Can laboratory tests at the time of admission guide us to the prognosis of patients with COVID-19?

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Keywords
Coronavirus • Mortality • Prognosis • Laboratory tests

Introduction. To enhance the COVID-19 patients’ care and to optimize utilizing medical resources during the pandemic, relevant biomarkers are needed for prediction of the disease’s progression. The current study was aimed to determine the factors that affect the mortality of COVID-19 patients admitted in Baharloo hospital in Iran.

Methods. In the current retrospective study, 56 survived patients and 56 patients who were died (a total of 112 cases) because of COVID-19 infection were randomly selected from those who were admitted to Baharloo hospital. Each patient who was diagnosed with COVID-19 and had recovered from it matched with each non-survived patient in the term of age. Laboratory tests of all these patients at the time of admission were recorded and compared. All analyses performed using spss version 22 by considering α = 0.05 as a significant level.

Results. There was no statistical difference in the age and gender distribution between the two groups (p > 0.05). The prevalence of diabetes among survived patients was 37.5% and among non-survived patients was 26.8% and there was no statistical difference between two groups regarding this comorbidity (p = 0.22). Also, there was no statistical difference in the prevalence of hypertension and coronary heart diseases between two groups (p > 0.05). Lymphocyte percentage, blood oxygen level, and platelet (PLT) count was significantly higher in patients who had recovered (P < 0.05).

Conclusions. LDH level, Lymphocyte percentage, PLT count, and blood Oxygen saturation have associations with severe forms of COVID-19 infection and can be used as predictors to assess the patients who are suspected of infection with COVID-19 at the time of admission.

Introduction

Since the emerging of novel Corona virus disease 2019 (COVID-19) in December, 2019, this virus has affected nearly 160 million people and caused about 3.25 million deaths worldwide. In Iran, more than 245,000 people are affected which has lead to 11,000 deaths in the country up to 7 July 2020 [1]. The symptoms of the COVID-19 are wide from asymptomatic to severe forms of pneumonia and multi organ failure [2-4]. Fever, cough, and fatigue are the most common symptoms of COVID-19 [2]. Case fatality rate is 3.8% and 25.6% of the patients experience the severe forms of the disease [2, 5]. COVID-19 is a highly contagious disease. Human to human transmission is the main cause of COVID-19 transmission and close contact with infected patients may transmit the virus to others [6]. Secondary attack rate of this infection is about 35% [7] and the virus spreads rapidly in populations. Rapid increase in the number of patients impose excess burden on the health care systems and increases the costs [8]. To enhance the patients’ care and to optimize utilizing medical resources during this pandemic, relevant biomarkers are needed for prediction of the disease’s progression and actively monitoring illness severity at the early stage [2, 3]. There are several studies on the factors which can predict the outcome in patients with COVID-19. Old age, low levels of lymphocytes, high levels of C reactive protein (CRP) and cardiac troponin, and D-Dimers levels higher than 1 μg/L were associated with poor prognosis in China [4, 9-11]. In a systematic review by Wynants et al, age, sex, computed tomography (CT) findings, lactate dehydrogenase (LDH), CRP, lymphocytes count, and presence of comorbidities were associated with the prognosis [12]. In previous studies on influenza, there had been differences between populations in the terms of the factors that have been related with mortality. Urea level in Macedonina [13], CRP in Tunisia, and Creatinine in Taiwan were associated with mortality in patients with influenza. Such may be applicable in
patients with COVID-19 and there may be differences in prognostic factors in different populations. As there are no studies available on the prognostic factors of COVID-19 in Iranian population, the current study aimed to determine the factors that affect the mortality of COVID-19 patients who were admitted in Baharloo hospital in Iran.

Materials and methods

Study population
Patients included in the current retrospective study were suspected of COVID-19 infection admitted in the Baharloo hospital. Baharloo hospital is a teaching hospital that located in Tehran and is affiliated to Tehran University of medical sciences medical school. This hospital has been COVID-19 referral center since the COVID-19 outbreak in Tehran. Inclusion criteria were: 1) clinical symptoms of COVID-19 such as fever, cough, fatigue, myalgia, dyspnea, chest pain, nausea, vomiting; 2) positive nasopharynx COVID-19 polymerase chain reaction (PCR) test; 3) lung imaging compatible with COVID-19 pneumonia. Patients who were diagnosed with bacterial pneumonia at the time of admission, those whose symptoms had started more than 7 days prior to admission and those whose medical records were incomplete were excluded from our study.

