Research Paper:
Routine Laboratory Parameters as a Tool for Predicting Death in Patients With COVID-19

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ABSTRACT

Background: The complexity of the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) makes the clinical course of the disease develop rapidly, causing severe and deadly complications. Identifying effective laboratory biomarkers able to predicting patients based on their risk. This study aimed to look for those serobiomarkers in hospitalized patients with Coronavirus Disease 2019 (COVID-19).

Materials and Methods: In this retrospective observational study, 114 patients with COVID-19, admitted to Valian hospital in Aligudarz, City, Iran from October to December 2020 were examined. The disease outcome was followed along with the hospital course of every patient at the time of analysis. Laboratory investigations of all patients were monitored at the time of admission. A comparative analysis was done between the survivors (n=73) and non-survivors (n=41). Statistical analysis was conducted using SPSS.

Results: Of the 114 patients, 40.4% (n=41) were non-survivor, and there were significant differences in Hemoglobin (Hb), Hematocrit (Hct), Platelet (PLT), Alkaline Phosphatase (ALP), Total Bilirubin, Fasting Blood Suger (FBS), Total Iron-Binding Capacity (TIBC), Lactate Dehydrogenase (LDH), Blood Urea Nitrogen (BUN), Creatinine (Cr), Albumin (ALB), and C-Reactive Protein (CRP) between survivors and non-survivors.

Conclusion: The laboratory parameters have fundamental roles in poor prognosis and mortality prediction rated among patients with COVID-19 in the first admission. Thus, it is highly recommended to collaborate among hematologists, health managers, and clinical especialists.

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1. Introduction

Recently, inhabitants in most countries globally are coping with one of the most life-threatening and highly contagious viral diseases with majorly respiratory disorders [1, 2], commencing from December 2019 in the Huanan seafood wholesale market of Wuhan City, Hubei Province, China [3]. International Committee on the Taxonomy of Viruses (ICTV), an international committee for the classification of viruses, named this newly introduced virus as a Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) [4]. It is sensibly recognized as responsible for the Coronavirus Disease-2019 (COVID-19) pandemic [5]. This pandemic is rapidly spreading worldwide with a constantly growing population. Moreover, it has socioeconomically attracted worldwide attention as a public health concern, especially for clinical specialists, clinical laboratory scientists, and occupational or public health managers [6]. Considerably, in this context, laboratory (serological & molecular tests) and clinical diagnosis for COVID-19 infection are paramount to act as the first line for the accreditation of clinical outcomes, increasing the sensitivity of diagnosis, and efficient therapeutic management of patients [7].

Accordingly, a wide array of clinical manifestations are recorded for patients with COVID-19, ranging from mild upper respiratory tract infection to Severe Acute Respiratory Distress Syndrome (SARDS) and sepsis [8, 9], resulting in Multiorgan Failure (MOF) and death. Based on results acquired from previous epidemiological studies on COVID-19, 80% of infected individuals were diagnosed as mild cases. However, 20% of patients became severely ill, and 2%-5% died due to the massive alveolar damage. From virological aspects, it seems that due to the distribution of Angiotensin-converting enzyme 2 (ACE2) receptors in various organs, including heart, kidney, liver, colon, esophagus, brain, testis, etc., there is possibilities for MOF development in patients with COVID-19 [10, 11]. Therefore, clinical specialists should pay more attention to a comprehensive viewpoint on the clinical interpretation of the results acquired from routine laboratory tests to reach clinical outcomes.

