Heliyon 10 (2024) e39976

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Novel tools for evaluating COVID-19 at the emergency department: Surfactant protein D level and CHARISMA score

Aykut Yucal [a,*], Mustafa Burak Sayhan [a], Ömer Salt [b], İlker Dıbırdık [c], Sinem Çalın [c]

[a] Trakya University School of Medicine, Department of Emergency Medicine, Edirne, Turkey
[b] Kayseri City Hospital, Department of Emergency Medicine, Kayseri, Turkey
[c] Trakya University School of Medicine, Department of Medical Biochemistry, Edirne, Turkey

ARTICLE INFO

Keywords:
Surfactant protein D
CHARISMA score
COVID-19
Pulmonary infiltration area
Quantitative volume measurement

ABSTRACT

Objectives: To investigate the serum surfactant protein D (SP-D) level required to determine the diagnosis and prognosis of coronavirus disease 2019 (COVID-19), and create a new scale for disease prognosis prediction.
Methods: This study was conducted among 64 patients with COVID-19 symptoms and 16 healthy volunteers. The participants were assessed by comparing "Controls/Patients", "PCR-negative/PCR-positive", "Simple COVID-19/Acute respiratory distress syndrome (ARDS)-accompanied COVID-19", "Mild ARDS/Moderate-severe ARDS", and "Survived/Dead" subgroups. Serum SP-D levels and pulmonary infiltration area (volume and percentage) measurements on CT were compared between the groups. A new scale, the "CHARISMA Score", was created by logistic regression method for a complete prognosis assessment. This includes confusion, heart rate, age, respiratory rate, percentage of infiltration on CT, serum SP-D level, mean arterial pressure and SaO_2.
Results: Serum SP-D levels differed significantly across the groups. There was a strong correlation between SP-D levels and infiltration volumes. CHARISMA scores were higher in the severe than in the mild ARDS group and in patients who died than in survivors. In the receiver operating characteristic curve analysis of the CHARISMA scores, a cutoff value of 4 indicated mortality.
Conclusion: Serum SP-D levels can be used to determine COVID-19 diagnosis and prognosis, and the CHARISMA score can be used to predict prognosis and mortality risk in patients with COVID-19 pneumonia.

1. Introduction

Surfactants are complex molecules containing key proteins and phospholipids located on the surface of the alveoli. They are synthesized by type-2 pneumocytes, and they reduce surface tension, facilitate diffusion, prevent alveolar collapse, and play a role in host defense. Surfactants are categorized into four subtypes: the hydrophilic group, including surfactant protein A (SP-A) and surfactant protein D (SP-D); and the hydrophobic group, including surfactant protein B (SP-B) and surfactant protein C (SP-C). SP-A and SP-D are both active in the immune system. SP-D synthesis increases in cases of infection and lung injury. SP-D allows pathogens to be

* Corresponding author. Trakya University School of Medicine, Department of Emergency Medicine, Specialist M.D, Edirne, Turkey.
E-mail addresses: dr.aykutyucal@gmail.com (A. Yucal), mustafaburak@yahoo.com (M. Burak Sayhan), dromersalt@gmail.com (Ö. Salt), ilkerdibirdik@trakya.edu.tr (İ. Dıbırdık), sinem.calin@gmail.com (S. Çalın).

https://doi.org/10.1016/j.heliyon.2024.e39976
Received 21 May 2024; Received in revised form 29 September 2024; Accepted 29 October 2024
Available online 7 November 2024

recognized and neutralized by macrophages and neutrophils. Normally, the alveolocapillary membrane acts as a tight barrier for SP-D. However, in lung injuries, the barrier is disrupted, causing SP-D to be present in the serum. SP-D has been studied as a marker, especially for coronavirus disease 2019 (COVID-19); however, there is no clear consensus, and no efficient scale of clinically significant serum levels has been determined [1–3].

COVID-19, caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), was declared a pandemic by the World Health Organization on March 11, 2023. The most common complication of COVID-19 is acute respiratory distress syndrome (ARDS) due to pneumonia, and rapid diagnosis and treatment of patients with ARDS, which has high mortality and morbidity rates, is critical. A reverse transcriptase polymerase chain reaction (RT-PCR) test is used to diagnose COVID-19; however, its requirements, sensitivity, and cost have led to research into alternative methods. Several clinical and radiological scoring tools are used for COVID-19. Radiological scoring may predict prognoses but can be subjective. However, using computed tomography (CT) interface software can yield more objective results through direct measurement of lesion volumes [4–9].

In this study, we aimed to evaluate the relationship between COVID-19 pneumonia infiltration sizes (quantitative volume and percentage measurement) and serum SP-D levels, which, to our knowledge, has not been previously examined. We also aimed to evaluate the significance of serum SP-D levels in the diagnosis of COVID-19 and the significance of the CHARISMA (C, Confusion; H, Heart rate; A, Age; R, Respiratory rate; I, Percentage of infiltration on CT; S, Serum SP-D level; M, Mean arterial pressure; and A, peripheral blood oxygen saturation [SaO_2] at admission) score, which was developed based on our results, in predicting COVID-19 prognoses and in-hospital mortality risks. In addition, the reason for investigating such a scoring system is that current diagnostic methods lack a universally applicable diagnostic tool that reflects the severity of lung injury with both radiologic, biochemical and clinical measurement results.

2. Methods

This was a single-center, cross-sectional, prospective methodological study. This study was conducted on a sample of 80 people, including 64 patients without any comorbidities who visited the emergency department with COVID-19 symptoms between August 15, 2022, and February 15, 2023, and 16 healthy volunteers without any symptoms.

The inclusion criteria were as follows: age >18 years, approval and signature of a written informed consent form by the participant or legal guardian, absence of comorbid diseases, and absence of pregnancy.

2.1. Design of groups

The participants were divided into five subgroups as follows.

- The first subgroup comprised the total study population (n = 80) classified as patients with respiratory tract infection (RTI) symptoms (n = 64) and healthy individuals (n = 16): the "Healthy Control" and "RTI Patients" groups, respectively.
- The second subgroup comprised patients with RTIs (n = 64) classified as those with positive PCR test results (n = 50) and those with negative PCR test results (n = 14): the “PCR(−)” and “PCR(+)” groups, respectively.
- The third subgroup comprised PCR(+) patients (n = 50) classified as those with simple COVID-19 (n = 19) and those with COVID-19 with ARDS (n = 31): The "Simple COVID" and "ARDS(+) COVID" groups, respectively.
- The fourth subgroup comprised PCR(+) patients (n = 50) classified as survivors (n = 37) and non-survivors (n = 13): the "Survived" and "Dead" groups, respectively.
- The fifth subgroup comprised patients with COVID-19 (n = 31) who developed ARDS classified as those with mild ARDS (n = 17) and those with moderate/severe ARDS (n = 14): the "Mild ARDS" and "Moderate/Severe ARDS" groups, respectively.

In the first two subgroups, we investigated whether SP-D levels had a diagnostic value in patients with RTIs or COVID-19. Other group comparisons were made in terms of serum SP-D levels, and clinical and radiological parameters.

