Predictors of Mortality Among COVID-19 Patients With or Without Comorbid Diabetes Mellitus

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Abstract- Late in 2019, the first case of COVID-19 was detected in China, and the disease caused a pandemic state worldwide. Up to now, many studies have investigated the impact of comorbid diseases, especially diabetes mellitus, on COVID-19 outcomes. In this study, we aimed to assess the para-clinic characteristics of COVID-19 patients with or without diabetes mellitus to identify factors indicative of poor prognoses. In this prospective study, 153 in-patients with COVID-19 were followed up from 1 March to 19 April. Paraclinical information of these patients was gathered from their medical records. Afterward, the association between these factors among both diabetic and non-diabetic patients was assessed in the correlation analyses. Discharge and expiration of 77.1% and 22.9% of the study participants resulted in a 1063 person-day follow-up for patients who were discharged healthily and 384 person-day follow-ups for expired patients. 41.8% of the participants had diabetes mellitus. Lymphocytopenia and Neutrolhilia prevalences increased during hospitalization; comparing with their initial prevalences. Thirty-seven patients got acute respiratory distress syndrome; of those, 35 died. The mean of the initial C reactive protein level was 42.49, and serum creatinine of 1.39. The study showed that higher initial neutrophil count, increasing neutrophil count more than 15000 and decreasing lymphocyte count below 1000 during hospitalization; development of acute respiratory distress syndrome and being intubated; initial C reactive protein and serum creatinine level were associated with higher mortality rates in COVID-19 victims.

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Introduction

Late in 2019, a novel virus from the *Coronaviridae* family was detected by the Chinese centers for disease control and prevention from the throat culture of patients with influenza-like manifestations, which was subsequently named Severe Acute Respiratory Syndrome CoronaVirus 2 (SARS-CoV-2) (1). The novel Coronavirus, attributed to causing multisystem involvement with especially leading to respiratory compromise, is spreading rapidly through the world, making its outbreak a pandemic, declared by the World Health Organization (WHO) on 11 March 2020 (2,3).

Several risk factors, including individuals' underlying

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diseases, had been shown to be associated with higher vulnerability to get SARS-CoV-2 infection (4-6). In this regard, Diabetes Mellitus (DM) is reported in a majority of studies to be among the most common comorbidities of patients with Coronavirus disease 2019 (COVID-19) (6). Although due to the immune system function dysregulation developed in the patients with DM and widely believing that these patients are at higher risk of being infected with SARS-CoV-2, published records did not allow us to determine whether DM would increase the infection rate certainly; it warrants further studies. However, it has been shown that, similar to other infectious diseases, having DM is associated with severe complications and poor prognosis in COVID-19 (7,8). In a systematic review of data of 1382 patients with SARS-CoV-2 infection, DM was found to increase the risk of multiorgan failure and ICU admission. Furthermore, the mortality rate was higher in these patients with concomitant DM and COVID-19 (9). However, data regarding the predictors of higher rates of complications and mortality in these patients with COVID-19 are still scant.

Here, we assessed the paraclinical data of patients with COVID-19 with or without diabetes and their relation with death as the clinical outcome in order to build a comprehensive body of information about the prognostic impact of diabetes and identify factors associated with more severe outcomes and mortality among them. Findings will help us to determine in which conditions a more aggressive treatment plan should be implemented.

Materials and Methods

Study design and setting

This is a prospective study conducted from 1 March to 19 April. Suspected COVID-19 patients who had clinical presentations of fever, cough, sore throat, and probable respiratory distress (10) and got hospitalized for at least 48 hours in Shohadaye Tajrish Hospital were included and followed up. Shohadaye Tajrish Hospital is a tertiary teaching hospital under the supervision of Shahid Beheshti University of Medical Sciences (SBUMS) and is located in Tehran, Iran. The approach to the disease and treatments were the same for all participants and were based on national health guidelines.

