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Research Article

External Validation and Modification of a New Score for Predicting Mortality in Patients with COVID-19 in High Altitude Patients. A Peruvian Study

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Abstract

This study aims to validate two predictive mortality scores for patients with COVID-19 to support clinical decision-making in those who require hospitalization. The tomographic patterns found can be added to the original scores to increase their predictive power. Retrospective, analytical, observational, and cross-sectional studies were carried out in two phases. 489 medical records of patients with COVID-19 hospitalized at "Daniel A. Carrión" Hospital in Huancayo (located at 3,250 meters above sea level) were reviewed to perform external validation. Two predictive scores, formed by nine (score 5) and ten variables (score 6) were evaluated. In a second step, a subgroup of 258 patients with chest CT scan results was

assessed to determine the association of tomographic findings with mortality. The diagnostic precision of SAWBPIL and SAWBPI scores was high and it was found between 80% and 85%, as expressed by an area under the curve (AUC) of SAWBPIL score of 0.843 and SAWBPI score (without DHL) of 0.822. This diagnostic precision was similar to those of the original study (AUC 0.838 and 0.826, respectively) and higher than that of the CALL score (AUC 0.756). The percentage of pulmonary involvement was 54.59% in the surviving patients and 66.6% in those who died (p-value = 0.000). The performance of the modified SAWBPI score (SAWBPI-CT1.0), formed when adding the percentage of pulmonary involvement and the presence or absence of septa, reached a diagnostic precision of 84.4%, while the SAWBPIL score (SAWBPIL-CT1.0) reached a precision of 90.3%. For a value of 3.75 severity points or more, the modified SAWBPIL score reached a sensitivity of 86.8% and a specificity of 70.1% to predict mortality from COVID-19. Two new mortality prediction scores were shown to maintain their predictive capacity in the population studied. Adding tomographic data, the diagnostic precision of the score that includes LDH values reached a value of 90.3%, higher than most currently used scores.

Keywords
COVID-19; mortality; prognostic score; validation; high altitude; Perú

1. Introduction

Globally, at least 15% of hospitalized patients will develop severe COVID-19 that will require management in intensive care units or lead to death [1]. The range of symptoms that the patient may present is highly varied, ranging from asymptomatic carrier to death due to multiple organ failure. Patients who have risk factors are most severely affected [2].

According to studies by Chen et al. [3] and Myrstad [4], severity scores should be an integral part of the management of patients with COVID-19 in each hospital and are essential to deciding the course of action to take in each case, both from the clinical and from the administrative point of view.

Mortality prognostic scores for COVID-19 vary depending on the country and the medical parameters used [3, 4]. These scores must be updated and proved appropriate to the different health systems and dissimilar geographic and demographic realities [5-8]. Most of the scoring systems come from China, a country with health and epidemiological characteristics very different from Latin American countries [9], where mortality and morbidity by SARS-CoV-2 have been much lower than in the southern hemisphere. Hence, the comparison between the clinical evolution of patients in both countries is difficult to assess. There is controversy regarding the effect of altitude on the evolution and severity of COVID-19. According to Abdelsalam et al. [10], mortality decreases, but according to Woolcott [11], it would increase in men over 65. Both studies included populations above 2000 but below 3000 meters above sea level. The performance of predictive scores in high-altitude populations is another aspect rarely investigated [12] even though some studies have evaluated clinical and laboratory features associated with severe COVID-19 at altitude [10-16].

In this context, evaluating new predictive scores for different geographical regions, including

high-altitude areas, is essential. The goals of this study are twofold: in the first phase, to validate a predictive mortality score for patients with COVID-19 developed in a high-altitude population and to support clinical decision-making in those patients who require hospitalization. In the second phase, a new mortality predictive score for patients with COVID-19 will be modified, evaluating it in the second population of hospitalized patients and adding chest tomography findings.

2. Materials and Methods

2.1 Study Design

This is a retrospective, analytical, observational, and cross-sectional study in which electronic medical records and chest CT scans were reviewed at the Daniel A. Carrión de Huancayo Hospital, 3,250 meters above sea level.

2.2 Sample Size Calculation

The sample size was calculated using the data obtained by Xiang et al. [9], who found an odds ratio (OR) of 2.26 for the correspondence between the presence of hypertension as a risk factor of death from COVID-19. With a statistical power of 80%, a degree of confidence of 95%, and a minimum one-to-one ratio, a minimum sample size of 130 cases was obtained, corresponding to 65 nonsurvivors and 65 survivors. It was decided to evaluate at least 300 patients per cohort to allow better discrimination of other less prevalent risk factors.

2.3 Data Set

Three groups of patients were evaluated. The derivation cohort consisted of 320 patients from 800 patients admitted with COVID-19 diagnosis to Ramiro Prialé Prialé National Hospital (RPPNH) between April and August 2020. The internal derivation cohort, or second group, comprised 300 patients from a population of 600 subjects with COVID-19 admitted to RPPNH between September and December 2020. This second population was exclusively formed by patients native to Huancayo and surrounding areas.

The external validation cohort, or third group, was obtained from Daniel A. Carrión Regional Hospital (DACRH), where around 1,200 patients with COVID-19 were admitted to the medical services during January to June 2022. From this population, a group of 500 medical charts of patients with COVID-19 were randomly evaluated. Eleven of the 500 charts were not included due to incomplete data, reaching a total of 489 medical charts (Table 1 compares the main characteristics of the three populations).

Table 1 Comparison of the Patient Characteristics of the Derivation, Internal Validation, and External Validation Cohorts.

Patient Characteristics	Derivation Cohort (n = 320)	Internal Validation Cohort (n = 300)	External Validation Cohort (n = 48)
Age (years)	60.58	61.08	56.33
Male Gender (%)	72.8	68.3	63.2
Length of stay (days)	10.91	10.58	9.26
$SatO_2$ (%)	81.9	81.5	78.10
FiO_2 (%)	38.12	36.76	49.91
Leukocytes per mm^3	12.455	12.319	10.782
Lymphocytes (%)	10.94	11.07	8.81
Platelets per mm^3	377,808	382,860	268,743
LDH (U/L)	625.65	647.22	604.22
CRP (mg/L)	136.34	179	130.61
$SatO_2/FiO_2$	279.1	282.21	338.24

$SatO_2$ = arterial oxygen saturation. $SatO_2/FiO_2$ = proportion of arterial oxygen saturation in relationship with the amount of oxygen administered (FiO_2 = inspired fraction of oxygen). CRP = C-reactive protein, LDH = lactate dehydrogenase.

