ORIGINAL ARTICLE

Identifying COVID-19 Confirmed Patients at Elevated Risk for Mortality and Need of Mechanical Ventilation Using a Novel Criteria for Hyperinflammatory Syndrome: A Retrospective Cohort, Single-center, Validation Study

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ABSTRACT

Background and Objectives. A mounting evidence links dysregulated immune response to cases of fatal pneumonia seen in COVID-19 infection. We aimed to validate the COVID-19-associated Hyperinflammatory Syndrome (cHIS) score, a novel clinical tool devised to identify those at risk for adverse outcomes, in a local population and investigate the relationship of cHIS score taken at admission and the risk of mortality and the need of mechanical ventilation.

Methods. This retrospective cohort study analyzed the sociodemographic, clinical, and laboratory data of 1,881 COVID-19 patients admitted at a tertiary hospital in Davao City, Philippines from January to December 2021. We calculated the cHIS score, composed of six clinical and laboratory criteria from admission, and used multivariate logistic regression to determine the risk of mortality and need of mechanical ventilation.

Results. The cHIS score taken at admission, regardless of cut-off value, was a significant predictor of mortality (OR 0.979 [99% CI 0.894-1.064]) and need of mechanical ventilation (OR 0.586 [99% CI 0.4975-0.6745]). Using the Youden Index, a cut-off cHIS score of 3 or more was a better predictor of mortality (sensitivity, 88.59%; specificity, 71.72%), and a cut-off score of 2 or more was a better predictor of need of mechanical ventilation (sensitivity, 84.02%; specificity, 70.82%) than other cut-off cHIS scores.

Conclusion. Among COVID-19 patients, the cHIS score at admission correlated with the risk of mortality and the need of mechanical ventilation. Cutoff scores of 3 and 2 had the optimal sensitivities and specificities to predict the risk of mortality and the need of mechanical ventilation, respectively.

Keywords: COVID-19, inflammation, mortality, mechanical ventilation, cytokine storm

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INTRODUCTION

Background of the Study

As of January 2023, the pandemic sparked by the Severe Acute Respiratory Coronavirus 2 (SARS-CoV-2) has claimed over 6.7 million lives worldwide, with an estimated 664 million people having already been infected. Since the start of the pandemic, the Philippines has logged 65,865 deaths, with at least 4.073 million confirmed cases and counting.[1]

The SARS-CoV-2, which was first documented in Wuhan, China in December 2019, is a novel enveloped RNA betacoronavirus that causes a systemic illness marked by fever, cough, and dyspnea, with predilection toward severity among the elderly and those with multiple comorbidities. As cellular targets of SARS-CoV-2 via the angiotensin-converting enzyme 2 (ACE2) receptor, macrophages and monocytes were shown in early studies to be aberrantly activated, leading to downstream immune dysregulation.[2]

Most of the infected patients were either asymptomatic or have mild presentations, but a significant number of these individuals would succumb to rapid clinical deterioration characterized by maladaptive elaboration of cytokines.[3,4] Interferon gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α) cause flu-like symptoms such as fever and chills, myalgias, dizziness, and fatigue, while interleukin-6 leads to vasculopathy, complement activation, and abnormal coagulation cascade, leading to disseminated intravascular coagulation (DIC).[5,6] In addition, these cytokines are linked to cardiomyopathy, lung injury, vascular leakage, and acute-phase protein synthesis.[5] Endothelial dysfunction from cytokine storm had previously been linked to coagulopathy, capillary leakage, and hypotension.[7]

An analysis of plasma cytokine levels in 41 COVID-19 patients in China in the early days of the outbreak revealed elevated levels of IFN-γ, TNF-α, interleukins, and other inflammatory cytokines. Among these patients, all developed pneumonia, a third received intensive care, and six expired.[8]

Virus-induced hyperinflammatory response plays a crucial role in the fatal pneumonia observed among COVID-19 patients. This hyperinflammatory state has been likened to that seen in secondary Hemophagocytic Lymphohistiocytosis (HLH), Macrophage Activation Syndrome (MAS), and Cytokine Release Syndrome (CRS).[9-11]

In December 2020, Webb et al. proposed the term COVID-19-associated hyperinflammatory syndrome (cHIS) to describe this immunologic disarray found among critically ill COVID-19 patients. An additive six-point scoring system called cHIS criteria, a clinical tool to identify those patients at risk for adverse outcomes, was developed. The variables for this criterion were derived from the clinical and laboratory features of conserved physiologic pathway of unchecked macrophage activation and cytokine production found in secondary HLH, MAS, and CRS.[12] The six components of this scoring system were *fever*, *macrophage activation*, *hematologic dysfunction, coagulopathy*, *hepatic injury*, and *cytokinemia*.[12]

An admission cHIS score of two or more was found to be significantly associated with in-hospital mortality or mechanical ventilation. The criteria appeared to have prognostic utility and might be useful for selection of patients for clinical trials and immunomodulatory therapy. Although this scoring system has been validated among patients in the Intermountain Prospective Observational COVID-19 (IPOC) registry in Salt Lake City, Utah, USA, further validity tests in large external cohorts are needed to enhance its applicability.[12]

In one of the first external validations of cHIS score among 370 critically ill COVID-19 confirmed patients in Turkey, an admission cHIS score of three or more was associated with mortality and invasive mechanical ventilation.[13] In another retrospective study among 57 COVID-19 confirmed patients with comorbid rheumatic diseases in USA, a cHIS score of 2 or more had higher odds of admission to intensive care, mechanical ventilation, and in-hospital mortality than patients with a peak cHIS of less than 2.[14]

Currently, there is no evidence-based system that is used to stratify patients according to their risk of mortality and need of mechanical ventilation. With the mounting evidence linking dysregulated immune response and clinical deterioration, a stratification system based on inflammatory markers, such as the cHIS score, should be pursued for local validation and application.

