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The Effectiveness of Laboratory Parameters in Predicting the in-Hospital Mortality of Iranian Patients with Coronavirus Disease 2019 (COVID-19)

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Key words: 2019-nCoV, Laboratory Characteristics, Mortality
Parole chiave: 2019-nCoV, Parametri di laboratorio, Mortalità

Abstract

Background. *The novel coronavirus 2019-nCoV (now SARS-CoV-2) has spread globally and affected healthcare systems worldwide. Due to lack of long-term immunization and effective specific treatments for the COVID-19 disease, there is a need of identifying the patients who are at the risk of a fatal outcome, according to the available epidemiological data and laboratory parameters.*

Objective. *Thus, we aimed to evaluate the prognostic value of epidemiological data and laboratory parameters for in-hospital case fatality in patients with COVID-19.*

Materials and Methods. *A retrospective cohort of patients with COVID-19 admitted to the Shahid Mostafa Khomeini Hospital of Ilam University of Medical Sciences from February 29 until March 29, 2020 was performed. Epidemiologic data and laboratory results were collected. Univariate and multivariate logistic regression models were performed to evaluate the prognostic value of the laboratory parameters for in-hospital death.*

Results. *A total of 256 Iranian COVID-19 patients were included in the evaluation; 38 of them died, resulting in a in-hospital case-fatality rate of 14.8%. The univariate analysis showed that advanced age [OR=1.04, 95% CI: 1.02, 1.06, P=0.001], smoking [OR=4.041, 95% CI: 1.546-10.563, P=0.004], white blood cells [OR=0.941, 95% CI: 0.904-0.980, P =0.003] and hematocrit [OR=1.060, 95% CI: 1.009-1.113, P=0.020] were positively associated with the risk of a fatal outcome. Multivariate logistic regression analysis revealed that COVID-19 patients with an elevated white blood cell count and elevated hemoglobin level had 1% and 9% greater risk of an in-hospital death for each elevated unit [OR=1.07; 95 %CI: 1.024-1.088, P =0.002 and OR=1.379; 95% CI 0.064-1.788, P =0.015, respectively].*

Conclusions. *An increase in white blood cell count and an increase in hemoglobin level might be independent risk factors for in-hospital death in Iranian patients with COVID-19. Further studies are necessary in order to conferm the prognostic value of the variables discussed.*

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Background

On December 8, 2019, an outbreak of pneumonia of due to an unknown agent, with an epidemiological link to a seafood market in Wuhan, Hubei province of China, was reported (1, 2). Shortly afterwards, the causative agent was isolated and characterized by whole genome sequencing and found to be a virus, member of the β Coronaviruses group 2B and it was named 2019-nCOV (1, 2). On January 30, 2020, the World Health Organization (WHO) declared that the epidemic of 2019-nCoV had become a public health emergency of international concern (PHEIC) (1, 2). Since then, the number of individuals infected with 2019-nCoV has dramatically mushroomed around the world (3, 4). Meanwhile, the 2019-nCOV has been internationally named SARS-CoV-2, and the associate disease COVID-19.

The main clinical symptoms of 2019-nCoV disease include fever, myalgia or fatigue, nonproductive cough, anosmia and dyspnea (3, 4). The patients' laboratory parameters include normal or reduced white blood cells, decreased lymphocyte count, increased neutrophils, thrombocytopenia, and abnormally elevated liver enzyme levels (5, 6). However, some characterizations and conclusions in the published relevant research were variable, limited, and controversial. At present, there is no worldwide available effective therapy that has been clinically approved for SARS-Cov-2; thus, it is important to categorize risk factors associated with the poor prognosis. In the current study, we aimed to predict the prognostic value of laboratory findings for in-hospital mortality in patients with COVID-19.

Material and methods

Ethics, Study Design, and Patient Selection

This retrospective cohort study was performed from March 20 to April 29, 2020 (the study period starts at the first patient admission and lasts until the last patient is discharged or dies), and included 285 patients with COVID-19 who were admitted to the Shahid Mostafa Khomeini Hospital in Ilam, Iran. The diagnosis of patients with COVID-19 was made according to the WHO interim guidance (7).

