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# Association between Laboratory Findings and Mortality of Hospitalized Patients with Covid-19 in Mashhad, Iran

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**ABSTRACT**

**Background & Objective:** *COVID-19* has enforced high burden on health systems universally. To better allocate limited health equipment, we aimed to investigate the prognostic impacts of laboratory parameters.

**Materials & Methods:** All *SARS-CoV-2* patients admitted to Imam-Reza University Hospital, Mashhad, Iran, during three *COVID19* peak periods in Iran (March to April 2020, July to August, and October to November 2020) were enrolled the study. Demographic and laboratory data were extracted and compared between survivors and non-survivors. Regression analyses and receiver operating characteristic (ROC curve) were used to identify risk factors and assess the ability of laboratory tests in predicting in-hospital mortality.

**Results:** A total of 2156 *COVID19* patients were included in the analysis, with a mean age of 60.20 (±18.8) years. Most patients were male (57%). Multiple regression analysis identified older age (OR=1.01), male sex (OR=2.34), lymphopenia (OR=2.12), LDH >500U/L (OR=2.17), hypernatremia (OR=9.7), urea >45mg/dL (OR=3.6), and BS >200mg/dl (OR=1.93) as significant risk factors for in-hospital death. Using ROC curve analysis, D-dimer (>1000ng/ml) as well as CK-Mb (>28U/L) both with sensitivities and specificities of more than 80% and PPV of about 90% were able to identify patients with higher possibility of in-hospital death.

**Conclusion:** Male sex, older age, lymphopenia, hypernatremia, increased Urea, increased LDH, and hyperglycemia may serve as potential risk factors for in-hospital death. D-dimer and CK-MB may be used in identifying patients with high probability of in-hospital death. These tests may be used in clinical decision-making in order to improve outcomes of patients with *COVID-19*.

**Keywords:** *COVID-19*, Laboratory tests, Mortality, Prognosis, Risk factors, *SARS-CoV-2*



## Introduction

IN December 2019, a new coronavirus, called *SARS-CoV-2*, was identified which was responsible for severe pneumonia cases in Wuhan, China and spread rapidly all around the world. Coronaviruses are a various group of RNA viruses that cause diseases with varying severity in humans and animals (1). Two other coronaviruses had emerged in recent years including severe acute respiratory syndrome coronavirus (*SARS-CoV*) and the Middle East respiratory syndrome coronavirus (*MERS-CoV*). The *SARS-CoV-2*, which causes a disease named *COVID-19*, is now a global pandemic and affecting most countries including Iran (2). *COVID-19* is a disease with a wide clinical spectrum from asymptomatic infection to severe viral pneumonia with respiratory failure and even death. Most patients have mild to moderate symptoms (3). Patients with underlying disorders such as chronic obstructive pulmonary disease, hypertension, diabetes, and cancer have been categorized as risk groups for worse outcomes (4). Many hematological and biochemical tests are being used at this time to predict outcomes of patients with *SARS CoV-2* infection. For example, a meta-analysis study indicated that non-survivor patients exhibited significantly higher white blood cell count (WBC), C-reactive protein (CRP), procalcitonin, erythrocyte sedimentation rate, interleukin-6, and interleukin-10 than survivors (5). Another meta-analysis study reported that older age, thrombocytopenia, lymphopenia, elevated levels of LDH, ALT, AST, PCT, Cr, and D-dimer are associated with severity of *COVID-19* and so may be utilized for predicting disease progression (6). In addition, combinations of some inflammatory markers, derived from complete blood count tests, have been used. For example, neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) claimed to be useful inflammatory markers in order to predict the outcome in patients with *COVID-19* (7). Regarding the high burden

of the pandemic to health systems worldwide and the shortage of health equipment, it is needed to categorize patients based on their risk for developing severe disease. Laboratory indicators may help predict the severity of the disease in the early stages of the infection (8) and be of significant importance in clinical decision making. As the clinical presentations and outcome of patients may be related to the genetic background and ethnicity, it is important that these factors being reevaluated in each region or country. There are some reports regarding to the association of some clinical and laboratory findings with outcome of patients with COVID19 from Iran (9-11), but they have some limitations. Most of these studies focused on clinical findings and no lab test or only limited number of lab tests are included in them. None of them has evaluated potential risk factors regarding to the diseases severity or death using a reliable statistical model such as regression analysis. In addition, the performance of different laboratory test in predicting poor outcome has not been assessed in any of them.

In this study, we aimed to investigate the association between laboratory findings of *Covid 19* patients in early hospitalization (within 24 hours) and their outcome (in-hospital death or discharge) in a referral university hospital in Mashhad, Iran in order to identify potential risk factors for disease severity and find most reliable lab tests in prediction of outcomes.

## Materials and Methods

### Study design and participant

In this retrospective cohort study, all patients with confirmed infection of SARS-CoV-2, admitted to Imam Reza University Hospital, Mashhad, Iran, during the time limits of the study were included. We selected time intervals with the highest number of covid-19 patients. This included three periods: from 20 March to 19 April 2020, 22 July to 5 August, and 22 October to 10 November 2020. The inclusion criteria were confirmed COVID-19 infection based on polymerase chain reaction (PCR) test and lung high-resolution computed tomography (HRCT) results and admission to the hospital. Patients who diagnosed with causes of pneumonia other than COVID-19 as well as ones with incomplete lab data or un-determined outcome were excluded from the study. Then, the patients were grouped into two separate cohorts for analyses: The first cohort included patients with Covid-19 who survived (n: 1486) and could hence be discharged, whilst the second group was composed of patients who died (670) within their hospital stay.

### Data collection

Demographic (age, sex, duration of hospital stay, residency) and laboratory data (complete blood counts (CBC), coagulation profile (PT, PTT, INR), D-dimer, serum biochemical tests (including renal and liver function tests), creatine kinase, lactate dehydrogenase, and serum electrolytes (including potassium, sodium and calcium), myocardial markers (cardiac troponin I, CK-MB) were collected from hospital electronic files. The first laboratory data, within 24 hours of admission, were included. The neutrophil-to-lymphocyte ratio (NLR) was obtained through dividing the neutrophil count by the lymphocyte count. The ratio should be less than 3 in healthy adults. In acute stress situations, the ratio increases above 3 and an NLR ratio of more than 9 is seen in sepsis. The platelet-to-lymphocyte ratio (PLR) was achieved through dividing the platelet count by the number of lymphocytes. In normal situations, the PLR is usually between 50 and 150, but shows variability across different populations (12).

Data were entered in to a computerized database and double-checked. The study protocol was approved by the Research Ethics Committee in Mashhad University of Medical Sciences

### Statistical analysis

Continuous and categorical variables were presented as mean (SD), frequencies and percentages. t- student test, $\chi 2$ test, or Fisher's exact test were used to compare differences between survivors and non-survivors where appropriate. In order to explore the risk factors associated with in-hospital death and their odds ratios (ORs), univariable and multivariable logistic regression models were used. Data were analyzed using statistical software Stata version 14. Variables that had a significance level of less than 0.2 in univariate analysis were introduced into the multiple logistic regression model using the stepwise backward method. Receiver operating characteristic (ROC curve), using MedCalc version 20.0.3 software, was used to examine the ability of different laboratory tests to distinguish between survivors and non-survivors. A p-value of $<0.05$ was considered statistically significant.

