Prediction of Cytokine Storm and Mortality in Patients with COVID-19 Admitted to ICU: Do Markers Tell the Story?

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Abstract

Introduction: COVID-19 has caused approximately one million deaths worldwide as of November 24, 2020. Markers of disease activity like ferritin, C-reactive protein (CRP), and D-dimers are frequently monitored to detect the best opportunity for intensive treatment. Methods: All patients of >18 years of age were included. The primary variables of interest, ferritin, CRP, and D-dimers, are frequently monitored to detect the best opportunity for intensive treatment. Results: The sample includes 235 records. More than 95% of patients have all markers on the day of admission to ICU were ferritin (median 1,278; IQR 1,424), D-dimer 1.21 (3.4), and CRP 129.5 (121). Daily average levels of markers were different from their admission day level: ferritin 1,395 (1,331), D-dimer 3.11 (5.52), and CRP 107 (75.8). Multiple logistic regression analysis determined that average CRP during the stay was the only predictor of survival. Discussion: Data on markers utilization to detect the acute phase of inflammation help clinicians focus on the opportunity window for intensive treatment. Conclusion: Average CRP during the stay in ICU is higher than CRP on admission. Average CRP is the only factor that predicts survival.
Optimal administration may prevent cytokine storms and abate the development of ARDS [6]. Markers of disease activity like ferritin, C-reactive protein (CRP), and D-dimers are frequently monitored to detect the best opportunity for intensive treatment [7]. Less commonly levels of interleukin 6 are used to detect and target the most intensive part of the disease phase although this test is expensive and only rarely available [8]. It may not be cost-effective for the developing world. Hence, identification of intense activity of virus and inflammation is of utmost importance.

Table 1. Sample characteristics (categorical variables)

| Categorical variable                        | Total (N = 235) (%) | Alive (N = 116) (%) | Died (N = 119) | p value* |
|---------------------------------------------|---------------------|---------------------|----------------|----------|
| Gender (male)                               | 206 (87.6)          | 100 (86)            | 106 (89)      | 0.30     |
| Nationalities (expatriates)                 | 229 (97.4)          | 113 (97.4)          | 116 (97.4)    | 0.60     |
| Diabetes, N (%)                             | 101 (42.9)          | 53 (45.6)           | 48 (40.3)     | 0.20     |
| Hypertension (yes)                          | 58 (24.6)           | 27 (23.2)           | 31 (26)       | 0.30     |
| CAD (yes)                                   | 18 (7.6)            | 4 (3.4)             | 12 (10)       | 0.03     |
| Prior renal impairment (yes)                | 28 (11.9)           | 7 (6)               | 21 (17.6)     | 0.01     |
| Outpatient dialysis (yes)                   | 16 (6.8)            | 6 (5.1)             | 10 (8.4)      | 0.24     |
| Tachycardia on admission (yes)              | 184 (78.2)          | 84 (72.4)           | 100 (84)      | 0.02     |
| Hypotension on admission (yes)              | 117 (49.7)          | 47 (40.5)           | 70 (58.8)     | 0.01     |
| Mechanical ventilation (yes)                | 200 (85.1)          | 96 (82.7)           | 104 (87.3)    | 0.20     |
| Vasopressors use (yes)                      | 186 (79.1)          | 84 (72.4)           | 102 (85.7)    | 0.01     |
| Dialysis required (yes)                     | 71 (30.2)           | 21 (18.1)           | 50 (42)       | 0.01     |
| Bacterial infection (yes)                   | 121 (51.4)          | 57 (49.1)           | 64 (53.7)     | 0.28     |
| Bacteremia (yes)                            | 94 (40)             | 41 (35.3)           | 53 (44.5)     | 0.11     |
| Chloroquine (yes)                           | 207 (88)            | 108 (93.1)          | 99 (83.1)     | 0.02     |
| Lopinavir/ritonavir (yes)                    | 85 (36.1)           | 34 (29.3)           | 51 (42.8)     | 0.01     |
| Favipiravir (yes)                           | 187 (79.5)          | 102 (87.9)          | 85 (71.4)     | 0.01     |
| Steroids (yes)                              | 212 (90)            | 110 (94.8)          | 102 (85.7)    | 0.01     |
| Received GI prophylaxis (yes)               | 225 (95.7)          | 112 (96.5)          | 113 (94.9)    | 0.37     |