Significance of the Study

A number of COVID-19 patients follow an initially benign clinical course, only to rapidly deteriorate, requiring intubation and mechanical ventilation. Most studies indicate that these patients are in a hyperinflammatory state, marked by excessive production of cytokines that lead to end-organ damage.[2-4,12] This subset of patients needs to be identified early using a valid criteria that employs readily available parameters.

Stratifying patients as mild, moderate, severe, and critical based on clinical and radiologic findings has been the local practice since the start of the pandemic, which is based on the WHO Clinical Management of COVID-19 Interim Guidance.[15] However, several patients have been re-stratified to higher levels of severity due to clinical deterioration that could have been predicted by better tools based on the elevated inflammatory markers at the time of admission.

The locally used "*Rule of 6*" is theoretically based on disordered immune response. Composed of universal values of Ferritin >60 ug/L, CRP >60 mg/ml, and LDH >600 ug/L in the first 48 hours of admission, it is convenient to use but is arbitrary at best and is not rooted on evidence-based studies.

The novel cHIS criteria, developed by Webb et. al, is a theoretically robust and validated criteria that can be applied locally. If locally validated, this criteria can help triage patients to the appropriate level of care at the time of admission. Limited resources and manpower can be properly allocated to the patients. Physicians and allied health workers can then monitor their patients better and institute more timely interventions, potentially resulting in better patient outcomes.

OBJECTIVES

General Objective

1. To correlate the admission cHIS score among COVID-19 confirmed patients with their risk of mortality and need of mechanical ventilation

Specific Objectives

1. To present the sociodemographic profile (i.e.; age, sex, body mass index, COVID-19 severity, and co-morbidities) of COVID-19 confirmed patients admitted at Southern Philippines Medical Center from January to December 2021
2. To establish the relationship between the patient's admitting cHIS score and the risk of mortality and need of mechanical ventilation
3. To determine the optimal cut-off value of cHIS score, including its sensitivity and specificity, as a predictor of mortality and need of mechanical ventilation

MATERIALS AND METHODS

Research Design, Setting, and Participants

This research was a retrospective cohort study among COVID-19 confirmed patients admitted at Southern Philippines Medical Center, a tertiary COVID-19 end referral center in Davao City, Philippines, from January 1 to December 31, 2021, meeting the following inclusion criteria:

Inclusion Criteria

1. Patients aged 19 and above with SARS-CoV-2 infection as confirmed by positive Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) done at SPMC or other Department of Health (DOH)-accredited laboratory in Davao City who were admitted, examined, worked-up and treated at SPMC from January 1 to December 31, 2021
2. Patients triaged and admitted either from the Main ER or Isolation ER of SPMC
3. Patients initially admitted at or transferred to a Temporary Treatment and Monitoring Facility (TTMF) but were referred back to Isolation ER for workup due to clinical deterioration
4. May be asymptomatic, mild, moderate, severe, or critical. Asymptomatic patients were classified under mild
5. Must be registered on SPMC Segworks Hospital Information System (SegHIS) Database

Exclusion Criteria

1. COVID-19 Suspects with pending RT-PCR results
2. COVID-19 Probable who were already being managed as COVID-19 Confirmed with negative RT-PCR confirmation (at least two samples)
3. COVID-19 Probable by virtue of positive RAgT test kits only
4. COVID-19 Confirmed persistently positive patients with positive SARS-CoV-2 IgG and those who were cleared by Infectious Disease Consultant as Recovered cases
5. COVID-19 Confirmed patients admitted and who had completed quarantine at a TTMF
6. COVID-19 Confirmed patients with medical or surgical problems initially admitted as non-COVID with negative RT-PCR, but were later found to have positive swabs on repeat in-patient RT-PCR at the wards (hospital-acquired COVID-19)
7. COVID-19 Confirmed but Recovered patients with ongoing medical problems and still admitted at the non-COVID wards
8. COVID-19 Confirmed End Stage Renal Disease (ESRD) patients admitted at a TTMF who were only referred to the Isolation Facility for their scheduled hemodialysis sessions
9. Adult patients who died at the outset and whose COVID-19 confirmed status was only discerned post-mortem
10. COVID-19 Confirmed patients with incomplete data and parameters for cHIS scoring

Sample Size and Sampling Procedure

The required sample size was computed via power analysis under the z tests family under logistic regression. The assumed null sensitivity of risk of mortality at 0.15 was taken from Abad et al. from a tertiary hospital in the Philippines.[16] A conservative alternative sensitivity of 0.20 was assumed, slightly below the studies of Salva et al. and slightly above Salamat et al. both in the Philippine context.[17,18] This resulted to an expected odds ratio of 1.51. The remaining parameter, α power was set at accepted levels of 0.05 and 0.95. Utilizing the statistical software G*Power 3, the sample size was determined to be 607 with an actual power of 0.95.[19] The authors utilized convenience sampling, enumerating all adult COVID-19 confirmed patients that met the inclusion and exclusion criteria covering the running census from January 2021 to December 2021.