## Results

### Basic characteristics and comparisons between two groups

From 20 March to 19 April, 22 July to 5 August and 22 October to 10 November 2020, 2274 patients with *COVID-19* were admitted to Imam Reza University Hospital, Mashhad, Iran. After exclusion of 118 patients with no available key information in their hospital records, 2156 patients were included in the final analysis. Of them, 1486 cases were discharged (survivors) and 670 (31%) of them died during hospitalization (non-survivors).

The median age of the study population was 60.20 ±18.8 years (range 1–96) and they were mostly male (n=1210 (57%)). Demographic and laboratory findings of patients (survivors and non-survivors) are reported in Tables 1 and 2. The mean age of those who died was significantly higher than survivors (67.60 vs. 56.87 years, P<0.001). Compared with survivors, non-survivors had significantly higher WBC counts, neutrophil counts, AST, ALT, ALP, LDH, CPK, CK-MB, CRP, BS, D-Dimer, urea, and creatinine concentrations. Eighty-three (44%) of 191 patients had

elevated concentrations of D-dimer more than 1000 ng /ml, where the rate was significantly higher in non-survivors than in survivors (P<0.001) (Tables 1 and 2). In addition, platelet counts, lymphocyte counts, albumin and Iron were significantly lower in non-survivors, comparing to survivors (Tables 1 and 2). Inflammatory markers such as NLR and PLR were calculated and compared between survivors and non-survivors. Both NLR and PLR were significantly higher in the non-survivor group (P<0.001 for both) (Table 1).

**Table 1. Demographic and hematological findings of patients on admission**

| Characteristic | All patient n (%) | Survivors n (%) | Non-Survivors n (%) | P value |
|---|---|---|---|---|
| | N=2156 | N= 1486 | N= 670 | |
| **Demographic** | | | | |
| **Age (years)** | | | | |
| **Mean (SD)** | 60.20 (18.8) | 56.87 (19.1) | 67.60 (15.8) | <0.001 |
| **Age Range (years)** | | | | <0.001 |
| **≤65** | 1240(58%) | 970(65%) | 270(40%) | |
| **>65** | 913(42%) | 514(35%) | 399(60%) | |
| **Sex** | | | | |
| **Female** | 944 (43%) | 684 (72%) | 260 (28%) | 0.002 |
| **male** | 1210 (57%) | 800 (66%) | 410 (34%) | |
| **Residency** | | | | |
| **Mashhad** | 1092(51%) | 743 (50%) | 349 (52%) | 0.77 |
| **counties** | 757(35%) | 529 (36%) | 228(34%) | |
| **Other provinces** | 305(14%) | 212 (14%) | 93 (13%) | |
| **median time of hospital stay, (IQR)** | 6 (3-11) | 6 (3-10) | 7 (3-13) | 0.007 |
| **Hematological findings** | | | | |
| **MCV (fl) Mean (SD)** | | | | |
| **Mean (SD), N:1779** | 84.9 (7.7) | 84.8 (7.7) | 85.1 (7.7) | 0.59 |
| **<80** | 303(17%) | 211 (17%) | 92(17%) | 0.923 |
| **80-96** | 1406(79%) | 965 (79%) | 441(79%) | |
| **96<** | 70(4%) | 49 (4%) | 21 (4%) | |
| **MCH (pg)** | | | | |
| **Mean (SD), N:1778** | 28.6 (2.8) | 28.6 (2.8) | 28.6 (2.7) | 0.72 |
| **<25** | 145 (8%) | 105 (9%) | 40 (7%) | 0.148 |
| **25-33** | 1580 (89%) | 1078 (88%) | 502 (91%) | |
| **33<** | 53 (3%) | 42 (3%) | 11 (2%) | |
| **MCHC (g/dl)** | | | | |
| **Mean (SD), N:1778** | 33.6 (1.9) | 33.6 (1.9) | 33.5 (1.9) | 0.31 |
| **<33** | 615 (35%) | 425 (35%) | 190(34%) | 0.160 |
| **33-36** | 1012 (57%) | 686 (56%) | 326 (59%) | |
| **36<** | 151 (8%) | 114 (9%) | 37 (7%) | |
| **RBC (x 10^6/µL)** | | | | |
| **Mean (SD), N:1778** | 4.6 (0.8) | 4.5 (0.9) | 4.6 (0.8) | 0.17 |

| Characteristic | All patient n (%) | Survivors n (%) | Non-Survivors n (%) | P value |
|---|---|---|---|---|
| | N=2156 | N= 1486 | N= 670 | |
| **<4.5** | 810(46%) | 540 (44%) | 270 (49%) | 0.013 |
| **4.5-5.9** | 898 (50%) | 644 (53%) | 254 (46%) | |
| **5.9<** | 70 (4%) | 41(3%) | 29 (5%) | |
| **Hct (%)** | | | | |
| **Mean (SD), N:1778** | 38.7 (6.3) | 38.4 (7.2) | 38.7 (6.3) | 0.38 |
| **<35** | 458 (26%) | 302 (25%) | 156 (28%) | 0.228 |
| **35-50.5** | 1258 (70%) | 882 (72%) | 376 (68%) | |
| **50.5<** | 62 (4%) | 41 (3%) | 21 (4%) | |
| **Hemoglobin (g/L)** | | | | |
| **Mean (SD), N:1778** | 129.8 (24.1) | 130.3 (23.2) | 128.9 (25.9) | 0.28 |
| **<120** | 551 (31%) | 363 (30%) | 188 (34%) | 0.116 |
| **120-17** | 1189 (67%) | 838 (68%) | 351 (63%) | |
| **175<** | 38(2%) | 24 (2%) | 14 (3%) | |
| **RDW-CV (%)** | | | | |
| **Mean (SD),1769** | 14.5 (2.2) | 14.4 (2.1) | 14.9 (2.4) | <0.001 |
| **≤15** | 1280 (72%) | 915 (75%) | 365 (66%) | <0.001 |
| **15<** | 489(28%) | 303 (25%) | 186 (34%) | |
| **PDW (fl)** | | | | |
| **Mean (SD), N:1693** | 13.3 (2.6) | 13.2 (2.5) | 13.5 (2.8) | 0.03 |
| **<9.8** | 62 (4%) | 44 (4%) | 18 (3%) | 0.062 |
| **9.8-17** | 1502 (89%) | 1057(90%) | 445 (87%) | |
| **17<** | 129 (7%) | 78 (6%) | 51 (10%) | |
| **MPV (fl)** | | | | |
| **Mean (SD), N:1690** | 10.0 (1.1) | 10.1 (1.1) | 10.0 (1.1) | 0.09 |
| **<8.6** | 125(7%) | 95 (8%) | 30 (6%) | 0.259 |
| **8.6-12-7** | 1545 (91%) | 1070(91%) | 475 (93%) | |
| **12.7<** | 20 (2%) | 13 (1%) | 7 (1%) | |
| **Platelet (x 10^3/µL)** | | | | |
| **Mean (SD), N:1775** | 217.3(95.7) | 220.2 (96.5) | 211.0 (93.9) | 0.06 |
| **<100** | 128 (7%) | 69 (6%) | 59 (11%) | <0.001 |
| **100≤** | 1647 (93%) | 1154(94%) | 493 (89%) | |
| **WBC (x 10^3/µL)** | | | | |
| **Mean (SD), N:1769** | 9.5 (5.2) | 9.1 (4.8) | 10.3 (6.0) | <0.001 |
| **<4** | 129 (6%) | 88 (7%) | 41 (7%) | 0.025 |
| **4-11.3** | 1173 (67%) | 834 (68%) | 339 (62%) | |
| **11.3<** | 467 (27%) | 300 (25%) | 167 (31%) | |
| **neutrophil count (x 10^3/µL)** | | | | |