CAD, coronary artery disease. *χ² test to assess the difference between groups.
Table 2. Sample characteristics (continuous variables)

| Continuous variable                        | Total (N = 235) | IQR | Alive (N = 116) | IQR | Died (N = 119) | IQR | p value<sup>¬</sup> |
|-------------------------------------------|-----------------|-----|-----------------|-----|----------------|-----|-------------------|
| Age, years                                | 49              | 13  | 49              | 14  | 48.5           | 16  | 0.38              |
| BMI, kg/m²                                 | 27.6            | 6.17| 27.3            | 7.3 | 28.1           | 5.26| 0.03              |
| Days to seroconversion                     | 13              | 17  | 18              | 19  | 15             | 9   | 0.01              |
| Ferritin admission, ng/mL                 | 1,278           | 1,424| 1,315           | 1,667| 1,352          | 1,204| 0.34              |
| Ferritin (average in ICU stay), ng/mL     | 1,395           | 1,331| 1,209           | 1,102| 1,665          | 1,605| 0.01              |
| D-dimer, ng/mL                            | 1.21            | 3.4 | 1.14            | 2.85 | 1.8           | 5   | 0.04              |
| D-dimer (average in ICU stay), ng/mL      | 3.11            | 5.52| 2.42            | 4.19 | 3.74          | 7.1  | 0.01              |
| CRP, mg/L                                 | 129             | 121 | 132             | 147 | 128           | 101  | 0.64              |
| CRP (average in ICU stay), mg/L           | 107             | 75.8 | 81.2            | 54.8 | 135          | 87.4  | 0.01              |
| Procalcitonin, ng/mL                      | 0.34            | 0.59 | 0.34            | 0.55 | 0.29        | 0.77  | 0.11              |
| Cr, mg/dL                                 | 0.9             | 0.35 | 0.9            | 0.3  | 0.9           | 0.85  | 0.01              |
| CPK, units/L                              | 231             | 616 | 207             | 577 | 310           | 623  | 0.04              |
| ABG PH                                    | 7.37            | 0.13 | 7.40            | 0.13 | 7.37        | 0.15  | 0.78              |
| PCO₂, Torr                                | 37.3            | 15.4 | 36.5            | 15.4 | 38.1        | 14.97 | 0.69             |
| PO₂, Torr                                 | 62.6            | 35.1 | 64.2            | 41.3 | 64.9       | 26   | 0.89              |
| Lactate, mmol/L                           | 1.7             | 1.1  | 1.5             | 1.1  | 1.85        | 1.4  | 0.03              |
| Bicarbonate, mEq/L                        | 21.6            | 5.3  | 22.5            | 4.7  | 22.1        | 5.7  | 0.74              |
| Magnesium, mg/dL                          | 2.04            | 0.36 | 2.04           | 0.37 | 2.06       | 0.35  | 0.46              |
| Platelets, 10<sup>9</sup>/mL              | 203             | 111 | 213             | 119 | 189           | 86   | 0.05              |
| Days on mech. vent                        | 11              | 19  | 16              | 20  | 16.5         | 19   | 0.13              |
| LOSICU, days                              | 14              | 22  | 20.5            | 23  | 17           | 18   | 0.07              |
| LOSH, days                                | 19              | 29  | 36.5            | 31  | 20           | 21   | 0.01              |
| APACHE 2 scores                           | 16              | 7   | 15              | 7   | 16           | 9    | 0.02              |

CRP, C-reactive protein; CPK, Cr phosphokinase; LOSICU, length of stay in the intensive care unit. <sup>¬</sup> Median test p value.
importance. Viral load monitoring is impractical. Inflammatory markers’ effectivity for disease monitoring and success of treatment and their cost-effectiveness is important and largely unknown.

Aims: We aim to measure the pattern of these markers’ usage, their relationship with the disease and with each other, and their prediction of disease activity and utility for treatment success and clinical outcomes. Moreover, we aim to detect the most active phase of the disease if one exists.

