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Novel biochemical prognostic indicators in COVID-19: Can CRP/albumin, urea/albumin, and LDH/albumin ratios be used to predict mortality and length of hospitalization?

Zeynep Ergenç[1], Hasan Ergenç[1]*, Songül Araç[2], Mustafa Usanmaz[3], Ersin Alkılınç[4], Gülsüm Kaya[5], Cengiz Karacaer[6], Ahmet Nalbant[6], Tezcan Kaya[6]

1 Department of Internal Medicine, Ayancık Government Hospital, Sinop, TR
2 Department of Emergency Medicine, University of Health Sciences, Diyarbakır Gazi Yaşargil Training and Research Hospital, Diyarbakır, TR
3 Department of Infectious Diseases and Clinical Microbiology, Gazi Government Hospital, Samsun, TR
4 Department of Pulmonology, Atatürk State Hospital, Sinop, TR
5 Department of infection control committee, Sakarya University Training and Research Hospital, Sakarya, TR
6 Department of Internal Medicine, Sakarya University Training and Research Hospital, Sakarya, TR

*** Corresponding Author:** Hasan Ergenc **E-mail:** dr.hasanergenc@hotmail.com

ABSTRACT

Objective: As the coronavirus disease 2019 (COVID-19) pandemic continues, clinical and laboratory predictors of progression to serious and lethal types of the illness are urgently needed. We aimed to investigate how well hematologic, biochemical, and immunologic biomarkers could distinguish between patients with and without severe or fatal COVID-19.

Material and Methods: This retrospective study was performed in the internal medicine departments of two institutions. Data were collected from the hospital database, and the medical files of 280 adult COVID-19 were reviewed. The relationship between hematologic and biochemical parameters which include C-reactive protein (CRP)/albumin, urea/albumin, and lactate dehydrogenase (LDH)/albumin ratios and length of hospitalization, disease severity, and survival were investigated.

Results: Our series consisted of 280 adult COVID-19 patients (147 women, 133 men) with an average age of 58.34 ± 18.64 (range: 19 to 93). Most patients (n=171, 61.1%) had mild-moderate disease, while severe disease was diagnosed in 109 cases (38.9%). A total of 36 patients died due to COVID-19 yielding a mortality rate of 12.9%. The average length of hospitalization was 8.98 ± 5.80 days (range: 1-55 days). We noted that (CRP)/albumin, urea/albumin, and lactate dehydrogenase (LDH)/albumin ratios were significantly associated with severity of disease, mortality, and length of hospitalization.

Conclusion: Several biomarkers have been established that could help with risk stratification models for predicting serious and fatal results of COVID-19 infection. We suggest that clinicians closely track CRP/albumin, urea/albumin, and LDH/albumin ratios in hospitalized patients with respiratory distress as indicators for possible critical illness progression.

Key words: COVID-19, CRP/albumin ratio, Urea/albumin ratio, LDH/albumin ratio, Mortality; Day of hospitalization

Research Article

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INTRODUCTION

To fight against the coronavirus disease (COVID-19), which is currently a global pandemic, laboratory and clinical predictors of progression to serious and lethal forms are critical. Such predictors can help stratify risk, guiding interventional trials of patients at a higher risk of developing a severe disease, and optimizing the use of scarce human and financial resources during the pandemic. Recognition of laboratory parameters that can distinguish between serious and mild cases is also essential. Improved clinical situational understanding would be possible for those exposed more or less to mortality (1). Procalcitonin and platelet count have previously been established as possible severity predictors of disease (2, 3). However, the higher amount of COVID-19 reports which are now available has allowed a more detailed review of laboratory results, which the medical and scientific communities desperately need (2, 3). In COVID-19 patients, reports indicated that white blood cell count, neutrophil count, levels of ALT, AST, total bilirubin, creatinine, lactate dehydrogenase (LDH), urea (blood urea nitrogen), creatine kinase-MB, myoglobin, prothrombin time, D-dimer, cardiac troponin I, and CRP levels erythrocyte sedimentation rate were increased.

On the other hand, lymphocyte, platelet, eosinophil counts, and serum albumin levels were decreased (1). Many people infected with COVID-19 indicate mild to moderate symptoms and are cured with adequate medical treatment (4).

However, moderate, or severe COVID-19 develops in 15–32% of cases, with a 1–15% mortality rate (5). COVID-19 patients have infrequently reported haematological defects (6). COVID-19 has different clinical symptoms, from a mild infection like flu to life-threatening types. Clinical presentation and mortality rates differ significantly across countries, and the reasons for these variations are still unknown. Variety of local testing methods, Genetic factors, and epidemiological reporting among countries can all play a role (7). To better understand this problem, it is critical to have a good image of the general characteristics of COVID-19 patients, as well as a meticulous review of clinical presentation and laboratory test results. There is also a lack of information regarding the clinical features of the infected patients admitted to hospitals (7). We aimed to examine the hematologic and biochemical laboratory anomalies in COVID-19 patients to determine which parameters can be useful to distinguish between those who are more likely to develop severe disease, and those less likely to survive. For this purpose, we investigated whether CRP/albumin, urea/albumin, and LDH/albumin ratios may be useful as prognostic indicators for patients infected with COVID-19.

