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Research Paper

Evaluation of Outcome in Patients With Moderate and Severe COVID-19 Via H-Score

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ABSTRACT

Background: Due to uncontrolled lymphocyte reaction, the overproduction of cytokines in COVID-19 patients can cause sepsis-like symptoms, suggesting sepsis, cytokine release syndrome (CRS), and secondary hemophagocytic lymphohistiocytosis (sHLH). Since different therapeutic approaches are used for each diagnosis, differentiation is essential. This study aims to use H-score as a possible prognostic tool in COVID-19 patients.

Methods: A sample of 64 moderate and severe COVID-19 patients was enrolled in this study. Clinical and laboratory findings were assessed. H-score was initially calculated and reevaluated among severe cases 72 hours later and among moderate cases showing severe features of COVID-19.

Results: Mortality of 31.3% was reported. Laboratory findings, including triglycerides (TG), ferritin, and aspartate aminotransferase (AST) showed significantly higher initial and follow-up laboratory assessment levels in severe cases than in moderate cases. Moreover, fibrinogen was significantly higher among severe cases than moderate cases at the initial assessment, but no significant difference was reported in the second fibrinogen assessment.

Conclusion: In this study, H-score was useful as a predictive tool for the initial evaluation of severe cases of COVID-19. H-score is much lower in these patients than in non-COVID-19 HLH patients may be due to the different underlying immunologic pathophysiology of COVID-19; thus, each H-score criterion must be evaluated for sensitivity and specificity in COVID-19 patients. The H-score cut-offs, H-score may be useful for diagnosing immune overreaction and determining the need for more exclusive immunomodulatory treatments.

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1. Introduction

As of February 11, 2022, an estimated 404 million confirmed cases of COVID-19 have been reported worldwide, with an estimated 5.8 million mortality cases globally due to its complications [1]. Fortunately, with the synthesis of the COVID-19 vaccine and increasing the rate of vaccination, the prevalence of infection has decreased. The disease mainly presents in less severe forms; however, COVID-19 still presents in various manifestations, from asymptomatic to critical cases requiring mechanical ventilation [2-4]. Various manifestations in different organs suggest that severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) is a multi-system infectious agent rather than a respiratory virus. Most of the COVID-associated mortalities are due to acute respiratory distress syndrome (ARDS) and multiple organ failure, with studies implicating hyperinflammatory conditions as the underlying causes of these life-threatening conditions [5]. Hyperinflammation in COVID-19 patients leads to a sepsis-like clinical manifestation called cytokine release syndrome (CRS) or cytokine storm (CS), which overwhelming production of inflammatory interleukins, including IL-2, IL-6 TNF-a, and MCP-1, can lead to increased vascular permeability, causing ARDS [6, 7].

Hemophagocytic lymphohistiocytosis (HLH) is a severe systemic inflammatory disease resulting from unbalanced cytokine production. Uncontrolled production of inflammatory cytokines occurs due to lymphocytic overreaction and natural killer (NK) cell deficiency to efficiently suppress and regulate reactive immune cells [7]. HLH is primarily divided into primary and secondary HLH. Many risk factors trigger secondary HLH (sHLH), including malignancies, immunosuppression, infection, etc. with viral infections contributing around 50% [8].

Epstein-Barr virus (EBV), cytomegalovirus (CMV), HIV, and influenza virus are among the most common viral etiology of sHLH. Previous studies suggest SARS and middle east respiratory syndrome (MERS), infections caused by members of the Coronaviridae family, to be infectious etiologies for sHLH progression. However, COVID-19 remains to be further evaluated [9].

H-score is a scoring system primarily developed in 1991 as a diagnostic criterion for familial hemophagocytic lymphohistiocytosis (FHL). The primary scoring system for HLH has been changed and updated and the most common H-score system was developed in 2014. Due to its parameters, and the reason for primary utilization, the H-score can provide us with the overall inflammatory status of the body [7].