Data Gathering

The patients' data were retrieved from Southern Philippines Medical Center (SPMC) COVID-19 Census and SPMC Segworks Hospital Information System (SegHIS) Database. The subjects' identifiable information were designated by alphanumeric code to provide anonymity. The subjects' data for use were: age, sex, body mass index, severity, comorbidities, incidence of mechanical ventilation, in-hospital all-cause mortality, and laboratory values.[20,21]

Direct communication was done with the originator of the cHIS scoring system, Dr. Brandon J. Webb from the Intermountain Medical Center in Salt Lake City, Utah, USA through electronic exchanges via e-mail. Permission was granted by the said author for the request to apply the six-point criteria to this local study.

COVID-19 Hyperinflammatory Syndrome (cHIS) was scored additively using a six-point scale as operationally defined in Appendix A.

Data Analysis

Descriptive statistics was used to summarize and report the sociodemographic profile of the subjects. Hot deck imputation was implemented on one percent of the missing data. Inferential statistics, specifically logistic regression, was used to determine the association between the admitting cHIS score with the risk of mortality and need of mechanical ventilation. Area under the receiver operating characteristic curve (AUROC) was used to assess the cHIS discrimination ability while Youden Index Analysis was used to determine the optimal cut-off values including the sensitivity and specificity of cHIS score. Following Mandrekar, an AUROC of at least 0.7 was acceptable.[22] To ensure robustness of the results, one-factor-at-a-time analysis by Czitrom was implemented.[23] Standard p-values were considered in the study, namely 0.1, 0.05, 0.01, and 0.001. The statistical software used was Stata.

Ethical Considerations

The study adhered to the Principles of the Declaration of Helsinki and conducted following the Guidelines of the International Conference on Harmonization - Good Clinical Practice (ICH-GCP) and the National Ethical Guidelines for Health and Health-Related Research (NEGHHRR).[24,25] The protocol and all relevant documents were reviewed and approved by the Institutional Ethics Review Committee. Individual information of patients remained strictly confidential. Patients were anonymized in the data collection form and only case numbers and code numbers were used. General data, clinical features, and laboratory results were abstracted from the hospital database and recorded. The investigators were responsible for the integrity of the data including its accuracy, completeness, legibility, originality, timeliness, and consistency. All study-related documents shall be kept and stored by the investigators for at least five years and will be discarded following prescribed measures.

RESULTS

Sociodemographic Profile of the Study Population

A total of 1,881 admitted patients that met the inclusion criteria was included in this study. A patient flow diagram is shown in Appendix B. Table 1 shows the sociodemographic profile of the study population.

Table 2 shows the frequency distribution of cHIS scores among the subjects. Patients with cHIS score of 0 comprised most of the population (29%), followed by those with a cHIS score of 1 (27.1%), cHIS score of 2 (18.6%), cHIS score of 3 (12.8%), cHIS score of 4 (7.5%), cHIS score of 5 (4%), and cHIS score of 6 (1%).

Relationship between the cHIS Score and the Risk of Mortality

Table 3 shows the logistic regression of cHIS score and the risk mortality across the sociodemographic profile.

The cHIS score at admission regardless of value was a strong independent predictor of mortality and was internally consistent and robust across multiple sensitivity analyses. Higher cHIS scores correlated with higher risk of mortality. For instance, a cHIS score of 1 was associated with 2.7-fold

Table 1. Sociodemographic Profile of the Study Population (N = 1,881)

	Frequency	Percentage (%)
Age		
Adult (19-44)	452	24.0
Middle Age (45-64)	831	44.2
Aged 65-80	526	28.0
Aged >80	72	3.8
COVID-19 Severity		
Mild	297	16.0
Moderate	401	21.6
Severe	663	35.7
Critical	497	26.7
Body Mass Index		
Underweight	47	2.5
Normal	943	50.1
Overweight	605	32.2
Obese	286	15.2
Sex		
Male	983	52.3
Female	898	47.7
Comorbidities		
Hypertension	992	52.7
Diabetes Mellitus	734	39.0
Chronic Kidney Disease	412	21.9
Cardiovascular Disease	341	18.1
Chronic Lung Disease	273	14.5
Neurologic Disease	121	6.4
Solid Cancers	72	3.8
Chronic Liver Disease	52	2.8
HIV-AIDS	13	0.7
Leukemias	5	0.3
Others	140	7.4

Table 2. Frequency Distribution of cHIS Scores among COVID-19 Confirmed Patients

cHIS Score	Frequency	Percentage (%)
0	545	29.0
1	509	27.1
2	350	18.6
3	241	12.8
4	142	7.5
5	75	4.0
6	19	1.0
Total	**1,881**	**100.0**

Table 3. Table of Logistic Regression for cHIS Score and Risk of Mortality

	Overall	cHIS ≥1	cHIS ≥2	cHIS ≥3	cHIS ≥4	cHIS ≥5	cHIS = 6
COVID-19 Hyperinflammatory Score (cHIS Score)							
Overall	**-0.979***** (0.0850)						
cHIS ≥1		**-2.723***** (0.458)					
cHIS ≥2			**-2.117***** (0.228)				
cHIS ≥3				**-2.087***** (0.200)			
cHIS ≥4					**2.236***** (0.270)		
cHIS ≥5						**-3.477***** (0.716)	
Body Mass Index (Control: Normal BMI)							
Underweight	**-1.612***** (0.539)	**-1.638***** (0.546)	**-1.840***** (0.520)	**-1.555***** (0.488)	**-1.374***** (0.508)	**-1.671***** (0.490)	**-1.614***** (0.493)
Overweight	-0.0290	-0.0468	-0.0578	-0.0145	-0.0637	-0.0819	-0.0728
Obese	-0.184	-0.188	-0.211	-0.158	-0.249	-0.257	-0.222
COVID-19 Severity (Control: Mild)							
Moderate	0.841*	1.112**	0.872*	0.583	0.560	0.637	0.647
Severe	0.849**	0.652*	0.705*	0.374	0.0809	-0.0595	-0.0568
Critical	**-2.982***** (0.385)	**-3.579***** (0.362)	**-3.348***** (0.377)	**-3.690***** (0.363)	**-4.099***** (0.355)	**-4.274***** (0.348)	**-4.411***** (0.344)
Comorbidities[a]							
Chronic Lung Disease	**-0.591**** (0.253)	**-0.544**** (0.247)	**-0.504**** (0.245)	**-0.601**** (0.247)	**-0.489**** (0.243)	**-0.554**** (0.241)	**-0.520**** (0.239)