COVID-19 confirmation, participants, and data collection

In the present study, we included 153 in-patients who had typical chest computed tomography (CT) scan findings, including distributed multifocal ground-glass opacities (GGO) and patchy consolidations. We considered CT scan for confirmation of COVID-19 because, at the time of the study, laboratory confirmation of the disease by Real-time reverse transcriptase-polymerase chain reaction (RT-PCR) was limited and based on previous shreds of evidence, the accuracy of chest CT scan was not inferior to RT-PCR; besides, chest CT scan could cause early detection of suspected cases (6,11,12). All the chest CT scans were interpreted by a trained specialized radiologist. After obtaining written consent, some demographic and clinical information from their medical records were gathered, and initial blood sampling for white blood cells and differentiation (WBC & diff), C reactive protein (CRP), serum creatinine level, and fasting blood sugar (FBS). Then, we followed these patients during their hospitalization period with WBC & diff. We reported maximum neutrophil count and minimum lymphocyte count as a representative for a surge in neutrophilia and lymphopenia during the course of the hospital. In this study, we excluded outpatients and also in-patients who were not able to be interviewed, including some patients in critical condition and patients with aphasia or other communication obstacles, except in cases that their liable family caregivers were available and consented. Furthermore, patients who received Continuous Renal Replacement Therapies (CRRT), Hemoperfusion, or end-stage renal disease (ESRD) patients who needed to be dialyzed were excluded from the study. Fasting blood sugar ≥126 was set as a marker for diagnosis of DM, besides the self-reported past medical history of DM.

Data analysis

Categorical variables were summarized as frequencies and percentages, and continuous variables were described as mean values. To be feasible comparing the groups, neutrophil counts were divided into three groups (≤7500, 7500-15000 and ≥15000), lymphocyte counts into three groups (≤500, 500-1000 and ≥1000), CRP into three groups (≤3, 3-10, and ≥10) and creatinine into two groups (≤1.2 and more than 1.2). Means of continuous variables were compared using the independent T-test, and the proportion of categorical variables were compared using the Chi-square test. Spearman's correlation was computed for investigating the correlation of continuous variables (maximum/minimum neutrophil count, maximum lymphocyte count, initial CRP, and initial creatinine) and expiration. All statistical analyzes were generated using Statistical Package for Social Sciences (SPSS Inc.,

Chicago, Illinois, USA) version 16.0. $P<0.05$ was set as a significant cut-off point.

Ethical consideration

All participants were informed about the purposes of the study, and written consent was obtained from patients or their liable family caregivers. All the participants were assured that their information would remain confidential. They also were informed about their right to withdraw from the study at any time they want. This study was approved by the Ethical Research Committee of Shahid Beheshti University of Medical Sciences (SBMUS).

Results

A total of 153 patients with a mean age of 61 were enrolled and followed up from 1 March to 19 April, resulting in a 1063 person-day follow-up for patients who were discharged healthily and 384 person-day follow-ups for expired patients. Up to 19 April, 118 patients were discharged, and 35 individuals expired, giving the total mortality rate of 22.9%. The majority of participants were male (71.2%), and 41.8% of the participants had DM. The diabetic state was associated significantly with a higher mortality rate. On admission, 45.8% of patients had lymphocytopenia (lymphocyte count under 1000), which increased to 71.9% during the monitoring period. Additionally, 24.9% had an initial neutrophil count of more than 7500, which increased to 53.6% at the end. During the follow-up time, 37 patients got acute respiratory distress syndrome (ARDS); of those, 35 died. The mean of the initial CRP level was 42.49, and serum creatinine of 1.39. Other laboratory data were shown in Table 1.

As illustrated in Figures 1 and 2 and Table 1, maximum neutrophil count of more than 15000 and minimum lymphocyte count of less than 1000 was significantly related to more mortality rates comparing dead and survived groups.

According to Table 2, maximum neutrophil count and minimum lymphocyte count during follow-up time, initial CRP, and initial serum creatinine level were significantly related to expiration and death.

Table 3 shows the comparison between diabetic and non-diabetic groups based on maximum neutrophil count and minimum lymphocyte count during the follow-up period, initial CRP, and initial serum creatinine level; the maximum neutrophil count was significantly higher in the diabetic group.

