Prognostic value of routine blood parameters in intensive care unit COVID-19 patients

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\section*{ABSTRACT}

\textbf{Introduction}
Laboratory medicine has an important role in the management of COVID-19. The aim of this study was to analyze routinely available blood parameters in intensive care unit COVID-19 patients and to evaluate their prognostic value.

\textbf{Patients and methods}
This is a retrospective, observational, single-center study including consecutive severe COVID-19 patients who were admitted into the intensive care unit of Ben Arous Regional Hospital in Tunisia from 28 September 2020 to 31 May 2021. The end point of the study was either hospital discharge or in-hospital death. We defined two groups based on the outcome: survivors (Group 1) and non-survivors (Group 2). Demographical, clinical, and laboratory data on admission were collected and compared between the two groups. Univariate
and multivariate logistic regression analysis were performed to determine the predictive factors for COVID-19 disease mortality.

Results
A total of 150 patients were enrolled. Eighty patients (53.3%) died and 70 (46.7%) survived during the study period. Based on statistical analysis, median age, Simplified Acute Physiology Score (SAPS II) with the serum levels of urea, creatinine, total lactate dehydrogenase (LDH), creatine kinase, procalcitonin and hs-troponin I were significantly higher in non-survivors compared to survivors. On multivariate analysis, LDH activity ≥ 484 U/L (OR=17.979; 95%CI [1.119-2.040]; p = 0.09) and hs-troponin I ≥ 6.55 ng/L (OR=12.492; 95%CI [1.691- 92.268]; p = 0.013) independently predicted COVID-19 related mortality.

Conclusion
Total LDH and hs-troponin I were independent predictors of death. However, further clinical investigations with even larger number of patients are needed for the evaluation of other laboratory biomarkers which could aid in assessing the prediction of mortality.

INTRODUCTION
The outbreak of the SARS-CoV-2 infection began in Wuhan, Hubei, China and spread rapidly around the world (1). Since March 2020, Coronavirus Disease 2019 (COVID-19) has been declared as a pandemic (2). The clinical manifestations of COVID-19 vary highly, ranging from asymptomatic or mild infection to severe forms of pneumonia requiring hospitalization at intensive care unit (ICU). In severe forms, respiratory distress syndrome may be often accompanied by life-threatening multi-organ failure (3). Several recent studies have investigated serum biomarkers closely associated with COVID-19 severity (4). However, only a few studies have focused on the prognostic role of laboratory findings in ICU COVID-19 patients.

Therefore, the aim of this study was to analyze routine blood parameters of severe COVID-19 patients and to explore the mortality predicting factors in these ICU patients.
The measurement of routinely available blood tests was performed on the date of ICU admission in the Central Laboratory of Ben Arous Regional Hospital. The laboratory tests included general parameters, such as C-reactive protein (CRP), procalcitonin (PCT), complete blood count and D-dimer. Hs-troponin I measurement was performed on admission since its prognostic value has been reported in several studies.

**Evaluation criteria**

Patients were followed up during their hospitalization. Our study’s primary endpoint was COVID-19 related mortality. The clinical and laboratory data were compared between the two study groups.

**Statistical analysis**

Statistical analysis was performed with SPSS version 25.0 software. Continuous variables were presented as median values with interquartile range (IQR) and were compared by the Student’s t-test or Mann-Whitney U-test according to the normality of the distribution. Qualitative variables were presented as counts and percentages and were compared by the Pearson $\chi^2$ and Fisher’s exact tests. Univariate and multivariate logistic regression analysis was used to determine the predictive factors for COVID-19 disease mortality. A $p$ value $< 0.05$ was considered to be statistically significant.

**RESULTS**

**Demographical and clinical characteristics of COVID-19 patients**

In this study, 150 patients, 88 men and 62 women (gender-ratio M/F=1.41), were enrolled. The median age was 64.5 years. Among study participants, 121 patients (80.66%) had at least one comorbidity, while 47 patients (31.3%) were mechanically ventilated during ICU treatment.

