A Comprehensive Appraisal of Laboratory Biochemistry Tests as Major Predictors of COVID-19 Severity

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● **Context.**—A relevant portion of coronavirus disease 2019 (COVID-19) patients develop severe disease with negative outcomes. Several biomarkers have been proposed to predict COVID-19 severity, but no definite interpretative criteria have been established to date for stratifying risk.

Objective.—To evaluate 6 serum biomarkers (C-reactive protein, lactate dehydrogenase, D-dimer, albumin, ferritin, and cardiac troponin T) for predicting COVID-19 severity and to define related cutoffs able to aid clinicians in risk stratification of hospitalized patients.

Design.—A retrospective study of 427 COVID-19 patients was performed. Patients were divided into groups based on their clinical outcome: nonsurvivors versus survivors and patients admitted to an intensive care unit versus others. Receiver operating characteristic curves and likelihood ratios were employed to define predictive cutoffs for evaluated markers.

Results.—Marker concentrations at peak were signifi-

cantly different between groups for both selected outcomes. At univariate logistic regression analysis, all parameters were significantly associated with higher odds of death and intensive care. At the multivariate analysis, high concentrations of lactate dehydrogenase and low concentrations of albumin in serum remained significantly associated with higher odds of death, whereas only low lactate dehydrogenase activities remained associated with lower odds of intensive care admission. The best cutoffs for death prediction were greater than 731 U/L for lactate dehydrogenase and 18 g/L or lower for albumin, whereas a lactate dehydrogenase activity lower than 425 U/L was associated with a negative likelihood ratio of 0.10 for intensive treatment.

Conclusions.—Our study identifies which biochemistry tests represent major predictors of COVID-19 severity and defines the best cutoffs for their use.

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At the end of 2019, an outbreak of atypical pneumonia of unknown cause was detected in Wuhan, the capital of the province of Hubei, China.[1] The etiologic agent of this disease was later identified to be a novel coronavirus, named "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2), phylogenetically similar but distinct from other coronaviruses known to cause disease in humans, such as human severe acute respiratory syndrome and Middle East respiratory syndrome.[2] The disease caused by SARS-CoV-2, named COVID-19, has since spread worldwide, with the World Health Organization recognizing it as a pandemic on March 11, 2020.[3]

Most patients infected with SARS-CoV-2 are asymptomatic or present with an uncomplicated mild illness charac-

terized by fever, dry cough, nausea, asthenia, and myalgia.[2] Up to 14% of patients, however, can evolve toward the development of a severe respiratory disease, characterized by radiologic findings of interstitial pneumonia and progressively worsening respiratory impairment requiring ventilatory assistance. About 5% of patients ultimately develop a full-on acute respiratory distress syndrome, requiring admittance to an intensive care unit (ICU) to administer invasive mechanical ventilatory support. These patients are also at risk of developing sepsis, septic shock, and multiorgan failure. Major risk factors for development of severe disease are old age, male sex, and comorbidities, such as metabolic and cardiovascular disease.[2]

Many laboratory test results have been reported to be significantly altered in patients with severe COVID-19. In addition to the acute-phase proteins, such as C-reactive protein (CRP), ferritin, and procalcitonin, studies have reported significant differences in levels of hematologic and hemostasis parameters, such as lymphocyte and neutrophil granulocyte count, and D-dimer, and differences in other biochemistry markers, such as lactate dehydrogenase (LDH), cardiac troponins, serum albumin, aminotransferases, and creatinine.[2,4–6] Most of these parameters are commonly requested in daily clinical practice; however, to the best of our knowledge, no specific interpretative criteria (ie, cutoffs able to aid in the evaluation of COVID-19 severity) have been reported so far. The aim of this study

Table 1. Baseline Characteristics of Coronavirus Disease 2019 (COVID-19) Patients Included in the Study

	Total	Nonsurvivors	Survivors	P	ICU	Non-ICU	P
Age, median (IQR)	61 (50–73)	73 (67–80)	58 (48–69)	<.001	64 (57–70)	61 (50–73)	.74
Sex, No./total (%)							
Female	134/427 (31)	19/89 (21)	115/338 (34)	.03	6/47 (13)	128/380 (34)	.006
Male	293/427 (69)	70/89 (79)	223/338 (66)		41/47 (87)	252/380 (66)	
Comorbidities, No./total (%)							
Hypertension	134/409 (33)	33/71 (46)	101/338 (30)	.01	11/34 (32)	123/375 (33)	.89
Cardiovascular disease	85/409 (21)	31/71 (44)	54/338 (16)	<.001	3/34 (9)	82/375 (22)	.009
Diabetes mellitus	56/409 (14)	17/71 (24)	39/338 (12)	.01	5/34 (15)	51/375 (14)	.94
Chronic respiratory disease	49/409 (12)	14/71 (20)	35/338 (10)	.047	3/34 (9)	46/375 (12)	.75
Obesity	10/409 (2)	6/71 (8)	4/338 (1)	.002	1/34 (3)	9/375 (2)	.69
HIV infection	9/409 (2)	0/71 (0)	9/338 (3)	.02	1/34 (3)	8/375 (2)	.76

Abbreviations: HIV, human immunodeficiency virus; ICU, intensive care unit; IQR, interquartile range.

was to obtain a comprehensive appraisal of the best performing laboratory biochemistry tests in predicting COVID-19 severity in a large group of patients and to define related cutoffs useful for their stratification in terms of prediction of ICU admission and mortality.