Table 1. Demographic and para-clinical characteristics of the study population in total and by survival status (N=153)

Factors		Total (N=153)	Deaths (N=35)	Survived (N=118)	*P*
Person-day follow-up		1447	384	1063	0.142 (t-test)
Age (mean (SD) years)		60.96 (17.01)	65.42 (42)	59.64 (17.45)	0.077 (t-test)
Gender	**Male**	109 (71.2%)	26 (74.3%)	83 (70.3%)	0.651 (chi-square)
	Female	44 (28.8%)	9 (25.7%)	35 (29.7%)	
Initial Neutrophil count (per µL)	**Under 7500 (normal range)**	115 (75.1%)	21 (60.0%)	94 (79.7%)	0.027* (chi-square)
	7500-15000	35 (22.9%)	12 (34.3%)	23 (19.5%)	
	15000<	3 (2.0 %)	2 (5.7%)	1 (0.8%)	
Initial Neutrophil count (mean (SD)) (per µL)		5866.07 (3433.42)	7600.11 (4003.39)	5351 (3080.76)	0.004* (t-test)
Maximum Neutrophil count during follow up (per µL)	**Under 7500 (normal range)**	71 (46.4%)	3 (8.6%)	68 (57.6%)	0.000* (chi-square)
	7500-15000	60 (39.2%)	16 (45.7%)	44 (37.3%)	
	15000<	22 (14.4%)	16 (45.7%)	6 (5.1%)	
Maximum Neutrophil count (mean (SD)) (per µL)		9163.02 (5230.12)	14467.60 (4959.01)	7589.63 (4180.48)	0.000* (t-test)
Initial Lymphocyte count (per µL)	**Under 500**	6 (4%)	2 (5.7%)	4 (3.4%)	0.478 (chi-square)
	500-1000	64 (41.8%)	17 (48.6%)	47 (39.8%)	
	1000<	83 (54.2%)	16 (45.7 %)	67 (56.8%)	
Initial Lymphocyte count (mean (SD)) (per µL)		1177.03 (600.41)	1068.77 (666.87)	1209.14 (578.41)	0.226 (t-test)

Cont. table 1

Minimum Lymphocyte count during follow up (per µL)	**Under 500**	27 (17.6%)	9 (25.7%)	18 (15.3%)	0.034* (chi-square)
	500-1000	83(54.3%)	22 (62.8%)	61 (51.6%)	
	1000<	43 (28.1%)	4 (11.5%)	39 (33.1%)	
Minimum Lymphocyte count (mean (SD)) (per µL)		846.10 (408.98)	659.61 (287.32)	901.42 (424.06)	0.000* (t-test)
Diabetes mellitus Type II	**Yes**	64 (41.8%)	21 (60.0%)	43 (36.4%)	0.013* (chi-square)
	No	89 (58.2%)	14 (40.0%)	75 (63.6%)	
Patients who developed ARDS and got intubated	**Yes**	37 (24.2%)	35 (100%)	2 (1.7%)	0.000* (chi-square)
	No	116 (75.8%)	0 (0.00%)	116 (98.3%)	
Initial C-reactive protein (mg/L)	**Normal (under 3)**	7 (4.6%)	1 (2.9%)	6 (5.1%)	0.832 (chi-square)
	Moderate (3-10)	19 (12.4%)	4 (11.4%)	15 (12.7%)	
	High (> 10)	127 (83.0%)	30 (85.7%)	97 (82.2%)	
Initial C-reactive protein (mean (SD)) (mg/L)		42.49 (35.21)	57.42 (44.2)	38.06 (30.89)	0.020 (t-test)
Initial Creatinine (mg/dL)	**Under 1.2**	74 (48.4%)	14 (40.0%)	60 (50.8%)	0.259 (chi-square)
	More than 1.2	79 (51.6%)	21 (60.0%)	58 (49.2%)	
Initial Creatinine (mean (SD)) (mg/dL)		1.39 (0.82)	1.53 (0.63)	1.35 (0.87)	0.242 (t-test)

