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

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Keywords

Critical · Infectious · Inflammatory markers · Medicine

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, for each patient throughout hospitalization were recorded. Primary clinical outcomes of length of stay in ICU and survival were recorded. **Demographics:** age, gender, BMI, and nationality. 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. **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.

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Introduction

COVID-19 has caused a million deaths as of November 24, 2020, worldwide [1]. COVID-19 (SARS CoV-2) spread rapidly via person to person contact and infect predominantly the pulmonary system [2]. Approximately 15% developed respiratory failure from ARDS, requiring mechanical ventilation and admission to ICU [3]. Progression to ARDS is unpredictable as the disease activity and intensity of inflammation is variable [4]. Therapy timing of anti-inflammatory agents and immune-suppressing medication is of utmost importance. This inflammation is dynamic in COVID-19 and most people get anti-inflammatory treatment, either from the beginning as a standard protocol or with the inflammatory markers monitoring

Fig. 1. K-P survival plot for ferritin level on admission.

Table 1. Sample characteristics (categorical variables)

Categorical variable	Total (N = 235) (%)	Alive (N = 116) (%)	Died (N = 119)	<i>p</i> 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, <i>N</i> (%)	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. * χ^2 test to assess the difference between groups.

[5]. 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 lev-

els 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

Fig. 2. K-P survival plot for average ferritin during ICU stay.

Table 2. Sample characteristics (continuous variables)

Continuous variable	Total (N = 235) median	IQR	Alive (N = 116) median	IQR	Died (N = 119) median	IQR	<i>p</i> value [†]
Age, years	49	13	49	14	48.5	16	0.38
BMI, kg/m ²	27.6	6.17	27.3	7.3	28.1	5.26	0.03
Days to seroconversion	13	17	18	19	9	15	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
PCO ₂ , Torr	37.3	15.4	36.5	15.4	38.1	14.97	0.69
PO ₂ , 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 ³ /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. [†] Median test *p* value.

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.

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-

Table 3. Logistic regression analysis (predictors of survival)

Variables	B	Odds ratio*	95% CI for odds ratio		p value
			lower	upper	
Age (years)	0.049	1.050	0.952	1.158	0.329
Gender (male/female)	-1.076	0.341	0.024	4.825	0.426
BMI, kg/m ²	0.005	1.005	0.933	1.083	0.892
Days swab test turns negative	-0.175	0.840	0.754	0.935	0.001
Diabetes	-0.291	0.747	0.151	3.707	0.722
Hypertension	0.444	1.559	0.126	19.268	0.729
CAD	-2.358	0.095	0.000	28.265	0.417
Dialysis (outpatient)	1.150	3.158	0.143	69.724	0.466
Mechanical ventilation	-1.765	0.171	0.002	14.335	0.435
Vasopressors	0.902	2.464	0.017	355.829	0.722
Bacterial infection	2.103	8.193	0.927	72.388	0.058
Chloroquine	-1.468	0.230	0.010	5.532	0.365
Lopinavir/ritonavir	2.106	8.216	0.998	67.629	0.050
Favipiravir	-0.741	0.477	0.030	7.697	0.602
Steroids	-2.688	0.068	0.002	2.699	0.152
Ferritin, ng/mL	0.000	1.000	0.999	1.001	0.833
D-dimer, ng/mL	0.016	1.016	0.936	1.102	0.708
Procalcitonin, ng/mL	-0.103	0.902	0.556	1.464	0.676
CRP, mg/L	-0.002	0.998	0.989	1.008	0.756
Cr	-0.133	0.875	0.526	1.456	0.608
Cr phosphokinase	0.000	1.000	0.999	1.001	0.560
ABG PH	-4.947	0.007	0.000	93.309	0.307
PCO ₂ , Torr	-0.010	0.990	0.894	1.095	0.841
PO ₂ , Torr	0.017	1.017	1.001	1.033	0.032
Platelets (10 ³ /mL)	-0.003	0.997	0.986	1.009	0.654
APACHE 2 score	-0.116	0.891	0.766	1.036	0.133
Average ferritin in ICU stay	0.000	1.000	1.000	1.000	0.599
Average D-dimer in ICU stay	-0.015	0.985	0.805	1.205	0.885
Average CRP in ICU stay	0.029	1.030	1.010	1.050	0.003

CAD, coronary artery disease; CRP, C-reactive protein. * For all categorical variables, odds ratios are for presence versus absence of the variable.

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 pressers, 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. χ^2 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, mul-

tiple 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-

Fig. 5. K-P survival plot for CRP level on admission. CRP, C-reactive protein.

Fig. 6. K-P survival plot for average CRP during ICU stay. CRP, C-reactive protein.

gression 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 pre-

dicts 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

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

Variable	Stand. coefficients beta	95% CI for beta lower bound	Upper bound	<i>p</i> value
Age (years)	-0.025	-0.010	0.008	0.830
Gender (male/female)	0.054	-0.159	0.271	0.602
BMI, kg/m ²	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/L	-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
PCO ₂ , Torr	-0.388	-0.024	0.001	0.077
PO ₂ , 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 (10 ³ /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.

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-

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.

gression analysis. Liu et al. [11] also found that CRP can effectively assess disease severity and predict outcomes in patients with COVID-19. Tan et al. [12] documented the role of CRP as a reliable biomarker for disease activity (not mortality) with “area under the curve” in the receiver operating analysis of 0.87 (95% CI, 0.10–1.00) where values 83 and 91% represent sensitivity and specificity, respectively.

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-

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.