Of these 489 charts, 258 had complete chest CT scan images with their corresponding radiologic report and were further evaluated to improve the two clinical scores (see Figure 1).

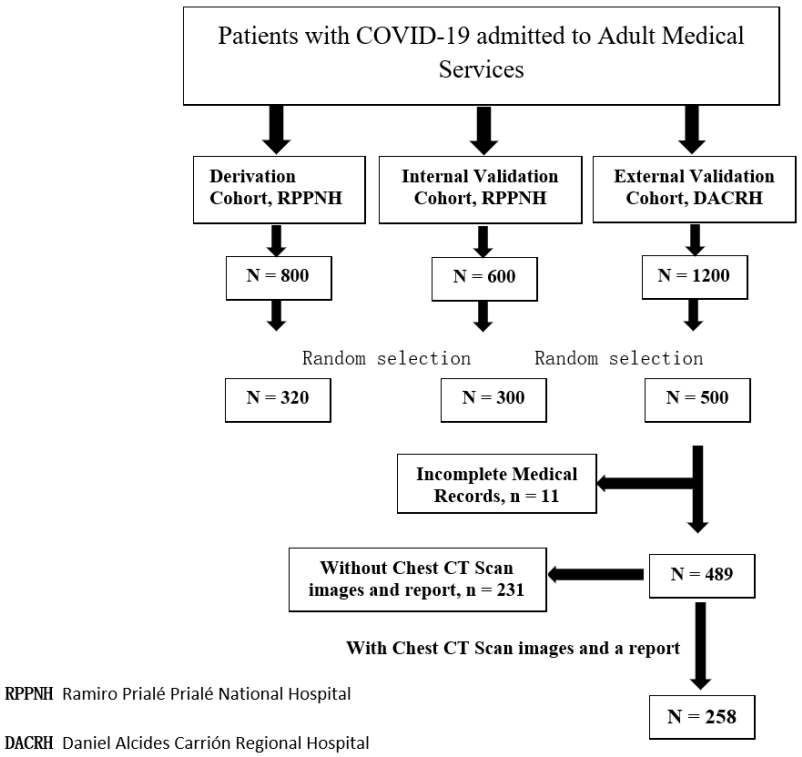

Figure 1 Flow of Subject Selection for the Derivation and Validation Cohorts.

2.4 Data Preprocessing

The list of patients admitted to both hospitals was reviewed. Charts corresponding to patients with confirmed COVID-19 were selected. Data profiling was performed, including all the known risk factors associated with COVID-19 mortality. Missing data regarding outcomes or main risk factors led to the exclusion of several medical charts. Laboratory values were considered only at admission to the hospital. Inconsistent data were suppressed if confirmation was not available. Data were organized according to clinical features, starting with epidemiological features, followed by prior medical history, onset symptoms, clinical presentation, hematological profile, biochemical profile, chest CT scan patterns, and percentage of lung compromise. Data were introduced to an Excel spreadsheet; the number of prior medical conditions and severe signs and symptoms were calculated. Data in Excel was transferred to an SPSS chart for subsequent analysis. Continuous variables were doublechecked with frequency analysis in SPSS for inconsistent values, conducing to the corresponding amendments.

2.5 Derivation of Severity Scores for Mortality from COVID-19

In the Derivation phase, 320 patients were included and a total of 35 predictors were collected, including 7 different symptoms, gender, a history of ILD, chronic renal disease, diabetes, malignancy, HIV, immunosuppression therapy, obesity, COPD, asthma, and eight ancillary test results.

The following 16 characteristics were identified as risk factors for mortality from COVID-19: age above 50 years, elevated values of lactic dehydrogenase (LDH), decreased values of platelets, lymphocyte proportion below 8%, decreased total lymphocytes, decreased oxygen saturation, decreased oxygen saturation to fractional expired oxygen ($SatO_2/FiO_2$) ratio, a low count lymphocyte count greater than 18,000, elevated C-reactive protein values (CRP), history of arterial hypertension, absence of five of six symptoms (sore throat, malaise, cough, fever sensation, anosmia and chest pain). Table 2 shows the risk above factors with their corresponding odds ratio.

Table 2 Risk Factors for Mortality Associated with COVID-19. Derivation Cohort.

Factor de Riesgo	OR	OR (95% CI)	P value
LDH > 880 UI	8.90	2.85-27.73	0.000*
Platelets < 135,000/mm^3	4.57	1.83-11.38	0.001*
Age > 65 years	3.59	2.23-5.78	0.000*
History of ILD	3.11	1.02-9.53	0.037*
Age > 70 years	3.09	1.82-5.24	0.000*
Leukocyte count > 18,200/mm^3	2.88	1.53-5.43	0.010*
Absence of chest pain	2.36	1.66-3.35	0.000*
Lymphocytes 7% or less	2.34	1.47-3.73	0.000*
$SatO_2/FiO_2$ < or = 182	2.18	1.27-3.74	0.001*
Age 51-64 years	2.14	1.61-2.84	0.001*
Absence of sore throat	2.0	1.34-2.97	0.000*
Absence of fever	1.69	1.28-2.23	0.000*
Hypertension history	1.41	1.04-1.92	0.008*
C-Reactive Protein < 13 mg/L	0.80	0.68-0.93	0.002*

Malaise	0.47	0.36-0.73	0.000*
Smell loss	0.40	0.24-0.68	0.0012*

*p < 0.05.

The corresponding Odds Ratio was calculated for all the risk factors, observing that it was higher for some of them, such as age greater than 70 years, lactate dehydrogenase (LDH) greater than 880 units, platelets less than 135,000/mm^3, excessive lymphocytosis above 2440 cells per cubic millimeter. As no statistical association was found with mortality for type 2 diabetes mellitus, COPD, and male sex, they were excluded from the model.

A multivariate analysis was performed using binary logistic regression. The association with mortality risk was confirmed only for age (p = 0.032) (Table 3).