Due to the similarities between the hyperinflammatory state of COVID-19 and sHLH, some studies propose the utilization of the H-score to assess the severity of COVID-19 using the H-score. Thus, this prospective study aims to evaluate the utility of the H-score as a stratification tool to evaluate outcomes in COVID-19 patients.

2. Materials and Methods

We enrolled all confirmed COVID-19 patients with moderate and severe disease admitted to Loghman-e-Hakim hospital and Labafinejad hospital in Tehran City, Iran from March 20, 2020, to September 20, 2020, in this study. Patients older than 18 years with laboratory polymerase chain reaction (PCR) for COVID-19 or spiral CT scan of the lung in imaging for COVID-19 with moderate and severe clinical features were included in this study. Patients were considered moderate and severe according to the National Institutes of Health (NIH) COVID-19 guidelines [10].

The patients were excluded if they met any of the following criteria, including transplant patients, patients with malignancy, leukemia, pancreatitis, patients receiving antipyretic for 48 hours before the enrollment, and patients receiving intralipid solution before enrolment. Pregnant and lactating patients and patients with critical conditions, including ARDS and multiple-organ failure were also excluded from this study.

Patients' medical history and clinical presentations were recorded. Laboratory investigations were conducted to assess H-score and to rule out other differential diagnoses, including ARDS, multiple organ failure (MOF), and pancreatitis [10].

Differentiated complete blood count (CBC), triglyceride (TG), ferritin, fibrinogen, aspartate transaminase (AST), alanine transaminase (ALT), albumin, coagulation profile, venous blood gases (VBG), lactate dehydrogenase (LDH), blood urea nitrogen (BUN), creatinine (Cr), lactate, amylase, and lipase were assessed using radioimmunoassay (RIA) technique. Patients were evaluated for organomegaly using abdominal sonography. Laboratory data were repeated in severe patients 72 hours after enrolment and in moderate patients after developing severe clinical features.

We also calculated patients' H-score according to H-score scoring system demonstrated in Table 1 [11]. Severe patients were reassessed for H-score 72 hours after enrolment. Moderate patients with progression to severe forms were also reevaluated. Patients who scored more than 90 were also candidates for bone marrow aspiration (BMA) [7].

We provided standard treatment consisting of oxygen and glucocorticoid therapy for moderate cases with additional use of high-dose corticosteroid therapy for the first three days for severe cases.

This study was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.RETECH.REC.1399.078). The study and its process were explained to each patient, and written informed consent was acquired.

Statistical Analysis

We used SPSS software v. 17 (SPSS Inc. Chicago, IL, USA) to analyze our data. The data sets were compared using the independent group t-test or Mann-Whitney U-test. Tests with a P value equal to or less than 0.05 were considered statistically significant.

3. Results

In this study, 64 patients, 40.63% of whom were women and 59.37% were men, were included. The Mean±SD age of the patients was 57.78±18.94 years, ranging from 39 to 77 years, patients with moderate and severe features in the initial evaluation were equally presented half and half. During the study, 12 moderate cases progressed to severe COVID-19, with 2, 3, and 15 mortality cases among moderate cases that remained moderate, moderate to severe cases, and severe cases, respectively. The most common comorbidities were hypertension (29.7%), diabetes mellitus (29.7%) followed by coronary heart disease (14.1%), and kidney disease (12.5%). Coronary heart failure was significantly lower among severe cases (P<0.046). In this study, splenomegaly was seen in 3 cases among severe cases (4.7%); however, no significant difference was seen between moderate and severe cases (P=0.207). No patients have undergone bone marrow biopsy. Immunosuppression was reported in 7 cases, including three moderate and four severe cases; however, no significant difference was demonstrated (P=0.388).