Standard errors (only shown for variables with significant and consistent correlation) in parentheses
*Levels of significance: ***p<0.01, **p<0.05, *p<0.1*
[a] Excludes comorbidities with nonsignificant correlation

increased likelihood of mortality compared to controls, while a cHIS score of 5 was associated with 3.5-fold increased likelihood of mortality compared to controls.

Among the sociodemographic data, being underweight or having a BMI of less than 18.5 kg/m^2, and the presence of a chronic lung disease both significantly correlated with mortality at p<0.01 and p<0.05, respectively, regardless of cHIS scores.

A COVID-19 stratification of critical at admission was also a significant risk of mortality regardless of cHIS scores at p<0.01.

Relationship between the cHIS Score and the Need of Mechanical Ventilation

Table 4 shows the logistic regression of cHIS score and the need of mechanical ventilation across the socio-demographic data.

The cHIS score at admission regardless of value was an independent predictor of the need for mechanical ventilation and was internally consistent and robust across multiple sensitivity analyses. For instance, a cHIS score of 3 was associated with 1.6-fold increased need of mechanical ventilation, even after controlling for age, sex, BMI, and severity.

A BMI of less than 18.5 kg/m^2, i.e., being underweight, and a stratification of critical both significantly correlated with the need of mechanical ventilation at p<0.01, regardless of cHIS scores, while no comorbidities were associated with increased need of mechanical ventilation.

Optimal Cut-off Values of cHIS Score, Including its Sensitivity and Specificity

Table 5 shows the optimal cutoffs of cHIS score in predicting mortality and need of mechanical ventilation.

Using the Youden Index, it was determined that a cHIS score of ≥3 was predictive of mortality with a sensitivity of 88.59% and a specificity of 71.72%, while a cHIS score of ≥2 was predictive of the need of mechanical ventilation with a sensitivity of 84.02% and a specificity of 70.82%. These cHIS values provided the best tradeoff between sensitivity and specificity in predicting the two adverse outcomes. Moreover, the AUROC analysis validated that they were within the acceptable discrimination value of at least 0.70.[22] The actual tables for AUROC are presented in Appendices C and D.

DISCUSSION

Even prior to SARS-CoV-2's explosion to pandemic level in early 2020, a mounting body of evidence has implicated

Table 4. Table of Logistic Regression for cHIS Score and Need of Mechanical Ventilation

	Overall	cHIS ≥1	cHIS ≥2	cHIS ≥3	cHIS ≥4	cHIS ≥5	cHIS = 6
COVID-19 Hyperinflammatory Score (cHIS Score)							
Overall	**0.586***** (0.0885)						
cHIS ≥1		**1.249***** (0.330)					
cHIS ≥2			**1.174***** (0.245)				
cHIS ≥3				**1.563***** (0.247)			
cHIS ≥4					**1.378***** (0.335)		
cHIS ≥5						**1.887***** (0.690)	
Body Mass Index (Control: Normal BMI)							
Underweight	**1.336***** (0.517)	**1.541***** (0.502)	**1.509***** (0.499)	**1.324***** (0.498)	**1.354***** (0.492)	**1.556***** (0.477)	**1.530***** (0.479)
Overweight	-0.392	-0.374	-0.360	-0.394	-0.361	-0.328	-0.344
Obese	-0.576	-0.569*	-0.548	-0.606*	-0.532	-0.513	-0.560*
COVID-19 Severity (Control: Mild)							
Moderate	-0.668	-0.815*	-0.630	-0.521	-0.491	-0.533	-0.538
Severe	-0.827**	-0.736*	-0.685*	-0.593	-0.356	-0.303	-0.296
Critical	**4.496***** (0.380)	**4.951***** (0.377)	**4.833***** (0.380)	**4.918***** (0.366)	**5.251***** (0.361)	**5.361***** (0.358)	**5.487***** (0.358)

Standard errors (only shown for variables with significant and consistent correlation) in parentheses
*Levels of significance: ***p<0.01, **p<0.05, *p<0.1*

dysregulated inflammatory response as the culprit in severe COVID-19 disease.[2,3,4,12] This observation has sparked numerous attempts to quantify the degree of immune dysregulation by using a combination of clinical and laboratory parameters to predict clinical outcomes. Among these were the COVID-19-associated Hyperinflammation (COV-HI); neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), and platelet-to-lymphocyte ratio (PLR); and the Ventilation in COVID Estimator (VICE) and Death In COVID-19 Estimator (DICE).[26-28] Meanwhile, the cHIS score has been externally validated in at least two studies, but has never been applied to a Southeast-Asian population.[13,14] To the authors' best knowledge, this study is the largest external validation of the cHIS score with 1,881 subjects, and the first one in the country.