Serum SP-D levels, infected tissue volumes on thoracic CT, and vital signs were used to create a new clinical scale that could be used to evaluate patients in the emergency department more effectively. While creating the scale, firstly univariate analysis was performed on the parameters that may be valuable for mortality. Then, multivariate analysis was performed for the significant variables. Since the sample size was small, the effectiveness of the model was tested for larger samples with the bootstrapping method. 5 alternative regression models were created and compared with each other. Considering diagnostic value, complexity and appropriateness, Model 1 was identified as the most appropriate clinical scale candidate. We named this scale, which we created using the logistic regression model, the CHARISMA Score. The scale includes the following parameters: C, confusion; H, heart rate; A, age; R, respiratory rate; I, infiltration percentage on thoracic CT; S, serum SP-D level; M, mean arterial pressure; and A, admission SaO_2. This scale was compared with other scales available in the literature regarding disease prognosis and in-hospital mortality risk prediction.

2.2. Data collection

The demographic and clinical characteristics of the participants were recorded. The clinical severity scores, CT severity scores, radiographic severity scores, and serum SP-D levels were recorded.

Measurement of SP-D Levels: Serum SP-D levels were determined using enzyme-linked immunosorbent assay (ELISA) methods in a biochemistry laboratory. The Human SP-D ELISA Kit (Catalog no: ELK1072) (ELK Biotechnology CO. Ltd. Denver, USA), with a

detection range of 0.63–40 ng/mL, was used for the procedure. Venous blood samples were collected from all patients. After clotting for 2 h, the mixture was centrifuged at 1000 rpm for 20 min. The serum SP-D levels of 80 samples were recorded.

Measurement of Imaging Data: The SIEMENS SOMATOM Definition AS 128 CT Scanner (SIEMENS AG, Munich, Germany), with a slice thickness of 5 mm, and Shimadzu Radspeed R-300 UL Collimator (566-10100-04) (Shimadzu Corporation, Kyoto, Japan) were used for the radiographic imaging. The SECTRA IDS7® PACS, v25.1 system (SECTRA AB, Linköping, Sweden) was used for the evaluation of imaging results. All patient data were collected using the Enlil® v3.23.01.1_20230116 system (Mergen Software Inc. Eskisehir, Turkey). Visual assessment scores and quantitative volume measurement results from the CT and radiographic data were evaluated by three experienced physicians who were blinded to the study. The physicians determined the lesion and lung borders for each patient separately using the radiologic data management system and performed a computer-based volume measurement assessment (infiltration volume and percentage) based on the contrast difference with the surrounding tissues. The results obtained by the three physicians were compared. The means of these data, which showed no significant differences, were calculated and recorded separately for each patient.

2.3. Statistical analysis

Data were statistically evaluated using Statistical Package for the Social Sciences (SPSS) v22.0 (IBM Corp., Armonk, NY, USA) and Python programming language (version 3.12.0, Python Software Foundation, USA). Distribution analysis for continuous variables was performed using the Kolmogorov–Smirnov test. Categorical data are presented as numbers (n) and percentages (%), normally distributed continuous data as means ± standard deviations (SDs), and non-normally distributed continuous data as medians (minimum–maximum). Relationships between categorical variables were analyzed using the chi-squared test. Differences between continuous variables were analyzed using the Mann–Whitney *U* test and the independent samples *t*-test, according to appropriateness.

Table 1
Comparisons of study groups and ROC analyses of serum SP-D levels.

Group Comparisons							
Parameters	**Study Groups**				**Patient Groups (RTI)** *(for COVID-19 Diagnosis)* **(n = 64)**		
	Total (n = 80)	**Control Group** *(Healthy Volunteers)* **(n = 16)**	**Patient Group (RTI)** *(Symptomatic Patients)* **(n = 64)**	**p**	**PCR (−) Group (n = 14)**	**PCR (+) Group (n = 50)**	**p**
Age (years)	57,4 ± 14,5	55,8,0 ± 6,2	57,7 ± 15,9	0,45[a]	58,9 ± 9,7	61,2 ± 15,6	0,078[a]
Sex Female	33 (41,3)	7 (43,8)	26 (40,6)	0,820[b]	13 (43,3)	20 (40,0)	0,769[b]
Male	47 (58,8)	9 (56,3)	38 (59,4)		17 (56,7)	30 (60,0)	
Temperature (°C)	37,5 ± 0,7	36,5 ± 0,2	37,8 ± 0,5	**<0,001**[a]	37,1 ± 0,7	37,8 ± 0,6	**<0,001**[a]
MAP (mmHg)	85,4 ± 14,5	97,8 ± 4,4	82,3 ± 14,5	**<0,001**[a]	98,9 ± 5,4	77,3 ± 12,0	**<0,001**[a]
Respiratory Rate (/min)	23,7 ± 11,4	12,6 ± 1,5	26,5 ± 11,1	**<0,001**[a]	12,7 ± 1,5	30,3 ± 9,4	**<0,001**[a]
Heart Rate (bpm)	95,9 ± 21,9	79,2 ± 3,0	102,7 ± 19,2	**<0,001**[a]	73,4 ± 5,4	109,5 ± 16,0	**<0,001**[a]
O_2 Saturation (%)	90,7 ± 7,5	97,8 ± 0,8	88,9 ± 7,3	**<0,001**[a]	97,4 ± 1,3	86,7 ± 6,7	**<0,001**[a]
SP-D (ng/mL)	16,8 ± 8,7	6,89 ± 0,6	19,3 ± 7,9	**0,001**[a]	7,5 ± 1,3	22,2 ± 6,3	**<0,001**[a]

Evaluation of Serum SP-D Levels in Subgroups											
Groups	**Group Comparisons**		**ROC Analysis**								
	SP-D (ng/mL) (mean ± SD)	**p**[a]	**Cut-off value (ng/mL)**	**AUC**[c]	**95 % CI**	**SE (%)**	**SP (%)**	**PPV (%)**	**NPV (%)**	**+LR**	**-LR**
Control (n:16)	6,89 ± 0,6	**0,001**	7,74	0,997	0,948–1000	100	96,9	88,9	100,0	32,0	0,0
Patient (n:64)	19,3 ± 7,9										
PCR(−) (n:14)	7,5 ± 1,3	**<0,001**	11,12	0,997	0,948–1000	96,0	100	100	93,7	6,7	0,05
PCR(+) (n:50)	22,2 ± 6,3										
Simple COVID (n:19)	16,4 ± 3,0	**0,001**	19,53	0,986	0,904–1000	93,6	94,7	96,7	90,0	17,8	0,07
ARDS + COVID (n:31)	25,8 ± 4,9										
Mild ARDS (n:17)	22,3 ± 2,5	**0,001**	25,91	0,966	0831-0,999	85,7	94,1	92,3	88,9	14,6	0,2
Severe/Moderate ARDS (n:14)	29,9 ± 3,7										
Survived (n:37)	19,5 ± 4,3	**0,001**	25,69	0,956	0,858–0,994	84,6	91,9	78,6	94,4	10,4	0,2
Dead (n:13)	30,0 ± 3,9										

[a] independent samples *t*-test.
[b] chi-squared test, **SP-D:** surfactant protein D; **MAP:** mean arterial pressure; **ARDS:** acute respiratory distress syndrome.
[c] :ROC analysis; **AUC:** area under the curve; **95 % CI:** 95 % confidence interval; **SE:** sensitivity; **SP:** specificity; **PPV:** positive predictive value; **NPV:** negative predictive value; **LR:** likelihood ratio. **SD:** standard deviation. **Note:** Data in the table are expressed as means ± standard deviations and n (%) as applicable.