Table 3 Multivariant Analysis of Risk Factors for Mortality in COVID-19 Patients.

Risk Factors	Coefficient (Beta)	P Value	OR	OR (95% CI)
$SatO_2/FiO_2$ < 183	-0.002	0.913	0.998	0.962-1.035
LDH > 880 U/ml	0.012	0.167	1.012	0.995-1.029
CRP < 13 mg/L	0.020	0.094	1.020	0.997-1.044
Age > 65 years	-0.023	0.032*	1.034	1.003-1.067
Hypertension history	0.024	0.961	1.025	0.384-2.736
Platelets < 135,000/mm^3	-0.033	0.108	0.968	0.930-1.007
FiO_2 > 0.40	0.059	0.478	1.061	0.902-1.248
Arterial Oxygen Saturation < 80%	-0.128	0.258	0.880	0.704-1.098
History of ILD	-0.195	0.823	0.823	0.148-4.562
Leucocytes > 18,200	-0.406	0.269	0.666	0.325-1.368
Linfocytes < 7%	-0.409	0.278	0.664	0.317-1.390
Chest pain	0.806	0.097	2.240	0.8064-5.806

*p < 0.05.

A total of 11 variables were selected: age, which had a significant association in the multivariate analysis, as well as lymphocyte count and proportion, leukocyte count, low $SatO_2/FiO_2$, hypertension history, low platelet count, high LDH, low CRP (as a protective factor), a history of ILD, and the absence of symptoms. Each numerical variable was evaluated with an ANOVA test, identifying the mortality rate point-by-point according to each cut-off value, leading to the proposed value of each risk factor, from 1 to 3 points.

Through a process of essay and error, by testing at least 30 possible combinations, 8 final models were obtained.

2.6 Derivation of Scores 5 and 6 for Mortality Prediction of COVID-19

Four scores included LDH level determination (models 2, 4, 6, and 8), and the other four did not include LDH values models (1, 3, 5, and 7). The models were compared using ROC curves. Models 1 and 2 did not include the proportion of lymphocytes; models 3 and 4 included a CRP value of <13 mg/L as a protective factor; models 7 and 8 excluded the absence of symptoms. ROC values obtained were 0.822, 0.819, 0.838, and 0.826 for models 2, 4, 6 and 8, respectively. ROC values for models 1,

3, 5, and 7 were 0.802, 0.803, 0.826, and 0.815, respectively. Models 6 and 5 had the best ROC values (0.838 and 0.826, respectively), so they were selected for internal validation.

Model 5 includes all the variables shown in the table (see Table 4), but without adding LDH, and model 6 or Score 6, which is model 5 but includes LDH values.

Table 4 Components of SAWBPI Score and SAWBPIL Score for Predicting Mortality from COVID-19.

Clinical Data	Scoring System				
	0	**1**	**1.5**	**two**	**3**
Age	<51 years	51-64 years		65-69 years	70 or more
$SatO_2/FiO_2$	>263	201-263	183-200	<183	
Total lymphocyte count	601-2439	501-600	<501		
LDH*	<520	520-879			≥880
White blood cell count	<18200	≥18200			
Platelets	>135000	≤135000			
COVID-19 list of 5 symptoms	1 present	all absent			
Lymphocyte percentage	>7%	≤7%			
Hypertension	Absent	Present			
ILD history	Absent	Present			

Score 5 does not include LDH values. * Lacatate Dehydrogenase.

Model 5 was named SAWBPI for its components: $SatO_2/FiO_2$, age, white blood cell count (including lymphocyte count and platelets), blood pressure, and an ILD history.

Model 6 was named SAWBPIL for its components: $SatO_2/FiO_2$, age, white blood cell count (including lymphocyte count and platelets), blood pressure, ILD history, and increased LDH levels.

Severity score No. 5 had a ROC area under the curve of 0.826, and when the LDH values were added, the area under the curve increased by 0.835.

2.7 Internal Validation

The validation cohort consisted of 300 HNRPP patients from high-altitude areas, such as Huancayo, the Mantaro Valley, and Huancavelica. Patients from areas below 3000 masl (meters above sea level) or above 4000 masl were excluded.

When performing the ROC curves, it was found that the performance of the predictive scores was higher than that of the derivation cohort, with an area under the curve for score 5 of 0.831 and score 6 (with DHL) of 0.855.

2.8 External Validation and Chest CT Scan Images: Population and Sample

A group of 258 patients with COVID-19 were hospitalized at the Daniel A. Carrión Hospital during the months of January to June 2022, and their conditions were evaluated.

All patients had confirmation of the disease by rapid antigen test or molecular test (RT-PCR) as well as chest CT scan, with a CORADS score of 4 or higher. Chest CT scans were performed by radiologists from Hospital Carrión, who had experience reading more than five hundred cases of

COVID-19.

2.8.1 Chest CT Scan Features Added to SAWBPI and SAWBPIL Scores

Chest CT images were evaluated to determine if any CT scan findings could be associated with a lower or higher mortality risk. SAWBPI and SAWBPIL scores were modified according to chest CT scan findings.

The following chest CT scan abnormalities were added to both scores:

- Presence of thickened septa and lung compromise <55%: +0 points
- Presence of thickened septa and lung compromise >55%: +1 point
- Presence of bilateral lung compromise of <55%: +0 points
- Presence of bilateral lung compromise of 55 to 70%: +0.5 points
- Presence of bilateral lung compromise of 71 to 89%: +0.7 points
- Presence of bilateral lung compromise of 90% or more: +1 point

SAWBPI-CT0.5 and SAWBPI-CT0.5 scores were considered when there was the presence of thickened septa and lung compromise >55%, and only 0.5 points were added to the original score. With this modification, a maximum of 1.5 points could be added if the patient had a bilateral lung compromise of 90% or more plus thickened septa.

SAWBPIL-CT1.0 and SAWBPIL-CT1.0 modifications were considered when there was the presence of thickened septa and lung compromise >55%, and 1.0 points were added to the score. With this modification, a maximum of 2.0 points could be added if the patient had a bilateral lung compromise of 90% or more plus thickened septa.

2.9 Ethics Statement

The treatment of patient data was carried out by coding them to guarantee anonymity and confidentiality, respecting the rules of the Declaration of Helsinki. The study was approved by the Ethics and Research Committee of the Continental University and by the Ethics Committee of Daniel A. Carrión Hospital.