Accordingly, healthcare staff and clinical laboratory scientists should be knowledgeable about the results of paraclinical diagnostic approaches. Such a perception helps to differentiate the clinical stage in the immunopathophysiology of COVID-19, especially in patients with non-respiratory clinical manifestations. Those manifestations include severe gastrointestinal, neurological, renal, and cardiovascular symptoms. So, there should be a novel understanding of survivors' and non-survivors' laboratory parameters to predict severity and risk for mortality [12, 13]. A large body of literature revealed that several laboratory parameters, Erythrocyte Sedimentation Rate (ESR), and C-Reactive Protein (CRP), hematologic parameters, such as Platelets (PLT) count, Prothrombin Time (PT), International Normalized Ratio (INR), D-Dimer, urine biomarkers, and tissue-specific (liver, kidney, cardiac) damage indicators can help predict clinical course, severity, and need for hospital resources and patient's outcome in patients with COVID-19 [14, 15]. As a prime instance, increased neutrophils, higher serum nitrate, and decreased number of platelets and lymphocytes can be good indicators for mortality among patients with COVID-19 (non-surviving ones) [16]. Mortality prediction is also of significant clinical prominence for patients with COVID-19 concomitantly inflicted with predisposition immune disorders, like cancers [17]. A study on Pakistani cancerous patients with COVID-19 revealed that D-dimer values of ≥0.2 mg/L and increased levels of CRP were significantly associated with mortality among deceased cases [18].

Additionally, given the variety in the clinical severity of COVID-19, laboratory characteristics of patients at admission to the emergency departments play an essential role in the admission protocol assessment of disease staging. They need critical care support [19]. Identifying effective laboratory parameters is crucial for early detection, diagnosis, prognosis, and risk stratification for mortality. Some biomarkers, such as albumin, Lactate Dehydrogenase (LDH), Alanin Aminotransferase (ALT or SGPT), Aspartate Aminotransferase (AST or SGOT), Blood Urea Nitrogen (BUN), and Creatinine (Cr), have been associated with exacerbated outcomes in other viral infections. There is a tremendous research interest in investigating those factors in patients with COVID-19 [20, 21].

To assess the risk stratification of patients with COVID-19 through data acquired from laboratory parameters, the definition of the cut-off point for biomarkers (e.g. D-Dimer) should not be underestimated. Thus, this retrospective study aimed to explore the role of laboratory characteristics of patients at admission to the hospital in predicting adverse clinical outcomes during the COVID-19 pandemic. We hope the results of this study can simplify rapid identification of patients in the healthcare settings, provide predictive biomarkers for risk stratifying patients with COVID-19, and improve clinical management with reduced adverse outcomes in high-risk patients with COVID-19.

2. Materials and Methods

Ethical approval

An application for full ethical approval was made to the research Ethics Committee of Lorestan University of Medical Sciences (Lorestan, Iran) and Shahid Valian University Affiliated Hospital (Aligudarz, Lorestan, Iran), and ethics consent was received on 20th August. The ethics approval number is IR.IAU.AGZ.REC.1400.001. The medical record department was informed before reviewing the personal records. According to the type of study, there was no need for written consent. It is worth mentioning that all of the data supporting this study's findings are available in the context of this article.

This study was conducted retrospectively, commencing from October 2020 until December 2020 in Shahid Valian University Affiliated Hospital (Aligudarz, Lorestan, Iran). The hospital information management system obtained data related to the inpatient (hospitalized) cases. The studied population included 114 patients receiving therapeutic regimens for COVID-19 and presenting positive PCR tests in their admission. In this study, patients with any other chronic liver diseases, viral diseases, co-infections, and malignancies were excluded. Among laboratory findings, Complete Blood Count (CBC), coagulation factors, routine biochemical tests, and liver function tests were compared between two admitted groups (survivors and non-survivors).

SPSS was used for the bio-statistical analysis of acquired data. The Mann–Whitney U test and Independent Samples t-test were used to compare the study groups' quantitative variables (survivors & non-survivors). Pearson's Chi-squared test or Fisher's Exact test were used to assessing the relationship between categorical variables. The collected results were expressed as Mean plus-minus Standard Deviation (SD), median (interquartile range), or frequency (percentage), wherever appropriate. Receiver Operating Characteristic (ROC) curves were used to determine the predictability of biochemical markers for the disease outcome. The Youden index was used as a summary measure of cut-off values for the Area Under the Curve (AUC). The significant level was set as $P<0.05$.