MATERIALS AND METHODS

Study Population

We performed a retrospective, observational study on adult (age ≥18 years) COVID-19 patients admitted between February 21 and March 31, 2020, to the "Luigi Sacco" academic hospital in Milan, 1 of the 2 national reference centers for infectious diseases in Italy. Patients were hospitalized in 1 of the following isolation wards reserved exclusively for COVID-19 care: 1 ICU, 2 infectious disease units, 1 pulmonology unit, and 4 low-medium intensity care wards. All patients had clinical and/or radiologic findings highly suggestive for COVID-19 at admission, and SARS-CoV-2 infection was confirmed by detection of viral RNA on nasopharyngeal material, using a real-time reverse transcription polymerase chain reaction method. The Institutional Review Board approved this study.

Analytic Methods

Patients' data were extracted from the hospital information systems. The CRP, LDH, D-dimer, albumin, ferritin, and cardiac troponin T (cTnT) results were collected. Because more than 1 test result was available for each patient, the worst result of the whole hospitalization period was considered for analysis (ie, the highest result for all evaluated analytes except for albumin, for which the lowest result was selected). Albumin, CRP, and LDH were measured on the Alinity platform (Abbott Diagnostics) by using immunoturbidimetry (CRP and albumin) and enzymatic (LDH) assays, respectively. D-dimer was measured on the ACL TOP 750 platform (IL-Werfen) and results expressed in fibrinogen-equivalent units (FEUs). Ferritin and cTnT were measured using a chemiluminescent microparticle immunoassay on the Alinity platform and a high-sensitivity electrochemiluminescence immunoassay on a Cobas e601 platform (Roche Diagnostics), respectively. Data about analytic performance of employed methods were previously published.[7–13] Adult reference intervals (all derived from previously performed ad hoc local studies) are: CRP, up to 10 mg/L; albumin, 35 to 50 g/L; LDH, 125 to 220 U/L; D-dimer, up to 500 µg/ L FEU (age ≤50 years) and up to "age years × 10" µg/L FEU (age >50 years); ferritin, 100 to 250 µg/L; and cTnT, up to 15 ng/L.

Conversion factors from conventional units to SI units are: CRP, from mg/L to nmol/L multiply by 9.5238; albumin, from g/L to mmol/L multiply by 0.0150; LDH, from U/L to nkat/L multiply by 16.6667; ferritin, from µg/L to nmol/L multiply by 0.0022.
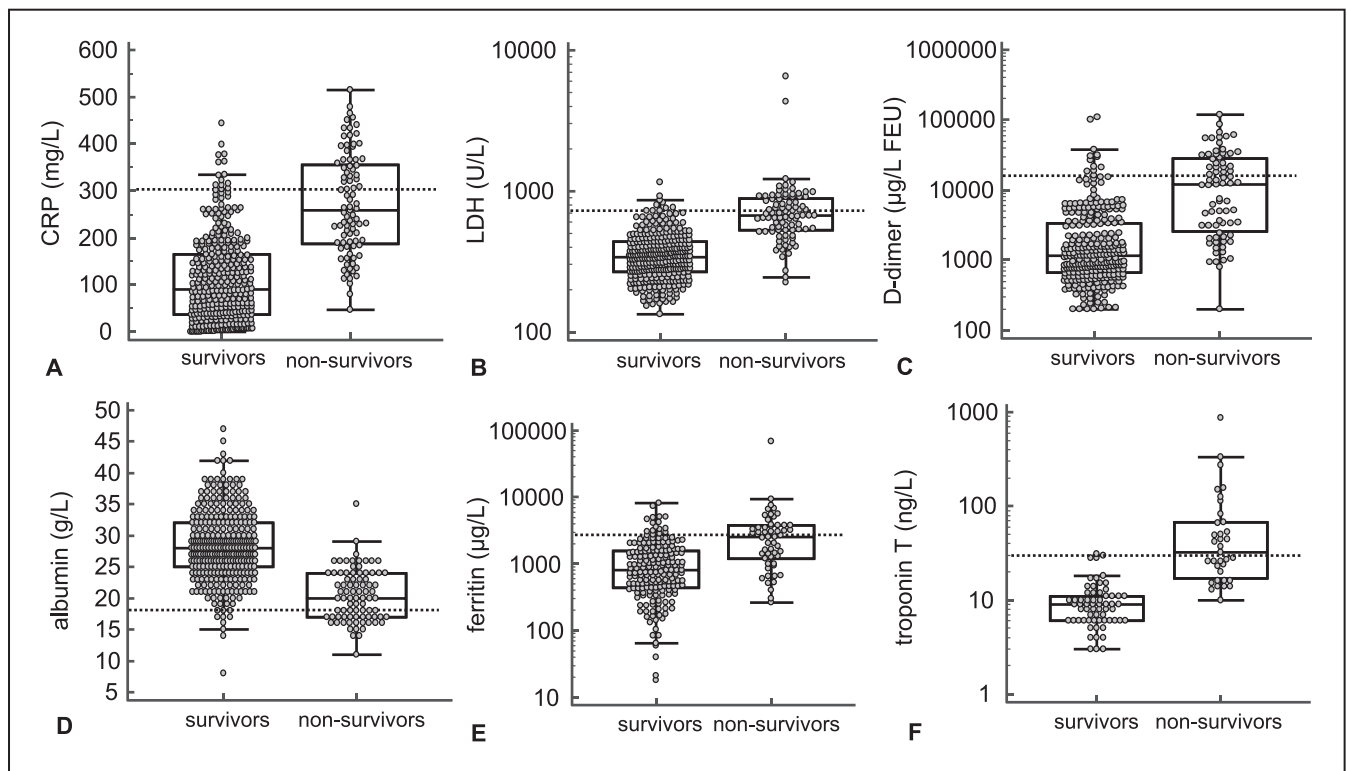
Statistical Analysis