3. Results

A total of 489 medical records were evaluated, 180 belonging to the female sex (36.8%) and 309 to the male sex (63.2%).

The majority of patients came from the city of Huancayo (78.4%), with 12.7% coming from other vicinities of the Mantaro Valley, 3.9% from the town of Chupaca, and the rest from various adjacent localities. The Mantaro Valley is a 70 kilometers territory, with an altitude ranging from 3100 to 3300 masl, which includes about twenty small boroughs and four major cities (Huancayo, Jauja, Concepción, and Chupaca) scattered at both sides of the Mantaro River in Junin.

Regarding past medical history, 39.7% of the patients had obesity, 16.8% had type 2 diabetes mellitus, 14.7% had high blood pressure, 2.5% were under immunosuppressive treatment, and 2% had a history of asthma, as well as chronic renal failure and pulmonary fibrosis, both with 1.6%.

3.1 Clinical Presentation and Oxygenation

The most frequent symptom was dyspnea (90.4%), followed by cough (71.8%), fever in 55.6%, headache in 26.8%, odynophagia in 20.2%, runny nose in 19.2%, myalgia in 14.3% and diarrhea in 11%.

The average age was 56.33 years, with a minimum age of 15 and a maximum of 95 years. The average heart rate was 96.83 beats per minute, with the maximum reached being 149 heartbeats per minute. The average respiratory rate was 24 breaths per minute, with a maximum value of 50 and a minimum of 14. The average temperature was 37.1°C. Mean systolic blood pressure was 115 mmHg and diastolic 72.5 mmHg. The BMI was elevated, with an average of 29 m^2/kg.

The average fraction of inspired oxygen (FiO_2) was 50%, with an average $SatO_2/FiO_2$ of 338.24. The average PaO_2 was 61.1 mmHg, with an average saturation of 88.8% according to the arterial blood gas study and 78.22% according to pulse oximetry. On average, arterial blood gases and PaO_2/FiO_2 were taken one to two hours after admission, particularly in those patients with oxygen saturations more significant than 85%. This difference may be because the arterial blood gases were taken at different times.

3.2 Ancillary Tests Results

The average hemoglobin level was 16.1 g/dL, with an average of 10,782 white blood cells per field, a mean of 9,405 neutrophils, 881 lymphocytes, and an average of 268,743 platelets per cubic millimeter.

The average ferritin level was 615.78, with a mean D-dimer of 3268 mg/L, DHL of 604 u/L, glucose of 154 mg/dL, urea of 44 mg/dL, creatinine of 0.95 mg/dL and average values of AST of 68 u/L and ALT of 75 u/L. Average albumin values were 3.35 g/dL and globulin 2.7 g/dL.

3.3 Prognosis and Complications

The average hospital stay was 9.26 days, with a minimum of 1 day and a maximum of 48. The most frequent complication was respiratory failure (94.9%), followed by acute heart failure (23.7%), coagulation disorder (18.4%), multiple organ failure (11.2%), and renal failure (8.8%). 39.5% of the patients (n = 193) died. Only 90 patients (18.4%) were intubated and connected to a mechanical ventilator.

3.4 SAWBPI and SAWBPIL Scores and COVID-19 Mortality Risk

Non-survivors had a mean of 4.9 points using the SAWBPI score, while survivors had a mean of 2.31 units. The difference was statistically significant (p-value = 0.00). Regarding the SAWBPIL score, non-survivors had an average of 6.14 and survivors 2.95 points. The difference was also statistically significant (Table 5)

Table 5 Relationship between SAWBPI and SAWBPIL with Risk of Mortality from COVID-19.

Severity Scores			
Outcome		SAWBPI	SAWBPIL
Survivor	Mean value	2.3193	2.9545
	Number of patients	296	253
	Standard. Deviation	1.87407	2.03952
Non-survivor	Mean value	4.9093	6.1410
	Number of patients	193	156
	Standard. Deviation	2.02287	2.37174
Total	Mean value	3.3415	4.1699
	Number of patients	489	409
	Standard. Deviation	2.31064	2.66603

The area under the ROC (receiver operator curve) was 0.843 for the SAWBPIL score and 0.822 for the SAWBPI score. The difference was statistically significant and revealed an excellent predictive capacity of both scores. Both scores were compared with the CALL score, which showed a ROC of 0.756 (Figure 2).

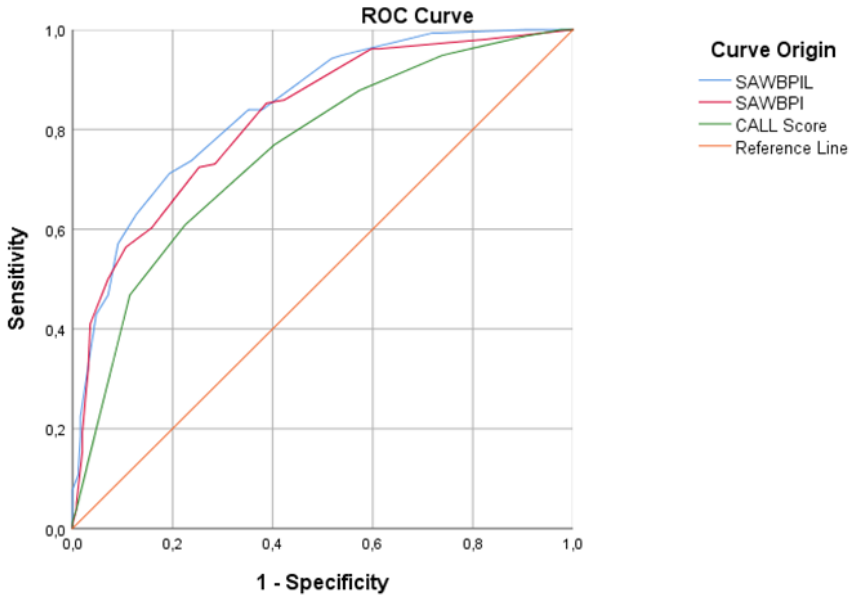

Figure 2 ROC Curves: CALL Score and SAWBPI (5) and SAWBPIL (6) Scores.