| Characteristic | All patient n (%) | Survivors n (%) | Non-Survivors n (%) | P value |
|---|---|---|---|---|
| | N=2156 | N= 1486 | N= 670 | |
| Mean (SD), N:1665 | 7.75 (5.5) | 7.3 (5.4) | 8.7 (5.5) | <0.001 |
| ≤ 6.46 | 826 (49%) | 644 (53%) | 216 (42%) | 0.85 |
| >6.46 | 839 (51%) | 510 (47%) | 295 (58%) | |
| neutrophil percentage | | | | |
| Mean (SD), N:1665 | 80.1(21.6) | 78.8(24.8) | 83.0 (10.9) | <0.001 |
| <45.5 | 32(2%) | 27 (2%) | 5 (1%) | <0.001 |
| 45.5-73.1 | 342(20%) | 278 (24%) | 64 (13%) | |
| 73.1< | 1291(78%) | 849 (74%) | 442 (86%) | |
| Lymphocyte count (10^3/µL) | | | | |
| Mean (SD), N:1689 | 1.37 (1.5) | 1.45 (1.6) | 1.19 (1.3) | 0.001 |
| ≤1 | 809(48%) | 512 (44%) | 297 (57%) | <0.001 |
| 1< | 880 (52%) | 657 (56%) | 223(43%) | |
| Lymphocyte percentage | | | | |
| Mean (SD), N:1689 | 15.7 (11.3) | 16.9(11.6) | 12.8(10.0) | <0.001 |
| <20 | 1245(74%) | 811 (69%) | 434 (84%) | <0.001 |
| 20-45 | 411(24%) | 332 (29%) | 79 (15%) | |
| 45< | 33(2%) | 26 (2%) | 7 (1%) | |
| INR | | | | |
| Mean (SD), N:1312 | 1.2 (0.7) | 1.2 (0.7) | 1.2 (0.7) | 0.85 |
| ≤1.2 | 942 (72%) | 674 (76%) | 268 (63%) | <0.001 |
| 1.2< | 370 (28%) | 214 (24%) | 156 (37%) | |
| PT (s) | | | | |
| Mean (SD), N:1317 | 13.8 (5.5) | 13.9(5.9) | 13.9 (4.5) | 0.41 |
| <13.5 | 891(68%) | 644 (72%) | 247 (58%) | <0.001 |
| 13.5≤ | 426 (32%) | 250 (28%) | 176 (42%) | |
| APTT (s) | | | | |
| Mean (SD), N:1315 | 36.6 (23.6) | 37.2 (23.9) | 36.8 (23.7) | 0.67 |
| ≤38 | 1087 (83%) | 741 (83%) | 346 (82%) | 0.485 |
| 38< | 228(17%) | 150(17%) | 78 (18%) | |
| ESR 1h (mm/h) | | | | |
| Mean (SD), N:584 | 51.0 (32.2) | 56.2 (32.3) | 52.4 (32.3) | 0.08 |
| ≤30 | 175(30%) | 133(31%) | 42 (27%) | 0.277 |
| 30< | 409 (70%) | 293 (69%) | 116 (73%) | |
| D-dimer (ng/ml) | | | | |
| Mean (SD), N:191 | 1967.7(1920.5) | 717.0 (879.7) | 3527.2 (1714.8) | <0.001 |
| ≤500 | 58(30%) | 56 (53%) | 2 (2%) | <0.001 |
| 500-1000 | 50(26%) | 41 (39%) | 9 (11%) | |

| Characteristic | All patient n (%) | Survivors n (%) | Non-Survivors n (%) | P value |
|---|---|---|---|---|
| | N=2156 | N= 1486 | N= 670 | |
| 1000< | 83(44%) | 9(8%) | 74 (87%) | |
| NLR, N: 1665 | | | | |
| Mean (SD) | 8.57(8.16) | 7.44(6.77) | 11.12(10.20) | <0.001 |
| <3 | 290 (17%) | 240 (21%) | 50 (10%) | |
| 3-9 | 836 (50%) | 611 (53%) | 225 (44%) | |
| >9 | 539 (33%) | 303 (26%) | 236 (46%) | |
| PLR, N: 1686 | | | | |
| Mean (SD) | 262.51(275.06) | 245.16(248.51) | 301.41(323.73) | <0.001 |
| <50 | 103 (6%) | 76 (6.5%) | 27 (5%) | |
| 50-150 | 510 (30%) | 372 (22%) | 138 (26.5%) | |
| >150 | 1073 (64%) | 718 (61.5%) | 355 (68.5%) | |

Data are expressed as mean (SD) or n/N (%), where N is the number of patients with available data. p values were calculated by t- student test, $\chi 2$ test, or Fisher's exact test, as appropriate. Abbreviations: RBC: red blood cells; HCT: hematocrit; MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; PLT: platelets; WBC: white blood cells; RDW-CV- Red Cell Distribution Width; PDW: Platelet Distribution Width; APTT: activated partial thromboplastin time; PT: prothrombin time; ESR: erythrocyte sedimentation rate; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio.

**Table 2. Biochemical findings of patients on admission**

| Biochemical findings | All patient n (%) | Survivors n (%) | Non-Survivors n (%) | P value |
|---|---|---|---|---|
| | N=2156 | N= 1486 | N= 670 | |
| | | | | |
| Total bilirubin(mg/dL) | | | | |
| Mean (SD), N:1364 | 0.9 (1.0) | 0.8 (1.0) | 0.9 (0.8) | 0.23 |
| ≤1.3 | 1193 (87%) | 818 (89%) | 375 (84%) | 0.002 |
| 1.3< | 171(13%) | 97 (11%) | 74 (16%) | |
| Direct bilirubin(mg/dL) | | | | |
| Mean (SD), N:1424 | 0.4(0.7) | 0.3 (0.5) | 0.4 (0.9) | 0.09 |
| ≤0.3 | 1010 (71%) | 708 (74%) | 302 (65%) | 0.001 |
| 0.3< | 414 (29%) | 252(26%) | 162 (35%) | |
| AST (U/L) | | | | |
| Mean (SD), N:1619 | 63.4 (150.7) | 52.7 (86.3) | 86.2(233.3) | 0.002 |
| ≤40 | 871 (54%) | 644 (59%) | 227 (44%) | <0.001 |
| 40< | 748 (46%) | 456 (41%) | 292 (56%) | |
| ALT (U/L) | | | | |
| Mean (SD), N:1609 | 53.1(144.7) | 46.4(95.2) | 67.2 (214.1) | 0.04 |
| ≤40 | 1091(68%) | 747 (68%) | 344 (67%) | 0.501 |
| 40< | 518 (32%) | 346 (32%) | 172 (33%) | |
| ALP(U/L) | | | | |
| Mean (SD), N:966 | 253.7 (214.0) | 232.1(184.2) | 292.0 (254.3) | <0.001 |