From those who were eligible to be included in our study, 56 patients who were died because of COVID-19 were randomly selected. Also the information of 56 patient who were recovered from the disease and were discharged from the hospital were selected as a control group. A code was dedicated to each patient and all data were recorded anonymously. We reviewed medical records of their recent admission because of COVID-19 infection. Demographic characteristics of patients as such as age, gender, and their underlying diseases were recorded. Laboratory and clinical parameters such as blood’s O2 Saturation, hemoglobin (Hb), white blood cell count (WBC), percentages of PMN and lymphocyte, platelet count, ESR, CRP, LDH, and serum vitamin D level at the time of admission to emergency department were extracted. The study design was approved by Tehran University of medical sciences ethical committee.

Statistical analysis
The descriptive analysis was performed using the mean (Standard Deviation) or frequency and percent for quantitative and qualitative variables, respectively. The differences in characteristics between survived and non-survived patients were examined using independent t-test for continuous variables and chi-squared test for categorical variables. All analysis performed using SPSS software version 22 by considering $\alpha = 0.05$ as a significant level.

Laboratory analysis
On the first admission day, 10 cc blood sample was obtained and sent to the hospital laboratory for CBC-diff (WBC count, Lymphocyte and PMN percents, Platelet count), LDH, CRP, ESR, and Vitamin D3 level. The automated hematology analyzer, Sysmex KX-21N, was applied for CBC-diff which counted cells and collected information on their size and structure (Lymphocyte, Neutrophil, Platelet). ESR test was made by Therma NE instrument; however, sometimes the western green tubes were used for measurement of sedimentation rate manually. CRP measurement was performed by immunoturbidimetry method using Hitachi 912 and LDH level was performed by enzymatic method using Hitachi 717. Vitamin D3 level was measured by high performance liquid chromatography (HPLC) method using Agilent instrument.

Results
In total 56 survived and 56 non-survived patients included in our study. Of these patients, 77 (68.8%) were males and 35 (31.3%) were female. In survived group 38 (67.9%) of cases were males and 18 (32.1%) of cases were females. In non-survived group 39 (69.6%) of cases were males and the 17 (30.4%) of cases were females. There was no significant difference in gender between two groups (P: 0.83).

The mean of ages among survived patients was 67.14 ± 10.54 and among death cases was 67.96 ± 14.60. There was no significant difference between two groups about age distribution (P = 0.73).

The prevalence of diabetes among among survided and non-survived patients were 37.5% and 26.5% respectively. There was no statistical difference between two group about this comorbidity (p = 0.22). Also there was no statistical difference in prevalence of hypertension and coronary heart diseases between two groups. More information has been shown in Table I.

Lymphocyte percentage was significantly higher in patients who had recovered from the disease as compared with the patients who died (22.76 vs 18%)(P = 0.001). PLT level in recovered patients was significantly higher than death cases (214,964 vs 167,196/microliter) (P = 0.003). LDH level was significantly higher in those who had not survived from COVID-19 infection compared to those who had recovered (587 vs 487 U/L) (P < 0.001). Also, Blood oxygen saturation was significantly higher in patients who survived COVID-19 compared to those who died (91 vs 82%)(P < 0.001). The more information about the Laboratory and clinical measures status in survived and non-survived patients was shown in Table II.

Discussion
COVID-19 pneumonia sometimes progress rapidly to Acute respiratory distress syndrome (ARDS) and even death. Unfortunately, until now, there is no definite treatment for the COVID-19 related illnesses. The
established laboratory markers to assess the illness severity are few and tentative [2, 14].