3. Results

During the study period (from 15th October 2020 to 15th December 2020), 114 patients with COVID-19 pneumonia admitted to the hospital were clinically diagnosed and included in this study. A complete laboratory data required for this study was assessed. Among them, 59(51.8%) were male, and 55(48.2%) were female. At the time of diagnosis, the Mean±SD age was 66.05±18.30 years (Table 1).

There were 183 patients (85 females and 98 males) with NCP en-rolled into the study, and these patients had complete clinical infor-mation and the laboratory data required for this study. The coagulation parameters on admission between survivors and non-survivors were compared he coagulation parameters on admission between survivors and non-survivors were compared.

The hematologic and coagulation parameters on the admission to the hospital were compared between the survivor and non-survivor groups (Table 1). The non-survivors revealed significantly lower mean Hemoglobin (Hb), Hematocrite (HCT), and PLT levels in our enrolled patients. Of note, D-dimer mean levels were also higher in non-survivors (3104.79±3069.38 ng/mL); however, those were not statistically significant compared to survivors (2776.60±3292 ng/mL).

The liver function tests mean differences, such as SGPT, SGOT, ALP, and total and direct Bilirubin between survivors and non-survivors, are also presented in Table 2. The mean±SD level of ALP in non-survivor was 331.07±149 IU/L, significantly higher than those in the surviving group (285.61±169 IU/L). Additionally, the total Bilirubin level was significantly different between the two groups; however, no significant difference was observed in SGPT and SGOT.

As per Table 3, the mean of Fasting Blood Sugar (FBS), total Iron-Binding Capacity (TIBC), LDH, BUN, and Cr levels were significantly higher in non-survivors Albumin was lower. The Mean±SD level of FBS in non-survivors was 212.29±83 mg/dL. 145.18±56 mg/dL in survivors. The Albumin levels in non-survivors were significantly lower than in survivors (2.7±0.37 vs. 3.2±0.53 g/dL).

The qualitative assessments on CRP and categories of survivor and non-survivor groups showed a significant association ($P<0.05$). Based on these findings, 69.8% of non-survivor had at least two positive results of the CRP test; however, 30.2% of them were CRP negative or 1 positive. Furthermore, the results acquired from investigating the relationship of sex and survival group variables were not statistically significant ($P>0.05$) 46(40.4%) of included population expired, of whom 19(41.3%) were female, and 27(58.7%) were male (Table 4).

Table 1. Hematologic and coagulation parameters in the surviving and non-surviving groups

Variable	Group	No.	Mean±SD		P
Age, y	Non-survivor	46	68.33±15.053	66.05±18.30	0.569
	Survivor	68	64.51±20.171		
WBC (cell/mm^3)	Non-survivor	46	11.426±6.5636	10.12±5.7	0.056
	Survivor	68	9.250±4.9424		
RBC (million/mm^3)	Non-survivor	46	4.0261±0.9599	4.42±1.1	0.514
	Survivor	68	4.8229±1.2585		
Hb (gr/dL)	Non-survivor	46	11.239±2.2874	12.24±2.81	0.002
	Survivor	68	12.921±2.9483		
HCT (%)	Non-survivor	46	34.904±6.7868	38.60±8.82	<0.001
	Survivor	68	41.101±9.2042		
PLT (cell/mm^3)	Non-survivor	46	175.39±105.017	200.19±109.24	0.012
	Survivor	68	216.97±109.596		
D-Dimer (ng/mL)	Non-survivor	46	3104.79±3069.38	2909.03±31	0.145
	Survivor	68	2776.60±3292.06		
PT (s)	Non-survivor	44	17.211±4.7797	17.63±4.98	0.859
	Survivor	66	17.920±5.1299		
PTT (s)	Non-survivor	44	38.136±19.7973	35.11±13.59	0.384
	Survivor	65	33.071±6.1716		
INR	Non-survivor	43	1.3588±0.31758	1.33±0.28	0.624
	Survivor	65	1.3218±0.26322		
ESR (mm/h)	Non-survivor	17	52.12±30.377	46.28±31.83	0.268
	Survivor	43	43.98±32.448		

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WBC: White Blood Cell; RBC: Red Blood Cell; Hb: Hemoglobin; HCT: Hematocrit; PLT: Platelet; PT: Prothrombin Time; PTT: Partial Thromboplastin Time; INR: International Normalized Ratio; ESR: Erythrocyte Sedimentation Rate.