| Biochemical findings | All patient n (%) | Survivors n (%) | Non-Survivors n (%) | P value |
|---|---|---|---|---|
| | N=2156 | N= 1486 | N= 670 | |
| **≤258** | 700 (72%) | 478 (77%) | 222 (64%) | <0.001 |
| **258<** | 266 (28%) | 140 (23%) | 126 (36%) | |
| **LDH (U/L)** | | | | |
| **Mean (SD), N:1290** | 726.4(437.6) | 681.4(434.8) | 823.1 (428.2) | <0.001 |
| **≤500** | 396 (31%) | 304(35%) | 92 (22%) | <0.001 |
| **500<** | 894 (69%) | 576 (65%) | 318 (78%) | |
| **CPK (U/L)** | | | | |
| **Mean (SD), N:187** | 407.1 (722.4) | 305.9(595.2) | 601.6 (892.4) | 0.02 |
| **≤170** | 98 (52%) | 72 (59%) | 26 (41%) | 0.020 |
| **170<** | 89 (58%) | 51 (41%) | 38 (59%) | |
| **CRP (mg/L)** | | | | |
| **Mean (SD), N:1534** | 115.8 (113.6) | 106.8(118.5) | 135.8 (98.9) | <0.001 |
| **≤75** | 617 (40%) | 472 (45%) | 145 (31%) | <0.001 |
| **75<** | 917(60%) | 587 (55%) | 330 (69%) | |
| **Sodium (mEq/L)** | | | | |
| **Mean (SD), N:1983** | 136.8 (5.1) | 136.8 (4.6) | 136.4 (6.0) | 0.12 |
| **<135** | 559 (28%) | 349 (25%) | 210 (34%) | <0.001 |
| **135-145** | 1356 (68%) | 984 (72%) | 372(61%) | |
| **145<** | 68 (4%) | 37 (3%) | 31 (5%) | |
| **Potassium (mEq/L)** | | | | |
| **Mean (SD), N:1962** | 4.3 (0.7) | 4.2 (0.6) | 4.4 (0.7) | <0.001 |
| **<3.5** | 129 (7%) | 89 (7%) | 40 (7%) | <0.001 |
| **3.5-5.5** | 1745 (89%) | 1222 (90%) | 523 (86%) | |
| **5.5<** | 88 (4%) | 44 (3%) | 44 (7%) | |
| **BS (mg/dL)** | | | | |
| **Mean (SD), N:1787** | 151.2 (91.0) | 144.3(85.9) | 165.9 (99.8) | <0.001 |
| **<70** | 79 (4%) | 52 (4%) | 27 (5%) | 0.003 |
| **70-200** | 1342 (75%) | 944 (78%) | 398 (70%) | |
| **200<** | 366 (21%) | 223 (18%) | 143 (25%) | |
| **Urea (mg/dL)** | | | | |
| **Mean (SD), N:2008** | 51.7 (39.2) | 46.2 (33.80) | 63.6 (46.78) | <0.001 |
| **≤45** | 1174 (58%) | 899 (65%) | 275 (44%) | <0.001 |
| **45<** | 834 (42%) | 482 (35%) | 352 (56%) | |
| **creatinine (mg/dL)** | | | | |
| **Mean (SD), N:1976** | 1.4 (1.4) | 1.2 (1.22) | 1.6 (1.69) | <0.001 |
| **≤1.4** | 1582 (80%) | 1145 (84%) | 437 (71%) | <0.001 |
| **1.4<** | 394 (20%) | 216 (16%) | 178 (29%) | |

| Biochemical findings | All patient n (%) | Survivors n (%) | Non-Survivors n (%) | P value |
|---|---|---|---|---|
| | N=2156 | N= 1486 | N= 670 | |
| **cTnI (ng/l)** | | | | |
| **Mean (SD), N:214** | 19.8 (48.6) | 6.4 (13.6) | 40.0 (70.9) | <0.001 |
| **≤100** | 205 (96%) | 128 (99%) | 77 (91%) | 0.002 |
| **100<** | 9 (4%) | 1 (1%) | 8 (9%) | |
| **CK-MB(U/L)** | | | | |
| **Mean (SD), N:183** | 37.9(25.9) | 23.3 (13.8) | 45.9 (27.4) | <0.001 |
| **≤25** | 71(39%) | 49 (75%) | 22 (19%) | <0.001 |
| **25<** | 112 (61%) | 16 (25%) | 96 (81%) | |
| **Total protein(g/dL)** | | | | |
| **Mean (SD), N:46** | 3.7 (1.8) | 3.5(1.7) | 4.1 (2.0) | 0.33 |
| **< 6** | 38 (83%) | 29 (88%) | 9 (69%) | 0.196 |
| **6 ≤** | 8 (17%) | 4 (12%) | 4 (31%) | |
| **Albumin (g/l)** | | | | |
| **Mean (SD), N:244** | 31.1 (7.0) | 32.6 (6.1) | 29.2 (7.6) | <0.001 |
| **<35** | 164 (67%) | 82 (60%) | 82 (76%) | 0.010 |
| **35≤** | 80 (33%) | 54 (40%) | 26 (24%) | |
| **Calcium (mg/dL)** | | | | |
| **Mean (SD), N:324** | 8.1 (0.9) | 8.2 (0.9) | 8.0 (0.9) | 0.19 |
| **<8.5** | 228 (70%) | 137 (68%) | 91(75%) | 0.189 |
| **8.5-10.5** | 91 (28%) | 63 (31%) | 28 (23%) | |
| **10.5<** | 5 (2%) | 2 (2%) | 3 (2%) | |
| **Magnesium (mg/dL)** | | | | |
| **Mean (SD), N:170** | 2.3 (0.5) | 2.3 (0.4) | 2.2 (0.4) | 0.33 |
| **<1.7** | 11(6%) | 4 (5%) | 7 (9%) | 0.418 |
| **1.7-2.7** | 127 (75%) | 67 (74%) | 60 (75%) | |
| **2.7<** | 32 (19%) | 19 (21%) | 13 (16%) | |
| **Phosphorus (mg/dL)** | | | | |
| **Mean (SD), N:210** | 4.0(1.6) | 4.1(1.6) | 3.9 (1.5) | 0.41 |
| **< 2.7** | 25 (12%) | 10 (8%) | 15 (19%) | 0.041 |
| **2.7-4.5** | 132 (63%) | 88 (67%) | 44 (56%) | |
| **4.5<** | 53 (25%) | 33 (25%) | 20 (25%) | |
| **FBS (mg/dL)** | | | | |
| **Mean (SD), N:92** | 135.2(76.6) | 127.9 (72.3) | 151.6 (84.8) | 0.17 |
| **<70** | 6 (7%) | 5 (8%) | 1 (4%) | 0.397 |
| **70-125** | 49 (53%) | 36 (56%) | 13(46%) | |
| **126≤** | 37 (40%) | 23(36%) | 14 (50%) | |
| **Iron (micg/dL)** | | | | |

