Disease and Diagnosis

Dis Diagn. 2021; 10(3): 91-98

doi 10.34172/ddj.2021.18

Original Article

COVID-19 Severity and Comorbidities in Diabetic Patients

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Abstract

Background: This study aimed to investigate the demographic factors, comorbidities, and laboratory results of diabetic patients with coronavirus disease 2019 (COVID-19) severity.

Materials and Methods: This cross-sectional study enrolled 171 diabetic patients with COVID-19 admitted based on chest CT scan findings to the COVID-19 ward of Shahid Mohammadi Hospital in Hormozgan, Iran from 1 March to 1 June, 2020. Reverse-transcriptase polymerase chain reaction (RT-PCR) test was performed, and the patients were divided into three groups (mild, moderate, and severe) based on the severity of disease. Then we investigated the demographic factors, comorbidities, and laboratory results of diabetic patients with severe COVID-19 severity.

Results: Regarding comorbidities, there was no significant difference between the three groups. Moreover, there was a significantly lower lymphocyte count in the severe group compared to moderate and mild groups ($P=0.001$). We showed the increase in blood urea nitrogen (BUN) and creatinine to be significantly associated with increased disease severity ($P=0.001$ and $P=0.009$, respectively). We also showed a significant difference in aspartate aminotransferase (AST) levels between different groups of patients ($P=0.002$) with a higher level of AST in the severe group ($P=0.020$). Lactate dehydrogenase (LDH) and troponin were also significantly associated with an increase in COVID-19 severity in patients with diabetes ($P=0.013$ and $P=0.002$, respectively).

Conclusion: There was a significant association between disease severity and BUN, creatinine, AST, LDH, and troponin levels in diabetic patients with COVID-19. There was no significant association between different groups regarding severity of disease and comorbidities.

Keywords: Diabetes mellitus, COVID-19, Severity, Laboratory findings

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Received: November 18, 2020, Accepted: February 17, 2021, ePublished: September 30, 2021

Introduction

Caused by severe acute respiratory syndrome coronavirus-2 (SARS-COV-2), coronavirus disease 2019 (COVID-19) is a viral disease that affects the lower respiratory tract and causes pneumonia in patients (1, 2). The disease spread rapidly around the world after the outbreak in late 2019 and became one of the challenges of healthcare systems by turning into a pandemic (3-5). Older adults and patients with underlying diseases such as cardiovascular diseases, hypertension, and diabetes are at higher risk for COVID-19 and require more care (5, 6). The importance of diabetes lies in its prevalence among older adults and the general population in terms of creating a burden on the special care system during the COVID-19 pandemic (5, 7). Diabetes is also one of the most common comorbidities among patients with COVID-19, which is considered a risk factor for these patients (6, 8).

However, the association between diabetes and respiratory distress syndrome (RDS) is not yet fully understood (9, 10). While some studies suggested that diabetes is not related to RDS, some others reported pulmonary dysfunction following diabetes (9-11). However, respiratory failure in RDS can be considered as one of the mechanisms of pancreatic damage in COVID-19 patients (12). It is also unclear what factors are associated with the greater severity of the disease and the critical condition of COVID-19 patients with diabetes.

In previous pneumonia (2003), coronavirus (SARS-CoV) was identified as a potential target tissue not only in lung, liver, kidney, and intestinal tissues but also in the pancreas (13). Moreover, the angiotensin converting enzyme 2 (ACE2) receptor is highly expressed in the pancreatic islets, and SARS-CoV infection has caused islet cell damage and subsequent acute diabetes (14). However, the cytopathic effect of SARS-CoV-2, in addition to the effects on the inflammatory system and respiratory failure, is thought to lead to pancreatic damage in COVID-19 patients (12).

This study aimed to investigate the demographic factors, comorbidities, and laboratory results of patients with diabetes and the severity of COVID-19, as well as to determine the prognostic factors in these patients.

Materials and Methods

This cross-sectional study enrolled 171 diabetic patients with COVID-19 admitted based on chest CT scan findings to the COVID-19 ward of Shahid Mohammadi Hospital in Hormozgan, Iran from 1 March to 1 June, 2020. Reverse-transcriptase polymerase chain reaction (RT-PCR) test was performed, and the patients were divided into three groups (mild, moderate, and severe) based on the severity of the disease. Then we investigated the demographic factors, comorbidities, and laboratory results (on the day of admission) of diabetic patients with severe COVID-19.