The median time from symptom presentation to referral to the hospital was five days, with a median hospital stay of 8 days. This study reports mortality of 31.3%, with significantly higher mortality among severe cases (P<0.018). Fever was seen in one patient among moderate cases and no significant difference was seen among different groups (P=0.327)

Table 2 presents patient laboratory results. TG, ferritin, and AST showed significantly higher initial laboratory assessment (P<0.001, P<0.002, and P<0.008, respectively) and follow-up (P<0.043, P<0.006, and P<0.004, respectively) in severe cases than in moderate cases. Moreover, fibrinogen was significantly higher among severe cases than in moderate cases at the initial assessment (P<0.025) but no significant difference was reported in the second fibrinogen assessment (P=0.241). LDH was also significantly higher among severe cases than moderate cases in the initial laboratory assessment (P<0.017). Cytopenia was seen in 8 cases with three cell lineage cytopenia in one severe case, two lineage cytopenia in 3 moderate cases, and 4 severe cases with no significant difference among moderate and severe groups (P<0.163). Table 2 presents initial and follow-up laboratory assessments with significant differences among moderate and severe cases.

Laboratory follow-up in severely surviving patients revealed a significant decrease in hemoglobin (from 12.7 g/dL to 11.9 g/dL [P<0.002]), and a significant increase in triglyceride (from 146 mg/dL to 165 mg/dL [P<0.006]). No significant difference was identified in other laboratory tests (Table 3). Progression of moderate to severe cases showed a significant increase (from 104 mg/dL to 120 mg/dL [P<0.022]) in TG in the follow-up laboratory findings (Table 4).

The initial Mean±SD H-score of this study in moderate and severe patients was 29.89±27.56 and 52.26±7.08, respectively. Follow-up Mean±SD H-score evaluation revealed an H-score of 47.83±37.42 in moderate cases and Mean±SD H-score of 63.72±27.60 among severe cases. In this study, the initial H-score was significantly higher among severe cases compared to moderate cases (P<0.001) while no significant difference was observed in the follow-up assessment (P=202). H-score was significantly higher in the initial assessment between demising patients with an H-score of 50.20±24.04 compared to the surviving with an Mean±SD H-score of 35.64±30.64 (P<0.045); however, no significant difference was seen between the demising (H-score=68.60±26.79), and the surviving patients (H-score=53.58±32.67) in the follow-up assessment (P=0.139).

Table 1. H-score scoring system

Variables	Parameter	Score
Temperature (°C)	<38.4	0
	38.4-39.4	33
	39.4<	49
Organomegaly	None	0
	Hepatomegaly or splenomegaly	23
	Hepatomegaly and splenomegaly	38
Cytopenia*	One linage	0
	Two linages	24
	Three linages	34
Triglycerides (mg/dL)	<58	0
	58-155	44
	>155	64
Fibrinogen (g/L)	>2.5	0
	≤2.5	30
Ferritin (ng/mL)	<2000	0
	2000-6000	35
	>6000	50
AST (U/L)	<30	0
	≥30	19
Known immunosuppression**	No	0
	Yes	18
Bone marrow hemophagocytosis	No	0
	Yes	35

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AST: aspartate aminotransferase; Hb: hemoglobin; WBC: white blood cell; Plt: platelet; HIV: human immunodeficiency virus.

* Hb≤9.2 g/dL or WBC<5000/ml or Plt<110.000/ml.

** HIV-positive or long-term immunosuppressive therapy.

4. Discussion

Based on different COVID-19 therapeutic guidelines, corticosteroids are the most agreed-upon immunosuppressive drugs; however, since HLH is an exaggerated immune system response and a CRS outcome, HLH evaluation can be used to determine the different severity of COVID-19 and to determine the proper time for exclusive immunomodulatory treatment in COVID-19 patients.

Introduced in 1952, HLH is generally categorized as primary and secondary. Primary HLH or familial HLH is primarily due to genetic predisposition and is mostly diagnosed in pediatric patients. Secondary HLH, also called reactive HLH, is the uncontrolled production of inflammatory cytokines secondary to infection, malignancy, and im-