The following medication was administered before ICU admission: antibiotic therapy (n=104, 69.3%), corticosteroid therapy (n=148, 98.6%),

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**Table 1**  Drugs and other ICU treatment administrated in both study groups

|                         | Group 1 (n=70) | Group 2 (n=80) | p value | RR [95% CI]     |
|-------------------------|---------------|---------------|---------|----------------|
| Prone position          | 10            | 59            | 0.000   | 2.636 [1.639; 4.240] |
| Dialysis                | 3             | 12            | 0.017   | 1.691 [1.214; 2.356] |
| Antibiotic therapy      | 48            | 56            | 0.193   | 1.06 [0.731 ; 2.157] |
| Corticosteroid therapy  | 73            | 75            | 0.515   | 1.66 [0.932 ; 1.873] |
| Curative anticoagulation| 35            | 69            | 0.000   | 3.898 [2.043; 7.436] |
| Mechanical ventilation  | 16            | 73            | 0.000   | 12.713 [4.903; 32.966] |
| Tracheotomy             | 5             | 4             | 0.149   | 0.68 [0.521 ; 2.147] |
curative anticoagulation (n=104, 69.3%), and mechanical ventilation (n=89, 59.3%) (Table 1). Eighty patients (53.3%) in Group 2 died of COVID-19 and 70 individuals (46.7%) survived and were discharged from the hospital (Group 1) (Table 2). The median hospitalization duration in ICU was 10 days for non-survivors (IQR [6, 17.5] days). Mortality causes were the following: hypoxemia (n=99, 66%), septic shock (n=32, 21.3%), cardiogenic shock (n=1, 0.7%), and multi-organ failure (n=18, 12%). We noted one case of coronary syndrome in Group 2 during the hospitalization in ICU.

Comparison of clinical characteristics between the two groups is presented in Table 2. The median age and the SAPS II score were significantly

| Characteristics                      | Total (n=150) | Group 1 (n= 70) | Group 2 (n=80) | p value |
|--------------------------------------|--------------|-----------------|---------------|---------|
| Age (years) median (IQR)             | 64.5 [20-92] | 61 [20-92]      | 65[31-68]     | 0.004   |
| Gender, n (%)                        |              |                 |               |         |
| Male                                 | 88 (58.7%)   | 38(54.3%)       | 50 (62.5%)    | 0.324   |
| Female                               | 62 (41.3%)   | 32(45.7%)       | 30 (37.5%)    |         |
| Median SAPS II score                 | 32 [27-38]   | 29 [24-33]      | 34 [29-46]    | <0.001  |
| Comorbidities, n (%)                 | 121 (80.6%)  | 58 (82.8%)      | 63 (78.7%)    | 0.52    |
| Hypertension, n (%)                  | 68 (45.3%)   | 27 (38.6%)      | 41 (51.2%)    | 0.14    |
| Diabetes mellitus, n (%)             | 61(40.7%)    | 28 (40%)        | 41 (51.2%)    | 0.876   |
| Dyslipidemia, n (%)                  | 19 (12.7%)   | 9 (12.9%)       | 10 (12.5%)    | 0.948   |
| Coronary disease, n (%)              | 24 (16%)     | 11 (15.7%)      | 13 (16.3%)    | 0.929   |
| Renal disease, n (%)                 | 10 (6.7%)    | 4 (5.7%)        | 6 (7.5%)      | 0.752   |
| Respiratory disease, n (%)           | 23 (15.3%)   | 11 (15.7%)      | 12 (15%)      | 0.904   |
| Thyroid disorders, n (%)             | 8 (5.3%)     | 5 (7.1%)        | 3 (3.8%)      | 0.474   |
| Obesity, n (%)                       | 13 (8.7%)    | 7 (10%)         | 6 (7.5%)      | 0.772   |
| Mechanical ventilation, n (%)        | 97 (64%)     | 20(28%)         | 77 (96%)      | <0.001  |

IQR: interquartile range; SAPSII: Simplified Acute Physiology Score. Bold p values mean statistically significant difference.
higher in Group 2 vs Group 1. There was no significant difference in terms of gender and comorbidities (hypertension, diabetes mellitus, dyslipidemia, coronary heart disease, kidney disease, respiratory disease, thyroid diseases and obesity) between the two groups. Mortality ratio was significantly higher in invasive ventilated patients.