3.5 Validation Subgroup with Chest CT Scan Evaluation

The population comprised 65.5% males (n = 169) and 34.5% females (n = 89). Older adults represented 38% of the population (n = 98). 34.9% (n = 98) of the evaluated population were non-survivors and 65.1% (n = 168) were survivors.

Regarding the patterns of lung injury, 26.4% had multilobar involvement, and ground glass lesions could be observed in 94.2% of the patients. 13.2% of the subjects evaluated presented atelectasis, and 38.8% had a crazy paving pattern.

The mean age of the patients was 55 years, with a maximum age of 94 years. The mean lymphocyte count was 932 cells per cubic millimeter, the mean leukocytes were 11,143 per cubic millimeter, and the mean platelets were 270,855 per cubic millimeter.

The average diameter of the pulmonary artery in those patients in whom the measurement could be made was 27.1 mm, with a maximum value of 38 mm and a minimum of 18 mm. The percentage of lung involvement was a mean of 52.87%, with a maximum of 99%.

3.6 Chest CT Scan Findings and Mortality

Non-survivors had a mean CORADS score of 4.93, and those who survived had an average of 4.76. This difference was barely statistically significant (p-value = 0.049). The average diameter of the pulmonary artery was 28.85 mm in non-survivors and 26.12 mm in survivors. The difference was statistically significant (p-value = 0.012). The percentage of lung involvement was 54.59% in survivors and 66.6% in those who died (p-value = 0.000).

The ground glass pattern was found in most chest CT scans, both in deceased patients and survivors. Regarding the other patterns, it was found that those who presented atelectasis had a lower mortality (11.8%) than those who did not (38.4%). The crazy paving pattern and thickening of the septa were associated with a risk of increased mortality.

The crazy paving pattern was observed in 100 patients and the thickened septal pattern in 124. Mortality among those who presented a crazy paving pattern was 46% and in those with thickened septa, it was also 46%, unlike 27.8% among those who did not have a crazy paving pattern and 24.6% for those who did not have thickened septa (Table 6 and Table 7). The presence of unilateral consolidations was not associated with higher mortality, but bilateral consolidations were associated with lower mortality (31% vs 45%) ($p > 0.05$).

Table 6 Crazy Paving Pattern and Mortality.

			Mortality		Total
			No	Yes	
Crazy Paving pattern	Absent	Count	114	44	158
		%	72.2	**27.8**	100.0
	Present	Count	54	46	100
		%	54.0	**46.0**	100.0
Total		Count	168	90	258
		%	65.1	34.9	100.0

Table 7 The Presence of Thickened Septa and Mortality.

			Mortality		Total
			No	Yes	
Thickened septa	Absent	Count	101	33	134
		%	75.4	**24.6**	100.0
	Present	Count	67	57	124
		%	54.0	**46.0**	100.0
Total		Count	168	90	258

%	65.1	34.9	100.0

When comparing the area under the Receiver Operator Curve (ROC) of SAWBPIL and SAWBPI scores, an AUC of 0.877 was found for the first and 0.849 for the second (Figure 3). The performance of the SAWBPI score, modified to take into account the percentage of lung compromised and the presence of septa - which was termed as SAWBPI-CT1.0 - reached an AUC of 0.884, while the modified SAWBPIL score (SAWBPIL-CT1.0) reached an AUC of 0.903 (Table 8). It was determined that the new scores worked better when one point - and not half a point - was added when thickened septa were found.

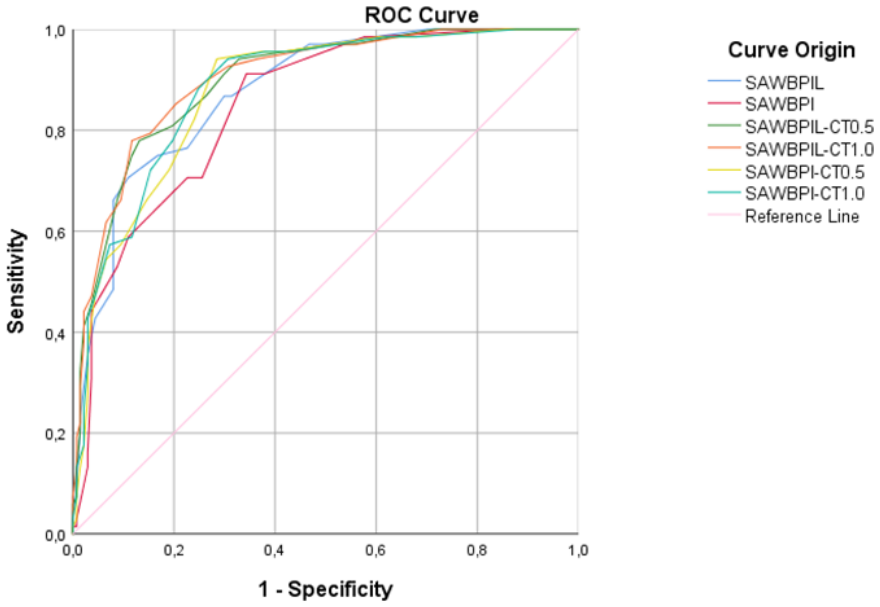

Figure 3 ROC Curves: Prognostic Scores of Mortality in COVID-19.

Table 8 Comparison of Six Predictive Scores for Mortality in COVID-19.

The area down the curve		95% confidence interval asymptotic	
SAWBPIL		0.877	
SAWBPI	0.849	Lower limit	Upper limit
SAWBPIL-CT0.5	0.898	0.830	0.924
SAWBPIL-CT1.0	0.903	0.797	0.902
SAWBPI-CT0.5	0.878	0.854	0.941
SAWBPI-CT1.0	0.884	0.860	0.945

The mortality rate of the patients who had a SAWBPIL CT0.5 score of 8 points or more was 90.3%, while the mortality rate of those individuals who had a SAWBPIL CT0.5 score of 7 points or less was 22.5% (p = 000) (Table 9).

Table 9 SAWBPIL-CT0.5 ≥ 8 and Mortality Risk in COVID-19 Patients. Contingency Table.