Receiver Operating Curve (ROC) analysis for fatalities due to COVID-19 showed Hb at a cut-off value of >14 gr/dL (AUC: 0.674, P<0.05), HCT at a cut-off value of <36% (AUC: 0.707, P<0.05), PLT at a cut-off value of <179 ×10^3 /µL (AUC: 0.640, P<0.05), LDH at a 639.2 U/L cut-off value (AUC: 0.652, P<0.05), BUN at a cut-off value of 21 mg/dL (AUC: 0.679, P<0.05) ,Cr at a cut-off of 1.19 mg/dL (AUC: 0.623, P<0.05), Albumin at a cut off value of <3 g/dL (AUC: 0.768, p<0.05) total Bilirubin at a cut-off of 0.74 mg/dL (AUC:0.676, P<0.05), and ALP at a cutoff value of 266 IU/L (AUC: 0.633, P<0.05) were the suggested biomarkers predicting death at admission (Table 5). ROC curves for laboratory characteristics of patients with COVID-19 are shown in Figures 1 and 2.

4. Discussion

The most disastrous viral Pandemic, COVID-19, has affected millions of individuals with augmented immunopathology, high morbidity, and high mortality. In addition to pulmonary complications, COVID-19 causes severe damages to other body systems, including the cardiovascular system, liver, and kidneys, as reported

Table 2. Liver function indexes in the surviving and non-surviving groups

Liver Function Tests	Group	No.	Mean±SD		P
SGPT (IU/L)	Non-survivor	38	42.50±32.261	48.80±55.64	0.784
	survivor	53	53.32±67.589		
SGOT(IU/L)	Non-survivor	42	53.38±35.887	60.10±56.87	0.722
	survivor	61	64.72±67.577		
ALP (IU/L)	Non-survivor	42	331.07±149.880	303.97±162.67	0.021
	Survivor	62	285.61±169.513		
Total Bilirubin (mg/dL)	Non-survivor	36	1.3803±0.90745	1.32±1.70	0.007
	survivor	44	1.2875±2.15401		
Direct Bilirubin (mg/dL)	Non-survivor	36	0.5167±0.51517	0.48±0.51	0.443
	Survivor	42	0.4576±0.52263		

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SGPT: Serum Glutamic Pyruvic Transaminase; SGOT: Serum Glutamic-Oxaloacetic Transaminase; ALP: Alkaline Phosphatase.

Table 3. Biochemical factors in the survivors and non-survivors

Variable	Group	No.	Mean±SD		P
FBS (mg/dL)	Non-survivor	17	212.29±83.165	174.44±76.27	0.003
	Survivor	22	145.18±56.573		
TIBC (µg/dL)	Non-survivor	5	298.80±28.595	267.54±56.80	0.04
	Survivor	8	248.00±62.694		
Serum Iron(µg/dL)	Non-survivor	4	24.75±9.106	54.92±75.11	0.063
	Survivor	9	68.33±88.170		
LDH (U/L)	Non-survivor	40	1008.223±612.2388	873.94±558.00	0.013
	Survivor	52	770.656±494.1399		
BUN (mg/dL)	Non-survivor	44	36.86±22.760	30.81±20.25	0.002
	Survivor	62	26.52±17.201		
Cr(mg/dL)	Non-survivor	43	1.9079±1.87008	1.60±1.44	0.033
	Survivor	61	1.3884±1.01275		
Ferritin (µg/L)	Non-survivor	12	483.4833±339.41944	375.68±292.00	0.162
	Survivor	25	323.9400±258.46249		
Albumin (g/dL)	Non-survivor	8	2.7238±0.37535	3.05±0.53	0.040
	Survivor	14	3.2443±0.53386		

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FBS: Fasting Blood Sugar; TIBC: Total Iron-Binding Capacity; LDH: Lactate Dehydrogenase; BUN: Blood Urea Nitrogen; Cr: Creatinine.