MATERIAL and METHODS

Study design: This retrospective study was performed in the internal medicine departments of two institutions between April 1, 2021 and August 1, 2021. The local institutional review board approved the trial (date/no). Written informed consent was received from patients or their immediate relatives. Data were collected from the hospital database and the medical files of 280 adults diagnosed with COVID-19 were reviewed. The baseline descriptives, clinical variables, laboratory data, and treatment outcomes were recorded.

Patients: On admission for COVID-19 infection, nasal and pharyngeal swabs were tested using a quantitative real-time reverse transcriptase-polymerase chain reaction (qPCR). COVID-19 infection positivity was diagnosed and treated per World Health Organization interim guidelines and the Turkish Ministry of Health's COVID-19 Diagnosis and Treatment Program (8-10). The clinical conditions during admission were classified as severe condition which requires intensive care or an oxygen saturation <90% or mild-to-moderate condition not needing ICU or oxygen saturation >90% (11). Patients were subjected to routine blood tests, chemical and immunological tests, and chest CT scanning to determine the COVID-19 severity. Following that, every other day, a serial chest CT scan was performed to monitor disease progression and treatment effectiveness. In one commercial multi-detector CT scanner, a single inspiratory phase (Optima CT540, GE Healthcare, U.S.A.) chest CT scans were performed with. To reduce motion and artifacts, patients were instructed to hold their breath. Computed tomography images were obtained using the following parameters: effective tube current, 110– 250 mAs; detector collimation, 0.625 mm; slice thickness, 1 mm; slice interval, 1 mm ; and tube voltage, 100–120 kVp;.

To analyse blood samples, standard methods in the laboratory of our hospital were used. Blood samples were analysed using a standard procedure. A routine blood examination was carried out and the Mindray BC-5390 device was used to count blood cells, classify white blood cells, and calculate biochemical parameters and haemoglobin concentrations (Shenzhen, China). Albumin, CRP, LDH, creatinine, blood urea nitrogen, calcium, sodium, potassium, alanine aminotransferase (ALT), aspartate transaminase (AST), D-dimer, and cardiac troponin I were among the biochemical tests which were performed in the VITROS 5600 Integrated Immunodiagnostic System (VITROS 5600, Johnson, New Jersey, USA).

Statistical analysis: Our data were analysed with IBM Statistical Package for Social Sciences (SPSS) Statistics 20 software (SPSS Inc., Chicago, IL, USA). Logistic regression and ROC analysis were performed to assess diagnostic tests and predictive models and to assess and compare the accuracy between tests and predictive models. Spearman's rank correlation coefficient (Spearman’s rho) was employed as a non-parametric measure of rank correlation and statistical dependence in the rankings of two variables. A p-value of below 0.05 was statistically significant.

Outcome parameters: The baseline descriptive and clinical variables under investigation included age, sex, comorbidity, survival status, disease severity, chief complaint at admission, length of hospitalization, disease severity, and quantitative polymerase chain reaction (qPCR) test results. The hematologic and biochemical lab results involved white blood cell count, haemoglobin level, platelet and lymphocyte counts, serum levels of urea (blood urea nitrogen), creatinine, LDH, AST, ALT, CRP, albumin, sodium, potassium, calcium, cardiac troponin I, D-dimer as well as CRP/albumin, urea/albumin, and LDH/albumin ratios. The results of lab tests performed on the first and fifth days after hospitalization were noted and the correlation between the disease severity, survival status, hematologic and biochemical parameters was sought.

RESULTS

Our series consisted of 280 adult COVID-19 patients (147 women, 133 men) with an average age of 58.34 ± 18.64 (range: 19 to 93). An overview of baseline and demographic data is presented in **Table 1**. Most patients (n=171, 61.1%) had mild-moderate disease while sever disease was diagnosed in 109 cases (38.9%). A total of 36 patients died due to COVID-19 yielding a mortality rate of 12.9%. The average length of hospitalization was 8.98 ± 5.80 days (range: 1-55 days). The most frequent comorbidities were hypertension (n=119, 73.9%), diabetes mellitus (n=67, 41.6%), chronic obstructive pulmonary disease (n=28, 17.4%), congestive heart failure (n=23, 14.3%), and coronary atherosclerotic heart disease (n=22, 13.7%). The most common chief complaints at admission were cough (n=132, 47.1%), fever (n=98, 35.0%), dyspnea (n=92, 32.8%), and fatigue (n=80, 28.6%), respectively. Table 2 demonstrates the results of the evaluation of the clinical variables as for the outcome for survival status. White blood cell and lymphocyte counts, serum levels of urea, creatinine, LDH, CRP, albumin levels were higher on the first and fifth days after admission in patients ending up with mortality. Similarly, serum levels of

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AST and cardiac troponin I were increased on the first day after admission in patients who died due to COVID-19. In contrast, sodium levels on the first day and albumin levels on both the first and fifth days were lower in patients who were lost during treatment. Notably, all three parameters under focus, CRP/albumin, urea/albumin, and LDH/albumin ratios, were remarkably higher in the mortality subgroup (**Table 2**).

The results of the evaluation of the clinical variables per disease severity are shown in Table 3. Accordingly, White blood cell count and serum levels of urea, creatinine, LDH, CRP and ratios of CRP/albumin, urea/albumin, and LDH/albumin, were significantly increased on the first and fifth days after admission in patients with severe disease. The hemoglobin and albumin serum levels were significantly decreased on the first and fifth days in patients with severe disease. ALT, sodium, and cardiac troponin I Serum levels were lower on the first day after admission in COVID-19 patients with severe disease (Table 3).