**Laboratory parameters of COVID-19 survivors and non-survivors**

Blood routine parameter results studied on admission are presented and compared between the two groups in Table 3. The levels of blood glucose, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyltranspeptidase (GGT), alkaline phosphatases (ALP), total bilirubin, sodium, potassium, chloride, calcium, magnesium, phosphorus, total protein, N-terminal prohormone of brain natriuretic peptide (NT-proBNP), D-dimer, CRP, hemoglobin, white blood cells (WBC), neutrophils, lymphocytes and platelets were not significantly different between the two groups (Table 3). In contrast, blood urea, creatinine, Lactate dehydrogenase (LDH), Creatine kinase (CK), PCT and hs-troponin I levels were significantly higher in Group 2 (non-survivors) than in Group 1 (survivors).

**Multivariate analysis**

Variables with statistically significant differences between the two groups (median age, SAPS II score, BUN, creatinine, LDH, CK, PCT and hs-troponin I) were included in logistic regression analysis. Accordingly, LDH ≥ 484 U/L (OR=17.979; 95%CI [1.119-2.040]; p = 0.09) and hs-troponin I ≥ 6.55 ng/L (OR=12.492; 95%CI [1.691- 92.268]; p = 0.013) were independent predictors for mortality.

| Laboratory tests, median (IQR) | Total (n=150) | Group 1 (n=70) | Group 2 (n=80) | p value |
|-------------------------------|-------------|---------------|---------------|--------|
| Glucose, mmol/L               | 9.72 (6.64-15.41) | 8.87 (6.04-15.64) | 10.35 (7.28-15.2) | 0.36   |
| ALT, U/L                      | 30 (18.5-44) | 33 (20-48.5) | 28(18-42) | 0.115 |
| AST, U/L                      | 41(27-58) | 36 (25-55) | 42(28-60) | 0.245 |
| GGT, U/L                      | 50.5 (27.7-77.7) | 49 (27-78.5) | 52(28-80) | 0.904 |
| ALP , U/L                     | 65 (52-86.2) | 60.5 (49.7-84.2) | 69(57-89) | 0.055 |
| Total bilirubin, µmol/L       | 9.05 (6.9-12.7) | 8.75 (6.6-12.10) | 10 (7.7-13.1) | 0.225 |
| Urea, mmol/L                  | 6.85 (5.2-10.95) | 5.65(4.45-8.22) | 8.85(6.37-13.47) | <0.01 |
| Creatinine, µmol/L            | 71.9 (61.1-104.4) | 66.5(55.1-86-1) | 77.85(66.5-123.2) | <0.01 |
| LDH, U/L                      | 528.5 (411.25-660.75) | 480(361-587) | 608 (472-740) | <0.01 |
| Parameter                  | ALP (U/L)   | ALT (U/L)   | AST (U/L)   | CK (U/L)   | CRP (mg/L) | NT-proBNP (pg/mL) | PCT (ng/mL) | D-dimer (ng/mL) | Hemoglobin (g/dL) | WBC (*10^3/µL) | Neutrophils (*10^3/µL) | Lymphocytes (*10^3/µL) | Platelets (*10^3/µL) |
|---------------------------|-------------|-------------|-------------|-----------|------------|------------------|-------------|----------------|------------------|----------------|----------------------|----------------------|---------------------|
| Alkaline phosphatases    | 69.5 (42-209.25) | 55.5 (39.2-146.2) | 91 (48.5-346.2) | **0.011** |            |                  |             |                |                  |                |                      |                      |                     |
| Alanine aminotransferase | 137 (134-140) | 136.5 (133-139) | 138 (136-141) |           | 108 (52.8-120) | 376 (137-1277) | 0.22 (0.0057-0.597) |            | 1305 (738.8-2784.2) | 12.2 (10.87-13.4) | 10.58 (7.43-13.5) | 9.41 (6.21-12.04) | 251 (197-313) |
| Aspartate aminotransferase| 4.2 (3.9-4.62) | 4.15 (3.8-4.6) | 4.25 (3.9-4.7) |           |           |                  |             |                |                  |                |                      |                      |                     |
| Creatine kinase          | 102 (99.75-105) | 101 (99.75-104) | 102 (99.25-105) |           |           |                  |             |                |                  |                |                      |                      |                     |
| Gamma-glutamyl-transpeptidase |           |           |           |           |           |                  |             |                |                  |                |                      |                      |                     |
| Lactate dehydrogenase    | 2.08 (1.95-2.21) | 2.09 (2.00-2.22) | 2.04 (1.93-2.2) |           |           |                  |             |                |                  |                |                      |                      |                     |
| N-terminal prohormone of brain natriuretic peptide |           |           |           |           |           |                  |             |                |                  |                |                      |                      |                     |
| Procalcitonin            | 0.9 (0.8-1.0) | 0.9 (0.8-1.0) | 1.0 (0.9-1.1) |           |           |                  |             |                |                  |                |                      |                      |                     |
| Procalcitonin            | 0.95 (0.81-1.21) | 0.91 (0.79-1.14) | 0.96 (0.82-1.28) |           |           |                  |             |                |                  |                |                      |                      |                     |
| CRP, mg/L                | 66 (59-70.75) | 67 (61-71) | 65 (57-70) |           |           |                  |             |                |                  |                |                      |                      |                     |
| hs-Troponin I, ng/L      | 12.1 (4.6-57.3) | 5.5 (3.1-19.4) | 21.6 (7.4-125.5) |           |           |                  |             |                |                  |                |                      |                      | <0.001              |
| NT-proBNP, pg/mL         | 376 (137-1277) | 245 (90.5-738.7) | 565 (177-1608) |           |           |                  |             |                |                  |                |                      |                      |                     |
| Neutrophils, *10^3/µL    | 0.77 (0.53-1.09) | 0.84 (0.60-1.07) | 0.69 (0.48-1.13) |           |           |                  |             |                |                  |                |                      |                      |                     |
| Total protein, g/L       | 10.58 (7.43-13.5) | 9.87 (6.77-12.85) | 10.89 (8.02-14.5) |           |           |                  |             |                |                  |                |                      |                      |                     |
| Lymphocytes, *10^3/µL    | 251 (197-313) | 277 (217-327) | 232 (184-306) |           |           |                  |             |                |                  |                |                      |                      |                     |
| Platelets, *10^3/µL      | 251 (197-313) | 277 (217-327) | 232 (184-306) |           |           |                  |             |                |                  |                |                      |                      |                     |