Pearson's and Spearman's correlation tests were used to determine the relationships between continuous parameters. The discrimination of the parameters was made using receiver operating characteristic (ROC) curve analysis. Sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios were calculated for each parameter. The predictive value for the

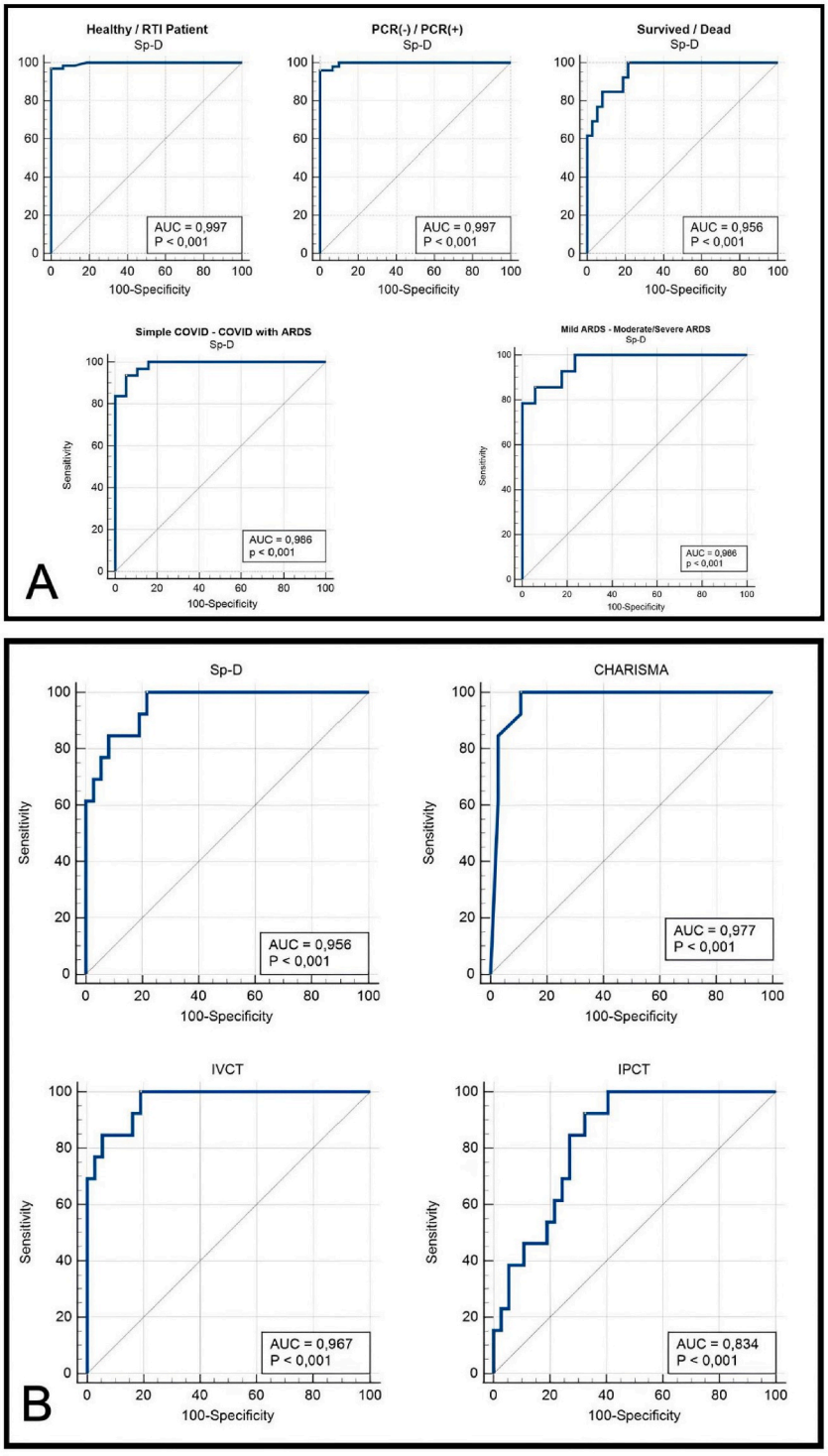

Fig. 1. A: Receiver operating characteristic (ROC) curves of serum surfactant protein D (SP-D) levels according to discrimination between groups. **B:** ROC analyses of SP-D levels, infiltration volume on computed tomography (IVCT), infiltration percentage on CT (IPCT), and CHARISMA scores for the risk of in-hospital mortality.

analysis was determined using the Youden index. MedCalc® v20.015–64 bit (MedCalc Software Ltd, Ostend, Belgium) was used for the ROC curve analyses. Binary logistic regression analysis was performed to determine whether SP-D levels and other significant parameters were independent predictors of mortality risk and to identify new scale models that could be used in this regard. Because of the small sample size, bootstrapping was used to increase the reliability of the results. Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), log-likelihood, nagelkerke R^2 and ROC analysis of the 5 models were performed for comparison. In order to determine the prediction error level of the CHARISMA score, the sample size was increased to 1000 by first applying an expansion simulation. Cross-validation analysis was performed on this sample. The scale was found to be quite successful with an average error of 2 %. Statistical significance was set at $p < 0.05$.

3. Results

3.1. Diagnostic and prognostic value of SP-D levels

Serum SP-D levels, clinical data, and pneumonia severity scores were analyzed in all subgroups. The mean age of the participants was 57.4 years with a standard deviation (SD) of 14.5 years, and more than half were male (58.8 %). The mean serum SP-D level of the total study population was 16.8 ng/mL with a standart deviation of 8.7 ng/mL. Serum SP-D levels were higher in patients with symptomatic RTIs and those with positive PCRs ($p < 0.05$) than in their respective counterparts. Serum SP-D levels, demographic data, and vital signs were compared between the groups to evaluate the diagnostic significance of serum SP-D levels (Table 1).

Serum SP-D levels were higher in symptomatic patients, PCR-positive patients, COVID-19 patients with ARDS, patients with severe/moderate ARDS, and patients who died than in their respective counterparts. The ability of using SP-D levels to discriminate between groups was evaluated using ROC analysis (Fig. 1). ROC analyses of serum SP-D levels according to cut-off values, areas under the curve (AUCs), confidence intervals, sensitivity, specificity, negative and positive predictive values, and likelihood ratios between the groups are shown in Table 1.

3.2. Radiological measurement comparisons

The mean radiological severity scores and quantitative lesion volume measurements, which were calculated separately by three experienced physicians in patients with COVID-19, were compared. However, no significant difference was observed ($p > 0.05$) (Supplementary Table).

3.3. Correlation of serum SP-D levels with other clinical parameters

Serum SP-D levels were found to correlate with other pneumonia severity scales and laboratory parameters used to predict the prognosis of COVID-19 pneumonia ($p < 0.05$) (Table 2). In the correlation analysis, moderate positive correlations were observed between serum SP-D levels and age, chest CT scores (CCTS), troponin levels, lactate levels, infiltration percentages on CT (IPCT), body temperatures, respiratory rates, and heart rates, while moderate negative correlations were found with MAP (mean arterial pressure) and SaO_2. The parameters that exhibited high positive correlations with serum SP-D levels are presented in Table 2.

3.4. Evaluating the novel clinical severity score: CHARISMA

We aimed to create a new scale that could better indicate mortality risk and disease severity in patients as well as the need for hospitalization, in addition to serum SP-D levels. Parameters that were significant predictors of in-hospital mortality risk were included in the binary logistic regression analysis. Although infiltration volume on computed tomography (IVCT) was found to be a strong predictor alone, it was excluded from the model because it showed a high correlation with serum SP-D levels and other parameters ($r = 0.960$); the IPCT, which showed a low correlation, was used instead.