| Biochemical findings | All patient n (%) | Survivors n (%) | Non-Survivors n (%) | P value |
|---|---|---|---|---|
| | N=2156 | N= 1486 | N= 670 | |
| **Mean (SD), N:69** | 45.1(51.4) | 58.0 (62.5) | 28.4 (23.5) | 0.009 |
| **<60** | 55 (80%) | 27 (69%) | 28 (93%) | 0.037 |
| **60-150** | 11 (16%) | 9 (23%) | 2 (7%) | |
| **150<** | 3 (4%) | 3 (8%) | | |
| **Lipase (U/L)** | | | | |
| **Mean (SD), N:89** | 52.4(41.1) | 33.3(22.4) | 78.1(46.5) | <0.001 |
| **<60** | 61 (69%) | 46 (90%) | 15 (40%) | <0.001 |
| **60-120** | 24 (27%) | 5 (10%) | 19 (50%) | |
| **120-180** | 2 (2%) | - | 2 (5%) | |
| **180<** | 2 (2%) | - | 2 (5%) | |

Data are expressed as mean (SD) or n/N (%), where N is the number of patients with available data. p values were calculated by t- student test, $\chi 2$ test, or Fisher's exact test, as appropriate. Abbreviations: CRP: C-reactive protein; ALT: alanine aminotransferase; AST: aspartate aminotransferase; LDH: lactate dehydrogenase; CPK: Creatine phosphokinase; BS: blood sugar, FBS: Fasting blood sugar.CK-MB: Creatine Kinase-MB; cTnI: cardiac troponin I.

### Risk factor estimation of death

The univariate logistic regression was performed on the demographic and laboratory parameters (Table 3). Older age, male sex, increase in RDW, PDW, INR, PT, D-dimer, bilirubin (total and direct), AST, LDH, ALP, CPK, CRP, urea, creatinine, WBC counts (>11.3 x 10^3/ µL), neutrophil Counts (>6.46 x 10^3/µL), neutrophil percentage (>73.1%), RBC counts (> 5.9 x 10^6/µL), Na, K, BS, cardiac troponin I , CK-MB and lipase were associated with a significantly higher risk of death. In addition, inflammatory markers including NLR more than 3 and PLR greater than 150 were also related to a higher risk of death. Furthermore, a decrease in platelet counts (<100 x 10^3/µL), RBC counts (<4.5 x 10^6/µL), lymphocyte percentage (<20%), albumin, sodium (< 135 mEq/L), phosphorus, and iron showed significantly increased risks for death.

As the results of all laboratory data were not available for all patients, 352 patients with complete data for most variables (134 non-survivors and 218 survivors) were included in the multivariable logistic regression model (Table 3). Laboratory findings including D-dimer, lipase, CK-MB, and cardiac troponin I were not available for most patients, therefore they were excluded from the multivariable analysis. Twenty-two laboratory tests including age, gender, Hb, MPV, Platelet, WBC, neutrophil count, lymphocyte count, total bilirubin, direct bilirubin, ATS, ALP, LDH, sodium, K, BS, urea, creatinine, RDW-CV, CRP, PDW, and INR were inputted into the multiple regression analysis models. Older age, male sex, LDH (> 500 U/L), sodium (>145 mEq/L), urea (>45 mg/dL), BS (>200 mg/dl), and lymphopenia (<1x 10^3/µL) at admission proved to be associated with increased odds of death, in the multivariable regression analysis.

**Table 3. Risk factors associated with in-hospital death**

| Factors | Column2 | Univariable | | Multivariable | |
|---|---|---|---|---|---|
| | | OR (CI) | P value | OR (CI) | P value |
| **Age (y)** | | 1.03 (1.03-1.04) | <0.001 | 1.01 (1.00-1.01) | 0.042 |
| **gender (female vs. male)** | | 1.34 (1.12-1.62) | 0.002 | 2.34 (1.29-4.22) | 0.005 |
| **MCV** | <80 | 0.95 (0.73-1.25) | 0.733 | | |
| | 80-96 | (ref) | | | |
| | 96< | 0.94 (0.56-1.58) | 0.810 | | |
| **MCH** | <25 | 0.82(0.56-1.20) | 0.299 | | |
| | 25-33 | (ref) | | | |

| Factors | Column2 | Univariable | | Multivariable | |
|---|---|---|---|---|---|
| | | OR (CI) | P value | OR (CI) | P value |
| | 33< | 0.56(0.29-1.10) | 0.093 | | |
| MCHC | <33 | 0.94(0.76-1.17) | 0.579 | | |
| | 33-36 | 1(ref) | | | |
| | 36< | 0.68(0.46-1.01) | 0.058 | | |
| RBC | <4.5 | 1.27(1.03-1.56) | 0.024 | | |
| | 4.5-5.9 | 1(ref) | | | |
| | 5.9< | 1.79(1.09-2.95) | 0.021 | | |
| Hct | <35 | 1.21(0.96-1.52) | 0.099 | | |
| | 35-50.5 | 1(ref) | | | |
| | 50.5< | 1.20(0.70-2.06) | 0.505 | | |
| Hemoglobin | <120 | 1.24(1.00-1.53) | 0.054 | | |
| | 120-175 | 1(ref) | | | |
| | 175< | 1.39 (0.71-2.72) | 0.333 | | |
| RDW-CV | ≤15 | (ref) | | | |
| | 15< | 1.54 (1.24-1.92) | <0.001 | | |
| PDW | <9.8 | 0.97(0.56-1.70) | 0.920 | | |
| | 9.8-17 | 1(ref) | | | |
| | 17< | 1.55(1.07-2.25) | 0.020 | | |
| MPV | <8.6 | 0.71(0.47-1.09) | 0.116 | | |
| | 8.6-12-7 | 1(ref) | | | |
| | 12.7< | 1.21(0.48-3.06) | 0.683 | | |
| Platelet | <100 | 2.00 (1.39-2.88) | <0.001 | | |
| | 100≤ | 1(ref) | | | |
| WBC | <4 | 1.15(0.77-1.70) | 0.494 | | |
| | 4-11.3 | 1(ref) | | | |
| | 11.3< | 1.37 (1.09-1.72) | 0.007 | | |
| Neutrophil count | ≤ 6.46 | ref | | | |
| | >6.46 | 1.53(1.24-1.89) | <0.001 | | |
| Neutrophil % | <45.5 | 0.80(0.30-2.17) | 0.667 | | |
| | 45.5-73.1 | 1(ref) | | | |
| | 73.1< | 2.26(1.68-3.04) | <0.001 | | |
| Lymphocyte count | ≤1 | 1.7 (1.38-2.1) | <0.001 | 2.12 (1.16 -3.9) | 0.015 |
| | 1< | 1(ref) | | | |
| Lymphocyte % | <20 | 2.25(1.71-2.95) | <0.001 | | |
| | 20-45 | 1(ref) | | | |
| | 45< | 1.13(0.47-2.70) | 0.781 | | |
| INR | ≤1.2 | (ref) | | | |
| | 1.2< | 1.83(1.43-2.35) | <0.001 | | |