Table 5. Optimal Cutoff Values of cHIS Scores

cHIS Score	Outcomes			
	Risk of Mortality		Need of Mechanical Ventilation	
	Sensitivity	Specificity	Sensitivity	Specificity
cHIS ≥1	100.00	0.00	0.00	100.00
cHIS ≥2	100.00	0.00	**84.02**	**70.82**
cHIS ≥3	**88.59**	**71.72**	64.50	89.08
cHIS ≥4	96.89	43.91	37.48	96.65
cHIS ≥5	99.79	20.92	17.55	99.62
cHIS = 6	100.00	0.00	0.00	100.00

The main objective of this study was to correlate the cHIS score among COVID-19 confirmed patients taken on admission and their risk of mortality and need of mechanical ventilation.

By regression analysis, the one-time cHIS score was found to be associated with mortality and need of mechanical ventilation, and was consistently robust across multiple sensitivity analyses. This was consistent with the three previous studies linking patient cHIS score to adverse clinical events.[12-14]

Noteworthy was the conservation of the relationship even when certain components of the cHIS score were excluded from analysis as they were not tested for all patients at the time of admission. Under the cHIS parameter of cytokinemia, we decided to omit serum triglyceride as it was not routinely taken as a non-fasting test on admission, and the IL-6 as it was not locally available. Thus, only CRP was the surrogate marker used for cytokinemia in this study.

Further analysis showed that cutoff cHIS scores of 3 and 2 can be used as a predictor of mortality and need of mechanical ventilation, respectively. This result was comparable to the original findings by Webb et al. which showed that a threshold score of 2 or more was predictive of both mortality (sensitivity 95%, specificity 59%) and mechanical ventilation (sensitivity 96%, specificity 49%).[12] Meanwhile, the validation study by Yildirim et al. demonstrated a cHIS score of 3 or more to be associated with ICU mortality (sensitivity 63%, specificity 50%) and invasive mechanical ventilation (sensitivity 61%, specificity 51%).[13] Among COVID-19 patients with

rheumatic diseases, Hsu et al. found that a cHIS score of 2 or more had higher odds of intensive care unit admission (OR 3.45 [95% CI 1.98–5.99]), mechanical ventilation (66.20 [8.98–487.80]), and in-hospital mortality (16.37 [4.75–56.38]) compared with those with a cHIS of less than 2.[14]

The strength of the cHIS score in predicting adverse outcomes stems from the theoretical robustness of its six components, which reflect physiologic features of archetypal hyperinflammatory states, such as HLH, MAS, and CRS.[12] Several studies had previously correlated the individual components of the cHIS score, namely fever;[29,30] macrophage activation;[31,32] hematologic dysfunction;[33-36] coagulopathy;[37] hepatic injury;[38-42] and cytokinemia,[43-47] to adverse clinical outcomes, but a composite of these clinical features had never been used as a triaging and prognostication tool up until Webb et al. came up with the said scoring system.

An interesting finding in this study was the association of underweight, but not obesity, with the risk of mortality and need of mechanical ventilation across all cHIS scores. Although obesity is more commonly linked to poor outcomes in COVID-19, some studies have in fact shown that being underweight, being associated with malnutrition, can be contributory to unfavorable clinical outcomes.[48-51] Since malnutrition is prevalent among COVID-19 patients, ranging from 27.5% to 82.6%, the European Society for Clinical Nutrition and Metabolism (ESPEN) has recommended providing an energy level of 27–30 kcal/kg body weight and a protein intake of more than one gram per kilogram body weight for COVID-19 patients.[52-57]

This study also showed that among the comorbidities, the presence of chronic lung disease was a significant independent predictor of mortality across all cHIS scores. Indeed, several studies have linked chronic lung disease to severe outcomes in COVID-19; the pathophysiologic explanation is that angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine-2 (TMPRSS2), which are cellular targets of SARS-CoV-2, are widely expressed in the lung tissue.[57-60] Since smoking significantly increases the expression of ACE2, patients with COPD are also shown to have increased expression of ACE2 in the airway epithelium, and thus adverse outcomes.[61]

A stratification of critical was also found to be associated with mortality and need of mechanical ventilation, regardless of cHIS score. However, this may be explained by the fact that COVID-19 critical patients were either already intubated or in shock at the outset, and thus would correlate cleanly with the said outcomes.

A limitation of this study was that COVID-19 variants with their differential virulence were not taken into account as potential independent variables affecting the risk of mortality and need of mechanical ventilation, as genomic testing was not available locally during the study period. By 2021, at least five variants of concern have been documented, including Alpha, Beta, Gamma, Delta, and Omicron.[62] Another potential confounder that could have strong impact on the patients' outcomes but was not included in the study, was their vaccination status. Before the year 2021 ended, the vaccination rollout was at 55% for those who received at least one dose and 44% for those fully vaccinated.[63] On top of these, our study being retrospective in nature, was limited by its vulnerability to recall bias, selection bias, and incomplete data.[64]

CONCLUSION

Among COVID-19 patients, the cHIS score taken at admission correlated with the risk of mortality and the need for mechanical ventilation. With optimal sensitivities and specificities, a cut-off cHIS score of ≥2 can be used as a predictor of the need for mechanical ventilation while a cutoff cHIS score of ≥3 can be used as a predictor of mortality.

We recommend requesting the laboratory tests included in the cHIS scoring and applying the said score in the prognostication of all admitted COVID-19 patients. This cHIS scoring can be modified such that triglyceride and IL-6 can be safely omitted if these tests are not available. Prospective validation of the cHIS score should be the next direction of research in order to confirm these findings without the biases of a retrospective study. We also recommend considering the COVID-19 variant and the patient's vaccination status as independent variables in future studies.