Firstly, univariate regression analysis was performed. Gender was not significant in predicting mortality ($p > 0.05$). Heart rate, SaO2, serum SP-D level, respiratory rate, IPCT, MAP, confusion and age variables were significant for mortality prediction ($p < 0.05$). Multivariate regression analysis was then performed using these variables and possible regression models for the scale were created. Due to the small sample size, bootstrapping was used to evaluate the reliability and standard deviation of the values. Regression analysis was also performed on the expanded sample of 1000 people by bootstrapping. The results showed no significant difference between the normal and expanded sample analyses. These 5 regression models were compared in regard to compatibility, complexity and diagnostic value. In mortality prediction, model 1 has the highest diagnostic value. (AUC:0.977) Although model 1 was found to be the most complex model in the complexity analysis, there is no significant difference between it and other models in terms of BIC value. ($\Delta BIC<2$) In addition, we also performed a 5 fold cross-validation analysis for Model 1 on a bootstrapped sample of 1000 individuals to assess the risk of over/underfitting and generalizability. And the average error of model 1 was 2.1 % on the training dataset and 2.3 % on the test dataset. So it showed a very successful stability and generalizability performance. As a result of these evaluations, Model 1 was accepted as the main scale and named as “CHARISMA Score” by using acronym to improve memorability. The β regression coefficients and odds ratios were taken into account to determine the scoring criteria of the scale components; as there was no significant difference between the variables, each criterion was given an equal score of 1 point. All these scale building stages are given in Table 2 as detailed.

The results were then compared with those from other parameters in terms of disease severity and in-hospital mortality risk

Table 2
The CHARISMA Score Correlation and regression analysis of serum SP-D levels with other prognostically valuable parameters; the formation of CHARISMA score.

Correlation Analysis Between SP-D Levels and Other Parameters

	r	p		r	p		r	p
IVCT (cm^3)	0,960	**0,001**[c]	**A-DROP**	0,885	**0,001**[c]	**Age**	0,555	**0,034**[b]
NEWS2	0,954	**0,001**[c]	**REA-ICU**	0,807	**0,001**[c]	**SaO_2 (%)**	−0,526	**0,032**[b]
qSOFA	0,943	**0,001**[c]	**RALE**	0,803	**0,001**[c]	**Temperature (°C)**	0,482	**0,001**[b]
CURB-65	0,940	**0,001**[c]	**CTSS**	0,784	**0,001**[b]	**IPCT (%)**	0,479	**0,015**[b]
CRB-65	0,931	**0,001**[c]	**TSS**	0,766	**0,001**[b]	**Respiratory Rate(b/min)**	0,478	**0,039**[b]
CORB	0,925	**0,001**[c]	**BNP (pg/mL)**	0,729	**0,001**[b]	**Lactate (mg/dl)**	0,444	**0,001**[b]
PSI	0,906	**0,001**[b]	**BRIXIA**	0,704	**0,001**[b]	**Heart Rate (bpm)**	0,423	**0,042**[b]
SCAP	0,889	**0,001**[c]	**CCTS**	0,691	**0,001**[b]	**MAP (mmHg)**	−0,412	**0,043**[b]
SMART-COP	0,889	**0,001**[c]	**Troponin (ng/L)**	0,690	**0,001**[c]	-	-	-

Logistic Regression Analysis of a Model with 8 Variables for Mortality

Variables	**Univariate Regression Analysis**				**Multivariate Regression Analysis**									
					Normal Sample Analysis (n:50)					Bootstrapping Method Analysis (n:1000)				
	β	**OR**	**CI**	**p**[a]	**β**	**SD**	**OR**	**CI**	**p**[a]	**β**	**SD**	**OR**	**CI**	**p**[a]
Sex (female)	0,05	0,99	0,97-1,04	0,66	–	–	–	–	–	–	–	–	–	–
Heart Rate (>118 b/min)	0,746	2,12	1,5-3,1	0,001	0,427	0,09	1,51	1,27-1,79	0,033	0,413	0,08	1,52	1,19-1,82	0,036
SaO_2 (≤84 %)	0,701	2,01	1,47-2,79	0,001	0,403	0,09	1,49	1,20-1,82	0,027	0,399	0,07	1,47	1,18-1,9	0,026
Serum SP-D Level (≥25 ng/mL)	0,682	1,98	1,43-2,82	0,004	0,395	0,06	1,43	1,71-1,92	0,031	0,392	0,07	1,39	1,16-1,95	0,035
Respiratory Rate (>35 b/min)	0,642	1,92	1,35-2,68	0,005	0,378	0,09	1,38	1,18-1,69	0,036	0,375	0,1	1,37	1,15-1,74	0,039
IPCT (>23 %)	0,611	1,86	1,30-2,53	0,01	0,362	0,1	1,34	1,13-1,71	0,039	0,361	0,12	1,35	1,16-1,77	0,039
MAP (≤74 mmHg)	0,599	1,82	1,23-2,42	0,016	0,344	0,12	1,30	1,10-1,73	0,04	0,342	0,11	1,32	112-1,74	0,041
Confusion (yes)	0,582	1,79	1,24-2,29	0,02	0,327	0,09	1,29	1,11-1,56	0,041	0,326	0,1	1,30	1,10-1,63	0,042
Age (>65 years)	0,549	1,73	1,13-2,21	0,023	0,319	0,13	1,27	1,09-1,49	0,043	0,318	0,14	1,28	1,10-1,57	0,044
Constant (Model 1)	–	–	–	–	1,22	0,14	3,16	1,51-4,57	0,034	1,2	0,16	3,12	1,54-4,74	0,033

Comparison of Regression Analysis Models

Models	**AIC**	**BIC**	**Log-Likelihood**	**Nagelkerke R^2**	**ROC**		
					AUC	**Sensitivity**	**Specificity**
Model 1	140,4	149,2	−63,1	0,431	0,977	100	89,2
Model 2	139,7	148,7	−62,3	0,362	0,843	86,1	85
Model 3	139,5	148,5	−61,8	0,347	0,821	87,4	77,8
Model 4	139,2	148,2	−61,2	0,321	0,793	83,6	76,2
Model 5	138,8	147,7	−60,2	0,314	0,782	79,5	75,3

CHARISMA Score (min=0; max=8 points) (Model 1)

Acronym	**Parameters**	**β**	**OR**	**Point**
C	Confusion (Yes)	0,33	1,30	1
H	Heart Rate >118 b/min	0,41	1,52	1
A	Age >65 years	0,32	1,28	1
R	Respiratory Rate >35 b/min	0,38	1,37	1
I	Infiltration percentage on thorax CT > 23 %	0,36	1,35	1
S	Serum SP-D level ≥25 ng/mL	0,39	1,39	1
M	MAP ≤74 mm/Hg	0,34	1,32	1
A	Admission SaO_2 ≤ 84 %	0,40	1,47	1

5-Fold Cross-Validation Results (Training ve Test) for Bootstrapped Sample Data

Folds	**Training Data Set**					**Test Data Set**				
	Data Size	**ROC**			**Average Error(%)**	**Data Size**	**ROC**			**Average Error(%)**
		AUC	**Sen(%)**	**Spe(%)**			**AUC**	**Sen(%)**	**Spe(%)**	
1	800	0,980	97,5	90,2	2,0	200	0,975	98,0	89,0	2,5
2	800	0,979	97,0	89,8	2,1	200	0,978	96,5	89,2	2,2