Biomarkers were evaluated according to the following outcomes: (1) death during hospitalization (nonsurvivors) versus hospital discharge after clinical recovery (survivors), and (2) hospitalization in ICU versus hospitalization in nonintensive wards. Demographic, clinical, and laboratory characteristics were compared between patients separated in these categories. Data were reported as percentages for categoric variables and median with interquartile range (IQR) for quantitative variables. Differences between variables in different categories were assessed by applying a χ^2 test (categoric) and Mann-Whitney rank-sum test (quantitative).

Optimum biomarker cutoffs both for predicting death and for excluding necessity for intensive care were extrapolated from a receiver operating characteristic (ROC) analysis, by maximizing specificity (outcome 1) and sensitivity (outcome 2), respectively. Likelihood ratios (LRs) and predictive values (PVs) associated with selected cutoffs were then derived. Univariate logistic regression was used to estimate variables' odds ratios (ORs) and their 95% confidence intervals (CIs) in relation to the selected outcome. A multivariate logistic regression model was then applied to variables significant at the univariate analysis. Final selection of variables included in the multivariate model was done by applying a stepwise approach. A P value <.05 denoted statistical significance. All analyses were performed using MedCalc software.

RESULTS

In the evaluated period, 518 COVID-19 patients were admitted. Of these, 91 patients were excluded from further analysis because they were still hospitalized as of April 13, 2020, when we started the collection of data. A total of 427 COVID-19 patients with definite clinical outcomes were therefore included in the final analyses. Of these, 89 patients (20.8%) died during the hospitalization period, whereas 338 were discharged after clinical recovery. Furthermore, 47 of the 427 patients (11.0%) required admission to the ICU, whereas 380 stayed in non–intensive care COVID units during the entire hospitalization period. Median age for all patients was 61 years (IQR, 50–73 years), and 293 of the 427 patients (69%) were male.

Demographic and medical history data for the studied population are shown in Table 1. Information about past medical history could not be retrieved for 18 patients (13 in the ICU group and 5 in the non-ICU group) who died suddenly. The most frequent comorbidity was hypertension, present in 134 of the 409 patients with complete data available, followed by cardiovascular disease (85 of the 409