Table 4. CRP and Categorical variables in the survivors and non-survivors

Variable	Category	No. (%)		Total	P-Value (Pearson's Chi-Squared)
		Non-Survive Group	Survive Group		
Gender	Female	19(41.3)	36(52.9)	55(48.2)	0.22
	Male	27(58.7)	32(47.1)	59(51.8)	
CRP*	Neg	4(9.3)	18(29.5)	22(21.2)	0.024
	1+	9(20.9)	9(14.8)	18(17.3)	
	2+	13(30.2)	8(13.1)	21(20.2)	
	3+	17(39.5)	26(42.6)	43(41.3)	

*C-Reactive Protein (CRP) test is qualitative

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Table 5. ROC analysis of clinical laboratory data to predict in-hopital death

Variable	AUC	Sensitivity	Specificity	95%CI	P
Hb	0.647	35.29	93.48	0.579-0.758	<0.05
Hct	0.690	75.00	60.87	0.614-0.789	<0.05
PLT	0.656	57.35	73.91	0.544-0.727	<0.05
D-Dimer	0.581	57.35	65.22	0.484-0.672	0.13
PT	0.510	84.85	25.00	0.413-0.607	0.86
PTT	0.549	64.62	74.73	0.451-0.645	0.38
ESR	0.592	67.44	58.82	0.458-0.717	0.26
ALB	0.768	64.29	87.50	0.541-0.919	<0.05
Total Bili	0.715	56.82	80.56	0.562-0.776	<0.05
ALP	0.633	70.97	61.90	0.533-0.726	<0.05
LDH	0.664	63.46	62.50	0.545-0.748	<0.05
BUN	0.718	56.45	72.73	0.582-0.767	<0.05
Cr	0.623	63.93	60.47	0.522-0.716	<0.05

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Hb: Hemoglobin; Hct: Hematocrit; PLT: Platelet; PT: Prothrombin time; PPT: Partial Thromboplastin Time; ESR: Erythrocyte Sedimentation Rate; ALB: Albumin; Total Bili: Total Bilirubin; ALP: Alkaline Phosphatase; LDH: Lactate Dehydrogenase; BUN: Blood Urea Nitrogen; Cr: Creatinine.

during the SARS pandemic in 2003 [22]. Hospitalized patients with immune predisposition disorders and elderlies are the ones that should be highly considered for risk stratification [23, 24]. Routine laboratory tests provide helpful information about the progression and severity of COVID-19. Alterations in the serum levels of several biomarkers play an indispensable role in determining the disease's prognosis and staging.

In this study, biochemistry and hematology markers were retrospectively evaluated in two groups of patients, including the survivors and the non-survivors of COVID-19. LDH is an intracellular enzyme involved in the interconversion of pyruvate to lactate with five isoenzymes. LDH is found in almost all tissues; however, it is more concentrated in kidneys, muscles, and hepatocytes [25]. It is increased after tissue damage, cancer, and in-