(*continued on next page*)

Table 2 (*continued*)

5-Fold Cross-Validation Results (Training ve Test) for Bootstrapped Sample Data										
Folds	**Training Data Set**					**Test Data Set**				
	Data Size	**ROC**			**Average Error(%)**	**Data Size**	**ROC**			**Average Error(%)**
		AUC	**Sen(%)**	**Spe(%)**			**AUC**	**Sen(%)**	**Spe(%)**	
3	800	0,978	97,2	89,7	2,2	200	0,977	97,0	89,3	2,3
4	800	0,979	97,3	90,0	2,1	200	0,976	98,5	88,9	2,4
5	800	0,977	97,1	89,5	2,2	200	0,978	97,5	89,1	2,2
Average	–	0,978	97,2	89,8	2,1	–	0,977	97,5	89,1	2,3

- Model 1: SP-D + IPCT + SaO2+ Heart Rate + Respiratory Rate + MAP + Confusion + Age.
- Model 2: SP-D + IPCT + SaO2+ Heart Rate + Respiratory Rate + MAP.
- Model 3: SP-D + IPCT + SaO2+ Heart Rate + Respiratory Rate.
- Model 4: SP-D + SaO2+ Heart Rate.
- Model 5: SP-D + IPCT.

[a] Binary logistic regression test, **β:** beta regression coefficient, **SD:** Standard Deviation, **CI:** Confidence Interval, **OR:** odds Ratio, **SP-D:** surfactant protein D.

[b] Pearson's correlation test.

[c] Spearman's correlation test; **r:** correlation coefficient; **AIC:** Akaike Information Criterion; **BIC:** Bayesian Information Criterion; **ROC:** Receiver Operating Characteristic; **AUC:** Area Under the Curve; **IPCT:** infiltration percentage on computed tomography; **IVCT:** infiltration volume on computed tomography, **TSS:** total severity score, **CTSS:** computed tomography-severity score, **CCTS:** chest computed tomography score**, NEWS2:** National Early Warning Score 2, **PSI:** Pneumonia Severity Index, **qSOFA:** quick Sequential Organ Failure Assessment, **SCAP:** Severe Community-Acquired Pneumonia Score, **REA-ICU:** Risk Stratification of Early Admission to the Intensive Care Unit, **RALE:** Radiographic Assessment of Lung Edema, **MAP:** mean arterial pressure.

prediction. Patients with COVID-19 were grouped by disease severity and outcome, with no significant sex difference between the groups. The mean age was higher in patients whose COVID-19 progressed to ARDS, patients with moderate ARDS, and patients who died, compared with their respective counterparts. This finding was similar for serum SP-D levels, IVCT, IPCT, and CHARISMA scores. Comparisons of other clinical and radiological severity scores and vital parameters are presented in Table 3.

ROC analysis was used to discriminate the serum SP-D level, IVCT, IPCT, CHARISMA score, and other pneumonia severity scores in terms of in-hospital mortality risk (Fig. 1). The optimal cutoff values of all parameters and the AUC, sensitivity-specificity, negative-positive predictive values, and likelihood ratios determined according to these values are shown in Table 4. The CHARISMA score was the most predictive parameter for in-hospital mortality risk, with an AUC of 0.977. Points greater than four on this scale predicted the risk of in-hospital mortality, with 100 % sensitivity and 89.2 % specificity.

4. Discussion

The specificity of RT-PCR for the diagnosis of COVID-19 has been reported as 100 % in many studies, with a sensitivity of approximately 83 %. Thoracic CTs, radiography, and laboratory tests are also effective for both diagnoses and prognosis predictions. These methods are used for diagnostic evaluation and prognostic prediction in centers where RT-PCR tests cannot be performed [10, 11]. In the present study, we evaluated serum SP-D levels, which may be an alternative for the diagnosis and prognostic assessment of COVID-19 pneumonia. There are studies focusing on this point in the literature, but they have neither been comprehensively compared with other clinical and radiological severity scales of pneumonia nor evaluated together with the 3D (Three-Dimensional) volume measurement of the lesion on thoracic CTs, which is directly used to calculate the extent of damage/infiltration in the lung [12–14]. We aimed to evaluate the association between serum SP-D levels and infiltration volumes to understand the predictive power of this volume measurement for pneumonia severity and mortality, with the aim of creating a novel scale that could provide more significant results with the combination of these two datasets.

When SP-D is detected in the blood due to a leak from the alveolocapillary membrane, which is disrupted by lung damage, pulmonary damage may be indicated. Salvioni et al. [2] and Saito et al. [15] found that COVID-19 patients had higher serum SP-D levels than patients without COVID-19. In our study, serum SP-D levels were higher in the RTI (symptomatic patients) group than in the control (healthy volunteers) group. In addition, higher serum SP-D levels were detected in the PCR(+) RTI patients than in the PCR(−) patients. Based on these results, we suggest that serum SP-D levels may serve as a guide for evaluating lung damage caused by COVID-19 pneumonia.

COVID-19 pneumonia may progress to ARDS owing to massive lung damage. Previous studies have revealed that serum SP-D levels indicate the presence of lung damage due to COVID-19 and are associated with the severity of this damage. Saito et al. [15] reported a mean serum SP-D level of 61.9 ng/mL in patients with simple COVID-19 and 237 ng/mL in those with severe COVID-19 with ARDS. In the same study, patients with ARDS were divided into three groups: mild, moderate, and severe ARDS, with mean SP-D levels of 29.87 ng/mL, 32.67 ng/mL, and 55.04 ng/mL respectively. Similar to these studies, our study showed that serum SP-D levels significantly increased with the severity of ARDS. Based on these data, we believe that increased serum SP-D levels can be an effective biomarker for evaluating the severity of ARDS in patients with COVID-19 pneumonia, which may be supported by more comprehensive studies with larger case series in this field.

Table 3
Evaluation of important data on disease severity and prognosis.