*significant, SD= standard deviation, ARDS= acute respiratory distress syndrome

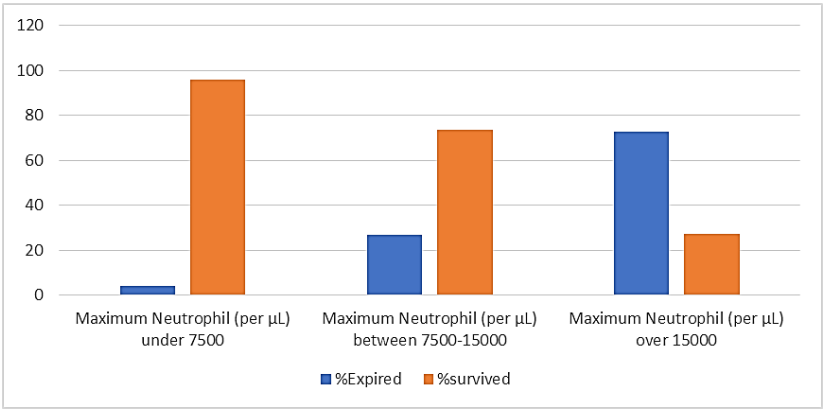

Figure 1. Comparison of mortality rate (%) based on Maximum Neutrophil groups during follow up

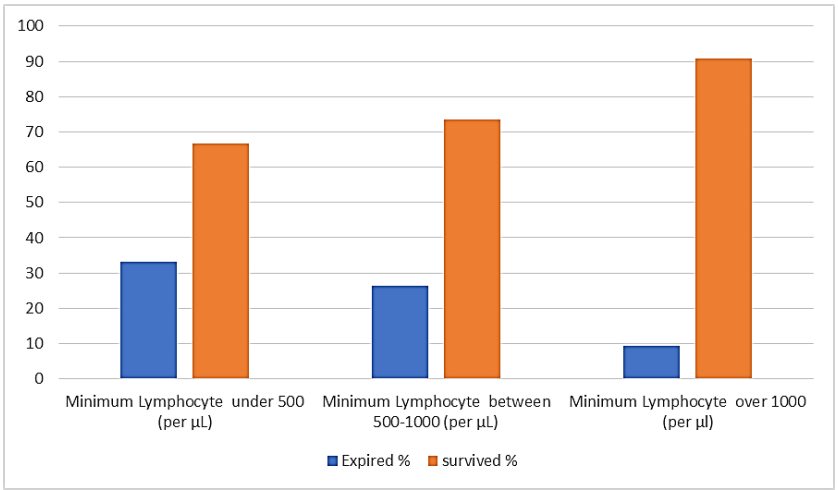

Figure 2. Comparison of mortality rate (%) based on Minimum lymphocyte groups during follow up

Table 2. The correlation of Maximum neutrophil count, Minimum Lymphocyte count, initial CRP, and initial creatinine with expiration in COVID-19 patients by Spearman's correlation analysis

	Expiration	
	r	***P***
Maximum neutrophil count (per µL)	0.52	0.0001*
Minimum Lymphocyte count (per µL)	-0.25	0.002*
Initial CRP (mg/L)	0.18	0.026*
Initial Creatinine (mg/dL)	0.16	0.048*

*significant, CRP= C reactive protein

Table 3. Comparison of mean age, FBS, Maximum neutrophil count, Minimum Lymphocyte count, initial CRP, and initial creatinine between diabetic and non-diabetic patients by Independent t-test

	Diabetic patients	Non-diabetic patients	*P*
Mean age (year)	65.40 (13.41)	57.77 (18.61)	0.004*
Mean FBS (mg/dL)	168.67 (67.97)	89.80 (9.25)	0.0001*
Mean maximum neutrophil count (per µL)	10273.15 (5353.66)	8364.72 (5018.78)	0.027*
Mean minimum Lymphocyte count (per µL)	847.53 (425.00)	845.08 (399.50)	0.971
Mean Initial CRP (mg/L)	47.14 (39.30)	39.15 (31.76)	0.162
Mean Initial Creatinine (mg/dL)	1.38 (0.80)	1.40 (0.84)	0.867

*Significant, FBS= fasting blood sugar, CRP= C reactive protein

Discussion

Beginning early after the epidemic of SARS-CoV-2, a chain of studies, as well as ours, was initiated to assess a variety of prognostic factors in patients infected with SARS-CoV-2. Higher initial and maximum neutrophil count, minimum lymphocyte count, DM as a comorbid disease, development of acute respiratory distress syndrome, and being intubated were associated with higher mortality rates. The maximum neutrophil count was also significantly higher among diabetic patients compared to non-diabetic ones.