| Factors | Column2 | Univariable | | Multivariable | |
|---|---|---|---|---|---|
| | | OR (CI) | P value | OR (CI) | P value |
| PT | <13.5 | (ref) | | | |
| | 13.5≤ | 1.84(1.44-2.34) | <0.001 | | |
| PTT | ≤38 | (ref) | | | |
| | 38< | 1.11(0.82-1.51) | 0.485 | | |
| ESR 1h | ≤30 | (ref) | | | |
| | 30< | 1.25 (0.83-1.89) | 0.278 | | |
| D-dimer | ≤500 | 1(ref) | | | |
| | 500-1000 | 6.15 (1.26-29.97) | 0.025 | | |
| | >1000 | 230.22 (47.85-1107.71) | <0.001 | | |
| total bilirubin | ≤1.3 | (ref) | | | |
| | 1.3< | 1.66(1.20- 2.31) | 0.002 | | |
| Direct bilirubin | ≤0.3 | (ref) | | | |
| | 0.3< | 1.51(1.19-1.91) | 0.001 | | |
| AST | ≤40 | (ref) | | | |
| | 40< | 1.82(1.47-2.24) | <0.001 | | |
| ALT | ≤40 | (ref) | | | |
| | 40< | 1.08(0.86-1.35) | 0.502 | | |
| ALP | ≤258 | (ref) | | | |
| | 258< | 1.94(1.45-2.59) | <0.001 | | |
| LDH | ≤500 | (ref) | | | |
| | 500< | 1.82 (1.39 -2.39) | <0.001 | 2.17(1.09-4.35) | 0.025 |
| CPK | ≤170 | (ref) | | | |
| | 170< | 2.06(1.12-3.81) | 0.021 | | |
| CRP | ≤75 | (ref) | | | |
| | 75< | 1.83(1.45-2.30) | <0.001 | | |
| Sodium | <135 | 1.59(1.29-1.96) | <0.001 | | |
| | 135-145 | 1(ref) | | | |
| | 145< | 2.22(1.36-3.62) | 0.002 | 9.7 (1.32-71.19) | 0.025 |
| Potassium | <3.5 | 1.05(0.71-1.55) | 0.804 | | |
| | 3.5-5.5 | 1(ref) | | | |
| | 5.5< | 2.34(1.52-3.59) | <0.001 | | |
| BS | <70 | 1.23(0.76-1.99) | 0.395 | | |
| | 70-200 | 1(ref) | | | |
| | 200< | 1.52(1.20-1.93) | 0.001 | 1.93 (1.01- 3.68) | 0.044 |
| Urea | ≤45 | (ref) | | | |
| | 45< | 2.39(1.97- 2.89) | <0.001 | 3.60 (1.78-2.26) | <0.001 |
| Creatinine | ≤1.4 | (ref) | | | |
| | 1.4< | 2.16(1.72-2.71) | <0.001 | | |

| Factors | Column2 | Univariable | | Multivariable | |
|---|---|---|---|---|---|
| | | OR (CI) | P value | OR (CI) | P value |
| cTnI I | ≤100 | (ref) | | | |
| | 100< | 13.30(1.63-108.38) | 0.016 | | |
| CK-MB | ≤25 | (ref) | | | |
| | 25< | 13.36(6.44-27.73) | <0.001 | | |
| Total protein | < 6 | 1.20(0.84-1.72) | 0.320 | | |
| | 6 ≤ | 1(ref) | | | |
| Albumin | <35 | 2.08(1.19-3.63) | 0.010 | | |
| | 35≤ | 1(ref) | | | |
| Calcium | <8.5 | 1.49(0.89-2.51) | 0.128 | | |
| | 8.5-10.5 | 1(ref) | | | |
| | 10.5< | 3.37(0.53-21.33) | 0.196 | | |
| Magnesium | <1.7 | 1.95(0.55-7.01) | 0.304 | | |
| | 1.7-2.7 | 1(ref) | | | |
| | 2.7< | 0.76(0.35-1.68) | 0.503 | | |
| Phosphorus | < 2.7 | 3.00(1.25-7.22) | 0.014 | | |
| | 2.7-4.5 | 1(ref) | | | |
| | 4.5< | 1.21(0.62-2.35) | 0.570 | | |
| FBS | <70 | 0.55(0.06-5.20) | 0.605 | | |
| | 70-125 | 1(ref) | | | |
| | 126≤ | 1.69(0.67-4.22) | 0.265 | | |
| Iron | <60 | 6.22 (1.27-30.44) | 0.024 | | |
| | 60≤ | 1(ref) | | | |
| Lipase | <60 | ref | | | |
| | 60≤ | 12.65 (4.10-38.98) | <0.001 | | |
| NLR | <3 | ref | | | |
| | 3-9 | 1.768 (1.257-2.486) | 0.001 | | |
| | >9 | 3.738(2.637-5.300) | <0.001 | | |
| PLR | <50 | 0.957(0.592 - 1.548) | 0.860 | | |
| | 50-150 | 1(ref) | | | |
| | >150 | 1.332 (1.055-1.682) | 0.015 | | |

**Abbreviations:** OR=odds ratio, CI= confidence interval**,** RBC - red blood cells; HCT – hematocrit; MCV - mean corpuscular volume; MCH - mean corpuscular hemoglobin; MCHC - mean corpuscular hemoglobin concentration; PLT – platelets; WBC – white blood cells ; RDW-CV- Red Cell Distribution Width; PDW-Platelet Distribution Width; APTT: activated partial thromboplastin time; PT: prothrombin time; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; ALT: alanine aminotransferase; AST: aspartate aminotransferase; LDH: lactate dehydrogenase; CPK: Creatine phosphokinase; BS: blood sugar ;FBS: Fasting blood sugar; CK-MB : Creatine Kinase-MB; cTnI: cardiac troponin I;NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio

### ROC analysis

The ROC analysis of all laboratory parameters was done, where five laboratory tests and two inflammatory markers were selected based on area under curve (AUC), sensitivity, specificity, and positive predictive value (PPV) (Table 4 as well as Figures 1). D-dimer showed largest AUC (AUC: 0.932) at the cut-off value of >1000 (sensitivity = 87.0% and specificity = 91.5%). The second test with highest AUC was lipase at the cut-off value of >34 (AUC= 0.860, sensitivity = 89.4% and specificity = 75.5%). D-Dimer, lipase, CK-MB, and cardiac troponin I showed acceptable PPV for

mortality. Iron and cardiac troponin I were found to be the most sensitive biochemical markers (AUC = 0.675, sensitivity = 90.0%) and (AUC = 0.832, sensitivity = 97.6%), respectively. Regarding CBC findings, NLR had significantly higher AUC than WBC (P = <0.001), PLR (P = <0.001) and lymphocytes percentage (P: 0.001) while the AUC of the neutrophils percentage was close to the AUC of NLR (Table 4).