ALP: Alkaline phosphatases; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CK: Creatine kinase; CRP: C-reactive Protein; GGT: Gamma-glutamyl-transpeptidase; LDH: Lactate dehydrogenase; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; PCT: Procalcitonin; WBC: White blood cells. Bold p values mean statistically significant difference.
DISCUSSION

COVID-19 is now recognized as a multisystem disease that can cause a complex disorder affecting many organs, which may require ICU hospitalization (6). Our study investigated the demographical profile, pre-existing comorbidities and routine blood parameters of 150 COVID-19 patients hospitalized in ICU comparing survivors and non-survivors. The clinical features in our study were comparable with other studies (7). Mortality reported in the literature ranges from 30 to 80% (8–13). These differences can be explained by the wide variety and population heterogeneity in different clinical studies. Economic and organizational obstacles in some countries may also partly explain the worse outcomes. For instance, the reduced number of ICU beds in developing countries may delay the hospitalization of severe COVID-19 patients in ICU wards.

As in other cohorts, the demographical and clinical risk factors for mortality were the age, SAPS II score and need for mechanical ventilation. Comorbidities did not significantly influence the COVID-19 related mortality in our study. Many authors showed that comorbidities were associated with a higher risk for death in patients with COVID-19. Estenssoro et al. identified cardiovascular disease, chronic kidney disease and diabetes as important mortality risk factors in mechanically-ventilated COVID-19 patients (14). The gender role in mortality was observed in different series; male gender was associated with worse outcomes and death (7). In our study, non-survivors were predominantly males (50 vs. 30). These non-significant differences can be explained by the retrospective nature of the study and the relatively low number of recruited patients.