Prognostic Comparison on COVID									
Parameters	Progression of COVID			Severity of ARDS			Mortality of COVID		
	Simple COVID (n = 19)	ARDS + COVID (n = 31)	p	Mild (n = 17)	Moderate/Severe (n = 14)	p	Survived (n = 37)	Dead (n = 13)	p
Age (years)	49,9 ± 12,4	68,1 ± 13,2	**<0,001**[a]	61,9 ± 14,4	75,6 ± 5,8	**0,002**[a]	56,7 ± 15,2	74,0 ± 7,6	**<0,001**[a]
Sex Female	9 (47,4)	11 (35,5)	0,405[c]	6 (35,3)	5 (35,7)	0,981[c]	15 (40,5)	5 (38,5)	0,895[c]
Male	10 (52,6)	20 (64,5)		11 (64,7)	9 (64,3)		22 (59,5)	8 (61,5)	
Temperature (°C)	37,9 ± 0,4	37,7 ± 0,6	0,077[a]	37,6 ± 0,7	37,8 ± 0,6	0,422[a]	37,8 ± 0,6	37,9 ± 0,5	0,471[a]
MAP (mmHg)	89,3 ± 8,9	69,9 ± 6,2	**<0,001**[a]	73,9 ± 2,7	65,1 ± 5,9	**<0,001**[a]	81,6 ± 10,6	65,2 ± 5,3	**<0,001**[a]
Respiratory Rate (b/min)	20,3 ± 5,3	36,4 ± 5,0	**<0,001**[a]	32,9 ± 3,7	40,6 ± 2,6	**<0,001**[a]	26,7 ± 8,2	40,4 ± 3,1	**<0,001**[a]
Heart Rate (b/min)	92,8 ± 8,9	119,7 ± 9,4	**<0,001**[a]	113,2 ± 4,7	127,6 ± 7,4	**<0,001**[a]	103,0 ± 12,9	127,9 ± 7,6	**<0,001**[a]
SaO_2 (%)	92,2 ± 1,9	83,4 ± 6,4	**<0,001**[a]	87,4 ± 3,5	78,4 ± 5,6	**<0,001**[a]	89,7 ± 3,9	78,3 ± 5,9	**<0,001**[a]
PSI	78,9 ± 27,2	169,7 ± 47,2	**0,001**[a]	136,0 ± 32,8	210,6 ± 22,9	**0,001**[a]	111,3 ± 48,3	203,2 ± 31,3	**0,001**[a]
CURB-65	0,0 (0,0–1,0)	4,0 (3,0–5,0)	**0,001**[b]	3,0 (2,0–3,0)	5,0 (5,0–5,0)	**0,001**[b]	1,0 (0,0–3,0)	5,0 (5,0–5,0)	**0,001**[b]
CORB	0,0 (0,0–4,0)	3,0 (2,0–4,0)	**0,001**[b]	2,0 (2,0–3,0)	4,0 (4,0–4,0)	**0,001**[b]	1,0 (0,0–2,0)	4,0 (4,0–4,0)	**0,001**[b]
CRB-65	0,0 (0,0-0,0)	3,0 (2,0–4,0)	**0,001**[b]	2,0 (1,0–2,0)	4,0 (4,0–4,0)	**0,001**[b]	0,0 (0,0–2,0)	4,0 (4,0–4,0)	**0,001**[b]
qSOFA	0,0 (0,0–1,0)	3,0 (2,0–3,0)	**0,001**[b]	2,0 (2,0–3,0)	3,0 (3,0–3,0)	**0,036**[b]	1,0 (0,0–2,0)	3,0 (3,0–3,0)	**0,001**[b]
SCAP	5,0 (5,0–10,0)	38,0 (27,5–44,5)	**0,001**[b]	30,1 ± 10,2	47,5 ± 8,2	**0,001**[a]	18,0 (5,0–30,0)	43,0 (41,0–54,0)	**0,001**[b]
SMART-COP	3,0 (3,0–5,0)	8,0 (6,5–10,0)	**0,001**[b]	7,0 (6,0–7,0)	10,5 (8,0–11,0)	**0,001**[b]	5,0 (3,0–7,0)	10,0 (8,0–11,0)	**0,001**[b]
REA-ICU	5,0 (4,0–6,0)	9,0 (7,0–10,5)	**0,001**[b]	7,1 ± 1,9	10,7 ± 1,6	**0,001**[a]	6,0 (4,0–7,0)	10,0 (9,0–11,0)	**0,001**[b]
NEWS2	3,0 (2,5-4,5)	12,0 (9,0–13,0)	**0,001**[b]	9,0 (8,0–12,0)	13,0 (12,0–14,0)	**0,001**[b]	6,4 ± 3,8	13,1 ± 1,4	**0,001**[a]
A-DROP	1,0 (0,0–1,0)	3,0 (2,0–4,0)	**0,001**[b]	2,0 (2,0–2,0)	4,0 (4,0–5,0)	**0,001**[b]	1,0 (1,0–2,0)	4,0 (4,0–4,0)	**0,001**[b]
CCTS	9,1 ± 3,6	15,6 ± 3,4	**0,001**[a]	13,8 ± 3,1	17,7 ± 2,4	**0,001**[a]	11,9 ± 4,6	16,6 ± 2,8	**0,001**[a]
TSS	6,0 ± 2,58	13,0 ± 3,23	**0,001**[a]	11,1 ± 2,6	15,4 ± 2,2	**0,001**[a]	8,9 ± 4,2	14,2 ± 2,9	**0,001**[a]
CTSS	10,8 ± 4,4	24,8 ± 6,1	**0,001**[a]	20,9 ± 4,6	29,6 ± 3,8	**0,001**[a]	16,8 ± 7,9	27,2 ± 5,9	**0,001**[a]
BRIXIA	5,6 ± 2,7	11,7 ± 2,8	**0,001**[a]	10,2 ± 2,5	13,5 ± 1,9	**0,001**[a]	8,2 ± 3,8	12,5 ± 2,8	**0,001**[a]
RALE	2,0 (2,0–3,0)	5,0 (4,0–6,0)	**0,001**[b]	4,0 (3,0–4,0)	6,0 (5,0–7,0)	**0,001**[b]	3,0 (2,0–4,0)	6,0 (5,0–7,0)	**0,001**[b]
SP-D (ng/mL)	16,4 ± 3,0	25,8 ± 4,9	**0,001**[a]	22,3 ± 2,5	29,9 ± 3,7	**0,001**[a]	19,5 ± 4,3	30,1 ± 3,9	**0,001**[a]
IVCT (cm^3)	555,8 (504,3–617,3)	876,2 (749,4–973,5)	**0,001**[b]	768,9 (669,1–875,2)	977,4 (947,9–1186,7)	**0,001**[b]	672,0 ± 147,9	1075,9 ± 211,1	**0,001**[a]
IPCT (%)	18,47 ± 6,79	30,83 ± 11,54	**0,001**[a]	27,9 ± 11,4	34,3 ± 11,1	0,129[a]	19,4 (15,2–28,3)	34,3 (28,3–40,5)	**0,001**[b]
CHARISMA Score	0,3 ± 0,1	4,8 ± 2,9	**<0,001**[a]	2,7 ± 1,9	7,3 ± 1,2	**<0,001**[a]	1,7 ± 0,9	7,4 ± 1,1	**<0,001**[a]

[a] independent samples *t*-test.
[b] Mann–Whitney *U* test.
[c] chi-squared test. **IPCT:** infiltration percentage on computed tomography; **IVCT:** infiltration volume on computed tomography, **TSS:** total severity score, **CTSS:** computed tomography severity score, **CCTS:** chest computed tomography score, **NEWS2:** National Early Warning Score 2, **PSI:** Pneumonia Severity Index, **qSOFA:** quick Sequential Organ Failure Assessment, **SCAP:** Severe Community-Acquired Pneumonia Score, **REA-ICU:** Risk Stratification of Early Admission to the Intensive Care Unit. **RALE:** Radiographic Assessment of Lung Edema. **Note:** Data in the table are expressed as means ± standard deviations, n (%) or medians (minimum-maximum) as applicable.

Table 4
ROC analyses of serum SP-D levels, CHARISMA Scores, and other parameters that are descriptive for in-hospital mortality risk.