Table 2. Patients' laboratory results

Variables	Mean±SD			P	Range
	Descriptive	Disease Level			Normal Value
	Total (N=64)	Moderate (n=32)	Severe (n=32)		
Age (y)	57.78±18.94	61.13±18.29	54.44±19.28	0.268	-
Start of Symptoms (d)	5.86±3.28	6.16±3.50	5.56±3.08	0.692	-
Hospitalization (d)	7.67±4.32	6.41±3.37	8.94±4.83	0.062	-
WBC 1 (x10^3/mm^3)	11.15±0.38	12.84±12.88	9.47±6.88	0.177	4-11
WBC 2 (x10^3/mm^3)	8.24±5.12	9.73±6.04	7.63±4.67	0.298	
Hb 1 (g/dL)	11.94±2.13	11.98±2.15	11.90±2.14	0.786	Male:14-18 Female:12-16
Hb 2 (g/dL)	11.37±2.00	11.75±1.62	11.21±2.15	0.439	
Plt 1 (x10^3/mm^3)	213.68±100.46	217.41±102.28	209.96±100.10	0.803	150.000-450.000
Plt 2 (x10^3/mm^3)	218.93±107.77	228.50±119.13	214.97±104.69	0.719	
TG 1 (mg/dL)	133.16±66.30	103.41±32.46	162.91±77.80	0.001	Up to 150
TG 2 (mg/dL)	173.23±90.17	134.08±66.78	190.63±94.74	0.043	
Ferritin 1 (ng/mL)	452.27±271.29	338.00±227.46	566.53±266.23	0.002	Male: 12-300 Female: 12-150
Ferritin 2 (ng/mL)	580.05±268.85	407.92±278.46	656.56±230.39	0.006	
Fibrinogen 1 (mcg/dL)	331.63±102.57	314.47±121.38	348.78±77.71	0.025	200-400
Fibrinogen 2 (mcg/dL)	347.46±70.12	339.50±81.35	351.00±65.91	0.241	
AST 1 (U/L)	56.48±49.27	37.75±27.79	75.22±58.62	0.008	8-33
AST 2 (U/L)	74.20±76.08	36.54±18.18	92.33±86.48	0.004	
Initial laboratory assessment					
Albumin (g/dL)	3.53±0.57	3.59±0.49	3.48±0.65	0.181	3.5-5.5
LDH (U/L)	506.03±308.21	411.56±189.36	600.50±372.53	0.017	140-280
BUN (mg/dL)	51.58±33.45	52.66±32.32	50.50±35.01	0.895	6-24
Cr (mg/dL)	1.61±1.44	1.91±1.77	1.31±0.93	0.245	Male:0.7-1.3 Female: 0.6-1.1
Amylase (U/L)	66.81±74.92	54.97±18.10	78.66±103.87	0.411	40-140
PT (s)	13.89±7.71	12.34±1.47	15.38±10.58	0.125	11-13.5
PTT (s)	34.33±12.66	30.63±11.27	38.38±13.17	0.01	30-40
pH	7.41±0.07	7.41±0.07	7.40±0.07	0.820	7.35-7.45
Lactate (mg/dL)	22.71±8.72	23.08±5.64	22.10±11.39	0.603	4.5-20
Lipase (U/L)	21.08±17.18	17±2.25	24.93±24.09	0.091	10-140

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WBC: white blood cell; Hb: hemoglobin; Plt: platelets; TG: triglyceride; AST: aspartate aminotransferase; LDH: lactate dehydrogenase; BUN: biologic urea nitrogen; Cr: creatinine; PTT: partial thromboplastin time; PT: prothrombin time; AST: aspartate aminotransferase.

Table 3. Comparison of laboratory parameters in severe cases

Laboratory Parameters	Mean±SD		P	Reference Range
	First Examination	Second Examination		
WBC (x10³/mL)	9.47±6.88	7.63±4.67	0.198	4-11
Hb (g/dL)	11.90±2.14	11.21±2.15	0.002	M:14-18 F:12-16
Plt (x10³/mL)	209.96±100.10	214.97±104.69	0.256	150000-450000
TG (mg/dL)	162.91±77.80	190.63±94.74	0.006	Up to 150
Ferritin (mcg/L)	566.53±266.23	656.56±230.39	0.081	Male: 12-300 Female: 12-150
Fibrinogen (mg/dL)	348.78±77.71	351.00±65.91	0.258	200-400
AST (IU/L)	75.22±58.22	92.33±86.48	0.970	8-33

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WBC: white blood cell; Hb: hemoglobin; Plt: platelets; TG: triglyceride; AST: aspartate aminotransferase.

munosuppression. Due to its progressing and exacerbating essence, early diagnosis is crucial to establish rapid immunosuppression therapy in these patients [7].