There were no post-discharge follow-ups. Out of the 285 patients, 29 were excluded for the following reasons: pregnancy, missing data and/or hematological disease. This study was approved by the Ethics Committee of the Ilam University of Medical Sciences (http://ethics.research.ac.ir/ir.medilam.rec.1399.021).

Data collection

The informations were collected on a customized form from the hospital information system and included epidemiological data, clinical symptoms, laboratory and radiographical findings. Blood samples were collected on admission, or during the hospital stay, and were evaluated at the central clinical laboratory of Shahid Mostafa Khomeini Hospital according to standard operative procedures. The routine blood tests (including white blood cell count [WBC], leukocyte subtypes, hemoglobin level and platelet count) were made using the Sysmex KX-21 automated hematology analyzer (Sysmex Corporation, Kobe, Japan). Throat swab samples were analyzed for the presence of SARS-CoV-2 using the Chinese Center for Disease Control and Prevention (c-CDC) recommended Kit (BioGerm, Shanghai, China) and followed the WHO guidelines for qRT-PCR (8, 9). The BT3000 Automatic biochemistry analyzer (Autoanalyzer BT3000, Biotechnica, Italy) was used to assess the biochemical parameters. Blood coagulation tests were assessed by Nycomed® Pharma (Nycocard®, Abbott Laboratories, Illinois, United States). Patients were diagnosed clinically (lung radiographical features) and their diagnosis was confirmed by using

laboratory-based data (RT-PCR) on throat and nose swab specimens from the upper respiratory tract).

Statistical analysis

Epidemiological and clinical characteristics of all the patients were expressed as frequencies and proportions for categorical variables; we used the mean ± SD for continuous variables. The relationship between categorical variables was assessed using the chi-squared test and a T-test was used to compare the groups regarding their outcome. Univariate and multivariate logistic regressions were performed to assess the effectiveness of laboratory parameters. Adjusted and unadjusted odds ratio (ORs) and 95% confidence intervals (CIs) were assessed in these models. In the multivariate-adjusted model, age, smoking status, white blood cell count, hematocrit level, C-reactive protein level (CRP), and the hemoglobin level were included. For statistical analyses, R-software v 3.5.2 available at http://www.R-project.org and SPSS 17.0 software (SPSS Inc, Chicago, USA) were used; $P < 0.05$ was considered as statistically significant.

Results

Demographic characteristics

Out of the 256 patients that had a confirmed COVID-19 diagnosis, the mean (standard deviation) age was 55.78 (18.61) years, and 50.4% (n=127) were male. Two hundred and eighteen patients recovered and 38 patients (14.8%) died. Table 1 depicts the baseline epidemiological and clinical features of the patients with COVID-19 included in this study.

The correlation between variables and COVID-19 mortality

The univariate analysis showed that *age* (OR=1.04, 95% CI: 1.02-1.06, *P*=0.001), *smoking* (OR=4.041, 95% CI: 1.546-10.563, *P*=0.004), *white blood cells* (OR=1.063, 95% CI:1.02-2.80, *P*=0.003) and *hematocrit* (OR=1.060, 95% CI: 1.009-1.113, *P*=0.020) were positively associated with the risk of an in-hospital death. No significant correlation was found between any other variables with the risk of in-hospital death (Table 2).

In a multivariate logistic regression, there was a 1% increase in the risk of in-hospital mortality per unit increase in white blood cell count in the adjusted model (OR=1.07; 95% CI: 1.024- 1.088 *P*=0.002). On the other hand, there was an important relationship between white blood cell count and death in the unadjusted model (OR=1.063; 95% CI: 1.02-2.80, *P*=0.003) (Table 3).