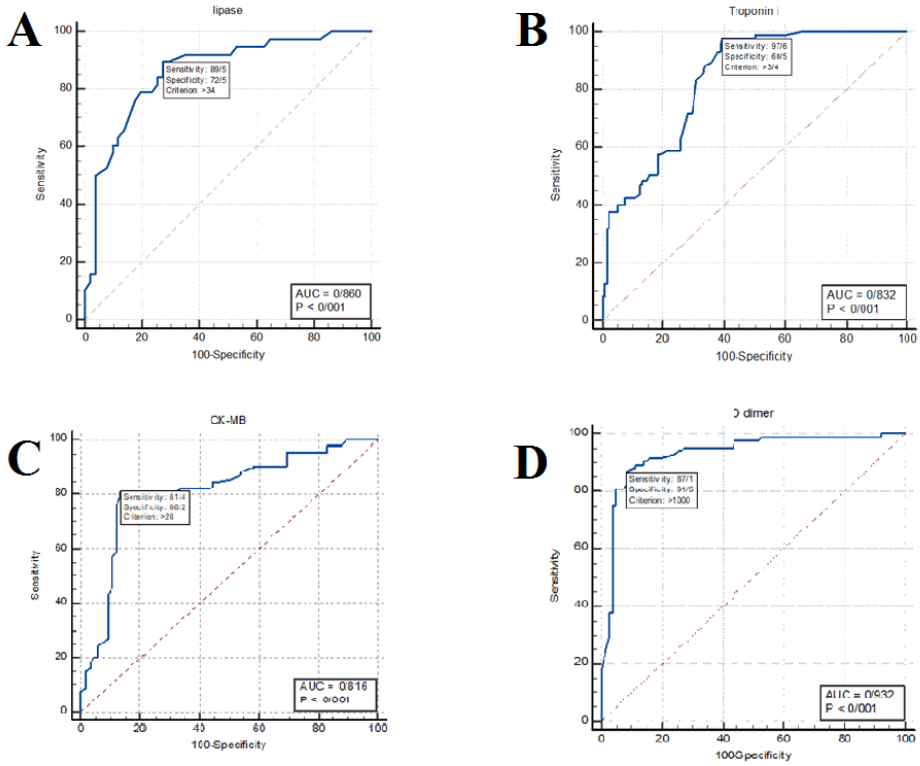


**Figure 1. Receiver operating characteristic (ROC) curves of patient's laboratory test at admission for predicting in-hospital mortality. A, B, C and D show the ROC curves for Lipase, cardiac Troponin I, CK-MB and D-dimer respectively. D-dimer exhibites the largest area under the curve (AUC).**

**Table 4. ROC analysis of laboratory parameters for the prediction of mortality**

| Test (unit) | Cut off | AUC | S.E | 95% CI | Sensitivity | Specificity | PPV | NPV | P-value |
|---|---|---|---|---|---|---|---|---|---|
| **WBC** | >8.69 | 0.551 | 0.015 | 0.52-0.57 | 53.3% | 57.2% | 57.2% | 1.25% | <0.001 |
| **Neutrophil%** | >84.79 | 0.644 | 0.014 | 0.62 - 0.66 | 56.1% | 65.6% | 42.0% | 77.2% | <0.001 |
| **Lymphocyte%** | ≤10 | 0.641 | 0.014 | 0.61-0.66 | 49.4% | 71.2% | 43.3% | 76.0% | <0.001 |
| **NLR** | >8.66 | 0.645 | 0.014 | 0.62- 0.66 | 49.7% | 72.1% | 44.2% | 76.4% | <0.001 |
| **PLR** | >214.51 | 0.559 | 0.015 | 0.53- 0.58 | 52.5% | 59.0% | 34.4% | 73.6% | 0.001 |
| **cTnI** | >3.4 | 0.832 | 0.026 | 0.77 -0.87 | 97.6% | 60.4% | 61.9% | 97.5% | <0.001 |
| **D-dimer** | >1000 | 0.932 | 0.019 | 0.88 - 0.96 | 87.0% | 91.5% | 89.2% | 89.8% | <0.001 |
| **Ck-mb** | >28 | 0.816 | 0.034 | 0.75 - 0.86 | 81.3% | 86.1% | 91.4% | 71.8% | <0.001 |
| **Iron** | ≤38 | 0.675 | 0.0662 | 0.55 - 0.78 | 90.0% | 51.2% | 58.7% | 87.0% | 0.008 |
| **Lipase** | >34 | 0.860 | 0.040 | 0.77 - 0.92 | 89.4% | 72.5% | 70.8% | 90.2% | <0.001 |

**Abbreviations:** PPV: Positive predictive value; NPV: Negative predictive value; AUC: Area under curve; S.E: Standard error of mean; ROC: Receiver operating characteristic; CI: confidence interval; cTnI: cardiac troponin I; NLR: Neutrophil-to lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio.

## Discussion

A total of 2156 hospitalized patients with *COVID-19* were evaluated in this study, with the hope to find demographic and laboratory factors predicting the higher risk of in-hospital death. Non-survivor patients were older compared with survivors (p<0.001), which suggest that older-aged people are more susceptible to life-threatening *COVID-19* infection. Using multiple regression analysis, older age proved to be an independent risk factor for in-hospital death (OR=1.01, P=0.042). In the study by Hu L et al, older age was an independent risk factor for (OR=3.54, p=<0.001) **(13)**. In addition, several studies such as Guan WJ et al **(14)** and Wang Z et al **(15)** studies indicated that the age of patients with severe *COVID-19* infection was significantly older than those with non-severe infection. Researchers have proposed that this finding might be associated with age-dependent defects in T-cell and B-cell functions as well as more comorbidities in older patients **(16)**. The function of immune system shows some decline in older individuals, which is associated with overproduction of type 2 cytokines, causing a defect in controlling viral replication and prolonged pro-inflammatory responses, which might be implicated in the poor clinical prognosis of *COVID-19* infection **(17)**. In this study, the male gender had higher odds of *COVID-19* mortality after adjustment for potential cofounders (OR=2.34, P=0.005). Yu C et al. also found similar results **(18)**. In contrast, few reports, including Liu k et al. study, evaluating 137 patients, did not find such an association **(19)**. This might be due to the smaller sample size of their study or in part different geographical and racial backgrounds. Furthermore, some previous studies have indicated that *MERS-COV* and *SARS-COV* have been found to infect more males than females **(20)**.

In this study, we found that elevated LDH levels had obvious association with in-hospital death due to COVID-19 (LDH>500, OR=0.46, P=0.025). This result is in line with those reported by Huang C et al **(21)** and Li C **(22)**. LDH is an intracellular enzyme found in almost every tissue especially in the kidneys, skeletal muscle, heart, liver, RBCs, brain, and lungs. Since LDH is not a tissue-specific marker, thus total LDH level is not a precise indicator of a specific disease and cannot designate damage to a certain organ. *COVID-19* by involving the lungs as well as other tissues leads to tissue hypoxia and inflammation. Theoretically, hypoxia or inflammation gives rise to an increase in the level of serum LDH. Thus, elevated serum LDH can be an important laboratory indicator for evaluating the severity of *COVID-19 i*nfection **(23)**. Guan WJ et al in their study on 1099 patients indicated that high levels of LDH in *COVID19* patients were associated with tissue damage and inflammation **(14)**.