Figure 1. Box and whisker plots showing the distribution of results of (A) C-reactive protein (CRP), (B) lactate dehydrogenase (LDH), (C) D-dimer, (D) albumin, (E) ferritin, and (F) troponin T in studied coronavirus disease 2019 (COVID-19) patients, according to outcome 1 (death during hospitalization [nonsurvivors] versus hospital discharge after clinical recovery [survivors]). The dashed lines indicate the cutoffs selected by maximizing the specificity—that is, reducing the number of false positives—of each test. Note that, except for CRP and albumin, the scale in y-axis is logarithmic.
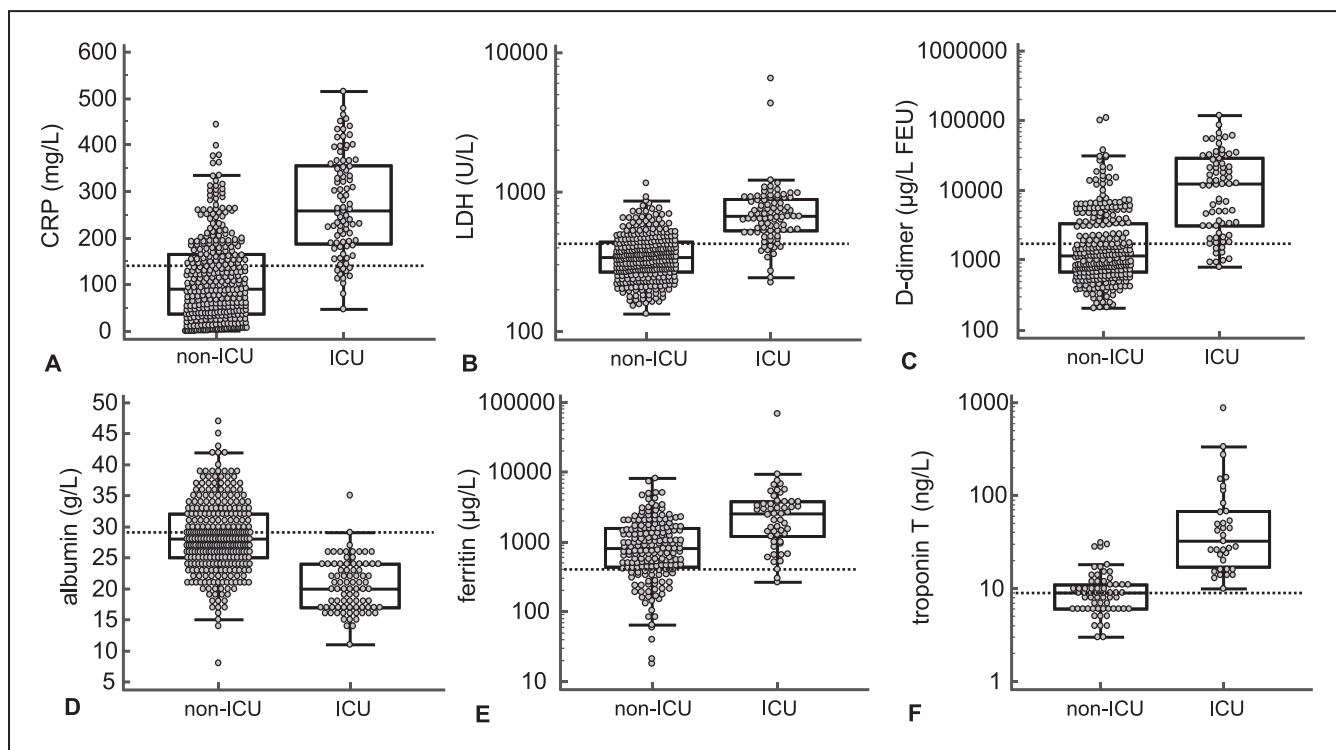
patients; 21%) and diabetes mellitus (56 of the 409 patients; 14%). In nonsurvivors, age and the frequency of all comorbidities, except for human immunodeficiency virus infection, which was more frequent in survivors, were significantly higher than in surviving patients. On the other hand, no significant differences in age and frequency of comorbidities were found between patients admitted to the ICU and other patients, except for cardiovascular disease, which was more frequent in the non-ICU group (Table 1).

Values of selected laboratory tests were significantly different between groups for both the examined outcomes (Figures 1 and 2; Table 2). Figure 3 shows ROC curves for the evaluated tests according to the ability to predict the 2 selected outcomes. For predicting patient death, cTnT displayed the best accuracy, with an area under the ROC curve (AUC) of 0.94 (95% CI, 0.90–0.98), followed by LDH, albumin, and CRP (Table 3).[14] The best cutoffs maximizing clinical specificity and minimizing false-positive test results in predicting patient death are reported in Table 3 (and displayed in Figures 1 and 2), together with the corresponding positive LR and positive PV. In this regard, the results showed a relevant capability for cTnT greater than 30 ng/L (positive LR, 31.9; 95% CI, 4.4–228.8) and LDH greater than 731 U/L (positive LR, 19.7; 95% CI, 9.1–42.7) to foresee death in COVID-19 patients. It should be noted, however, the wide CI associated with cTnT due to the relatively low number of patients (n = 98) who underwent measurements of this biomarker. Given the relevant association found between elevated cTnT and mortality, we checked the death causes of the 35 deceased patients for whom cTnT was

measured during hospitalization. For 34 of these patients (97%), the main cause of death was respiratory failure due to pneumonia complications, with no direct evidence of mortal cardiac events. Only 1 patient—who, however, had a relatively low peak cTnT measurement of 14 ng/L—died of cardiac arrest after the insurgence of a nonshockable arrythmia unresponsive to manual cardiopulmonary resuscitation.

The best power to predict ICU admission was found for serum albumin, with an AUC of 0.89 (95% CI, 0.84–0.94), followed by CRP and LDH (Table 4). Using a cutoff of 29 g/L or greater, albumin displayed the best accuracy to exclude the need for ICU admission. Here, in evaluating the test performance, sensitivity was favored to minimize the risk of false-negative results, that is, patients with test results lower (higher for albumin) than cutoff who are actually admitted to ICU.

At univariate analysis, ORs for death during hospitalization were significantly higher for older patients and patients with concentrations of all evaluated tests above the selected cutoffs (under the selected cutoff for albumin; Table 5). On the other hand, patient age was not a significant predictor of ICU admission, whereas all the evaluated laboratory tests were (Table 6). In the multivariate analysis, done by including only the 72 patients who had complete data for all considered variables, age, high serum concentrations of LDH, and low serum concentrations of albumin remained significantly associated with high OR of death, whereas only LDH concentrations less than 425 U/L were significantly associated with low OR for ICU admission (Tables 5 and 6).