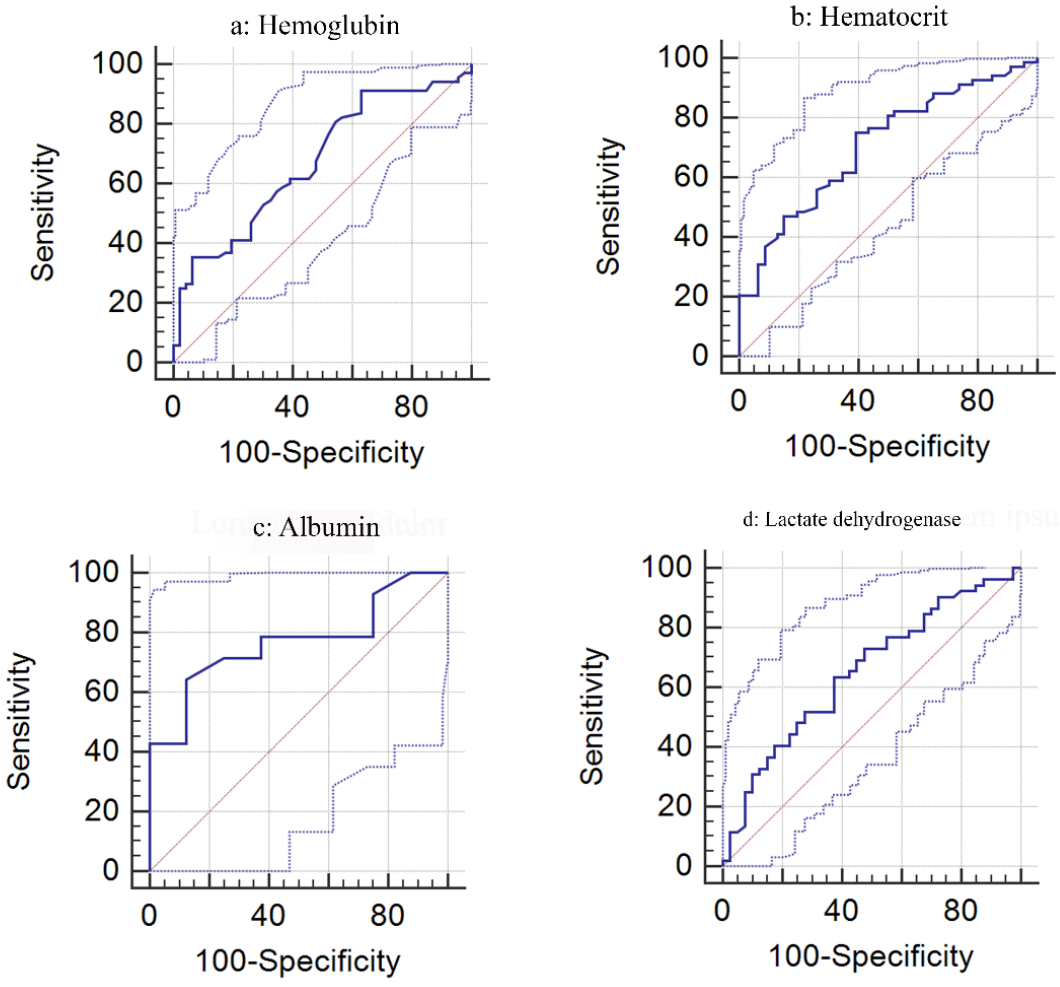

Figure 1. Roc for laboratory characteristics of COVID-19 patients (Hb, HCT, Albumin, LDH)

fections [26, 27]. According to our results, it was found that LDH has risen significantly in the non-survivors compared to the survivors, i.e., in line with the results from a study conducted by Elena Aloisio and associates. LDH levels in non-surviving individuals increased significantly compared to the surviving group [28]. It seems that significantly increased LDH can be considered a potential biomarker in predicting the severity of COVID-19 [26, 29].

Liver dysfunction is a complication of COVID-19, which can be due to the direct tissue damage through viral pathogenesis or possible side effects of administrated drugs [30]. The liver impairment in COVID-19 is not a prominent feature; however, the mechanism and importance of elevated ALP and total Bilirubin must be considered in the association of prognosis. Accordingly, numerous cases of changes in liver enzymes have been reported in patients with COVID-19, including increased ALT, AST, LDH, Y-Gammaglutamyl Transferase (GGT), Superoxide Dismutase (SOD), ALP, and total Bilirubin [31, 32]. We found that ALP levels were higher in non-survivor. A mild increase in ALP was observed in a study of liver function tests in COVID-19 patients [33, 34].