In Table 4, the relationship between clinical variables and length of hospitalization was demonstrated. Serum D-dimer level on the first day, hemoglobin levels, lymphocyte counts, levels of LDH, CRP, potassium as well as CRP/albumin and LDH/albumin ratios on the fifth day and serum albumin levels on both the first and fifth days seem to be associated with length of hospitalization (**Table 4**).

The performances of clinical variables for discrimination of survival status and severity of disease are shown in Table 5. Our data indicated that hemoglobin level, white blood cell count, lymphocyte count, serum levels of urea, creatinine, LDH, CRP, albumin, cardiac troponin I and D-dimer as well as CRP/albumin, urea/albumin, and LDH/albumin levels may have important implications as predictors of disease severity and mortality (**Table 5**).

The performances of CRP/albumin, urea/albumin, and LDH/albumin levels to predict disease severity and survival are shown in **Graphs 1 and 2**.

Table 1. Demographic and clinical characteristics of patients in our series (n=280).

Variable		Statistics n (%)
Age (mean±standard deviation (min-max))		58.34 ± 18.64 (19 – 93)
Sex	**Female**	147 (52.5)
	Male	133 (47.5)
Comorbidity	**No**	99 (38.1)
	Yes	161 (61.9)
Comorbidity types	**HT**	119 (73.9)
	DM	67 (41.6)
	COPD/asthma	28 (17.4)
	CAHD	22 (13.7)
	CHF	23 (14.3)
	CRF	6 (3.7)
	CVO	4 (2.5)
	Dementia	1 (0.6)
	Hypercholesterolemia	7 (4.3)
	Goitre	5 (3.1)
	Other	21 (13.0)
Chief complaint(s) at admission	**Fever**	98 (35.0)
	Angina pectoris	5 (1.8)
	Cough	132 (47.1)
	Diarrhea	8 (2.9)
	Sore throat	33 (11.8)
	Dyspnea	92 (32.8)
	Sputum	9 (3.2)
	Headache	15 (5.4)
	Myalgia	23 (8.2)
	Dysgeusia	2 (0.7)
	Nausea	11 (3.9)
	Fatigue	80 (28.6)
	Ageusia	2 (0.7)
	Back pain	29 (10.4)
	Arthralgia	10 (3.6)
	Pain	10 (3.6)
	Loss of appetite	9 (3.2)
	Other (otalgia, shivering, sweating, etc.)	14 (5.0)
Survival status	**Alive**	244 (87.1)
	Dead	36 (12.9)
Length of hospitalization (mean±standard deviation (min-max))		8.98 ± 5.80 (1 – 55)
Disease severity	**Mild**	171 (61.1)
	Severe	109 (38.9)
qPCR test result	**Negative**	105 (37.5)
	Positive	175 (62.5)

(Abbreviations: HT: hypertension; DM: diabetes mellitus; COPD: chronic obstructive pulmonary disease; CAHD: coronary atherosclerotic heart disease; CHF: congestive heart disease; CRF: chronic renal failure; CVO: cerebrovascular disease; qPCR: quantitative polymerase chain reaction)

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Table 2. Evaluation of the clinical variables per the outcome for survival (*: Difference was calculated as the alteration between fifth and first days).