In addition, regardless of cHIS scores, being underweight was predictive of mortality and need of mechanical ventilation, while the presence of chronic lung diseases was predictive of mortality. Thus, we strongly recommend SARS-CoV-2 vaccination among the underweight and those with chronic lung diseases in order to mitigate their higher risk for adverse outcomes compared to the general population.

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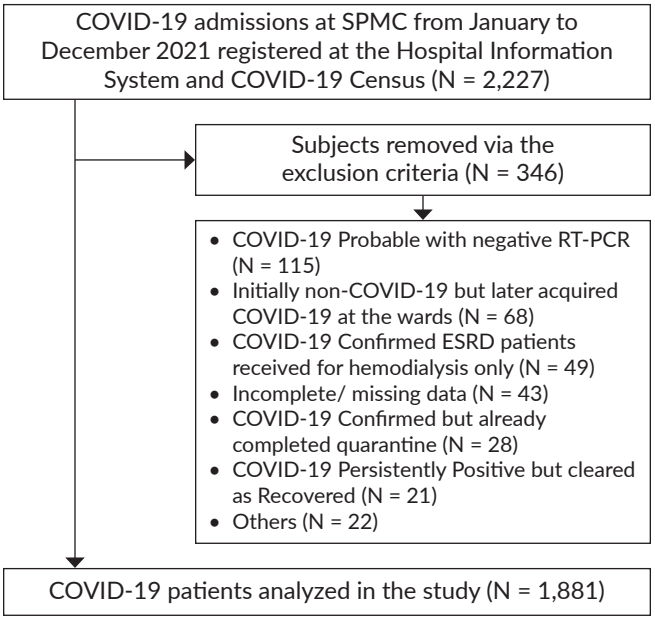
APPENDICES

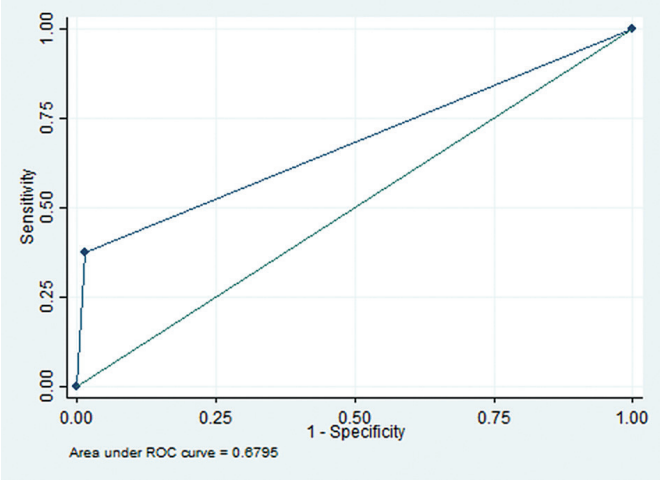
Appendix A. The six components of the COVID-19-associated hyperinflammatory syndrome (cHIS) criteria and the parameters used to score them

cHIS Parameters	Operational Definition
Fever	Temperature of >38.0°C
Macrophage Activation	Ferritin of ≥700 µg/L
Hematologic Dysfunction	Neutrophil-to-lymphocyte ratio of ≥10, OR Both hemoglobin of ≤9.2 g/dL, AND platelet count of ≤110×10^9 cells/L
Coagulopathy	D-dimer of ≥1.5 µg/mL
Hepatic Injury	Lactate dehydrogenase of ≥400 U/L, OR Aspartate aminotransferase of ≥100 U/L
Cytokinemia	C-reactive protein of ≥15 mg/dL, OR Triglyceride of ≥150 mg/dL[a], OR Interleukin-6 of ≥15 pg/mL[b]

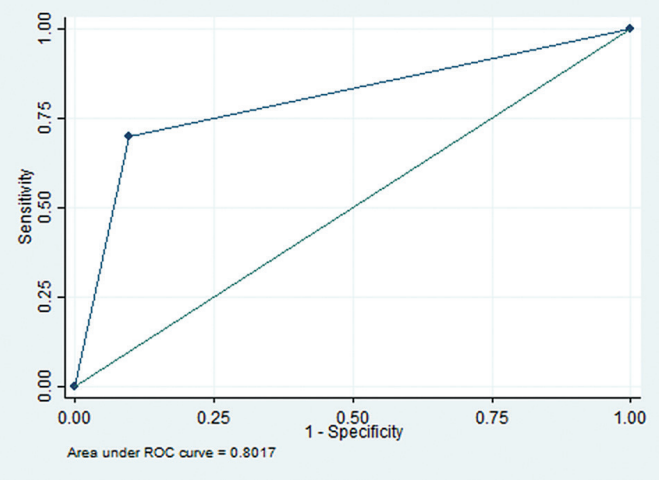
[a] *Excluded as a parameter as it is not routinely taken as a non-fasting lab at SPMC*
[b] *Excluded as a parameter as it was not available at SPMC during the study period*



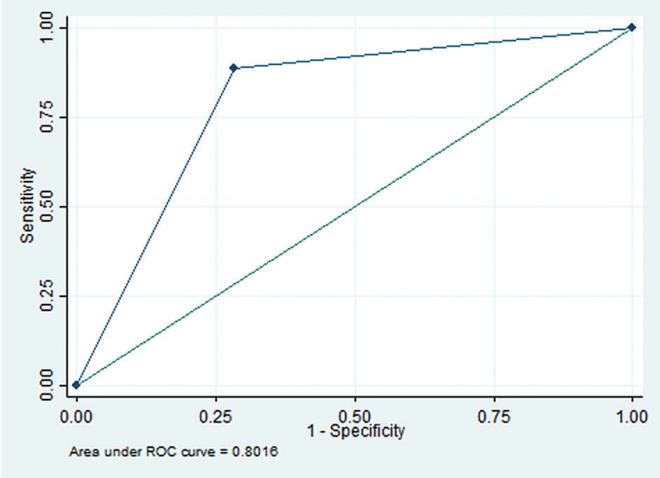
Appendix B. Flow diagram of the study participants.