		Mortality		Total
		Survivor	Deceased	
SAWBPIL-CT0.5 ≥ 8	Absent	138	40	178
		77.5%	22.5%	100.0%
	Present	3	28	31
		9.7%	90.3%	100.0%
Total		141	68	209
		67.5%	32.5%	100.0%

The mortality rate of the patients who had a SAWBPIL CT1.0 score of 8 points or more was 90.9%, while the mortality rate of those individuals who had a SAWBPIL CT1.0 score of 7 points or less was 21.6% (p = 000) (Table 10).

Table 10 SAWBPIL-CT1.0 ≥ 8 and Mortality Risk in COVID-19 Patients. Contingency Table.

		Mortality		Total
		Survivor	Deceased	
SAWBPIL-CT1.0 ≥ 8	Absent	138	38	176
		78.4%	21.6%	100.0%
	Present	3	30	33
		9.1%	90.9%	100.0%
Total		141	68	209
		67.5%	32.5%	100.0%

The mortality rate of the patients who had a SAWBPI CT0.5 score of 6.5 points or more was 87.2%, while the mortality rate of those individuals who had a SAWBPI CT1.0 score of 6 points or less was 23.2% (p = 000) (Table 11).

Table 11 SAWBPI-CT0.5 ≥ 6.5 and Mortality Risk in COVID-19 Patients. Contingency Table.

		Mortality		Total
		Survivor	Deceased	
SAWBPI-CT0.5 ≥ 6.5	Absent	162	49	211
		76.8%	23.2%	100.0%
	Present	6	41	47
		12.8%	87.2%	100.0%
Total		168	90	258
		65.1%	34.9%	100.0%

The mortality rate of the patients who had a SAWBPI CT1.0 score of 7 points or more was 88.1%, while the mortality rate of those individuals who had a SAWBPI CT1.0 score of 6.5 points or less was 24.5% (p = 000) (Table 12).

Table 12 SAWBPI- CT1.0 ≥ 7 and Mortality Risk in COVID-19 Patients. Contingency Table.

		Mortality		Total
		Survivor	Deceased	
SAWBPI-CT1.0 ≥ 7	Absent	163	53	216
		75.5%	24.5%	100.0%
	Present	5	37	42
		11.9%	88.1%	100.0%
Total		168	90	258
		65.1%	34.9%	100.0%

The mortality rate of patients with a SAWBPIL score of 7 points or more was 82.9%, while the mortality rate of those who had a SAWBPIL score of 6.5 points or less was 22.4% (p = 000) (Table 13).

Table 13 SAWBPIL ≥ 7 and Mortality Risk in COVID-19 Patients. Contingency Table.

		Mortality		Total
		Survivor	Deceased	
SAWBPIL ≥ 7	Absent	135	39	174
		77.6%	22.4%	100.0%
	Present	6	29	35
		17.1%	82.9%	100.0%
Total		141	68	209
		67.5%	32.5%	100.0%

The mortality rate of patients with a SAWBPI score of 6 points or more was 88.5%, while the mortality rate of those who had a SAWBPI score of 5.5 points or less was 24.5% (p = 000) (Table 14).

Table 14 SAWPI ≥ 6 and Mortality Risk in COVID-19 Patients. Contingency Table.

		Mortality		Total
		Survivor	Deceased	
SAWPI ≥ 6	Absent	163	53	216
		75.5%	24.5%	100.0%
	Present	5	37	42
		11.9%	88.1%	100.0%
Total		168	90	258
		65.1%	34.9%	100.0%

The mortality rate of the patients who had a SAWBPIL CT1.0 score of points or more was 72.3%, while the mortality rate of those individuals who had a SAWBPIL CT1.0 score of 3.5 points or less was 10.3% (p = 000) (Table 15).

Table 15 SAWBPIL-CT1.0 ≥ 4 and Mortality Risk in COVID-19 Patients. Contingency Table.

			SAWBPIL-CT1.0 ≥ 4		Total
			0.00	1.00	
Mortality	Absent	Count	39	102	141
		% within mortality	27.7%	72.3%	100.0%
	Present	Count	61	7	68
		% within mortality	89.7%	10.3%	100.0%
Total		Count	100	109	209
		% within mortality	47.8%	52.2%	100.0%

A SAWBPIL-CT0.5 score ≥ 8 and a SAWBPIL-CT1.0 ≥ 8 showed the maximal specificity for mortality (97.9%), having the latter a higher positive predictive value than the former (90.9% versus 90.3%), but with low sensitivity (44.1% versus 41.2%). The performance of the other four scores was similar (see Table 16). For a value of 4 or more points, the modified SAWBPIL score (SAWBPIL-CT1.0) achieved a sensitivity of 89.7% and a specificity of 72.3% for predicting mortality from COVID-19.

Table 16 Sensitivity, Specificity, Negative Predictive Value, and Positive Predictive Value for the 6 scores.

Predictive Score	**OR**	**OR (95% CI)**	**S (%)**	**Sp (%)**	**NPV**	**PPV**	**p-Value**
SAWBPIL-CT0.5 ≥ 8	32.2	9.30-111.45	41.2	97.9	77.5	90.3	0.000
SAWBPIL-CT1.0 ≥ 8	36.31	10.51-125.48	44.1	97.9	78.4	90.9	0.000
SAWBPI-CT0.5 ≥ 6.5	22.59	9.05-56.37	45.6	96.4	76.8	87.2	0.000
SAWBPI-CT1.0 ≥ 7	22.77	8.51-60.88	41.1	97.0	75.5	88.1	0.000
SAWBPIL ≥ 7	16.73	6.48-43.19	42.6	95.7	77.6	82.9	0.000
SAWPI ≥ 6	22.76	8.50-60.88	41.1	97.0	75.5	88.1	0.000
SAWBPIL-CT1.0 ≥ 4	22.79	9.59-54.12	89.7	72.3	61	93.6	0.000

PPV = Positive Predictive Value. **NPV** = Negative Predictive Value. **OR** = Odds Ratio. **Sp** = Specificity. **S** = Sensitivity.

4. Discussion

The population evaluated in the present study had different characteristics from the original population from which the COVID-19 mortality risk score was derived. The original population had a predominance of older adults hospitalized in the medical service and intensive care unit, treated during the pandemic's first wave, and mainly diagnosed by a medical board and even by rapid antibody tests [8]. The population of the present study, in which the score above has been validated, had an average age of 54 years; the patients were hospitalized during the second wave of the pandemic between January and June of the year 2021, and they mainly were diagnosed through a rapid antigen test and even had confirmation with a molecular test.