Figure 2. *Box and whisker plots showing the distribution of results of (A) C-reactive protein (CRP), (B) lactate dehydrogenase (LDH), (C) D-dimer, (D) albumin, (E) ferritin, and (F) troponin T in studied coronavirus disease 19 (COVID-19) patients according to outcome 2 (hospitalization in intensive care unit [ICU] versus hospitalization in nonintensive wards). The dashed lines indicate the cutoffs selected by maximizing the sensitivity—that is, reducing the number of false negatives—of each test. Note that except for CRP and albumin, the scale in the y-axis is logarithmic.*

After multivariate analysis, cTnT maintained borderline significance ($P = .06$) as a predictor of death.

DISCUSSION

Months after the initial spread of SARS-CoV-2–related disease in China, it is now evident from published studies that, together with age and other risk factors such as comorbidities, alterations of different laboratory markers can be useful to assess disease severity and risk of evolution toward critical stages.[15] However, available studies only reported purely descriptive analyses of the studied populations, and no clear interpretative criteria for commonly
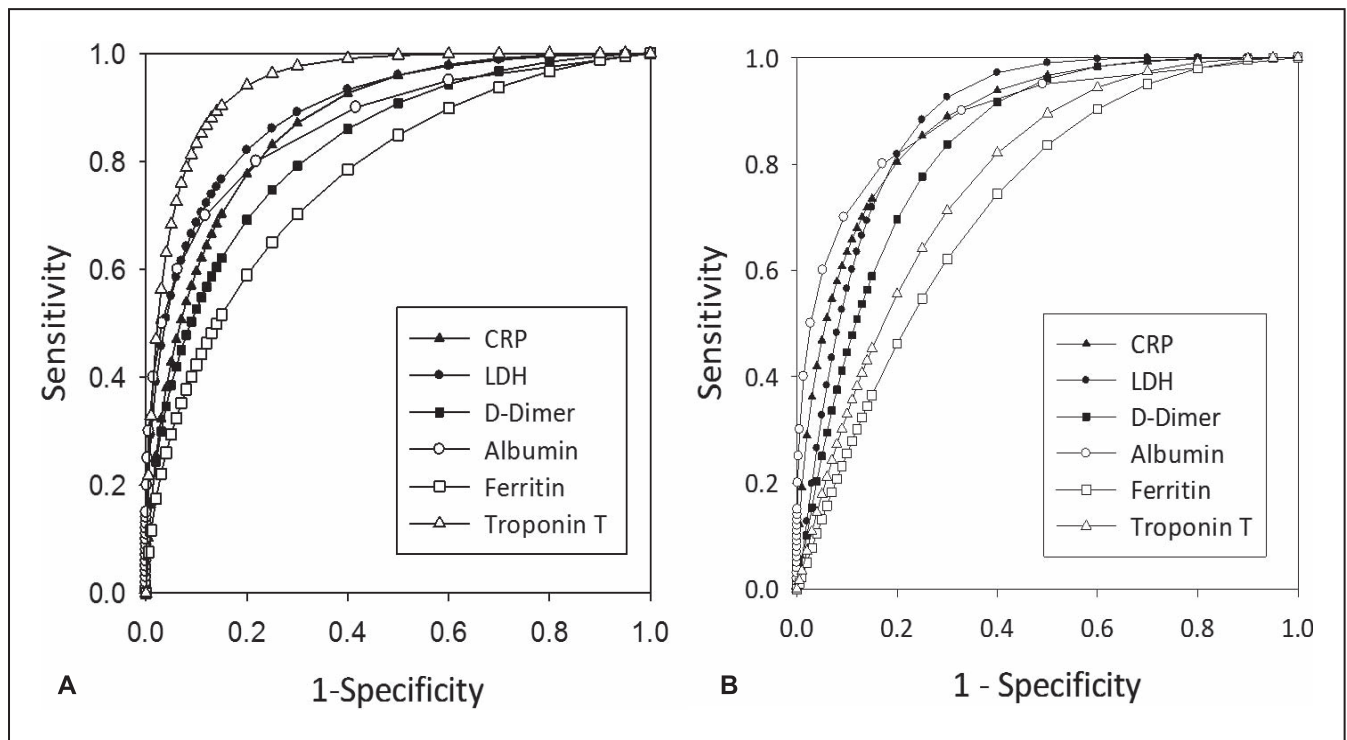
Table 2. Laboratory Findings in Coronavirus Disease 2019 (COVID-19) Patients Included in the Study[a]