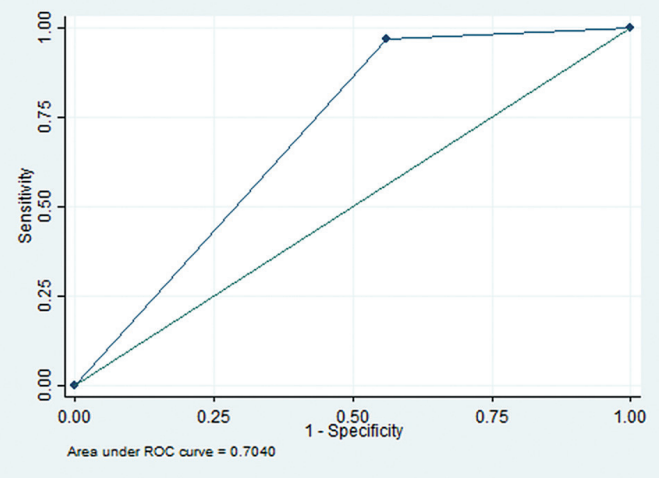
A. cHIS ≥1



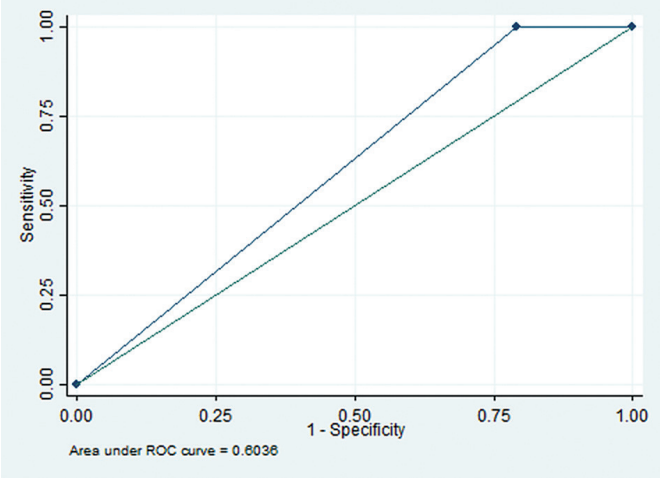
B. cHIS ≥2



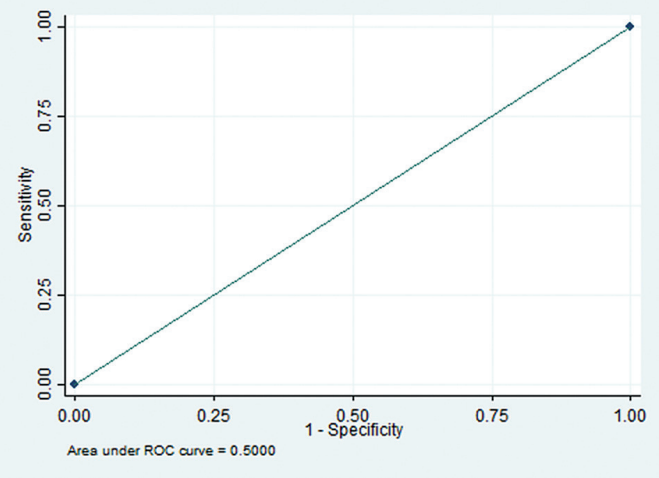
C. cHIS ≥3



D. cHIS ≥4

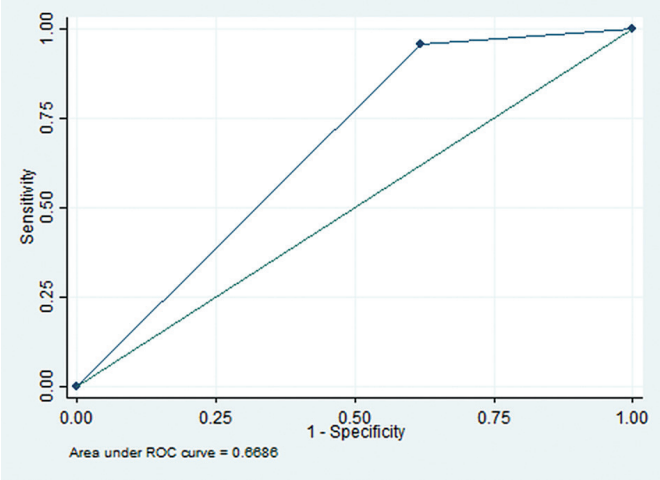


E. cHIS ≥5

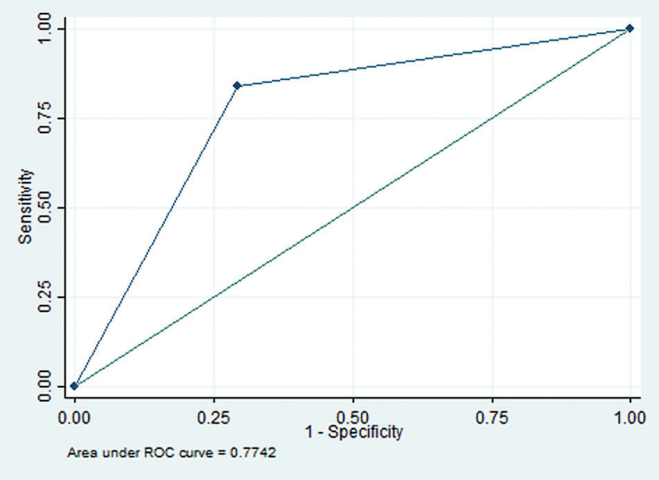


F. cHIS = 6

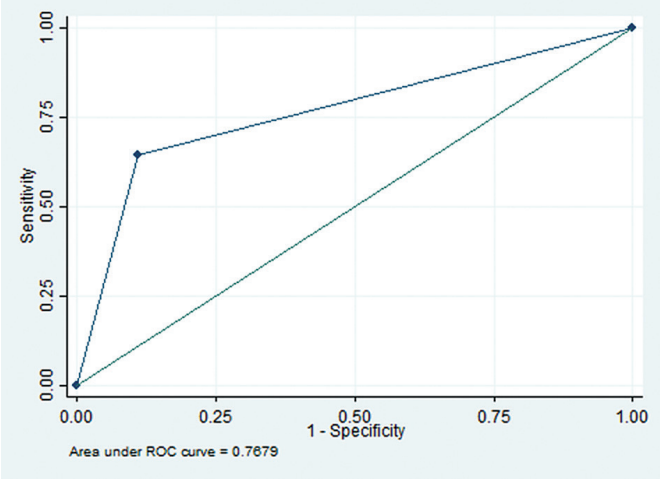