		Survival status		
		Alive (n=242)	Dead (n=36)	p
WBC (/µl)	**1st day**	5.84 [4.6 – 7.6]	7.25 [5.35 – 9.14]	**0.013**
	5th day	6.10 [4.6 – 7.61]	9.16 [6.0 – 11.85]	**<0.001**
	Difference*	-0.1 [-1.69 ; 1.0]	1.83 [-0.27 ; 2.92]	**0.002**
Hb (g/dl)	**1st day**	13.4 [12.1 – 14.63]	13.15 [11.35 – 14.53]	0.282
	5th day	12.8 [11.45 – 13.9]	12.3 [10.6 – 13.7]	0.109
	Difference*	-0.60 [-1.30 ; -0.1]	-1.1 [-1.6 ; -0.30]	0.178
Plt (/µl)	**1st day**	198 [160.75 - 249]	188 [142.25 – 225.5]	0.151
	5th day	232.5 [168 - 301]	218 [147 - 256]	0.290
	Difference*	28.5 [-9.25 ; 76.25]	26.0 [-15.0 ; 55.0]	0.721
Lymph (/µl)	**1st day**	1.30 [0.9 – 1.71]	0.93 [0.59 – 1.2]	**<0.001**
	5th day	1.40 [1.0 – 2.02]	0.70 [0.5 – 1.2]	**<0.001**
	Difference*	0.10 [-0.20 ; 0.35]	-0.03 [-0.4 ; 0.11]	0.085
Urea (mg/dl)	**1st day**	28.0 [22.0 – 34.0]	44.55 [32.78 – 79.63]	**<0.001**
	5th day	26.0 [20.4 – 34.0]	53.6 [26.0 – 82.8]	**<0.001**
	Difference*	-2.0 [-8.9 ; 3.95]	16.1 [-8.0 ; 25.0]	**0.001**
Creatinine (mg/dl)	**1st day**	0.80 [0.7 – 1.0]	1.10 [0.87 – 1.49]	**<0.001**
	5th day	0.77 [0.68 – 0.89]	0.96 [0.7 – 1.33]	**0.010**
	Difference*	-0.03 [-0.12 ; 0.01]	0.0 [-0.13 ; 0.20]	0.150
LDH (U/l)	**1st day**	248 [200 - 317]	307.5 [220.25 – 438.25]	**0.004**
	5th day	232 [185 - 324]	449.5 [248.25 – 606.5]	**<0.001**
	Difference*	-15.5 [-71.0 ; 56.3]	125 [-56.25 ; 247.5]	**0.009**
CRP (mg/l)	**1st day**	19.5 [5.23 – 73.98]	108.8 [55.63 – 152.3]	**<0.001**
	5th day	20.0 [3.95 – 57.75]	132.2 [72.0 – 171.0]	**<0.001**
	Difference*	0.0 [-19.5 ; 18.0]	21.0 [-32.7 ; 71.1]	0.264
AST (U/l)	**1st day**	24.0 [19 - 34]	31.0 [21.5 – 45.0]	**0.019**
	5th day	25.0 [18 - 37]	33.0 [18.0 – 48.0]	0.159
	Difference*	-1.0 [-7.0 ; 9.0]	1.0 [-9.0 ; 21.0]	0.468
ALT (U/l)	**1st day**	20.0 [14 - 30]	19.5 [13.25 – 27.75]	0.647
	5th day	25.0 [15 - 36]	21.0 [15.0 – 26.0]	0.239
	Difference*	1.5 [-3.75 ; 9.0]	-1.0 [-6.0 ; 11.0]	0.357
Albumin (g/dl)	**1st day**	43.0 [40 - 46]	39.5 [37.0 – 42.0]	**<0.001**
	5th day	40.0 [36 - 42]	33.0 [28.0 – 36.0]	**<0.001**
	Difference*	-3.5 [-6.0 ; -1.0]	-6.0 [-8.0 ; -3.5]	**0.010**
Sodium (mEq/l)	**1st day**	137 [135 - 139]	135.5 [133 - 138]	**0.031**
	5th day	139 [137 - 140]	138 [134 - 141]	0.406
	Difference*	1.0 [0.0 – 4.0]	2.0 [-2.0 ; 3.0]	0.429
Potassium (mEq/l)	**1st day**	4.1 [3.8 – 4.4]	4.17 [3.60 – 4.43]	0.640
	5th day	4.2 [3.889 – 4.49]	4.1 [3.6 – 4.43]	0.210
	Difference*	0.10 [-0.30 ; 0.40]	-0.10 [-1.0 ; 0.51]	0.131
Calcium (mg/dl)	**1st day**	8.7 [8.3 – 9.0]	8.65 [8.33 – 9.0]	0.875
	5th day	8.5 [8.2 – 8.8]	8.5 [8.24 – 8.98]	0.596
	Difference*	-0.20 [-0.50 ; 0.16]	-0.20 [-0.90 ; 0.10]	0.298
Cardiac troponin I (ng/ml)	**1st day**	0.10 [0.007 – 0.10]	0.1 [0.029 – 0.106]	**0.008**
D-Dimer (ng/ml)	**1st day**	86 [0.79 - 210]	1.63 [0.8 - 417]	0.495
CRP / albumin	**1st day**	0.45 [0.12 – 1.84]	2.83 [1.49 – 4.51]	**<0.001**
	5th day	0.51 [0.10 – 1.58]	3.67 [2.65 – 5.83]	**<0.001**
	Difference*	0.004 [-0.46 ; 0.52]	0.96 [-0.26 ; 2.24]	**0.026**
Urea / albumin	**1st day**	0.65 [0.49 – 1.02]	1.12 [0.81 – 1.95]	**<0.001**
	5th day	0.64 [0.5 – 0.86]	1.52 [0.98 – 2.89]	**<0.001**
	Difference*	0.02 [-0.19 ; 0.14]	0.51 [-0.09 ; 0.95]	**0.001**
LDH / albumin	**1st day**	5.92 [4.57 – 7.83]	8.55 [5.84 – 14.99]	**<0.001**
	5th day	6.31 [4.62 – 8.26]	14.62 [6.52 – 22.63]	**<0.001**
	Difference*	0.11 [-0.17 ; 1.92]	5.62 [-1.57 ; 10.79]	**0.004**

(Abbreviations: WBC: White blood cell count; Hb: hemoglobin level; Plt: platelet count; Lymph: lymphocyte count; LDH: lactate dehydrogenase level; CRP: C-reactive protein level; AST: aspartate transaminase level; ALT: alanine transaminase level)

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Table 3. Evaluation of the clinical variables per the disease severity (* Difference was calculated as the alteration between the fifth and first days).