	Nonsurvivors		Survivors		
	No.	Median (IQR)	No.	Median (IQR)	*P*
CRP, mg/L	89	258 (188–355)	338	93 (38–165)	<.001
LDH, U/L	89	671 (528–885)	332	340 (267–436)	<.001
D-dimer, μg/L FEU	75	12 227 (3070–29 031)	294	1173 (673–3370)	<.001
Albumin, g/L	83	20 (17–24)	307	28 (25–32)	<.001
Ferritin, μg/L	54	2526 (1210–3762)	189	504 (433–1573)	<.001
Troponin T, ng/L	35	32 (17–68)	63	9 (6–11)	<.001
	ICU		Non–ICU		
	No.	Median (IQR)	No.	Median (IQR)	*P*
CRP, mg/L	47	313 (208–387)	380	108 (42–188)	<.001
LDH, U/L	47	660 (553–907)	374	353 (274–472)	<.001
D-dimer, μg/L FEU	47	11 870 (3614–28 919)	322	1263 (726–3896)	<.001
Albumin, g/L	47	18 (16–20)	381	27 (24–32)	<.001
Ferritin, μg/L	33	2062 (1247–3473)	210	884 (458–1762)	<.001
Troponin T, ng/L	17	27 (14–58)	81	10 (7–18)	<.001

Abbreviations: CRP, C-reactive protein; FEU, fibrinogen-equivalent units; ICU, intensive care unit; IQR, interquartile range; LDH, lactate dehydrogenase.

[a] Conversion factors to SI units: CRP, from mg/L to nmol/L multiply by 9.5238; albumin, from g/L to mmol/L multiply by 0.0150; LDH, from U/L to nkat/L multiply by 16.6667; ferritin, from μg/L to nmol/L multiply by 0.0022.

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Figure 3. *Receiver operating characteristic (ROC) curves for the evaluated tests according to the ability to predict the 2 selected outcomes. A, Death outcome. B, Intensive care unit admission outcome.*

requested biochemistry parameters were defined for use in COVID-19 patients to predict negative outcomes with a defined probability.[2,4–6,16–20] In our study, we depicted this probability by deriving LR and PV associated with selected cutoffs. Positive LR expresses the quotient between the probability that a value of the test overlapping with the indicated cutoff is associated with the defined outcome and the probability that it does not associate with such an outcome. Negative LR, on the other hand, expresses the quotient between the probability that a value of the test lower (higher in the case of albumin) than the indicated cutoff is associated with a negative outcome and the probability that it does not associate with such an outcome.[14] Positive and negative PVs are 2 essential calculations that provide insight into the accuracy of positive or negative test results within the population tested. These

values are based on the test sensitivity and specificity, but they also incorporate and are dependent on the prevalence of selected outcomes in the studied population. In our study, positive PVs reported in Table 3, last column, indicate the number of deceased COVID-19 patients that a test accurately identifies out of the total number of dead patients within our population. On the other hand, negative PVs listed in Table 4 define the accurate detection of cases that did not require intensive treatment. Our cutoff values were specifically selected to have a high specificity (ie, rule-in ability) in detecting patients at risk for in-hospital death, and a high sensitivity (ie, rule-out ability) in detecting patients not at risk for ICU admission.

To our knowledge, this study is the largest case series of COVID-19 patients in Italy so far, and one of the largest worldwide. In terms of population description, our findings

Table 3. Receiver Operating Characteristic (ROC) Curve Analysis and Diagnostic Ability of Evaluated Tests to Predict In-Hospital Death in Studied Coronavirus Disease 2019 (COVID-19) Patients Using the Best Cutoff Maximizing Clinical Specificity[a]

Test	AUC (95% CI)	Selected Cutoff	Specificity (95% CI)	LR+ (95% CI)[b]	PPV (95% CI)
Troponin T	0.94 (0.90–0.98)	>30 ng/L	0.98 (0.91–1.00)	31.9 (4.4–228.8)	0.89 (0.58–1.00)
LDH	0.89 (0.86–0.93)	>731 U/L	0.98 (0.96–0.99)	19.7 (9.1–42.7)	0.84 (0.70–0.93)
Albumin	0.87 (0.84–0.91)	≤18 g/L	0.97 (0.94–0.98)	12.2 (6.3–23.7)	0.76 (0.61–0.88)
CRP	0.87 (0.83–0.91)	>303 mg/L	0.96 (0.93–0.98)	10.4 (5.8–18.7)	0.73 (0.59–0.85)
D-dimer	0.84 (0.80–0.89)	>16 280 µg/L FEU	0.96 (0.93–0.98)	10.7 (5.6–20.3)	0.74 (0.58–0.86)
Ferritin	0.77 (0.70–0.84)	>2824 µg/L	0.93 (0.88–0.96)	6.3 (3.5–11.2)	0.62 (0.45–0.78)

Abbreviations: AUC, area under the ROC curve; CI, confidence interval; CRP, C-reactive protein; FEU, fibrinogen-equivalent units; LDH, lactate dehydrogenase; LR+, positive likelihood ratio; PPV, positive predictive value.

[a] Conversion factors to SI units: CRP, from mg/L to nmol/L multiply by 9.5238; albumin, from g/L to mmol/L multiply by 0.0150; LDH, from U/L to nkat/L multiply by 16.6667; ferritin, from µg/L to nmol/L multiply by 0.0022.