Methods

All patients with confirmed COVID-19 admitted to ICU of Dubai Hospital between January 1, 2020, and June 30, 2020, were included. We excluded patients <18 years of age. The primary variable of interest, ferritin, CRP, and D-dimers, on admission to ICU and for each patient throughout the hospitalization were also recorded. Primary clinical outcomes of length of stay in the intensive care unit (LOSICU) and survival were also recorded. Demographics: age, gender, BMI, and nationality. Comorbidities: diabetes, hypertension, coronary artery disease (CAD), renal failure, and out-

**Fig. 3.** K-P survival plot for D-dimer level on admission.

**Fig. 4.** K-P survival plot for average D-dimer during ICU stay.
patient dialysis were recorded. Immune status, smoking status, and alcohol use were also recorded. Inpatient clinical evaluation details including vital signs, fever, tachycardia, blood pressure, hypoxia, use of mechanical ventilation, use of pressors, or dialysis were also recorded. Laboratory parameters for evidence of infection: WBC and bacteremia were also recorded. Therapy on admission: chloroquine, antivirals, and steroids were recorded. The APACHE 2 scores calculated within 24 h of admission to ICU were recorded to assess the severity of illness. Ferritin, CRP, and D-dimers were recorded daily if available for the whole ICU stay, and all other variables were recorded on admission day to ICU.

Statistical Analysis
All the variables were analyzed and found that they were not normally distributed; therefore, median with interquartile ratios was calculated. The average level of the marker was determined by adding all values available and dividing by the number of days values available. χ² test was performed to detect the difference between variables if they were categorical, and median test was performed if the variable was continuous. For survival analysis, multiple logistic regression was performed with survival (mortality) as dependent variables and all other variables as independent predictors.

Since LOSICU is very skewed and the variance of LOSICU across the levels of CRP was heterogeneous, data were transformed into log LOSICU and least square regression was performed for log LOSICU and markers (CRP) only for survivors. We used IBM SPSS Statistics for Windows, version 26 (IBM Corp., Armonk, NY, USA).

Results
Characteristics of the sample $N = 235$ are described in Tables 1 and 2. More than 95% of patients have all markers on the day of admission to ICU. Average levels of markers were different from their admission day level which suggest levels were changing. Multiple logistic re-

| Table 3. Logistic regression analysis (predictors of survival) |
|-------------------------------|-----------------|-----------------|-----------------|
| Variables                     | B               | Odds ratio      | 95% CI for odds ratio |
| Age (years)                   | 0.049           | 1.050           | 0.952 to 1.158    |
| Gender (male/female)          | −1.076          | 0.341           | 0.024 to 4.825    |
| BMI, kg/m²                    | 0.005           | 1.005           | 0.933 to 1.083    |
| Days swab test turns negative | −0.175          | 0.840           | 0.754 to 0.935    |
| Diabetes                      | −0.291          | 0.747           | 0.151 to 3.707    |
| Hypertension                  | 0.444           | 1.559           | 0.126 to 19.268   |
| CAD                           | −2.358          | 0.095           | 0.000 to 28.265   |
| Dialysis (outpatient)         | 1.150           | 3.158           | 0.143 to 69.724   |
| Mechanical ventilation        | −1.765          | 0.171           | 0.002 to 14.335   |
| Vasopressors                  | 0.902           | 2.464           | 0.017 to 355.829  |
| Bacterial infection           | 2.103           | 8.193           | 0.927 to 72.388   |
| Chloroquine                   | −1.468          | 0.230           | 0.010 to 5.532    |
| Lopinavir/ritonavir           | 2.106           | 8.216           | 0.998 to 67.629   |
| Favipiravir                   | −0.741          | 0.477           | 0.030 to 7.697    |
| Steroids                      | −2.688          | 0.068           | 0.002 to 2.699    |
| Ferritin, ng/mL               | 0.000           | 1.000           | 0.999 to 1.001    |
| D-dimer, ng/mL                | 0.016           | 1.016           | 0.936 to 1.102    |
| Procalcitonin, ng/mL          | −0.103          | 0.902           | 0.556 to 1.464    |
| CRP, mg/L                     | −0.002          | 0.998           | 0.989 to 1.008    |
| Cr                            | −0.133          | 0.875           | 0.526 to 1.456    |
| Cr phosphokinase              | 0.000           | 1.000           | 0.999 to 1.001    |
| ABG PH                        | −4.947          | 0.007           | 0.000 to 93.309   |
| PCO₂, Torr                    | −0.010          | 0.990           | 0.894 to 1.095    |
| PO₂, Torr                     | 0.017           | 1.017           | 1.001 to 1.033    |
| Platelets (10³/mL)            | −0.003          | 0.997           | 0.986 to 1.009    |
| APACHE 2 score               | −0.116          | 0.891           | 0.766 to 1.036    |
| Average ferritin in ICU stay  | 0.000           | 1.000           | 1.000 to 1.000    |
| Average D-dimer in ICU stay   | −0.015          | 0.985           | 0.805 to 1.205    |
| Average CRP in ICU stay       | 0.029           | 1.030           | 1.010 to 1.050    |