There was a 9% increase in the risk of an in-hospital death per unit increase in hemoglobin level in the adjusted model (OR=1.379; 95% CI: .064-1.788, *P*=0.015) (Table 3). Thus, an increase in the white blood cell count and hemoglobin level were independent influencing factors in a fatal outcome of COVID-19 patients.

When the differences in laboratory parameters that predicted a fatal outcome by gender and age group (<30, 30-50, and >50 years) were analysed, a significant association between patients older than 50 years of age with an increased CRP > 3 mg/L and in-hospital mortality was found (*P*=0.028). In addition, a fatal outcome was associated with an increased WBC and being female (*P*=0.038).

Further, the in-hospital mortality was related to the thrombocytopenia and thrombocytosis in both genders (*P*=0.049) and in patients over 50 years of age (*P*=0.023). The risk of mortality related to the decreasing and increasing of activated partial thromboplastin time was more significantly associated with males than females (*P*<0.0001) and in patients over 50 years (*P*=0.027).

Table 1 - The epidemiological and laboratory characteristics of 256 patients with COVID-19

Characteristics	All patients (n=256) Mean± standard deviation (SD)	Recovered (n:218) Mean± standard deviation (SD)	Died (n=38) Mean± standard deviation (SD)	P value
Demographic				
Age, years	55.78±18.61	54.07±18.49	65.52±16.32	<0.001
Male (%)	127 (49.6%)	108 (50.5%)	21 (55.3%)	0.515
Female (%)	129 (50.4%)	110 (49.5%)	17 (44.7%)	
BMI (kg/m^2)	25.63±3.32	25.7±0.23	25.06±0.54	0.268
Smoking	21 (8.2%)	13 (61.9%)	8 (38.1%)	0.004
Laboratory findings				
White blood cells, 10^9/L	9.5±10.15	8.334±7.72	16.33±17.44	0.008
Lymphocyte (%)	22.75±57.00	23.06±13.04	20.96±9.88	0.344
Neutrophil (%)	75.81±40.00	75.39±13.037	78.21±9.935	0.205
NLR	4.78±6.38	4.73±0.62	5.13±1.34	0.815
Red blood cells, 10^{12}/L	4.38±0.05	4.39±0.95	4.27±1.26	0.481
Hemoglobin, gm/dL	12.79±1.85	12.87±1.94	12.32±2.27	0.122
Platelet, 10^9/L	229.05±177.50	226.61±184.89	242.99±128.4052	0.601
ALT, U/L	64.66±110.65	65.100±107.52	61.67±133.46	0.903
AST, U/L	66.34±115.30	67.04±115.46	61.67±117.25	0.851
LD, U/L	697.69±600.48	655.943 ±363.76	958.667±1331.38	0.279
CK, U/L	220.09±335.41	231.47±356.176	148.47±134.499	0.345
ALP, U/L	234.20±164.48	224.828±161.78	279.888±181.21	0.394
Glucose, mg/dL	141.84±109.55	140.56±114.094	149.75±76.892	0.704
Blood urea nitrogen, mg/dL	40.76±32.37	40.30±31.99	43.43±34.77	0.582
Creatinine, mg/dL	1.55±1.68	1.625±1.825	1.19±0.38	0.459
D-dimer, mg/L	0.58±0.51	0.652±0.52	0.20±0.20	0.01
PT, sec	12.84±1.95	12.733±1.97	13.461±1.78	0.100
APTT, sec	10.56±15.68	9.6247±14.21	15.988±22.02	0.183
Total bilirubin, mg/dL	6.98±18.57	4.54±10.53	22.34±41.99	0.306
Erythrocyte sedimentation rate, mm/hr	48.07±33.8	48.99±34.59	42.65±28.428	0.292
Hematocrit (%)	37.76±6.6	38.17±6.40	35.42±7.27	0.018
Calcium, mg/dL	9.7±5.63	9.80±6.10	9.34±0.50	0.647
Sodium, mEq/L	137.3±4.65	137.17±4.89	138.36±2.76	0.145
Potassium, mEq/L	4.04±1.99	4.09±2.1507	3.77±0.4402	0.367
Albumin, g/dL	4.03±1.14	4.14±1.23	3.60±0.59	0.351
Comorbidities				
Hypertension (%)	74 (28.9%)	59 (79.7%)	15 (20.3%)	0.282
Chronic liver disease (%)	6 (2.3%)	4 (66.7%)	2 (33.3%)	0.271