		Disease severity		
		Mild (n=171)	Severe (n=109)	p
WBC (/µl)	**1st day**	5.77 [4.61 – 7.45]	6.80 [4.83 – 8.98]	**0.035**
	5th day	6.03 [4.6 – 7.36]	7.06 [5.26 – 9.19]	**0.002**
	Difference*	-0.03 [-1.27 ; 1.11]	0.17 [-1.7 ; 2.4]	0.950
Hb (g/dl)	**1st day**	13.6 [12.3 – 14.9]	12.8 [11.6 – 14.2]	**0.007**
	5th day	13.1 [11.8 – 14.3]	11.9 [10.7 – 13.0]	**<0.001**
	Difference*	-0.5 [-1.2 ; 0.1]	-1.1 [-1.6 ; -0.30]	**0.002**
Plt (/µl)	**1st day**	208.5 [170.8 - 251]	181.5 [142.25 – 227.5]	**0.003**
	5th day	238 [175.5 – 300.8]	223 [146 - 311]	0.116
	Difference*	28.0 [-12.0 ; 75.0]	28.5 [-4.5 ; 78.0]	0.873
Lymph (/µl)	**1st day**	1.44 [1.1 – 1.88]	0.97 [0.61 – 1.2]	**<0.001**
	5th day	1.59 [1.19 – 2.19]	0.90 [0.7 – 1.3]	**<0.001**
	Difference*	0.16 [-0.10 ; 0.43]	-0.10 [-0.30 ; 0.11]	**0.001**
Urea (mg/dl)	**1st day**	26.0 [21.0 – 33.8]	41.1 [29.55 – 65.25]	**<0.001**
	5th day	24.0 [20.0 – 30.3]	36.2 [24.03 – 58.5]	**<0.001**
	Difference*	-1.0 [-7.0 ; 3.4]	-2.55 [-14.48 ; 15.58]	0.953
Creatinine (mg/dl)	**1st day**	0.78 [0.68 – 0.90]	1.0 [0.85 – 1.41]	**<0.001**
	5th day	0.73 [0.66 – 0.81]	0.70 [0.9 – 1.22]	**<0.001**
	Difference*	-0.03 [-0.1 ; 0.03]	-0.1 [-0.20 ; 0.00]	**0.008**
LDH (U/l)	**1st day**	233 [197.5 – 303.3]	289 [218 – 374.5]	**<0.001**
	5th day	229 [185.3 – 308.0]	264 [188 – 394]	**0.035**
	Difference*	-11.0 [-62.0 ; 51.0]	1.0 [-7.0 ; 15.0]	0.574
CRP (mg/l)	**1st day**	11.5 [2.58 – 35.68]	96.85 [35.8 – 139.78]	**<0.001**
	5th day	12.5 [2.4 – 35.7]	65.5 [29.1 – 129.6]	**<0.001**
	Difference*	0.0 [-15.33 ; 14.1]	0.35 [-53.2 ; 39.53]	0.747
AST (U/l)	**1st day**	24.0 [19 - 34]	27.0 [20.0 – 38.5]	0.066
	5th day	24.5 [18 - 35]	29.5 [18.0 – 47.75]	0.052
	Difference*	-2.0 [-7.0 ; 6.0]	1.0 [-7.0 ; 15.0]	0.063
ALT (U/l)	**1st day**	21.0 [15 - 30]	18.0 [13.0 – 26.0]	**0.022**
	5th day	25.0 [16 - 35]	21.0 [14.0 – 39.75]	0.251
	Difference*	1.0 [-4.0 ; 10.0]	2.5 [-3.75 ; 13.0]	0.308
Albumin (g/dl)	**1st day**	44.0 [41 - 47]	40.0 [37.0 – 42.0]	**<0.001**
	5th day	41.0 [38 - 43]	35.0 [31.0 – 38.0]	**<0.001**
	Difference*	-3.0 [-5.25 ; -1.0]	-4.0 [-6.5 ; -1.0]	0.112
Sodium (mEq/l)	**1st day**	138 [136 - 139]	136.0 [133 - 138]	**<0.001**
	5th day	139 [137 - 140]	139 [136 - 141]	0.752
	Difference*	1.0 [-1.0 ; 3.0]	3.0 [0.0 ; 5.0]	**0.016**
Potassium (mEq/l)	**1st day**	4.1 [3.82 – 4.37]	4.1 [3.79 – 4.50]	0.689
	5th day	4.2 [3.9 – 4.49]	4.11 [3.8 – 4.42]	0.200
	Difference*	0.13 [-2.0 ; 0.48]	-0.10 [-0.58 ; 0.32]	**0.008**
Calcium (mg/dl)	**1st day**	8.7 [8.4 – 9.0]	8.70 [8.25 – 9.0]	0.685
	5th day	8.57 [8.29 – 8.8]	8.5 [8.1 – 8.87]	0.286
	Difference*	-0.10 [-0.40 ; 0.20]	-0.40 [-0.90 ; 0.01]	**0.002**
Cardiac troponin I (ng/ml)	**1st day**	0.10 [0.018 – 0.10]	0.03 [0.006 – 0.1]	**0.002**
D-Dimer	**1st day**	126 [1.16 – 239.8]	1.21 [0.60 – 165.8]	**<0.001**
CRP / albumin	**1st day**	0.24 [0.06 – 0.79]	2.40 [0.92 – 3.94]	**<0.001**
	5th day	0.31 [0.06 – 0.94]	2.07 [0.81 – 3.71]	**<0.001**
	Difference*	0.04 [-0.27 ; 0.38]	0.16 [-1.29 ; 1.44]	0.735
Urea / albumin	**1st day**	0.57 [0.47 – 0.78]	1.03 [0.73 – 1.63]	**<0.001**
	5th day	0.59 [0.49 – 0.78]	1.04 [0.66 – 1.62]	**<0.001**
	Difference*	0.03 [-0.13 ; 0.14]	-0.04 [-0.33 ; 0.49]	0.774
LDH / albumin	**1st day**	5.42 [4.29 – 6.84]	7.43 [5.74 – 9.79]	**<0.001**
	5th day	5.69 [4.52 – 7.82]	6.89 [5.92 – 12.17]	**<0.001**
	Difference*	0.14 [-88 ; 1.65]	0.46 [-2.17 ; 4.19]	0.649

(Abbreviations: WBC: White blood cell count; Hb: hemoglobin level; Plt: platelet count; Lymph: lymphocyte count; LDH: lactate dehydrogenase level; CRP: C-reactive protein level; AST: aspartate transaminase level; ALT: alanine transaminase level)

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Table 4. The relationship between clinical variables and length of hospitalization.