Consistent with previous findings, univariate analysis showed that urea, creatinine, PCT, total LDH, CK and hs-troponin I were significantly different between the two groups. Renal injury was frequently reported in patients with COVID-19, even in those who had no underlying kidney disease (15). The systemic immune response to the SARS-COV-2 leading to so-called a cytokine storm can be an explanation for the high prevalence of kidney injury in patients with COVID-19 (16,17). Therefore, kidneys may be a susceptible target of the SARS-COV-2 infection. Elevated level of urea at admission maybe an indicator for early kidney injury. Consequently, early detection of acute kidney injury may facilitate appropriate treatment, including avoiding nephrotoxic drugs and adequate fluid therapy (2).

We also found that PCT was significantly associated with death without being an independent factor of mortality. Similarly, a study investigating this marker as a COVID-19 mortality predictor, showed an upward trend of acute-phase proteins, including PCT in non-survivors, and a stable or downward trend in survivors (18). PCT levels appeared to be disease-severity-dependent and may be associated with bacterial co-infection (19). In addition, a recent study hypothesized that a progressive increase in PCT levels may predict a worse prognosis (20). Consistently to other studies, CK, a marker of muscle tissue damage, was associated with an increased mortality in patients with COVID-19 (21,22).

It is relatively common that COVID-19 patients have clinical signs of dehydration and hypovolemia. This may contribute to renal impairment and consequently to a mild increase in CK levels. In addition, muscle damage and CK elevation, even without respiratory symptoms, should be considered as a potential COVID-19 manifestation. Consequently, it is important to monitor CK levels in COVID-19 patients, especially when they complain of muscle pain and weakness (23).
We used logistic regression analysis to screen independent significant factors associated with in hospital–mortality in ICU. LDH ≥ 484 U/L (OR=17.979; [95% CI: 1.119-2.04]; p = 0.09) was an independent predictor for mortality. LDH, an ubiquitous enzyme, is well recognized as a prognostic marker related to the severity of several pathologies. LDH elevation in COVID-19 occurs in cell lysis syndrome and may reflect the extent of lung and other tissue damage (24-26). Additionally, LDH levels are elevated in thrombotic microangiopathy, which is associated with renal failure and myocardial injury (25). In the latter, the elevation of LDH can be associated to the elevation of troponin. In our study, hs-troponin I ≥ 6.55 ng/L (OR=12.492; 95% CI [1.691-92.268]; p = 0.013) was an independent predictor of mortality. Interestingly, a meta-analysis concluded that cardiac injury biomarkers mainly increased in COVID-19 non-survivors (26).

Data on acute myocardial injury associated with COVID-19 shows a very strong independent association between increased troponin concentrations and disease severity, including mortality. It has been hypothesized that the acute inflammatory response in COVID-19 disease can cause rupture of atherosclerotic plaques leading to ischemia. Inflammation also causes endothelial dysfunction and increases the procoagulant activity of the blood, which can contribute to the formation of an occlusive thrombus over a ruptured coronary plaque (27,28).

In contrast to other studies, we did not find any prognostic value of CRP. However, Zhang et al. did not find any significant difference in CRP levels between survivors and non-survivors on ICU admission. However, at 1-3 days after admission CRP levels were significantly altered between the two groups (29). Interestingly, D-dimer did not differ between our two groups.

The same results were reported by a multicentric study including 1260 patients (30). However, this marker has been considered as a prognostic marker in COVID-19 (31). Survival analysis by Zhang et al. find an association between 14-day mortality and an increase in D-dimer with no difference in 7-day mortality rate. Monitoring CRP and D-dimer levels during hospitalization would be interesting to evaluate the prognostic role of these markers.

Our study has several limitations. First, this was a retrospective single center investigation with a relatively low number of patients. Therefore, the only evaluated event was mortality. Second, laboratory parameters were analyzed only at admission. The evaluation of the kinetics of some biological markers would be interesting, thus further studies are needed to overcome these limitations.

In conclusion, our study showed that the levels of LDH and troponin on admission, were independent predictors of mortality. This can help clinicians to predict disease prognosis and perform early therapeutic interventions.

Ethical approval

The study was approved by the Institutional Ethics Committee and was in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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