In the present study, some simple and available biomarkers are investigated and compared between survivor and non-survivor groups. Neutrophil and Lymphocyte counts, neutrophil to lymphocyte ratio, platelet count, LDH and CRP levels usually are economic, rapid and usable laboratory parameters that could straightforwardly discriminate between COVID patients with and without severe disease. Neutrophil count in severe COVID-19 cases were likely to be higher in contrast with lymphocyte count that were lower compared with non-severe patients in previous studies [15]. In MERS coronavirus leukocyte population change was found to be an important factor tied with severity and outcome of the patients [16]. COVID-19 infection causes dysregulation of immunological response and cytokine storm. This phenomenon enhances the neutrophil production and stimulates the lymphocyte apoptosis. On the other hand, severe viral infection may lead to bacterial co-infection, therefore neutrophil count would be raised [15]. NLR, absolute neutrophil count divided by absolute lymphocyte count, is a simple indicator. NLR is a predictor for mortality in malignancies, collagen vascular diseases, infectious diseases, acute coronary syndrome and intracranial hemorrhage. A research showed that higher NLR was tied with mortality in admitted COVID-19 patients [17] but there was no association between severity of the disease and NLR in our study, We found that Lymphocyte count was lower in those who experienced severe forms of the disease. The decrease of Lymphocyte count might be explained by the following mechanisms; direct invasion of lymphocyte through ACE-2 receptor by virus, destruction of lymphoproliferative systems (Spleen, Thymus) by COVID-19, apoptosis of lymphocyte with pro-inflammatory cytokines and suppression of lymphocytes proliferation by lactic acidosis in severe infection [18]. The present study found significant differences in Lymphocyte count between non-survivor and survivor groups (P < 0.05). Neutrophil to lymphocyte ratio in the survivors was less than non-survivor, however this difference was not significant (P > 0.05) . Platelet count (PLT) was significantly higher in those who had recovered from COVID-19 compared to those who had not in our study. Although, this novel coronavirus is

### Tab. I. Comparison some factors among survived and non survived cases.

| Variables          | Total (n = 112) | Survived (n = 56) | Non-survived (n = 56) | P-value |
|-------------------|----------------|------------------|----------------------|---------|
| **Age group**     |                |                  |                      |         |
| < 60              | 36 (32.1%)     | 17 (47.2%)       | 19 (52.8%)           | 0.68    |
| > 60              | 76 (67.9%)     | 39 (51.5%)       | 37 (48.8%)           |         |
| **Gender**        |                |                  |                      | 0.85    |
| Males             | 77 (68.8%)     | 38 (50.6%)       | 39 (49.4%)           |         |
| Females           | 35 (31.2%)     | 18 (51.4%)       | 17 (48.6%)           |         |
| **O2 status**     |                |                  |                      | 0.008   |
| < 93              | 66 (84.6%)     | 36 (54.5%)       | 30 (45.5%)           |         |
| ≥ 93              | 12 (15.4%)     | 12 (100%)        | 0 (0.0%)             |         |
| **Comorbidity**   |                |                  |                      |         |
| Asthma            | 2 (1.8%)       | 0 (0.0%)         | 2 (100%)             | 0.15    |
| Diabetes          | 36 (32.1%)     | 21 (37.5%)       | 15 (26.8%)           | 0.22    |
| Hypertension      | 34 (30.4%)     | 19 (35.9%)       | 15 (26.8%)           | 0.411   |
| Coronary artery disease | 16 (14.3%) | 6 (10.7%)       | 10 (17.9%)           | 0.28    |