		Length of hospitalization (n=280)	
		r	p
WBC	**1st day**	-0.053	0.376
	5th day	0.061	0.349
Hb	**1st day**	-0.105	0.079
	5th day	-0.212	**0.001**
Plt	**1st day**	0.031	0.610
	5th day	-0.068	0.302
Lymph	**1st day**	-0.071	0.238
	5th day	-0.327	**<0.001**
Urea	**1st day**	-0.053	0.382
	5th day	0.002	0.979
Creatinine	**1st day**	-0.061	0.311
	5th day	-0.053	0.418
LDH	**1st day**	0.035	0.560
	5th day	0.205	**0.002**
CRP	**1st day**	0.070	0.247
	5th day	0.410	**<0.001**
AST	**1st day**	-0.060	0.315
	5th day	0.067	0.302
ALT	**1st day**	-0.108	0.073
	5th day	-0.058	0.378
Albumin	**1st day**	-0.144	**0.016**
	5th day	-0.353	**<0.001**
Sodium	**1st day**	-0.034	0.570
	5th day	-0.099	0.131
Potassium	**1st day**	-0.033	0.580
	5th day	-0.129	**0.048**
Calcium	**1st day**	0.041	0.491
	5th day	-0.068	0.301
Cardiac troponin I	**1st day**	0.027	0.677
D-Dimer	**1st day**	0.184	**0.002**
CRP / albumin	**1st day**	0.072	0.232
	5th day	0.444	**<0.001**
Urea / albumin	**1st day**	-0.009	0.887
	5th day	0.100	0.127
LDH / albumin	**1st day**	0.107	0.074
	5th day	0.324	**<0.001**

Table 5. The performances of clinical variables for discrimination of survival status and disease severity (*: lesser values are consistent with increased mortality or severe disease).

Variable	Interval	Survival status	Disease severity
WBC	**1st day**	0.646 (0.534 – 0.759)	0.587 (0.506 – 0.669)
	5th day	0.747 (0.635 – 0.859)	0.623 (0.543 – 0.703)
Hb*	**1st day**	-	0.615 (0.537 – 0.693)
	5th day		0.686 (0.616 – 0.756)
Lymph*	**1st day**	0.720 (0.607 – 0.834)	0.735 (0.667 – 0.804)
	5th day	0.785 (0.678 – 0.892)	0.798 (0.739 – 0.858)
Urea	**1st day**	0.725 (0.623 – 0.828)	0.751 (0.682 – 0.819)
	5th day	0.774 (0.651 – 0.897)	0.724 (0.649 – 0.798)
Creatinine	**1st day**	0.695 (0.589 – 0.801)	0.779 (0.711 – 0.846)
	5th day	0.664 (0.526 – 0.802)	0.704 (0.627 – 0.782)
LDH	**1st day**	0.600 (0.451 – 0.749)	0.586 (0.504 – 0.667)
	5th day	0.756 (0.607 – 0.904)	0.585 (0.504 – 0.666)
CRP	**1st day**	0.792 (0.689 – 0.896)	0.795 (0.735 – 0.856)
	5th day	0.801 (0.683 – 0.918)	0.782 (0.721 – 0.843)
Albumin*	**1st day**	0.741 (0.648 – 0.834)	0.794 (0.734 – 0.855)
	5th day	0.825 (0.736 – 0.914)	0.842 (0.785 – 0.898)
Cardiac troponin I	**1st day**	0.64 (0.532 – 0.747)	0.608 (0.531 – 0.686)
D-Dimer	**1st day**	-	0.632 (0.557 – 0.706)
CRP / albumin	**1st day**	0.794 (0.682 – 0.905)	0.804 (0.743 – 0.864)
	5th day	0.822 (0.699 – 0.945)	0.803 (0.744 – 0.863)
Urea / albumin	**1st day**	0.743 (0.641 – 0.845)	0.788 (0.724 – 0.853)
	5th day	0.818 (0.710 – 0.926)	0.774 (0.704 – 0.844)
LDH / albumin	**1st day**	0.705 (0.571 – 0.839)	0.677 (0.601 – 0.752)
	5th day	0.778 (0.627 – 0.928)	0.669 (0.593 – 0.744)

(Abbreviations: WBC: White blood cell count; Hb: hemoglobin level; Lymph: lymphocyte count; LDH: lactate dehydrogenase level; CRP: C-reactive protein level)