[b] The strength of the indication for the presence of the selected outcome provided by the positive result of the test is relevant when LR+ ≥10, modest when 5 ≤ LR+ < 10, and poor when 2 ≤ LR+ < 5.[14]

Table 4. Receiver Operating Characteristic (ROC) Curve Analysis and Diagnostic Ability of Evaluated Tests to Exclude the Need for Admission in Intensive Care Unit in Coronavirus Disease 19 (COVID-19) Patients During Hospitalization Using the Best Cutoff Maximizing Clinical Sensitivity

Test	AUC (95% CI)	Selected Cutoff	Sensitivity (95% CI)	LR− (95% CI)[a]	NPV (95% CI)
Albumin	0.89 (0.84–0.94)	≥29 g/L	0.98 (0.89–1.00)	0.07 (0.01–0.50)	0.99 (0.95–1.00)
CRP	0.88 (0.84–0.93)	<141 mg/L	0.94 (0.83–0.99)	0.10 (0.03–0.30)	0.99 (0.94–1.00)
LDH	0.88 (0.84–0.92)	<425 U/L	0.94 (0.93–0.99)	0.10 (0.03–0.30)	0.99 (0.97–1.00)
D-dimer	0.84 (0.78–0.89)	<1704 μg/L FEU	0.94 (0.93–0.99)	0.10 (0.03–0.30)	0.99 (0.96–1.00)
Troponin T	0.77 (0.66–0.88)	<9 ng/L	0.94 (0.71–1.00)	0.13 (0.02–0.90)	0.98 (0.88–1.00)
Ferritin	0.73 (0.64–0.82)	<404 μg/L	0.97 (0.84–1.00)	0.15 (0.02–1.00)	0.98 (0.89–1.00)

Abbreviations: AUC, area under the ROC curve; CI, confidence interval; CRP, C-reactive protein; FEU, fibrinogen-equivalent units; LDH, lactate dehydrogenase; LR−, negative likelihood ratio; NPV, negative predictive value.

[a] The strength of the indication for the absence of the selected outcome provided by the negative result of the test is relevant when LR− ≤0.10, modest when 0.10 < LR− ≤ 0.20, and poor when 0.20 < LR− ≤ 0.50.[14]

are similar to those from other studies, mainly carried out on Chinese populations.[2,4–6,17–20] Among laboratory biochemistry tests, we included in our analysis those biomarkers, already proposed in previous descriptive studies, that appear to cover a relevant portion of pathophysiologic mechanisms potentially influencing the disease severity. Ferritin and CRP are acute-phase proteins that may reflect the hyperinflammatory state induced by SARS-CoV-2 active infection[21,22]; LDH activity in serum may reflect both lung damage and more widespread tissue damage[23]; D-dimer is associated with hemostasis disorders and disseminated intravascular coagulation, which are frequent in COVID-19 patients[24]; serum albumin levels are related to hepatic and renal functions as well as the nutritional status, which are often compromised during long and complicated hospitalizations[8]; finally, cardiac troponin levels may reflect both the presence of a preexisting cardiovascular condition, which is one of the major risk factors for developing severe COVID-19 (Table 1), and the insurgence of cardiac complications directly related to the viral infection or to the compromised pulmonary function.[25,26]

In terms of death prediction, the only test with an AUC above 0.90, the limit indicating high global accuracy,[27] was cTnT. COVID-19 patients with a peak cTnT value greater than 30 ng/L (corresponding to 2 times the upper reference limit selected at the 99th percentile of the reference population[28]) had a chance of dying that was more than 30 times higher than that of other patients. On the other hand, the cTnT value for predicting ICU admission was relatively poor. This is probably due to the fact that COVID-19 patients are generally admitted to the ICU following the development of respiratory impairment and acute respiratory distress syndrome, whereas the development of cardiac complications caused by SARS-CoV-2 infection, such as myocarditis, usually does not require intensive care treatment. Previous studies have shown that cardiac troponin I concentrations exceeding the 99th percentile upper reference limit can be observed in 8% to 12% of COVID-19 patients.[25] Only 1 study has previously measured cTnT, detecting elevated concentrations, defined as above the 99th percentile upper reference limit, in 27.8% of evaluated patients and showing that myocardial injury, as detected by a cTnT increase, is significantly associated with a fatal outcome of COVID-19.[26] Unfortunately, the assay used in the study was not specified and a fixed cut-point for marker application not stated, so results were not directly replicable in other settings. Our data confirm that COVID-19 patients displaying myocardial injury, revealed by elevated cTnT concentrations, are at high risk for death, and they enlarge the previous information by indicating the best biomarker cutoff associated with this outcome. Because of the relatively low number of patients tested, cTnT reached only borderline significance when a multivariable model was applied. The best-fitting variables for death prediction at multivariate logistic regression were patient age, LDH, and albumin concentrations. Markedly altered levels of these 2 laboratory parameters, reflecting a general impairment of the patient's health status and organ functions, independently predicted death during hospitalization.