Ranking of Prognostic Value	AUC[a]	95 % CI	Cut-off value	SE (%)	SP (%)	PPV (%)	NPV (%)	+LR	-LR
CHARISMA	0,977	0,881–0,998	4	100	89,2	76,5	100	9,3	0,0
IVCT (cm^3)	0,967	0,873–0,997	802,66	100	81,1	65,0	100	5,3	0,0
SMART-COP	0,956	0,858–0,994	7	92,3	89,2	75,0	97,1	8,5	0,1
SP-D (ng/dL)	0,956	0,858–0,994	25,69	84,6	91,9	78,6	94,4	10,4	0,2
NEWS2	0,942	0,837–0,988	9	100	81,1	65,0	100	5,3	0,0
SCAP	0,939	0,833–0,987	33	100	83,8	68,4	100	6,2	0,0
CURB-65	0,937	0,830–0,986	3	92,3	86,5	70,6	97,0	6,8	0,1
CORB	0,935	0,827–0,985	2	100	78,4	61,9	100	4,6	0,0
PSI	0,930	0,821–0,983	174	92,3	89,2	75,0	97,1	8,5	0,1
CRB-65	0,930	0,821–0,983	2	92,3	83,8	66,7	96,9	5,7	0,1
BNP (pg/mL)	0,916	0,802–0,976	134	76,9	89,2	71,4	91,7	7,1	0,3
A-DROP	0,914	0,799–0,974	2	92,3	86,5	70,6	97,0	6,8	0,1
qSOFA	0,914	0,799–0,974	2	92,3	86,5	70,6	97,0	6,8	0,1
REA-ICU	0,877	0,754–0,953	7	100	78,4	61,9	100	4,6	0,0
RALE	0,864	0,737–0,944	4	76,9	81,1	58,8	90,9	4,1	0,3
CTSS	0,846	0,716–0,933	23	84,6	75,7	55,0	93,3	3,5	0,2
TSS	0,843	0,712–0,930	12	76,9	70,3	47,6	89,7	2,6	0,3
IPCT (%)	0,834	0,701–0,927	23,34	92,3	67,6	50,0	96,2	2,9	0,1
Troponin (ng/L)	0,814	0,679–0,910	80	84,6	67,6	47,8	92,6	2,6	0,2
BRIXIA	0,813	0,677–0,909	11	69,2	81,1	56,3	88,2	3,7	0,4
CCTS	0,801	0,664–0,901	13	92,3	59,5	44,4	95,7	2,3	0,1
Lactate (mg/dl)	0,762	0,620–0,871	17	84,6	62,2	44,0	92,0	2,2	0,3

[a] ROC analysis; **AUC:** area under the curve; **95 % CI:** 95 % confidence interval**; SE**: sensitivity; **SP**: specificity; **PPV**: positive predictive value; **NPV**: negative predictive value; **LR:** likelihood ratio.

Predicting the risk of mortality is important for the successful management of patients with COVID-19. Agustama et al. [16] reported a mean serum SP-D level of 38.92 ng/mL in people who survived and 39.70 ng/mL in people who died, with no significant difference between the two groups. On the other hand, Salvioni et al. [2] reported a range of 173.8–220.3 ng/mL in patients who survived and 417.9–661.5 ng/mL in those who died, with a significant difference between groups. These findings are similar to that of our study, as serum SP-D levels were significantly higher in patients who died than those who survived (30.1 (SD:3.9) vs. 19.5 (SD:4.3) ng/mL, respectively). Based on these findings, we suggest that serum SP-D levels may be a predictor of early in-hospital mortality risk.

The CT severity score (CTSS), chest CT score (CCTS), total severity score (TSS), and radiographic assessment of lung edema (RALE) score, which have been used as radiologic pneumonia severity scales in the literature, were examined by Wasilewski et al. [8], and the Brixia score was examined by Setiawati et al. [17]. These scores have been reported to be associated with the severity of COVID-19. Our results are comparable to those reported in the literature regarding these scores. In addition, IVCT and IPCT calculations, which are obtained by computer-based lesion/infiltration volume measurement, were used in our study, in contrast to the scoring techniques that depend on the physician's experience. IVCT and IPCT measurement techniques, which are based on the contrast difference between normal lung parenchyma and the pneumonia infiltration area, are computer-based volume measurements. In our study, these measurements were also related to disease severity. In particular, IVCT was better than all other radiological severity scales in predicting the risk of in-hospital mortality. We believe that this method will contribute to the literature because it is minimally affected by the evaluator's experience, simple to use, easily accessible, noninvasive, and can be stored digitally and repeatedly.

An important finding in our study was that serum SP-D levels correlated with IVCT and IPCT, suggesting that serum SP-D levels are directly related to the volume of the damaged or infected pulmonary tissue. Accordingly, in our study, we developed a new clinical severity scale, the CHARISMA score, by including both serum SP-D levels and IPCT values, which is more appropriate for the regression model, together with vital signs that are important in predicting in-hospital mortality. The CHARISMA score created in our study includes laboratory, clinical, and radiologic severity parameters. In this respect, it is clearly superior to other existing scoring systems. Our motivation for creating a new scale is that it includes both a biochemical marker for lung injury and a radiologic variable that directly quantifies the amount of damaged tissue, calculated in a quantitative and practical way, unlike other scores that include only clinical assessment.

Many clinical and radiological severity scales in the literature have been used to evaluate the prognosis of COVID-19 pneumonia. They include the pneumonia severity index (PSI), CURB-65 (confusion, uremia, respiratory rate, blood pressure, age $\geq$65 years), CORB (confusion, oxygenation, respiratory rate, and blood pressure), CRB-65 (confusion; respiratory rate $\geq$30/min; blood pressure $\leq$90/60 mmHg; age $\geq$65 years), quick sequential organ failure (qSOFA), severe community-acquired pneumonia (SCAP), SMART-COP (systolic blood pressure, multilobar infiltrates, albumin, respiratory rate, tachycardia, confusion, oxygen, and pH), REA-ICU (risk stratification of early admission to the intensive care unit), national early warning score 2 (NEWS2), and A-DROP (age, dehydration, respiratory failure, orientation disturbance, pressure) scores, which are the most common clinical severity scales, and the CCTS, TSS, CTSS, Brixia, and RALE indices, which are radiologic severity scales [18–22]. The CHARISMA score created in our study includes laboratory, clinical, and radiologic severity parameters. The score provided successful results in discriminating simple COVID-19 from COVID-19 with ARDS, discriminating mild from moderate/severe ARDS, and predicting the risk of in-hospital mortality. We believe that patients with a CHARISMA score $\geq$5 are at a high risk of mortality and should, therefore, be followed up in hospitals.

4.1. Limitations

This was a single-center study that was carried out for a limited period during the COVID-19 pandemic. Serum SP-D levels were evaluated only upon admission. Another limitation is that the time between symptom onset and hospital admission could not be clearly determined. Additionally, we did not analyze how long the serum SP-D levels remained elevated or what type of trend it followed during the disease. In addition, the clinical implications of SARS-CoV-2 variants or mutations were not evaluated in this study. This was because at the time of our study, the detection and management differences of these variants had not yet entered clinical routine practice. More significant results will be obtained from larger studies with longer durations and comparative studies in multiple centers, following the trend of serum SP-D levels during the disease course, determining symptom onset times, and considering virus mutations.

5. Conclusion

The serum SP-D level is valuable for COVID-19 diagnosis, ARDS prediction, and ARDS severity determination. In addition, IVCT and IPCT may be used as innovative radiological approaches for the management and prognosis of COVID-19 pneumonia. The CHARISMA score may be suitable for use in emergency departments because it is easy to calculate, practical, and useful for predicting disease prognoses. This scale will provide more reliable results when evaluated using larger sample sizes and in multicenter studies. We believe that our study includes guiding results for further studies regarding the diagnosis and prognosis of COVID-19 in the emergency department.