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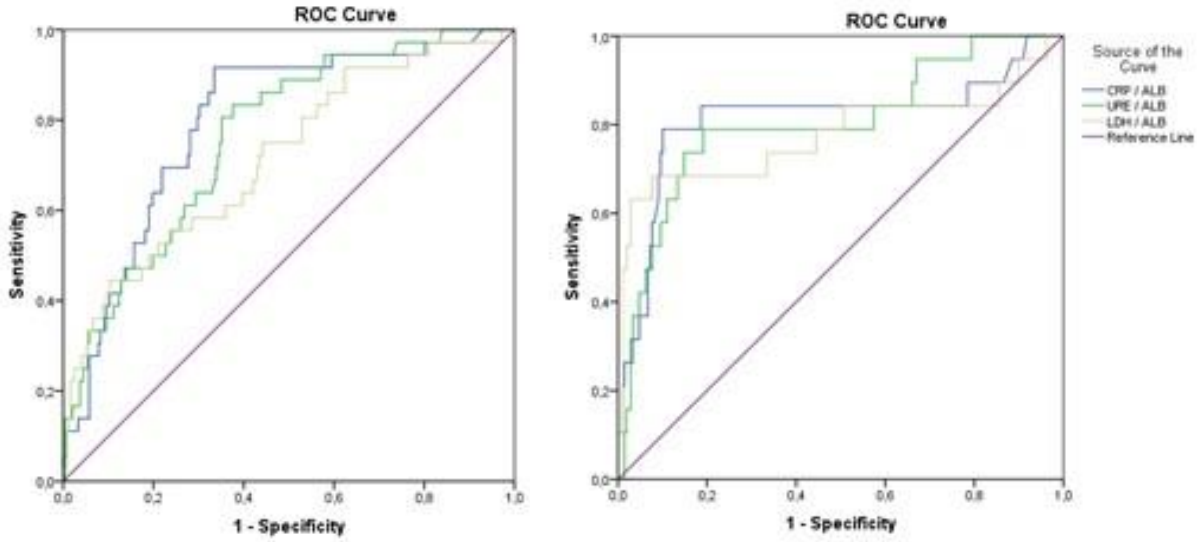
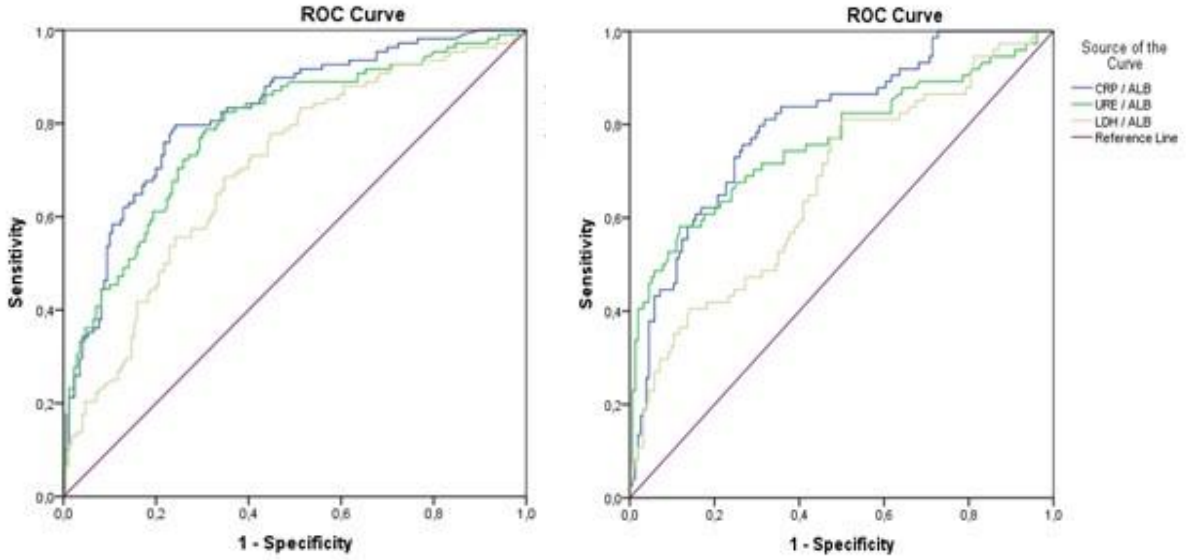


Graph 1. The performances of variables for discrimination of survival. a) Fort he first day, AUC= 0.794 (0.682 – 0.905) for CRP / albumin, AUC= 0.743 (0.641 – 0.845) for urea / albumin, AUC=0.705 (0.571 – 0.839) for LDH / albumin; b) Fort he fifth day, AUC= 0.804 (0.743 – 0.864) for CRP / albumin, AUC= 0.774 (0.704 – 0.844) for urea / albumin, AUC=0.677 (0.601 – 0.974) for LDH / albumin.



Graph 2. The performances of variables for discrimination of disease severity. a) For the first day, AUC= 0.823 (0.773 – 0.873) for CRP / albumin, AUC= 0.788 (0.732 – 0.844) for urea / albumin, AUC=0.704 (0.624 – 0.767) for LDH / albumin; b) For the fifth day, AUC= 0.801 (0.741 – 0.862) for CRP / albumin, AUC= 0.764 (0.691 – 0.836) for urea / albumin, AUC=0.669 (0.594 – 0.745) for LDH / albumin.

DISCUSSION

We assessed whether hematologic and biochemical markers might have significant prognostic value for COVID-19 patients. Our data yielded that LDH/albumin, urea/albumin, and CRP/albumin may have important clinical implications for predicting the prognosis, survival, disease severity, and length of hospitalization in this patient group in our population.