In a retrospective study by Clark et al., a median H-score of 52 was reported among 152 people in a population sample with 31 patients admitted to the intensive care unit (ICU). Similarly, no relationship was observed between elder age and higher H-score [8]; however, they did not discriminate between mortality and severe cases. Lorenz et al., assessing 19 COVID-19 ICU patients, reported a median H-score of 122 and 157 with and without BMA, respectively [12]. Meng et al. conducted a retrospective study enrolling 415 patients and reported a higher H-score to be associated with MOF [9]. They reported this finding despite MOF being a differential diagnosis for HLH. Meng M. et al. also reported no significant relationship between H-score and age and sex; however, Ardern-Jones et al. reported a strong negative correlation between H-score and age [13, 14]. In this study, the initial H-score among severe COVID-19 patients was 57.5, while an H-score of 19 was calculated for moderate cases. No significant relationship was observed between the severity of the disease and age, sex, or length of hospitalization.

Table 4. Comparison of laboratory parameters in moderate cases

Laboratory Parameters	Mean±SD		P	Reference Range
	First Examination	Second Examination		
WBC (x10³/mL)	11.15±10.38	9.73±6.04	0.754	4-11
Hb (g/dL)	11.98±2.15	11.75±1.62	0.147	Male:14-18 Female:12-16
Plt (x10³/mL)	217.41±102.28	228.50±119.13	0.374	150000-450000
TG (mg/dL)	103.41±32.46	134.08±66.78	0.022	Up to 150
Ferritin (mcg/L)	338.00±227.46	407.92±278.46	0.248	Male: 12-300 Female: 12-150
Fibrinogen (mg/dL)	314.47±121.38	339.50±81.35	0.937	200-400
AST (IU/L)	37.75±27.79	36.54±18.18	0.576	8-33

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WBC: white blood cell; Hb: hemoglobin; Plt: platelets; TG: triglyceride; AST: aspartate aminotransferase.

Ardern-Jones et al. reported H-score on days 1 to 4 as a strong predictor of the H-score in the entire admission [13]. We used H-score as a scoring system to assess outcomes in COVID-19 patients in a longitudinal evaluation. In this study, the initial H-score in severe cases was significantly higher than in moderate cases, while the second H-score was not significantly different in severe and moderate cases whose condition was exacerbated. Also, H-score was significantly higher among severe deceased cases compared to deceased moderate cases. This finding suggests that the initial H-score is a vital prognostic factor than the disease course. However, hospitalization and receiving high-dose corticosteroid therapy during the first three days of admission may contribute to a lack of differentiation between severe and moderate cases.

Bordbar et al. showed that H-score is significantly higher in deceased patients than the surviving patients, supporting its role in predicting patients' outcomes [15]. In Bordbar et al.'s study, the H-score did not reach the diagnostic threshold for sHLH, which was attributed to the lack of hepatosplenomegaly and high TG levels as common findings in COVID-19 patients; however, it's noteworthy to mention that these findings are not routinely evaluated in COVID-19 patients. Clark et al. also reported a significantly higher H-score among patients admitted to the ICU compared to non-ICU patients [8]. In this study, the initial evaluation of H-score among severe COVID-19 cases revealed a significant difference in patients' survival with a significantly higher H-score among deceased patients than the surviving patients; however, no significant difference was seen in the second evaluation of H-score between surviving and demising patients.

