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# Rate of secondary HLH and performance of H-score in patients with severe COVID-19

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## ABSTRACT

**Background:** Severe COVID-19 is thought to be caused by immune overdrive and cytokine storm. One of the cytokine storm syndromes frequently induced by infections is secondary hemophagocytic lymphohistiocytosis (HLH) which can be assessed using H-score. In this study, we aimed to evaluate the rate of patients with COVID-19 who meet HLH criteria based on H-score and the association of H-score with poor outcomes.

**Methods:** In a prospective cohort study of 19 patients with COVID-19 requiring ICU stay from March to May, 2020, we collected demographic and clinical data that focused on H-score's variables and COVID-19 outcomes. H-score  $\geq 169$  was used to determine the percentage of patients who met the HLH criteria. Mann-Whitney, Kruskal-Wallis, and Spearman rho tests and multiple regression analyses were carried out to evaluate the associated factors. The optimal H-score cut-off to predict poor COVID-19 outcome (need for intubation  $\pm$  ECMO) was determined using receiver operating characteristic (ROC) analysis.

**Results:** In 669 patients with severe COVID-19 with a mean  $\pm$  SD age of  $50.3 \pm 12.8$  years, which comprised 95% men; 66% required intubation, 4% ECMO, and 16% died. Only 2% had an H-score  $\geq 169$ . Patients with poor outcomes had a higher mean (SD) H-score than those without; intubation (96.0 [50.0] vs 75.0 [35.0],  $p < 0.01$ ), ECMO (113.0 [25.0] vs 93.0 [50.0],  $p < 0.01$ ) and death (98.0 [62.0] vs 93.0 [48.0],  $p < 0.01$ ). Factors associated with H-score were diabetes ( $\beta$  coeff =  $-10.4$ ,  $p < 0.01$ ), abdominal pain ( $\beta$  coeff =  $19.1$ ,  $p < 0.01$ ), duration of COVID-19 symptoms ( $\beta$  coeff =  $-0.7$ ,  $p = 0.049$ ), and days before ICU

admission ( $\beta$  coeff =  $-1.2$ ,  $p = 0.01$ ). H-score showed a fair ability to discriminate COVID-19 outcomes (AUC 0.61, 95% CI 0.54–0.67). An H-score of 85 was the optimal cut-off with a sensitivity 69% and 1-specificity 53%.

Conclusion: Despite its association with severity in COVID-19, H-score's ability to predict poor outcomes

was only fair, indicating differences in the cytokine storm faced in COVID-19 compared with that during secondary HLH.

Keywords: COVID-19, HLH, H-score