The tests that had the higher power for excluding the need for intensive care were serum albumin, CRP, and LDH, with an AUC of 0.88 to 0.89. Patients for whom these analytes did not show marked variations during the whole hospitalization period had a low probability of requiring admission to the

Table 5. Univariate and Multivariate Logistic Regression Analyses for Predictors of Death During Hospitalization of Coronavirus Disease 2019 (COVID-19) Patients

	Univariate Analysis		Multivariate Analysis	
	Odds Ratio (95% CI)	P	Odds Ratio (95% CI)	P
Age	1.09 (1.07–1.12)	<.001	1.14 (1.03–1.27)	.01
C-reactive protein	12.1 (6.39–22.8)	<.001	—	—
LDH	33.0 (14.0–78.0)	<.001	161.5 (2.28–11 422.8)	.02
D-dimer	13.1 (6.55–26.2)	<.001	—	—
Albumin	19.6 (9.09–42.3)	<.001	46.0 (3.54–596.8)	.003
Ferritin	10.8 (5.02–23.1)	<.001	—	—
Troponin T	32.3 (6.81–153.2)	<.001	10.3 (0.95–111.2)	.06

Abbreviations: CI, confidence interval; LDH, lactate dehydrogenase.

Table 6.   Univariate and Multivariate Logistic Regression Analyses for Predictors of Admission in an Intensive Care Unit of Coronavirus Disease 2019 (COVID-19) Patients During Hospitalization

	Univariate Analysis		Multivariate Analysis	
	Odds Ratio (95% CI)	*P*	Odds Ratio (95% CI)	*P*
Age	1.01 (0.98–1.02)	.86	—	—
C-reactive protein	0.04 (0.01–0.14)	<.001	—	—
LDH	0.03 (0.01–0.12)	<.001	0.06 (0.01–0.54)	.01
D-dimer	0.04 (0.01–0.14)	<.001	—	—
Albumin	0.10 (0.03–0.33)	<.001	—	—
Ferritin	0.12 (0.02–0.94)	.04	—	—
Troponin T	0.12 (0.01–0.94)	.004	—	—

Abbreviations: CI, confidence interval; LDH, lactate dehydrogenase.

ICU. This is not surprising because these markers reflect a combination of heightened inflammatory state and organ tissue damage and/or disfunction that could lead to worsening of clinical conditions and require intensive treatment. The possible role of LDH as the most powerful clinical predictor of outcome worsening in COVID-19 patients is indicated by the fact that this test is the only biomarker that remains significantly associated with both selected outcomes at the multivariate logistic regression analysis.

One of the strengths of our study is that all evaluated biomarkers, except for D-dimer, for which harmonization initiatives are still ongoing,[10,11] were determined using methodologies for which harmonization has been verified and validated. Ferraro et al[12] previously stressed how the issues of measurement standardization and harmonization represent an absolute priority for optimizing health care.[29] Only the use of assays providing harmonized results will allow the use of common reference intervals and decision limits, enabling the universal application of results of clinical studies undertaken in different locations or times and permitting their unambiguous interpretation. Accordingly, all the selected cutoffs reported in this study can be directly applied in other situations provided that the related institutions also use assays that produce harmonized results. With regard to this, it is worth mentioning that in this study, serum albumin was measured with an immunoturbidimetric assay, which is fully specific for the protein measurement, contrary to colorimetric methods, such as those based on protein dye-binding, for example, the bromocresol green methods, which are in use in most clinical institutions worldwide.[30] This explains why albumin concentrations reported in our study appear to be lower than other data reported in literature for COVID-19 patients.[18,20] On the other hand, we are aware that programs about harmonization of D-dimer assays are ongoing and that higher-order reference materials are still not available. However, preliminary studies comparing different D-dimer assays seem to support a certain grade of comparability between results.[10,11] It should also be noted that another confounding issue for D-dimer test is represented by the lack of homogeneity in reporting units of measurement. In this study, results were reported as μg/L FEU, which relate the mass of D-dimer to the mass of fibrinogen, as previously recommended.[31] Reporting values using alternative units could result in erroneous classification of normal and elevated results.

The major limitation of our study is represented by its retrospective nature. However, because the results were obtained on a large population of more than 450 COVID-19 patients, it is safe to say that they are statistically robust and may represent a significant aid in decision-making for prioritized treatment and more aggressive strategies in this still poorly known disease. Another potential confounder is represented by the possible inability of admitting all the patients to the ICU who would have required intensive care due to ICU capacity constraints. However, because of an effective territorial organization, no major obstacles to ICU admission when it was needed were experienced during the study period in our institution.

CONCLUSIONS

Performing risk stratification in COVID-19 patients based solely on clinical features is often difficult because signs and symptoms usually lack specificity. From the results of this study, it appears that some laboratory biochemistry parameters may represent an invaluable aid in identifying patients with low risk of disease progression and consequent need of ICU admission, and, conversely, patients with higher risk of mortality. The interpretative criteria for laboratory tests defined in this study were specifically selected to obtain accurate rule-out of patients who did not need intensive care treatment and rule-in of patients at higher risk of death. These 2 sets of test cutoffs should be optimally used in combination to perform an accurate evaluation of this serious disease.

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