White blood cell count increased just slightly in patients with acute disease, but it increased clinically significantly in patients who died. As a result, a large increase in WBCs in patients with severe disease could indicate clinical deterioration and an increased risk of a poor outcome. Increased neutrophils may drive the rise in WBCs, whereas lymphocytes, monocytes, and eosinophils can decrease. Lymphocytes are thought to be necessary for eliminating virally infected cells in the SARS virus (12), and survival in COVID-19 may depend on the virus's ability to replenish lymphocytes destroyed by the virus (13).

Patients with serious and fatal COVID-19 infection had increasedcardiac and muscle damage biomarkers. At presentation, patients who died had substantially increased cardiac troponin levels, indicating the possibility of cardiac injury from progression to multiple organ failure, viral myocarditis, and secondary cardiac injury from organ-targeted pathologies (e.g. rheumatoid arthritis).

An image of multiple organ failure occurs when large elevations in renal biomarkers (creatinine, blood urea nitrogen), liver enzymes (aspartate aminotransferase and alanine aminotransferase), and coagulation steps were combined (1).

Since growing evidence suggests that ROS are involved in clotting and platelet activation, both compartments may be overactivated in the case of albumin degradation/oxidation. Hypoalbuminemia is linked to thrombosis risk and poor survival because of oxidative stress/inflammation (14). So far, no data on the effect of serum albumin on mortality in patients with COVID-19 have been yet published.

There are several possible explanations for the connection between hypoalbuminemia and decreased survival. First, albumin can protect against the storm of cytokine and the resulting organ failure by acting as an antioxidant and anti-inflammatory protein; in this context, the reverse relationship between troponin levels and serum albumin is of interest. Albumin has anticoagulant properties and prevents clotting and platelet activation caused by oxidative stress. As a result, hypoalbuminemia's detrimental effect on activation of clotting may be another factor contributing to poor survival. Albumin and D-dimer levels have an inverse relationship in COVID-19, with the latter being a known marker of increased mortality and thrombotic risk. Albumin can be inversely correlated with in-hospital mortality as an inverse acute phase reactant precisely because it represents a more impaired clinical presentation of COVID-19. As a result, low levels of albumin should be viewed as an anomaly rather than a predictor of poor prognosis. Since hypoalbuminemia is a symptom of chronic and acute inflammation, and a reverse relationship between albumin levels and CRP was found in this study. Our finding indicates an underlying overactive inflammatory state. Other mechanisms such as higher albuminuria may be involved in lowering albuminemia in the COVID-19 clinical setting. However, hypoalbuminemia reflecting the concomitant acute liver failure can be fairly ruled out by the current and previous studies (14).

Early detection of a severe infection can allow for earlier intervention in therapeutics and supportive measures, resulting in better outcomes [20]. Higher ALT, leukocyte count, and AST, as well as increased LDH and finally increased procalcitonin, were all established as important markers of ICU entry. LDH was the only predictor in our study significantly predicting all three outcomes: ARDS, ICU entry, and mortality. LDH is a metabolic and immune surveillance prognostic biomarker that is released when a cell's cytoplasmic membrane is damaged. The immune response to the viral infection can be weakened by these changes, leading to a more severe disease in patients with high LDH levels. Higher procalcitonin may indicate bacterial coinfection, leading to COVID-19 complications and, as a result, higher ICU admission in these patients (15).

Plasma CRP levels were linked to the severity of COVID-19 pneumonia. Therefore, it may help distinguish mild COVID-19 pneumonia patients from those with moderate to severe COVID-19 pneumonia. These findings may be an early warning sign of severe disease, allowing doctors to better stratify patients for transfer to an intensive care unit (16).

When hepatocytes are stimulated by inflammation, CRP is produced quickly. It binds to a wide range of pathogens, allowing complement activation through the classical pathway, suggesting immune activation, lymphocyte invasion, inflammation outbreak, and immune molecule consumption. Higher CRP levels in COVID-19 patients slowly recovered could be early signs of nosocomial infections, allowing physicians to start empirical antibiotic therapy sooner and avoid a worsening outcome (16).

Pan et al. suggested that the clinical course of patients with severe COVID-19 varied from admission with different outcomes. Lymphocyte count, CRP, platecrit, and LDH dynamic monitoring may help predict the prognosis of severe patients. Furthermore, with the exception of ARDS, the fatal characteristic of COVID-19 is often due to extreme systemic inflammation with induced cardiac dysfunction (17).

Some limitations of the current study must be remembered. Retrospective design, relatively small sample size, and possible impacts of socioeconomical factors may influence our results. However, considering the rapidly emerging pandemic, these findings are clinically important and may aid clinicians in identification and treatment of patients who are under more risk for severe disease. Furthermore, we do not have an external validation cohort. As a result, our findings should be considered exploratory and preliminary. The correlations we note should not be presumed to be cause and effect because subjects who are more likely to die have significant differences in some of these co-variates.

CONCLUSION

As far as we know, this is the first study to provide a detailed insight into the prognostic significances of LDH/albumin, CRP/albumin, and urea/albumin levels in COVID-19 patients. We noted that these 3 novel indicators might possess important clinical implications and their analysis may aid in the early recognition of patients at higher risk for mortality and stratification of patients for intensive care unit transfer. Identification and validation of these novel prognostic indicators necessitate the implementation of further multicentric trials on larger series.

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Ethical approval: All procedures performed in studies involving human participants were in accordance with the institutional and/or national research committee's ethical standards and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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