A meta-analysis study conducted by Kazemi et al. comparing severe and non-severe cases of COVID-19 reported significant differences in AST, ferritin, and fibrinogen in severe and non-severe cases, which is consistent with our study. Moreover, in our study, TG was also significantly higher among severe cases than in moderate patients. Kazemi et al. also reported a significant reduction in lymphocyte count, platelet, and hemoglobin in severe cases compared to non-severe cases, which was not found in our study [6].

In our study, no significant difference was seen in WBC between severe cases of COVID-19 compared to moderate cases of COVID-19, while Ardern-Jones et al. showed that WBC was significantly lower among surviving patients compared to those who died [13]. Laboratory tests also showed that triglyceride, ferritin, and AST are significantly higher in both initial and secondary H-score evaluation, while fibrinogen is significantly higher only in initial H-score evaluation in severe cases.

Studies show that TNF-a secretion can reduce triglyceride levels due to the activation of lipoprotein lipase [7, 14, 15]. In this study, the secondary assessment of triglyceride revealed a significant increase compared to the initial assessment. Moreover, alongside the easy accessibility of the TG level test, its significant difference between moderate and severe cases proposes TG as a possible inflammatory marker.

Studies also showed that comorbidities are associated with more severe cases [6, 12]; however, in this study, comorbidities were not associated with a higher score of the disease. Meng et al. reported a significantly higher autoimmune disease among patients with a higher H-score [14].

The utility of the H-score in the COVID-19 setting has been controversial. Some studies suggest the utilization of the H-score as diagnostic criteria for sHLH in COVID-19 patients, while some studies propose H-score as a tool for predicting the outcome of COVID-19 patients [16-18]. Organomegaly, hypofibrinogenemia, and cytopenia are common features among HLH patients, while COVID-19 patients mostly present with hyperfibrinogenemia, leukocytosis, and no sign of organomegaly. Moreover, despite hyperferritinemia in COVID-19 patients and HLH patients, COVID-19 patients usually do not reach the threshold for H-score [19].

In this study, the use of the H-score as a predictive prognosis tool for moderate and severe cases of COVID-19 was promising in severe patients. Initially, the mean H-score was 57.5 in severe cases. Assuming that all participants had a full score on the bone marrow (BM) item, the score would change to 92.5, which is much lower than the mean H-score in non-COVID-19 HLH patients. Meanwhile, the initial H-score was significantly higher in severe cases than in moderate cases. Thus, a modified H-score with a different cut-off or a new interpretation of the H-score should be determined.

This study has limitations. Although one of the first studies conducted in Iran using H-score as a prognostic factor for COVID-19 and was conducted in multiple centers, the small sample sizes, and different time intervals among moderate cases that were highly improved regarding H-score evaluation were among limitations. However, compared to other studies, our exclusion

criteria by excluding cases of MOF and ARDS were a crucial advantage for this study. Moreover, despite not reaching the H-score of 90 in any patients, as a result of not acquiring a bone marrow sample, assessing bone marrow samples due to their invasive nature was not favored. Moreover, recent studies questioned the use of BMA as an H-score criterion for sHLH diagnosis [20]. Thus, studies with larger sample sizes and repeated evaluation of H-score in moderate and severe cases in separate groups considering the exclusion criteria are recommended to provide us with a better understanding.

5. Conclusion

In this study, H-score was useful as a predictive tool for the initial evaluation of severe cases of COVID-19. H-score is much lower in these patients than in non-COVID-19 HLH patients, which may be due to the different underlying immunologic pathophysiology of COVID-19; thus, each H-score criterion should be evaluated for sensitivity and specificity in COVID-19 patients. Following that, with changes in the H-score cut-offs, H-score may be useful for diagnosing immune overreaction and determining the need for more exclusive immunomodulatory treatments. Moreover, a new term instead of HLH may be assigned to describe the resulting condition. Moreover, in this study, no significant difference was seen between moderate and severe cases during hospitalization, which could be attributed to high dose corticosteroid therapy in severe cases and other factors modulating H-score during hospitalization.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.RETECH.REC.1399.078).

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Authors' contributions

All authors equally contributed to preparing this article.

Conflict of interest

The authors declared to conflict of interest.

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