The area under the curve for the validation cohort for the SAWBPIL and SAWBPI scores was even higher than the one obtained for derivation. A patient who met all the clinical alterations included in the scores would reach a maximum value of 19 points, and a person who did not have any of

them would have a score of zero for the SAWBPIL score and a maximum value of 16 points for the SAWBPI score. Between both extremes, a series of severity levels need to be identified.

Shang et al. [10] evaluated scoring systems to predict complications and death in patients with COVID-19. In a population of 2,529 patients with COVID-19, they retrospectively found the following mortality predictors: age, diabetes, coronary disease, decreased percentage of lymphocytes, procalcitonin levels, elevated C - C-reactive protein, urea, and increased D-dimer. They developed a scoring system called CSS, with a high discriminative capacity and an area under the curve of 0.919.

Another score with high predictive capacity is the HNC-LL developed by Xiao et al. in China [11]. It was created after evaluating 690 patients in 2020, with validation with 442 medical records. They used the presence of arterial hypertension, neutrophil count, C-reactive protein, lymphocyte count, and lactic dehydrogenase. The area under the curve obtained was 0.861 in the derivation cohort in Honghu City. Validation was carried out in the same hospital with an area under the curve of 0.871.

At higher levels of LDH, more excellent activity of the lesion and more significant lung damage have been described [13]. Unfortunately, this test was unavailable in nearly half of our patients, which limits its applicability.

In studies carried out in China, for example, it was found that values above 320 U/L of LDH [14] were significantly associated with higher mortality. A new finding was identified in our population: mortality risk was recognized when LDH levels raised above 880 U/L, with a slight increase if the patient had values between 520 and 879 U/L. Future studies must clarify if this difference is due to a higher tolerance to hypoxia in high-altitude populations or a change in the excretion or production of LDH related to altitude conditions.

The radiographic patterns identified in the chest CT scan can be used to increase the diagnostic accuracy of the risk scores. A bilateral lung compromise greater than or equal to 55% was identified as a risk factor for developing severe disease and death. The tomographic patterns associated with a higher risk of death were the crazy paving patterns and the septa thickening. Paradoxically, atelectasis was associated with more remarkable survival (11.8% versus 38.4%). This would be because the majority of cases of atelectasis (41.1%) were identified in tomography scans performed during the absorptive phase of the disease, compared to the instances in which atelectasis was not found, of which only 12.4% were found in the absorptive phase.

To ensure that all the patients in the study had COVID-19, only cases with CORADS 4 or more were accepted. Therefore, CORADS was not evaluated as a risk factor for mortality in this study.

An unexpected result was that bilateral consolidations were associated with lower mortality than unilateral consolidations. Patients with bilateral consolidations had an average pulmonary involvement of 53.06%, similar to the 52.26% of those who did not have them. Bilateral lung involvement was mainly due to ground glass or crazy paving-type lesions if no bilateral consolidations were identified. Furthermore, most patients with non-bilateral consolidations were primarily in the peak and progressive phase (94.5%), unlike those with bilateral consolidations, where only 67.5% were in the peak phase, and 19.8% were already in the absorption or resolution phase.

When evaluating the chest CT scan characteristics associated with more significant mortality, three findings showed greater association: the percentage of lung compromised, the presence of crazy paving (also known as crazy cobblestone pattern), and the presence of septa thickening.

Septa thickening may be related to vascular congestion and cardiovascular deterioration [15], a highly recognized sign in acute cardiogenic pulmonary edema cases. When evaluating the crazy

paving pattern, it was found that it did not help improve the predictive capacity of SAWBPI and SAWBPIL scores since it was frequently seen in survivors.

Reviewing the chest CT scan patterns in detail, it was observed that there was a relationship between the percentage of lung involvement and the presence of thickening of the septum. Septal thickening occurred in both the deceased and the survivors. Still, it was noticed that in survivors, septal thickening did not increase mortality as long as the percentage of lung involvement was below 55%. For this reason, the presence of septal thickening was added as a risk variable only if the patient had a compromise on the chest X-ray greater than or equal to 55%, with which two new scores were obtained, one for SAWBPIL score (SAWBPIL-CT1.0) and another for SAWBPI score (SAWBPI-CT1.0).

Both new scores included determining the percentage of lung involvement with cut-off points at 55%, 70%, and 90%, as well as the presence or absence of septal thickening. With this modified score, the area under the curve of the SAWBPI score rose to 0.898, with a confidence interval that went from 0.854 to 0.941, while the SAWBPIL score raised its location under the curve to 0.903, with a confidence interval that ranged from 0.860 to 0.945. The addition of these chest CT scan findings has dramatically increased the predictive capacity of both scores studied.

When comparing the results obtained with other risk scores, differences were observed in the selected variables—the CANPT score, developed by Y. Chen in China [5] was tested in 582 patients and showed an area under the curve of 0.841 with a sensitivity of 89.6% and a specificity of 59.4%. When performing the corresponding validation, the score maintained its good predictive capacity at 0.85. The variables considered by the CANPT index are the presence of comorbidities, a temperature of 38.5°C or higher, an elevated neutrophil/lymphocyte ratio, decreased platelets, decreased albumin, increased total bilirubin, increased creatinine, and CPK (creatine phosphokinase) levels. This score is a little more difficult to apply because all these analyses are not routinely done in Perú.

Compared to the CALL score, the performance of our score was also superior, as was the case with the CANPT. The CALL score was developed in China and considers age over 60, lactic dehydrogenase (LDH) over 500 U/L, decreased lymphocytes below 1000, and at least one associated comorbidity as risk factors. With the severity of COVID-19 [16, 17]. The area under the curve originally found was 0.91 when Tong Ji developed the score, but when it was validated in a Turkish population, the area under the curve decreased to 0.59 [18]. The CALL score also decreased its predictive capacity when it was validated in a Chinese population, decreasing its area under the curve to 0.768.

Another group of Chinese researchers evaluated the CAN score, which assesses the values of creatine phosphokinase, creatinine, albumin, and the neutrophil/lymphocyte index. The performance of this score in Chen's study [5] was lower than the CANPT score and the CALL score, reaching an area under the curve of 0.766; for that reason, this score was preferred to those previously mentioned. Our score had a greater precision than the indicated scores.