Table 2 - The unadjusted association between baseline variables and all-cause death during hospitalization (n=256)

Variable	Statistics	Odds ratio (95% CIs)	*P*-value
Age, years	55.78±18.61	1.04 (1.02, 1.06)	0.001
Sex			
Male	127 (49.6%)	1.0	0.516
Female	129 (50.4%)	0.795 (0.4,1.60)	
BMI (kg/m^2)	25.63±3.32	1.063 (.955, 1.183)	0.267
Hypertension			
No	182 (71.1)	1.0	0.284
Yes	74 (28.9%)	1.481 (.722, 3.040)	
Smoking			
No	235 (91.8%)	1.0	0.004
Yes	21 (8.2%)	4.041 (1.546, 10.563)	
Chronic liver disease			
No	250 (97.7%)	1.0	0.298
Yes	6 (2.3%)	2.514 (0.444, 14.246)	
White blood cells, 10^9/L	9.5±10.15	1.063 (1.02, 2.80)	0.003
Lymphocytes (%)	22.75±57.00	1.015 (0.984, 1.048)	0.343
Neutrophils (%)	75.81±40.00	0.980 (0.949, 1.011)	0.204
NLR	4.78±6.38	0.991 (0.918, 1.069)	0.813
Red blood cells, 10^{12}/L	4.38±0.05	1.171 (0.758, 1.809)	0.478
Hemoglobin, gm/dL	12.79±1.85	1.149 (0.963, 1.372)	0.122
Platelet, 10^9/L	229.05±177.50	1.000 (0.996, 1.005)	0.607
ALT, U/L	64.66±110.65	1.000 (0.998, 1.001)	0.902
AST, U/L	66.34±115.30	1.000 (0.996, 1.005)	0.850
LDH , U/L	697.69±600.48	0.999 (0.999, 1.000)	0.090
CK, U/L	220.09±335.41	1.001 (0.999, 1.004)	0.362
ALP, U/L	234.20±164.48	0.998 (0.994, 1.002)	0.399
Glucose, mg/dL	141.84±109.55	0.999 (0.996, 1.003)	0.704
Blood urea nitrogen, mg/dL	40.76±32.37	0.997 (0.988, 1.007)	0.582
Creatinine, mg/dL	1.55±1.68	1.538 (0.435, 5.433)	0.504
Total bilirubin, mg/dL	6.98±18.57	0.966 (0.930, 1.004)	0.080
Erythrocyte sedimentation rate, mm/hr	48.07±33.8	1.006 (0.995, 1.018)	0.290
Hematocrit (%)	37.76±6.6	1.060 (1.009, 1.113)	0.020
Calcium, mg/dL	9.735±5.63	1.049 (0.816, 1.347)	0.711
Sodium, mEq/L	137.347±4.65	0.935 (0.858, 1.019)	0.124
Potassium, mEq/L	4.04±1.99	1.736 (0.877, 3.439)	0.114
Albumin, g/dL	4.036±1.14	3.334 (0.277, 40.116)	0.343
APTT, sec	10.56±15.68	0.978 (0.954, 1.002)	0.073
PT, sec	12.84±1.95	0.814 (0.639, 1.037)	0.095

Table 3 - Risk association between baseline age, smoking, white blood cells, hemoglobin and in-hospital death.

Variable	Unadjusted odds ratio (95% CIs)	Model 1ǂ Odds ratio (95% CIs)	† *P*-value
White blood cells	1.063 (1.02, 2.80)	1.07 (1.024, 1.088)	0.002
Hemoglobin	1.291 (1.014, 1.644)	1.379 (1.064, 1.788)	0.015

ǂ Model 1 was adjusted for age and smoking.
† *P*-value related with the multivariate model.