Appendix C. AUROC analysis per cHIS cutoff score for mortality outcome.



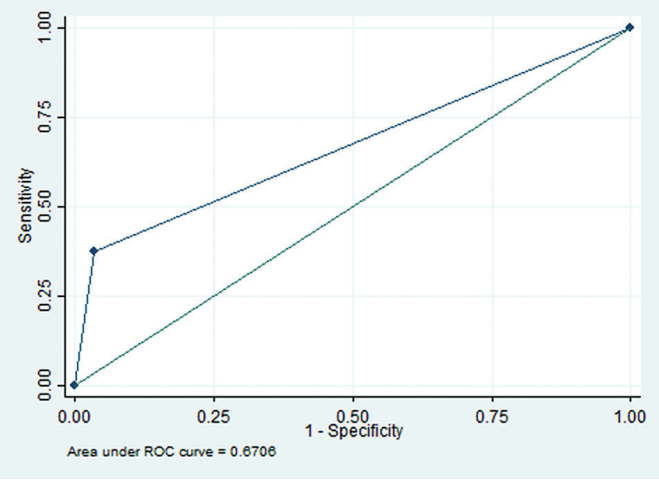
A. cHIS ≥1



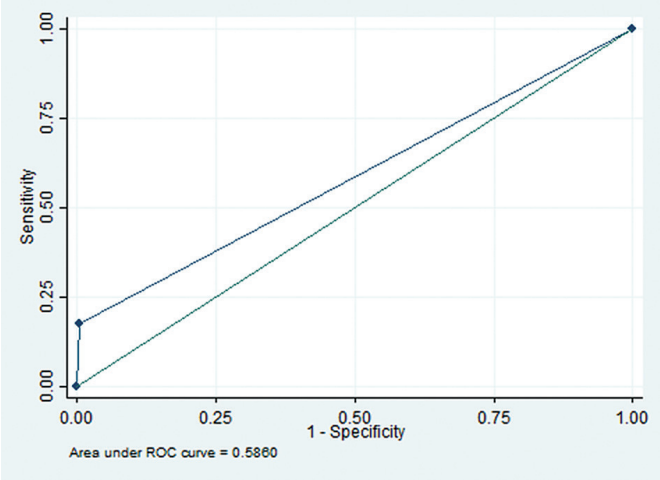
B. cHIS ≥2



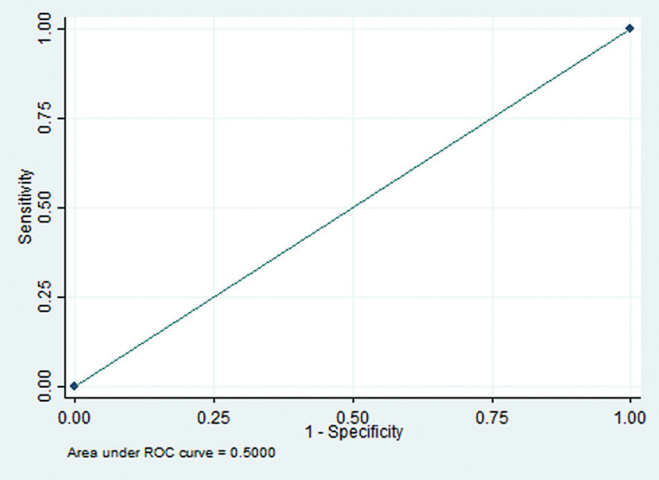
C. cHIS ≥3



D. cHIS ≥4



E. cHIS ≥5



F. cHIS = 6

Appendix D. AUROC analysis per cHIS cutoff score for need of mechanical ventilation outcome.