Alhambra in Kuwait [19] developed a new severity score that was externally validated in a population in Italy. Its derivation population was 417 patients, and the validation population consisted of 923 patients. As risk factors, the presence of asthma and the elevation of glucose above 126 and 200 mg/dL were considered, as well as male gender and not being born in Kuwait. The researchers found an area under the curve of 0.901. When internal validation in Kuwait was performed, the area under the curve fell to 0.826. When external validation was done in Italy, the

area under the curve fell even more, reaching 0.687. Although that study had an excellent predictive capacity, it showed two problems. The first was the large drop in performance of the score when applied to a population outside Kuwait; the second was its components. Since one of the variables was not being a citizen of Kuwait, to which 2.5 units were assigned in the score, all patients in other countries would already have two points of severity. The second problem found was that the male sex was included as a risk factor. In contrast, in our derivation cohort, it was found not to have a great association with mortality and, therefore, was not included in our predictive score. As for asthma, it is known that in high altitude populations, its rate is singularly low and when patients wheeze above 3000 masl it is more likely that they have a chronic obstructive pulmonary disease or heart failure than asthma. For this reason, due to the rarity of this finding, it was not included in the study.

Even though type II diabetes mellitus is associated with greater severity of COVID-19 and a higher risk of mortality, the association in our derivation cohort lost strength in the multivariate analysis, which is why it was withdrawn from the scheme. In this case, none of the Kuwaiti score variables are part of our score, and it is unlikely they can be successfully applied in our country.

A research group from Brescia [20], the Italian city where the first COVID-19 severity score was developed, combined radiological and clinical data, developing a severity assessment system for COVID-19 based on machine learning [21]. In that severity score, the levels of neutrophils, eosinophils, basophils, ferritin, C-reactive protein, fibrinogen, lactic dehydrogenase, and D-dimer, as well as certain pulmonary radiological characteristics were determined. The score obtained was called BS-ENM and had an area under the curve of 0.98, which decreased when it was validated, down to 0.83; that is, the validation performance of that highly complex score was inferior to that of our study.

The CCEDRRN [22] score, an acronym for the so-called Canada COVID-19 Emergency Department Rapid Response Network Study, was developed through a large population-based, multicenter study that included 2,100 patients in the referral cohort and 7,400 patients. in the validation cohort, totaling 8761 patients. The variables identified were age, sex, chest pain, severe liver disease, respiratory rate, and the level of respiratory support, the latter detailing whether the patient was intubated or not or if mechanical ventilation was used. The area under the curve in the derivation and validation cohorts was 0.92, higher than our study. A score of 6 in the CCEDRRN identified a low-risk patient with a negative predictive value of 99.9%; that is, it identified a patient who could be treated on an outpatient basis and referred home. The variables used for the score can be easily quantified and therefore, CCEDRRN could be an essential alternative to the score obtained by our research group.

The SEIMC score [23] was developed in 127 Spanish hospitals, with 4035 patients in its derivation cohort and 2126 patients in its validation cohort. The area under the curve found in the derivation cohort was 0.822, which increased to 0.842 in the validation cohort. The variables studied for the development of this score were age, neutrophil/lymphocyte ratio, age-adjusted oxygen saturation, glomerular filtration rate, presence or absence of dyspnea, and male gender. SEIMC score showed an area under a very similar curve, although lower than ours, and used, like other studies, the neutrophil/lymphocyte index. The approach of using age-adjusted oxygen saturation is entirely novel. It could also be adapted to our high-altitude environment since there are studies in which age-adjusted oxygen saturation has been calculated according to altitude levels [8]. The glomerular filtration rate would be more challenging to determine since it would involve a creatinine clearance

study. Male gender is also included in the SEIMC score, but, as was mentioned before, even though most hospitalized patients are male, gender is not universally associated with COVID-19 mortality.

5. Conclusions

Two prognostic scores were validated, SAWBPI with nine components and SAWBPIL with ten clinical data, which initially predicted the risk of death from COVID-19 with a global precision of 82.6% and 83.8%, respectively. When both scores were externally validated, the diagnostic accuracy of SAWBPI decreased to 82.2%, and SAWBPIL's rose to 84.3%. When compared with the CALL score (China) [16, 17], the CAN scale (China) [5], and Alhamarˈs score (Kuwait) [19], the performance of both scores was superior. Both new scores had a similar clinical precision as CANPT Score (China) [5], SEIMC (Spain) [23] and Brescia scale (Italy) [20], but were inferior to CCEDRRN (Canada) [22].

Using data from chest CT scan images, a maximum of 2 points were added for bilateral lung compromise greater than 55% with thickening of the septum. With that addition, the area under the precision increased to 90.3% for SAWBPIL, obtaining the SAWBPIL-CT1.0 score, and up to 88.4% for SAWBPI, obtaining the SAWBPI score, which does not include LDH values.

Considering that the external validation was successful, both scores can be used in clinical practice to evaluate the severity of COVID-19 patients. Those individuals with a SAWBPI-CT1.0 score of 2 units or less can be classified as low risk. They would be observed in the emergency room for 24 to 48 hours (less than 2% mortality). At the same time, those with 4 or more points would have a mortality risk more significant than 80% and should receive intensive management in the hospital.

In hospitals that do not have a CT scanner, the SAWPIL score may be used, and if the health center does not have LDH dosing, the SAWPI score will be used.

The diagnostic accuracy of predictive scores varies by country due to ethnic, epidemiological, and climatic differences. For this reason, although it is true that SAWBPIL-CT1.0 and SAWBPIL scores have proven to be helpful in evaluating COVID-19 severity in the Peruvian population, the scores developed abroad should be tested in the same population, just as the new scores could be prospectively assessed in other countries.

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Author Contributions

The idea of the manuscript was planned by WCG. The basic literature was brought together, and the first draft was prepared by KPS, MCA, and GTS. KPS and GTS collected and compiled the information. WCG edited the final draft and MCA, KPS, and GTS approved the final version of the manuscript. All the authors have read and approved the submission of the manuscript.

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Competing Interests

The authors have declared that no competing interests exist.

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