In the present study, hypernatremia was identified as an independent risk factor for mortality (OR=9.7, P=0.025). Trecarichi EM et al showed that hypernatremia two days after admission and exposure to hypernatremia at any time point during hospitalization increased the risk of death in *COVID-19* patients ((HR=2.34, P=0.001) and (HR=3.05, P=<0.001), respectively)) **(24)**. Hypernatremia has been introduced as a potential surrogate marker of sepsis, especially in the elderly, as a severe systemic infection can lead to reduced extracellular fluid volume. This high frequency of volume depletion in *COVID-19* illness might be explained by low oral intake due to anorexia or nausea, or fluid losses due to fever or diarrhea. In addition, some evidence suggests that sodium could have an important role in immune response, affecting the function of macrophages and T-lymphocytes **(25, 26)**.

Low lymphocyte count was found to be an independent risk factor for poor outcome of Covid-19 patients in the current study. In a meta-analysis study by Mingchun Ou et al, lymphopenia was shown to be associated with increased risk of severe disease and mortality in patients with *COVID-19* and the researchers suggested that lymphopenia could be a clinical indicator of worsening of the disease during hospitalization **(6)**. In addition, it has been reported that lymphopenia was seen in about 73.8% of patients with severe *COVID19* infection, and increased the risk of poor clinical outcomes **(27)**. Lymphocytes play a pivotal role in the elimination of most viral infections. Memory T and B cells, generated during infection, are a potent mechanism in protecting the host from severe disease upon re-exposure. While the attention has been mostly placed on humoral immunity, there is increasing evidence that T cells play the main role in determining the outcome of patients with *COVID-19* **(28)**.

D-dimer has been reported to be an independent risk factor for death in some reports **(17, 29)**. In the present study, D-dimer was significantly higher in the non-survivor group comparing to survivors (3527±1714 vs. 717±879, P<0.001), and using univariate regression analysis, D-dimer>1000 turned to be with 230 times increase in odds of in-hospital death. Unfortunately, because of some shortage in laboratory kits during the studied period, the results for D-dimer was only available for 191 patients, so we could not further analyze it using multivariate regression analysis. D-dimers are produced by degradation of fibrin and are not normally present in blood unless coagulation and fibrinolysis have occurred. High levels of D-dimers could be related to the presence of disseminated intravascular coagulation (DIC). On the other hand, *COVID-19* is strongly associated with various coagulopathies. Importantly, severe *COVID-19* disease is postulated to happen because of a crosstalk between inflammatory and coagulation systems. In this way, the production of pro-inflammatory cytokines (e.g. TNF-α, IL-1β or IL-6) leads to the up-regulation of tissue factor (TF), which results in a pro-coagulant activity. Thus, this marker has a promising potential for

determining mortality (30). In addition, the present study showed that elevated blood urea was associated with adverse clinical outcomes in hospitalized patients with *COVID-19*. Urea levels mostly is a marker for kidney function. Kidney involvement is known as a part of multiorgan dysfunction due to *SARS-CoV-2* virus infection and cytokine storm. The mechanism of kidney involvement of *SARS-CoV-2*, especially in those with mild to moderate disease conditions, remains unclear. However, a recent study by Wang et al. found that *SARS-CoV-2* enter cells by a novel route of CD147-spike protein and has been involved in various kidney diseases (31, 32).

NLR and PLR as novel markers for evaluation of inflammatory status are currently explored as predictors of mortality or severity in patients with *COVID-19*. In the current study, mean levels of NLR and PLR were higher in the non-survivor group compared to the survivors (P<0.001). In line with our study, Asghar MS et al. (7) indicated that levels of NLR and PLR were significantly higher in patients who died during hospitalization than those who survived (both P <0.05). Elevated NLR could occur due to dysregulation of inflammatory cytokines including TNF-α and IL-6, leading to aberrantly high production of neutrophils. In contrast, catecholamines, cortisol, and the increased pro-inflammatory mediators will bind to the lymphocytic surface leading to up-regulation of genes involved in lymphocytic apoptosis which might be responsible for the lymphopenia (33). In addition, the ROC analysis revealed that NLR at a cut-off value of >8.66 has 49.7% sensitivity and 72.1% specificity in predicting in-hospital mortality. In the present study as well as the study by Lin S et al, NLR revealed the highest AUC among other CBC based parameters (34).

Using ROC analysis, D-dimer, lipase, troponin I, and CK-MB showed acceptable AUCs (AUCs: 0.93, 0.86, 0.83 and 0.82, respectively) and may have good predictive value for identifying *COVID-19* patients with a higher risk of death. D-dimer at a cut-off of >1000 ng/ml, showed 87% sensitivity and 91.5% specificity in identifying patients at risk of death. In line with our results, Bastug A et al showed that D-dimer at a cut-off of ≥565 had a sensitivity of 85.7% and 80.6% specificity in identifying patients who will need ICU admission (AUC: 0.896) (35). Other studies including Mahmood Y et al reported that D dimers (>1500 ng/ml) and troponin (>13.5 ng/ml) could positively predict the admission to ICU in patients with *COVID-19* (36). According to recent studies, it has been reported that elevated cardiac troponins suggest that myocardial injury is a possible mechanism leading to severe disease and mortality in patients with *SARS-CoV-2* infection (37). Yang X et al in their study including 52 critically ill adult patients with *SARS-CoV-2* pneumonia admitted to ICU showed that 23% of patients had a cardiac injury and cardiac disease was more prevalent in non-survivor patients compared to survivor patients (28% vs 15%) (38).

To the best of our knowledge, the study population at the present study is the largest among similar studies, evaluating risk factors for identifying definite outcome of patients with *COVID-19*. Meanwhile, as the results of some laboratory tests including D-dimer were not available in most patients, their evaluation in multiple variate analysis was not possible. Further studies with large sample sizes that evaluate both the clinical data including signs and symptoms of patients as well as their past medical histories beside the laboratory findings could help identify patients with higher risk of worse outcome more precisely.

## Conclusion

In this retrospective cohort study, evaluating data of 2156 hospitalized *COVID-19* patients, older age, male sex, LDH >500 U/L, urea >45 mg/dL, lymphocyte <1 (x 10^3/µL), sodium >145 mEq/L, and BS>200 mg/dl were identified as independent risk factors for in-hospital death. In addition, D-dimer (>1000 ng/ml) as well as CK-Mb (>28 U/L) both with sensitivities and specificities of more than 80% and PPV of about 90% were able to identify patients with a higher possibility of in-hospital death. These results may help physicians in making more precise decisions regarding the patient's prognostic test results leading to better allocation of scarce medical resources.

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## Conflict of Interest

The authors declare that they have no competing interests.

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