CAD, coronary artery disease; CRP, C-reactive protein. * For all categorical variables, odds ratios are for presence versus absence of the variable.
Elevation of Inflammatory Markers in COVID-19 Infection

Regression model showed only elevated average CRP during ICU stay-predicted survival (Table 3). Comparing the effects of marker levels on survival, a Kaplan-Meier plot (Fig. 1–6) was constructed for all markers (4th quartile vs. 1st quartile). Only higher level of average CRP level predicts worse survival (Fig. 6). Ferritin and D-dimer do not predict survival differences. For LOSICU prediction, linear regression on log-transformed LOSICU showed that the days that the swab takes to turn negative, bacterial infection, Cr, and ABG PH on the day of admission to
ICU predicted LOSICU (Table 4). Specific regression for log LOSICU for CRP in the survivors’ group does not predict LOSICU (Fig. 7, 8).

Discussion

Inflammatory markers are frequently checked. Ferritin and D-dimer on admission do not predict mortality. Only average CRP level for ICU stay predicts mortality. Using the 4th quartile against the first quartile as a categorical variable, CRP predicts mortality. Ferritin and D-dimers do not. Zhou et al. [9] found that ferritin is significantly elevated in nonsurvivors than survivors, but they did not consider other factors predicting mortality; therefore, their results show the only association of ferritin with mortality. Zhang et al. [10] showed D-dimer on admission greater than 2.0 μg/mL (4-fold increase) predict in-hospital mortality in patients with COVID-19. They also did not adjust for confounding factors by re-

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Table 4. Regression for factors determining LOSICU (log LOSICU and predictor variables)

| Variable                        | Stand. coefficients beta | 95% CI for beta lower bound | Upper bound | p value |
|---------------------------------|--------------------------|----------------------------|-------------|---------|
| Age (years)                     | −0.025                   | −0.010                     | 0.008       | 0.830   |
| Gender (male/female)            | 0.054                    | −0.159                     | 0.271       | 0.602   |
| BMI, kg/m²                       | 0.123                    | −0.002                     | 0.008       | 0.181   |
| Days turn test negative         | 0.239                    | 0.001                      | 0.013       | 0.029   |
| Diabetes                        | 0.068                    | −0.101                     | 0.191       | 0.541   |
| Hypertension                    | −0.122                   | −0.280                     | 0.088       | 0.301   |
| CAD                             | −0.109                   | −0.679                     | 0.266       | 0.386   |
| Renal failure                   | 0.015                    | −0.263                     | 0.294       | 0.912   |
| Outpatient dialysis             | 0.209                    | −0.086                     | 0.537       | 0.153   |
| Immunosuppressed                | 0.045                    | −0.278                     | 0.411       | 0.701   |
| Mechanical ventilation          | −0.082                   | −0.452                     | 0.182       | 0.396   |
| Vasopressors                    | 0.096                    | −0.137                     | 0.354       | 0.380   |
| CRRT                            | 0.128                    | −0.070                     | 0.243       | 0.273   |
| Bacterial infection             | 0.464                    | 0.120                      | 0.543       | 0.003   |
| Bacteremia                      | 0.003                    | −0.229                     | 0.232       | 0.988   |
| Line infection                  | 0.009                    | −0.198                     | 0.210       | 0.953   |
| Chloroquine                     | 0.045                    | −0.208                     | 0.310       | 0.694   |
| Lopinavir/ritonavir             | −0.087                   | −0.213                     | 0.091       | 0.426   |
| Favipiravir                     | −0.097                   | −0.351                     | 0.120       | 0.329   |
| Steroids                        | 0.087                    | −0.164                     | 0.371       | 0.442   |
| WBC                             | 0.017                    | −0.015                     | 0.017       | 0.878   |
| Ferritin, ng/mL                 | −0.050                   | 0.000                      | 0.000       | 0.771   |
| D-dimer, ng/mL                  | 0.038                    | −0.006                     | 0.009       | 0.742   |
| Procalcitonin, ng/mL            | 0.043                    | −0.008                     | 0.013       | 0.657   |
| CRP, mg/dL                      | −0.095                   | −0.001                     | 0.000       | 0.404   |
| Cr, mg/dL                       | −0.338                   | −0.090                     | −0.009      | 0.017   |
| ABG PH                          | −0.442                   | −2.626                     | −0.079      | 0.038   |
| PCO₂, Torr                      | −0.388                   | −0.024                     | 0.001       | 0.077   |
| PO₂, Torr                       | 0.180                    | −0.001                     | 0.003       | 0.173   |
| Lactate, mmol/L                 | −0.218                   | −0.097                     | 0.013       | 0.128   |
| Bicarbonate, mEq/L              | 0.124                    | −0.018                     | 0.035       | 0.532   |
| Magnesium, mg/dL                | 0.030                    | −0.204                     | 0.272       | 0.777   |
| Platelets (10³/mL)              | −0.011                   | −0.001                     | 0.001       | 0.921   |
| APACHE 2 score                  | 0.095                    | −0.009                     | 0.019       | 0.493   |
| Average ferritin stay in ICU    | 0.014                    | 0.000                      | 0.000       | 0.906   |
| Average D-dimer stay in ICU     | 0.143                    | −0.010                     | 0.027       | 0.348   |
| Average CRP stay in ICU         | −0.183                   | −0.002                     | 0.000       | 0.088   |