CRediT authorship contribution statement

Aykut Yucal: Writing – review & editing, Writing – original draft, Validation, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Mustafa Burak Sayhan:** Visualization, Validation, Supervision, Project administration, Methodology, Formal analysis, Conceptualization. **Ömer Salt:** Visualization, Supervision, Resources, Methodology, Investigation. **İlker Dıbırdık:** Validation, Software, Resources, Data curation. **Sinem Çalın:** Validation, Supervision, Data curation.

Ethical Statement

The study was conducted with the approval of the Ethical Committee Presidency of Trakya University Faculty of Medicine (No.16/27, Protocol code: TUTF-GOBAEK 2022/311; August 8, 2022). The Declaration of Helsinki was fully complied with, and data required to protect patient privacy were obtained from clinical records without any clinical intervention. All participants (or their proxies/legal guardians) provided written informed consent to participate in the study and for their data to be published.

Funding

This study received no funding support from any person or organization. All costs of the study were covered by the author.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors wish to thank the volunteers for agreeing to participate in the study and the emergency service team for their help.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e39976.

References

[1] S. Han, R.K. Mallampalli, The role of surfactant in lung disease and host defense against pulmonary infections, Ann Am Thorac Soc 12 (2015) 765–774, https://doi.org/10.1513/AnnalsATS.201411-507FR.

[2] L. Salvioni, F. Testa, A. Sulejmani, F. Pepe, P. Giorgio Lovaglio, P. Berta, et al., Surfactant protein D (SP-D) as a biomarker of SARS-CoV-2 infection, Clin. Chim. Acta 537 (2022) 140–145, https://doi.org/10.1016/j.cca.2022.10.013.

[3] H. Sano, Y. Kuroki, The lung collectins, SP-A and SP-D, modulate pulmonary innate immunity, Mol. Immunol. 42 (2005) 279–287, https://doi.org/10.1016/j.molimm.2004.07.014.

[4] World Health Organization, Novel coronavirus Situation Report 2019–nCoV 1 (2020). https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200121-sitrep-1-2019-ncov.pdf?sfvrsn=20a99c10_4. (Accessed 18 April 2022).
[5] World Health Organization, Coronavirus disease 2019 (COVID-19) situation, Report–51, https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200311-sitrep-51-covid-19.pdf?sfvrsn=1ba62e57_10, 2020. (Accessed 18 April 2022).
[6] S. Chavez, B. Long, A. Koyfman, S.Y. Liang, Coronavirus Disease (COVID-19): a primer for emergency physicians, Am. J. Emerg. Med. 44 (2021) 220–229, https://doi.org/10.1016/j.ajem.2020.03.036.
[7] B. Long, B.M. Carius, S. Chavez, S.Y. Liang, W.J. Brady, A. Koyfman, et al., Clinical update on COVID-19 for the emergency clinician: presentation and evaluation, Am. J. Emerg. Med. 54 (2022) 46–57, https://doi.org/10.1016/j.ajem.2022.01.028.
[8] P.G. Wasilewski, B. Mruk, S. Mazur, G. Półtorak-Szymczak, K. Sklinda, J. Walecki, COVID-19 severity scoring systems in radiological imaging - a review, Pol. J. Radiol. 85 (2020) e361–e368, https://doi.org/10.5114/pjr.2020.98009.
[9] D. Sun, X. Li, D. Guo, L. Wu, T. Chen, Z. Fang, et al., CT quantitative analysis and its relationship with clinical features for assessing the severity of patients with COVID-19, Korean J. Radiol. 21 (2020) 859–868, https://doi.org/10.3348/kjr.2020.0293.
[10] B. Böger, M.M. Fachi, R.O. Vilhena, A.F. Cobre, F.S. Tonin, R. Pontarolo, Systematic review with meta-analysis of the accuracy of diagnostic tests for COVID-19, Am. J. Infect. Control 49 (2021) 21–29, https://doi.org/10.1016/j.ajic.2020.07.011.
[11] Coronaviridae Study Group of the International Committee on Taxonomy of Viruses, The species severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2, Nat Microbiol 5 (2020) 536–544, https://doi.org/10.1038/s41564-020-0695-z.
[12] S.S. Joni, R. Gerami, F. Pashaei, H. Ebrahiminik, M. Karimi, Quantitative evaluation of CT scan images to determinate the prognosis of COVID-19 patient using deep learning, Eur J Transl Myol 33 (2023) 11571, https://doi.org/10.4081/ejtm.2023.11571.
[13] P. Lyu, X. Liu, R. Zhang, L. Shi, J. Gao, The performance of chest CT in evaluating the clinical severity of COVID-19 pneumonia: identifying critical cases based on CT characteristics, Invest. Radiol. 55 (2020) 412–421, https://doi.org/10.1097/RLI.0000000000000689.
[14] Sectra, Time savings using the Sectra volume measurement tool: sectra AB. https://sectraprodstorage01.blob.core.windows.net/medical-uploads/2019/08/productivity-article1xxxvolume-measurement-2.0.pdf, 2019. (Accessed 23 May 2023).
[15] A. Saito, K. Kuronuma, K. Moniwa, K. Kodama, S. Takahashi, H. Takahashi, et al., Serum surfactant protein A and D may be novel biomarkers of COVID-19 pneumonia severity, Res Square (2020), https://doi.org/10.21203/rs.3.rs-29567/v1.
[16] A. Agustama, A. Surgean Veterini, A. Utariani, Correlation of surfactant protein-D (SP-D) serum levels with ARDS severity and mortality in Covid-19 patients in Indonesia, Acta Med Acad 51 (2022) 21–28, https://doi.org/10.5644/ama2006-124.366.
[17] R. Setiawati, A. Widyoningroem, T. Handarini, F. Hayati, A.T. Basja, A.R.D.S. Putri, et al., Modified chest x-ray scoring system in evaluating severity of COVID-19 patient in Dr. Soetomo General Hospital Surabaya, Indonesia, Int. J. Gen. Med. 14 (2021) 2407–2412, https://doi.org/10.2147/IJGM.S310577. https://orcid.org/0000-0002-0761-7471.
[18] R. Yang, X. Li, H. Liu, Y. Zhen, X. Zhang, Q. Xiong, et al., Chest CT severity score: an imaging tool for assessing severe COVID-19, Radiol Cardiothorac Imaging 2 (2020) e200047, https://doi.org/10.1148/ryct.2020200047.
[19] K. Li, Y. Fang, W. Li, C. Pan, P. Qin, Y. Zhong, et al., CT image visual quantitative evaluation and clinical classification of coronavirus disease (COVID-19), Eur. Radiol. 30 (2020) 4407–4416, https://doi.org/10.1007/s00330-020-06817-6.
[20] K. Li, J. Wu, F. Wu, D. Guo, L. Chen, Z. Fang, et al., The clinical and chest CT features associated with severe and critical COVID-19 pneumonia, Invest. Radiol. 55 (2020) 327–331, https://doi.org/10.1097/RLI.0000000000000672.
[21] K.L. Buising, K.A. Thursky, J.F. Black, L. MacGregor, A.C. Street, M.P. Kennedy, et al., Identifying severe community-acquired pneumonia in the emergency department: a simple clinical prediction tool, Emerg Med Australas 19 (2007) 418–426, https://doi.org/10.1111/j.1742-6723.2007.01003.x.
[22] G. Fan, C. Tu, F. Zhou, Z. Liu, Y. Wang, B. Song, et al., Comparison of severity scores for COVID-19 patients with pneumonia: a retrospective study, Eur. Respir. J. 56 (2020) 2002113, https://doi.org/10.1183/13993003.02113-2020.