Additionally, the extent of bilirubin in non-survivors had shown significantly increased levels. In similar studies, an increase in total bilirubin has been reported in patients with severe COVID-19 [31, 32]. In our study, the amount of albumin has decreased in the non-survivors, which was similar to the results of an investigation by Huang et al., who reported that serum albumin level <35 g/L at presentation increased the risk of death in COVID-19 by at least 6-fold [28].

On the other hand, a decrease in albumin levels is associated with a poor prognosis [35]. Oxidative stress is among coronaviruses' cell and tissue damage mechanisms [36].

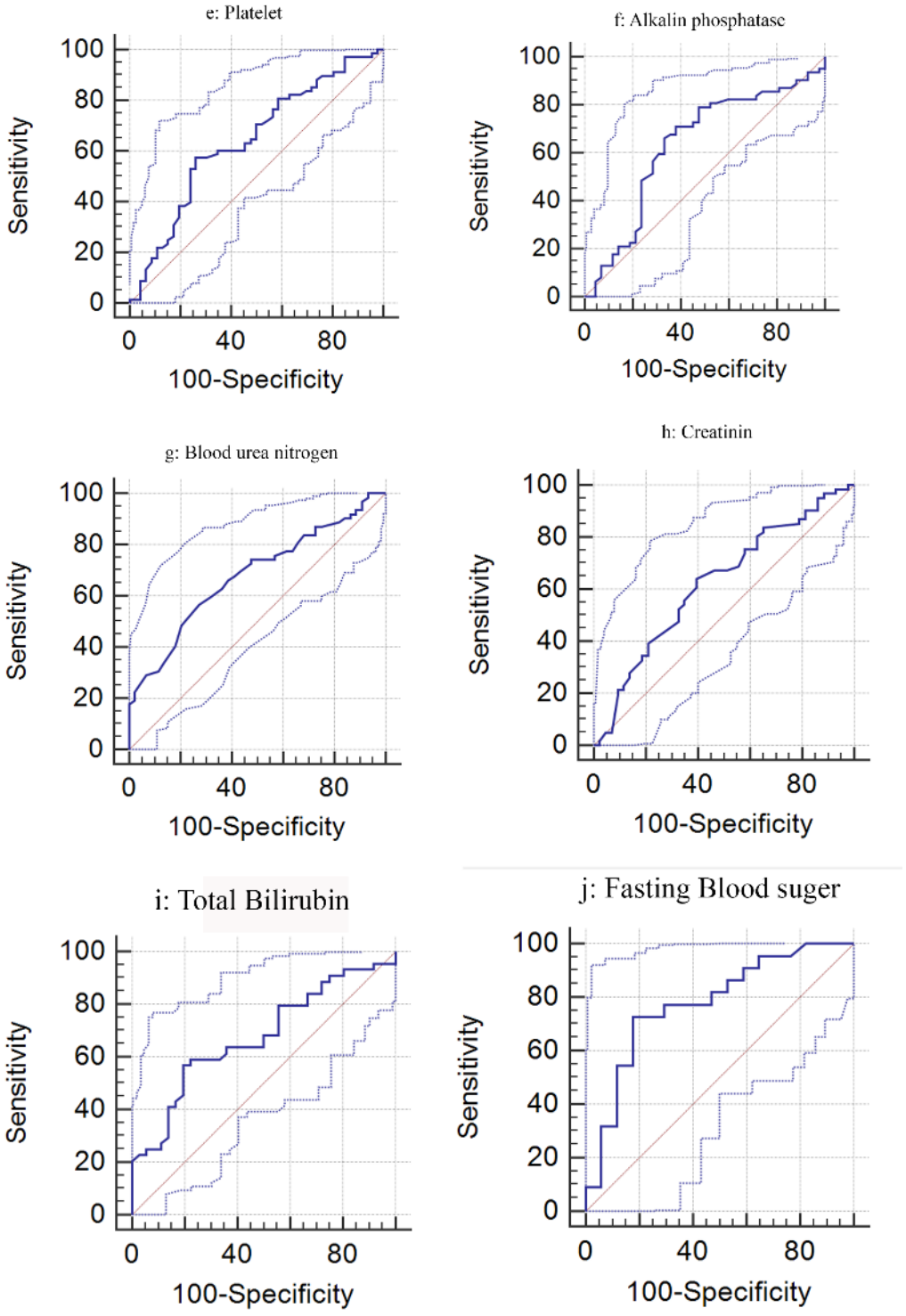

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Figure 2. ROC for laboratory characteristics of COVID-19 patients (PLT, ALP, BUN, Cr, Total Bilirubin, FBS)