LOSICU, length of stay in the intensive care unit; CRRT, continuous renal replacement therapy; CAD, coronary artery disease; CRP, C-reactive protein.
Elevation of Inflammatory Markers in COVID-19 Infection

We did not find that comorbid conditions such as CAD, renal failure, or secondary bacterial infections predict mortality. Barman et al. [13] found in their sample that CAD is an independent predictor of mortality. Cheng et al. [14] also found that kidney disease is associated with in-hospital death of patients with COVID-19. Ruan et al. [15] found that secondary infection was associated with high mortality in their 150 patients from Wuhan, China.

Other than ABG PH no factor predicted LOSICU including ferritin, CRP, CAD, and secondary bacterial infection. Moratto et al. [16] found that high ferritin level on admission is associated with prolonged duration of hospitalization. To our knowledge, we are not aware of a study that recorded daily ferritin level and determines the impact of average ferritin level on the length of ICU stay. Moreover, we performed linear regression analysis considering the impact of >20 significant confounding factors. This suggests that finding association in other studies may be from different methodology or from not adjusting for other significant variables.

We identify the following limitations. Small sample size and single-center retrospective study may have provided results, not generalizable to other populations. Our extensive daily record of all markers of the whole sample and on each patient provided the dynamic changes dur-

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**Fig. 7.** Linear regression for LOSICU and CRP on admission. LOSICU, length of stay in the intensive care unit; CRP, C-reactive protein.

**Fig. 8.** Linear regression for LOSICU and average CRP during ICU stay. LOSICU, length of stay in the intensive care unit; CRP, C-reactive protein.
ing ICU stay within a sample and for each patient therefore it provided more reliable measurements. Extensive including of confounding factors allowed us to estimate the real and actual impact of markers on the outcome.

**Conclusion**

Inflammatory markers are elevated in COVID-19 infection. A single level of CRP on admission does not predict outcome although the average CRP level during the stay in ICU predicts survival. Other markers do not predict survival.

**Statement of Ethics**

Ethical approval was provided by Emirates Institutional Review Board for COVID-19 Research, DSREC/2020/1324/approved on July 13, 2020.

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**Conflict of Interest Statement**

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**Author Contributions**

R.N.: conceived the research idea, proposal writing, data collection, data analysis, and manuscript writing. A.H.: conceived the idea, proposal writing, and review of the final manuscript. N.I.: idea conception and data collection. D.E.: data collection. Z.O., M.S., S.Z., R.A., S.E., C.S., N.A., W.A., M.A., and F.M.: idea conception and data collection. M.H.: data collection and manuscript writing.