Discussion

This retrospective cohort study included 256 COVID-19 patients, and the in-hospital mortality rate was 14.8%. A similar level of in-hospital mortality rate was reported in two cohorts of Chinese patients - 11.1% and 11.7% - from specialized departments where patients with a severe course of the disease had been transferred (8, 9). The high in-hospital mortality in our study could be also explained by the fact that, at the time of this study, neither specific treatments had been found, nor evidence-based treatment guidelines were available yet.

Based on the epidemiological data analyses, smoking and advanced age were identified as risk factors for in-hospital mortality.

The prevalence of smoking habits in our study was 8.2%, which is higher than reported in recent studies from Europe and the USA (10). A history of smoking as a risk factor associated with a fatal outcome has been reported previously for Chinese patients in Wuhan (11), where the prevalence of smoking was 6%. Thus, there is a potential risk for COVID-19 pneumonia in people who smoke (12).

In agreement with other studies (13, 14), old age was found to be a risk factor associated with a poor disease prognosis. (P=0.001). In recent meta-analyses of 611,583 patients from different continents, the highest rate of increase in fatality risk was observed in patients aged 60 to 69 years of age and this is consistent with our data, where the mean age of patients who died in our study was 65.52±16.32.

It is believed that a dysregulated immune cell response and subsequent immunologic abnormalities evoke a cytokine storm or hyper inflammation that causes extreme inflammation and even death (15). In our multivariate logistic regression analysis, we found that an increase in WBC is a risk factor associated with a poor disease progression (P=0.002). A similar result was observed in a retrospective study from a Wuhan single center that compared 125 Covid-19 non-survivors with 414 randomly selected COVID-19 survivors, where the WBC were found to be 7.85 versus 5.07×10^9/L, respectively (16). However, the bacterial co-infection in the COVID-19 patients could also result in the increase of WBC; based on the latest meta-analysis data, co-infection can be present in 6.9% (95% CI: 4.3-9.5%) of a COVID-19 patient cohort (17).

The alteration of leukocyte counts in Chinese patients with COVID-19 has been described in several studies; elevated levels of neutrophils and reduction in the number of lymphocytes have been suggested as a risk factors for in-hospital mortality (3, 14, 18-21). However, interestingly, in our study, we did not find a significant correlation between increased neutrophil count and in-hospital mortality (P=0.813). Thus, further research into this association is warranted.

It has been shown that COVID-19 damages hemoglobin by attacking the 1-beta chain of hemoglobin, capturing porphyrin and preventing heme metabolism. This, in turn, impairs the ability of red blood cells to transport oxygen throughout the body, affecting the lungs and leading to acute respiratory distress syndrome (ARDS). So far very little

clinical experience of infected patients with hemoglobin disorders has been recorded and most hemoglobin disorders are not related to respiratory conditions. However, complications involving the heart, lungs, and the immune system, can be present in these patients, and, in a patient with COVID-19, they may trigger very serious complications. Our multivariate logistic regression analysis showed that hemoglobin differences are a potential risk factor for in-hospital mortality of COVID-19 (P =0.015).

The hematocrit level is one of the most significant erythrocyte parameters that affects the viscosity of whole blood. However, reports that show that HCT can be considered as an independent risk factor for a poor prognosis of diseases have been reported rarely (22, 23). In our unadjusted logistic regression analysis, we found that the hematocrit level was positively associated with the risk of in-hospital mortality (P=0.020).

The outcomes of our study might have some clinical consequences. As white blood cells and hemoglobin can be rapidly assessed by a routine blood test, clinicians may identify high-risk patients at an earlier stage. Therefore, appropriate action can be taken to decrease the in-hospital mortality.