Serom albumin is an acute phase reactant with antioxidative properties. It provides an abundantsource of free thiols that can scavenge Reactive Oxidant Species (ROS). Under the condition of oxidative stress, albumin may undergo irreversible oxidation, which impairs the albumin's antioxidative property and cell damage [37].

Acute kidney injury is a relatively common complication of COVID-19 and is associated with patient mortality [38, 39]. In our study, data have revealed that the levels of BUN and Cr have significantly elevated in non-survivors. Along with the elevated levels of Bun, Cr, and LDH, COVID-19 associated renal failure probably

affects the prognosis. The results of a meta-analysis by Lichen Ouyang et al. indicated that BUN and Cr levels in non-survivor groups had elevated significantly. The prevalence of acute kidney injury in non-surviving patients was several times higher than in surviving ones. One possible mechanism for this complication is the increased expression of ACE2 in the renal tubules, which acts as a receptor for the virus and an uncontrolled immune response against the virus-infected tissues [38]. Another mechanism for causing acute kidney damage is the cytokine storm created following a viral infection that can lead to sepsis, shock, hypoxia, and rhabdomyolysis of the kidney in patients with COVID-19 [40]. The generation of microthrombosis in COVID-19, a pervasive complication in the body, can cause kidney damage by inducing ischemia in kidney tissue [41].

The results of the FBS evaluation were also remarkable. In the non-surviving group, the level of FBS has shown a significant increase compared to the surviving individuals. The results of other studies also indicate an increase in blood glucose with the severity of the disease and hyperglycemia, which is associated with a poor prognosis [13]. Regardingly, the immune system affects systemic glucose homeostasis through persistent inflammation and helps raise blood sugar, developing systemic insulin resistance [42, 43]. In this case, specific immune functions like activated integrins inhibit insulin secretion and function [44].

Evaluating hematological parameters has also has demonstrated a decrease in Hb, HCT, and PLT in non-surviving individuals. Consistent with our findings, several researchers in their meta-analysis study on 1582 patients with COVID-19 reported that patients in the severe group had significantly lower Hb levels than non-severe patients [45]. Seied Asadollah Mousavi et al. documented significant differences between low concentrations of Hb, admission to intensive care unit, and death [46]. Inflammation extremely affects erythropoiesis through abnormal iron metabolism. It inhibits erythroid progenitor and precursor cells and reduces erythrocyte lifespan [47]. Thrombocytopenia is a well-known disorder in patients with COVID-19 [48]. In this context, SARS-CoV-2 is thought to inhibit the hematopoiesis in the bone marrow through specific receptors to reduce the initial PLT formation and lead to thrombocytopenia [49].

5. Conclusion

According to the burgeoning rate of mortality and morbidity induced by COVID-19, it is essential to use comprehensive views on the usage of the laboratory biomarkers for patients with a high risk of COVID-19-associated death. Additionally, risk stratification should be assessed for patients with COVID-19 who have a developing progression from mild to severe disease. This point can make a prolonged time for targeted therapies. Considering hematologic and biochemical laboratory diagnostic tests in viral infections can prevent deteriorating clinical outcomes in hospitalized patients with COVID-19.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Ethics Committee of Lorestan University of Medical Sciences, Lorestan, and Shahid Valian University Affiliated Hospital, Aligudarz, Lorestan (Code: IR.IAU.AGZ.REC.1400.001). According to the type of study, there was no need for written consent.

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Authors' contributions

All authors equally contributed to preparing this article.

Conflicts of interest

The authors declared no conflict of interest.

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