The prevalence of DM in our patients was 41.8%. However, this is not reflective of the actual prevalence of diabetes in SARS-CoV-2 infected patients, as patients with mild forms of infection were not included in the current study. Based on a meta-analysis of twelve studies, it was concluded that having diabetes does not seem to increase the risk of contracting SARS-CoV-2 infection, and being of the most common comorbid diseases among these patients is due to its high prevalence in society, not because of higher susceptibility (13). Furthermore, studies have shown that hyperglycemia can be marked both as a poor prognostic factor and as a consequence of SARS-CoV-2 infection (14,15). SARS-Cov-2 induced hyperglycemia has been partly attributed to the pancreatic islets' injury due to the expression of angiotensin-converting enzyme 2 (ACE2) (15). Emerging evidence has demonstrated that glycemic state, as is particularly impaired in patients with diabetes, is associated with the severity of the disease, the speed of disease progression, and the mortality rate (6).

Similar to our study's results, in one meta-analysis on the prevalence of diabetes mellitus among SARS-CoV-2 infected patients, its prevalence was revealed to be significantly higher among those with severe conditions (16). In our study, the prevalence of diabetes mellitus was documented to have a significant association with mortality rate, being present among about 60% and 36.4% of those who died and those who survived, respectively. This association may be attributed to several reasons. A series of studies have documented that poorly controlled diabetes is associated with a significant decrease in pulmonary function (17,18). In one of these studies, it was concluded that in patients with diabetes mellitus type 2, there was a significant reduction in several pulmonary parameters, including forced vital capacity (FVC), Forced expiratory volume in one second (FEV1), forced expiratory flow (FEF), and peak expiratory flow rate (PEFR) (18). Microangiopathy (19), impaired chemotaxis (20), and decreased interleukins' production (21) are other mechanisms predisposing diabetic patients to develop more severe forms of infection. In another study on the clinical outcome of the patients with severe SARS-CoV-2 infection, it was shown that diabetic patients were more susceptible to receiving mechanical ventilation, admission to ICU, and higher mortality than others without diabetes (22).

Furthermore, the current study demonstrated that some other prognostic factors, including the patient's

neutrophil count on admission, initial CRP level, maximum neutrophil, and minimum lymphocyte counts during hospitalization, have a significant association with the outcome of these patients. It showed that maximum neutrophil and minimum lymphocyte counts were respectively significantly higher and lower in those who died compared to the survivors; hence, the neutrophil-to-lymphocyte ratios would be higher in patients with severe forms of infection. In the same way, some studies have concluded that the neutrophil-to-lymphocyte ratio (NLR) can be used as an independent biomarker for poor clinical outcomes, and surveillance of these markers will guide for better management (23). Furthermore, neutrophilia, which was revealed to have an association with the mortality rate of our patients, was found to be significantly more common in diabetic patients. Similarly, in another study, it was demonstrated that neutrophilia, especially in patients with the hyperglycemic state, is associated with a high mortality rate (24).

The limitation of this study is that the presence or absence of diabetes mellitus in the patients was determined by self-expression and whether or not they were under a physician's follow-up or treatment. With such an approach, some undiagnosed patients will be missed; however, all the patients were being tested for fasting blood sugar (FBS). The more standard approach to assess if they had DM was checking HbA1C level; because, as it was stated above, hyperglycemia could be elicited in critically ill patients (25).

Based on what was mentioned above, DM is a major comorbid disease affecting the prognosis of COVID-19 patients. The study showed that higher initial neutrophil count, increasing neutrophil count more than 15000 and decreasing lymphocyte count below 1000 during hospitalization; development of ARDS and being intubated; initial CRP and serum creatinine level were associated with higher mortality rates in COVID-19 victims.

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