### Tab. II. Comparison of clinical and laboratory measures of survived and non-survived patients.

| Variables          | Total (n = 112) | Survived (n = 56) | Non-survived (n = 56) | P |
|--------------------|----------------|------------------|----------------------|---|
| **Mean**           | **SD**         | **Mean**         | **SD**               | **Mean** | **SD** | **Mean** | **SD** | **Mean** | **SD** | **P** |
| WBC count/ microliter | 75.10±18.18  | 6470.58±2355.02 | 5257.14±1680.13 | 0.183 |
| Neutrophil %       | 75.58±15.42   | 71.32±10.86     | 77.14±7.44          | 0.515 |
| Lymphocyte %       | 17.56±8.77    | 22.76±6.13      | 18±7.11             | 0.001 |
| Neutrophil / Lymphocyte | 6.56±5.89    | 5.42±6.13       | 7.29±5.54           | 0.093 |
| Haemoglobin (g/dL) | 13.04±1.97    | 13.16±2.28      | 13.35±2.04          | 0.526 |
| PLT/ microliter     | 191080.35±85825.73 | 124964.28±89961.39 | 167196.42±74909.01 | 0.003 |
| ESR (mm/h)         | 66.13±29.19   | 70.58±23.22     | 58.71±27.18         | 0.397 |
| CRP (mg/L)         | 59.52±45.06   | 55.5±28.63      | 72.85±22.31         | 0.101 |
| LDH (U/L)          | 664.71±445.86 | 487.352±142.92  | 587.14±161.84       | < 0.001 |
| Vitamin D (ng/ml)  | 25.96±14.56   | 25.62±15.53     | 26.52±12.7          | 0.81  |
| Blood's oxygen Saturation % | 86.89±9.02 | 91±4.01         | 82.42±10.46         | < 0.001 |
different from SARS, the mechanism of decrease in PLT count might be similar. Thrombocytopenia in COVID-19 might be explained by platelet activation and aggregation when the virus starts immunological damage of lung tissue. The platelet consumption is increased in the injured area. Disseminated intravascular coagulopathy (DIC) might also be induced by COVID-19 and culminates in thrombocytopenia [14, 19-21]. Moreover, the virus may involve bone marrow directly to lead in the thrombocytopenia [2]. LDH is related with cytokine and chemokine functions. It enhances the immune responsive cells (e.g., CD4+ T cells) and Gamma-Interferon production [22]. Suppression of LDH is linked with decreasing effect of the inflammatory mediators [23]. Previous studies indicated that high LDH levels in some infection such as EBV, PCP, Influenza, H1N1 and even Zika virus were related to lung injury [22-25]. COVID-19 invades multiple organs (e.g., lung–intestines, liver, myocardium) through ACE 2 receptors. Therefore, high LDH level in COVID-19 patients might mean multiple organ damages not merely lung injury [22-26]. Our research showed that the LDH levels in non-survivors are significantly higher than the survivor group (P < 0.005). It might be due to the accelerating multi-organ failure in the former group as compared to the latter (P < 0.001). COVID-19 can directly involve multiple organs, trigger the severe inflammatory response, and produce cytokines (i.e., CRP, interleukins) [22, 23]. CRP activates the complement system and augments phagocytosis. CRP attaches to virus and prompt the phagocyte cells to eliminate microorganisms. These molecules can enhance the pro-inflammatory cytokines (IL1, IL6, IL8, TNF-a, CRP) effects [10, 27-29]. Statistically there was no significant difference in CRP between survival and non-survival groups in our study (P = 0.101), however CRP was higher in those who did not survive which may be clinically significant and means more inflammation due to severe infection [24]. The current study had some limitations. We focused on “death” as the index of severity of the disease but there are some other indicators such as admission in ICU that can be used as an indicator of severe form of the disease. Also the sample size in the current study was small and future studies are advised to evaluate the prognostic indicators of COVID-19 infection in larger Iranian populations.

Conclusions

Blood oxygen saturation, LDH level, Lymphocyte count and PLT count are reliable, low expense biomarkers for monitoring COVID-19 patients’ outcome. Having these available biomarkers in the first day of admission, can be useful for early management of patients. To confirm these results and identification of other biomarkers in poor outcome patients, other studies are necessary. The study has the following limitations. It is a unicentric retrospective observational study with a relatively small sample size. Biomarkers were measured only once at the time of admission, so we are unaware if the kinetics of biomarkers could improve or worsen the observed results. We provide several variables in our cohort; however, some variables may be missing, such as lung computed tomography scan information. Although viral presence was confirmed mainly by polymerase chain reaction assay, false positives and false negatives could be present.

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Conflict of interest statement

The authors declare no conflict of interest.

Authors’ contributions

Conceptualization: HH, HA. Data curation: All authors. Formal analysis: SA, ANA, YA and MK. Methodology: HA. Project administration: All authors. Writing – original draft: HA, HH. Writing – review & editing: HH, ANA. All authors read and approved the final version of the manuscript.

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