVID-19 course.48,49 Chen et al 50 conducted a retrospective cohort study in 478 critically-ill COVID-19 patients to enlighten whether inflammation degree determine the response to corticosteroid therapy. Investigators used nine inflammation markers (white blood cell count, high sensitivity CRP, IL-2R, IL-6, IL-8, IL-10, TNF-α, D-dimer and NLR) to determine hyperinflammatory phenotype. Although corticosteroid therapy did not improve survival overall, corticosteroid therapy was associated with reduced 28th day mortality in patients with hyperinflammation.7 In a secondary analysis of multicenter observational study, Moreno et al 50 investigated relationship between clinical phenotypes (A, B and C) of critically-ill COVID-19 patients and response to corticosteroid therapy. Authors found that only patients with phenotype C (with a higher inflammatory status) benefit from corticosteroid therapy consistent with the study by Chen et al.7 It has also been shown that immunomodulatory drugs (tocilizumab, sarilumab (IL-6 inhibitors) and anakinra (interleukin-1 inhibitor)) are associated with the reduced need for IMV, improve survival in critically-ill COVID-19 patients; whereas in patients with mild COVID-19 pneumonia, immunomodulatory drugs do not improve outcomes.51,52 Observational studies showed encouraging results on the use of IL-6 inhibitors in severe COVID-19 cases and a recent meta-analysis including 16 observational studies noted a decreased risk of death associated with the use of tocilizumab (OR 0.57 [95% CI 0.36-0.92]) compared to standard care.53 In another prospective observational study from Italy, 56 severe COVID-19 cases with elevated inflammatory markers were analyzed for efficacy of sarilumab. Twenty eight patients were treated with sarilumab and standard care while 28 patients received only standard care.9 Although sarilumab was associated with faster recovery (10 days vs 24 days), there was no differences in mortality between two groups. Despite these promising results of early observational studies, the CORIMUNO-19 and COVACTA randomized-controlled trials, which did not have inflammatory criteria for patient selection and did not use corticosteroid therapy as a component of standard care, showed no association between the use of tocilizumab and prognosis.10,11 Later randomized-controlled trials were able to meet their primary end-points. The REMAP-CAP trial, which assigned patients to receive tocilizumab, sarilumab or standard care, determined the number of respiratory and cardiovascular organ support–free days as primary outcome. Both tocilizumab and sarilumab were able to improve outcomes including survivals.54 These results have also been confirmed by the RECOVERY trial which includes participants with the evidence of systemic inflammation (CRP ≥75 mg/L).55 Corticosteroid therapy was a component of standard care in both REMAP-CAP and RECOVERY trial. RECOVERY investigators have also performed a randomized-controlled trial on efficacy of baricitinib, a Janus kinase (JAK) 1–2 inhibitor.12 At randomization, 95% of patients were receiving corticosteroid therapy and 23% were
receiving tocilizumab and baricitinib led 13% reduction in mortality in hospitalized COVID-19 patients.

All these findings suggest that determination of hyperinflammation and its severity are important for patient choice for immunomodulatory treatments. Immunomodulatory treatments should be considered as an adjunctive therapy to corticosteroid and should be decided individually. Therefore, admission chIS score in critically-ill patients may be a novel scoring system to distinguish hyperinflammatory COVID-19 patients who have poor prognosis and admission chIS score could be utilized in the course of further immunomodulatory treatment decision. Also, chIS score may be used for escalation of anti-inflammatory treatments. However, in the lack of randomized controlled trials which examine safety and efficacy of chIS score guided immunomodulatory treatment strategy, it is impossible to recommended clinicians strongly to decide using immunomodulatory drugs only based on chIS score.

Both our study and the previous study by Webb et al 5 that had proposed chIS criteria revealed that chIS criteria is associated with poor prognosis. On the other hand the present and the previous study 2 have some different features and results. First, previous study analyzed maximum daily chIS score of hospitalized 299 COVID-19 patients, while we evaluated admission chIS scores of 370 critically-ill COVID-19 patients. Therefore we were not able to compare maximum daily chIS score of our patients and those in the previous study.5 However; as COVID-19 patients are usually admitted to ICU when their clinical condition worsens, determining prognosis and deciding immunomodulatory treatment on admission are more helpful for intensive care physicians and more crucial for patients. Second, median daily maximum chIS score of patients was 2 in the previous study, whereas our patients’ admission median chIS score was 3. In our study, at a threshold of 2 or higher, chIS score has best sensitivity as well as in the previous study.5 If accuracy for both sensitivity and specificity is considered, admission chIS score is most useful at a threshold of 3 or higher. Therefore, we determined cut off value for chIS diagnosis as 3. In addition, more than half of the critically-ill patients with COVID-19 have fever or hematological dysfunction and nearly half of the patients have hepatic inflammation and cytopenia. Therefore, if chIS score ≥ 2 is accepted for chIS diagnosis, it may cause overdiagnosis in these patients. Further studies which investigate reliability and validity of chIS score among different patient cohorts are needed. Third, in the previous study by Webb et al 5 there was no data on disease severity scores and its relationship with chIS score. We found that patients who had an admission chIS score greater than 3 had worse disease severity scores and similar patient performance scores than others. It advocates that admission chIS score correlates with disease severity independently from patients’ performance status.

This study is important because this is the first study which investigate applicability and prognostic accuracy of admission chIS score in critically-ill patients. The limitations of this observational study are evident. First, due to its retrospective nature, temporal bias is a concern and chIS score could not have been validated prospectively. Second, we do not have chance to compare admission chIS scores and maximum daily chIS scores. Third, we do not entirely know the potential medications which patients received shortly before ICU admission such as steroids, non-steroidal anti-inflammatory drugs, antipyretics that may lead to changes in chIS score. Therefore, this limitation may underreflect the predictive accuracy of admission chIS score on prognosis.

Conclusion
This study revealed that critically-ill COVID-19 patients with admission chIS score ≥ 3 have worse clinical outcomes than other patients. These criteria may be useful to determine severity of disease and hyperinflammation in patients with COVID-19. To validate our findings, further prospective studies in different patient cohorts are needed.

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ORCID iDs
Mehmet Yildirim https://orcid.org/0000-0002-0526-5943
Burcin Halacli https://orcid.org/0000-0002-7216-7438

Supplemental Material
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