There were also some remarkable limitations in our study: (i) this study is a single-center with no external validation cohort; (ii) the number of recorded events is to some extent small, which limits the statistical power of our study; (iii) since all patients in this study were Iranian patients with COVID-19, the outcomes of this current study might not necessarily be applied to other ethnicities; (iv) although we have adjusted for potential confounders, unassessed confounding might not have been fully measured; (v) the experimental data are limited; (vi) this study was focused on laboratory characters and not every patient was monitored continuously for all clinical manifestations.

In conclusion, this retrospective study of Iranian patients with COVID-19, showed that an increase in white blood cell count and the level of hemoglobin were risk factors independently influencing in-hospital fatality. We assume that predicting the risk helps relieving the absence of medical resources and managing the patients with COVID-19. Further studies are necessary in order to confirm the prognostic value of the variables discussed.

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Consent for publication: Not applicable.
Availability of data and materials: Not applicable.

Abbreviations
Coronavirus Disease 2019 (COVID-19)
Odds ratio (OR)
Public health emergency of international concern (PHEIC)
2019 novel coronavirus (2019-nCoV-2)
SARS Corona Virus 2 (SARS-CoV-2)
White blood cell count (WBC)
Center for Disease Control and Prevention (CDC)
Confidence Intervals (CIs)
Acute Respiratory Distress Syndrome (ARDS)

Riassunto

L'efficacia dei dati di laboratorio nel predire la letalità nei pazienti iraniani di malattia da Coronavirus 2019

Premessa. Il nuovo Coronavirus 2019-nCoV (noto oggi come SARS-CoV-2) si è diffuso rapidamente in tutto il mondo, mettendo in crisi tutti i sistemi sanitari. In mancanza di vaccini capaci di immunizzare a lungo, e di

terapie specifiche efficaci, è necessario poter identificare i pazienti a maggior rischio di esito infausto mediante parametri epidemiologici o indicatori di laboratorio.

Obiettivo: Valutare il valore prognostico dei dati epidemiologici e dei parametri di laboratorio per predire la letalità in pazienti di COVID-19.

Materiali e metodi. È stato effettuato uno studio retrospettivo di coorte su pazienti di COVID-19 ricoverati nell'ospedale Shahid Mostafa Khomeini dell'Università di Scienze mediche di Ilam dal 29 Febbraio al 29 Marzo 2020. Da costoro sono stati raccolti dati epidemiologici e risultati di esami di laboratorio. Sono stati applicati modelli di regressione logistica sia uni- che multi-variata per valutare il valore prognostico dei dati di laboratorio nei confronti dell'esito letale.

Risultati. Sono stati 256 i pazienti iraniani ricoverati con COVID-19, dei quali 38 sono successivamente morti in ospedale (letalità: 14.8%). L'analisi univariata ha mostrato che *l'età avanzata* [OR=1.04, 95% CI: 1.02-1.06, *P*=0.001], *il fumo* [OR=4.041, 95% CI: 1.546-10.563, *P*=0.004], *la conta dei leucociti* [OR=0.941, 95% CI: 0.904-0.980, *P* =0.003] *e l'ematocrito* [OR=1.060, 95% CI: 1.009-1.113, *P*=0.020)] sono risultati associati positivamente al rischio di un esito infausto. L'analisi di regressione logistica multivariata ha rivelato che i pazienti di COVID-19 con *un'elevata conta di leucociti* ed *un elevato valore di emoglobina* mostravano un incremento, rispettivamente, dell'1% e del 9% del rischio di morte intra-ospedaliera per ogni unità di incremento [OR=1.07; 95% CI: 1.024-1.088; *P* =0.002] e [OR=1.379; 95% CI: 0.064-1.788, *P*=0.015)].

Conclusioni. Un incremento della conta leucocitaria, così come un incremento dei livelli di emoglobina possono rappresentare fattori di rischio, indipendenti tra loro, di morte intraospedaliera dei pazienti iraniani con COVID-19. Studi ulteriori, su casistiche più ampie, saranno necessari per confermare il valore prognostico di queste variabili.

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