The following blood tests were run for all the patients: a complete blood count (CBC) (Sysmex kx21), liver enzyme erythrocyte sedimentation rate (ESR) via Westergren method, blood urea nitrogen (BUN), and lactate dehydrogenase (LDH) (Mindray bs 800).

The glomerular filtration rate (GFR) was calculated via the following equation:

$$GFR = \frac{n(140 - Age) \times \text{body weight}}{Creatinin \times 72}$$

In this study, lymphocyte ≤1500 per mm3, LDH ≥ 500, U/L, alanine aminotransferase (ALT) (SGPT) ≥ 40 U/L, and aspartate aminotransferase (AST) (SGOT) ≥ 40 U/L were regarded as abnormal. Severe disease was defined as respiratory rate ≥ 30, systolic blood pressure < 90 mm Hg, and decreased level of consciousness (15).

Statistical Analysis

Qualitative variables were described by number (n) and percentage (%), while quantitative variables were described by mean and standard deviation (SD). Shapiro-Wilk test was applied to assess normality of quantitative variables.

Analysis of variance (ANOVA) and chi-square tests were applied to compare quantitative and qualitative variables in three groups, respectively. *P* value less than 0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics 22 software (IBM Corporation, Armonk, NY, USA).

Results

Out of 171 subjects, 45 patients were in the mild, 82 in moderate, and 44 in severe groups. The mean age of patients in the mild, moderate, and severe groups was 58±14, 58.6±15.3, and 58±12 years, respectively, which was not significantly different ($P=0.9$).

Out of 171 subjects, 26 (15.2%) patients died, of whom 14 (53.8%) were male and 12 (46.2%) were female. There was no significant difference between the proportion of dead in the two groups ($P=0.514$).

The results of Shapiro-Wilk test showed that all quantitative variables were normally distributed ($P>0.05$).

In terms of gender frequency, 48%, 55.6%, and 65.9% of patients were male in the mild, moderate, and severe groups, respectively, which was significantly different ($P=0.002$). In terms of place of residence (urban or rural), 88.3%, 86.7%, and 84.1%, of patients in the mild, moderate, and severe groups were living in urban areas, respectively, which was not significantly different ($P=0.43$) (Table 1). Regarding comorbidities, there was a history of hypertension in 52.6%, 55.6%, and 51.2% of patients in the mild, moderate, and severe groups, respectively ($P=0.89$). There was a history of ischemic heart disease in 73.3%, 63.3%, and 75% of patients in the mild, moderate, and severe groups, respectively, which was not significantly different ($P=0.68$). History of asthma was reported in 6.7%, 11%, and 6.8% of patients in the mild, moderate, and severe groups, respectively, ($P=0.62$). Hyperlipidemia was reported in 13.3%, 2.7%, and 15.9% of patients in the mild, moderate, and severe groups, respectively, ($P=0.54\%$). History of chronic kidney disease was reported in 6.7%, 8.5%, and 18.2% of patients in the mild, moderate, and severe groups, respectively, which was not significantly different ($P=0.15$). There was a significant association between mortality and severity of disease, so that mortality rate in patients with severe disease was higher than mild and moderate groups ($P<0.001$) (Table 2).

Regarding laboratory findings, hemoglobin was 12.5±2.3 g/dL, 11.9±2.4 g/dL, and 11.2±2.4 g/dL in the mild, moderate, and severe groups, respectively, which was not significantly different ($P=0.55$). White blood cell was $7.3\pm4.1\times10^9$/L, $8.1\pm4.4\times10^9$/L, and $11.9\pm9.7\times10^9$/L in the

Table 1. Demographics and Social Characteristics of Diabetic Patients With COVID-19 in Different Groups of Severity

Characteristics		All Patients (n=171) No. (%)	Mild (n=45) No. (%)	Moderate (n=82) No. (%)	Severe (n=44) No. (%)	*P* Value
Age (y)	20-29	5 (2.9)	2 (4.4)	2 (2.4)	1 (2.3)	0.829
	30-39	15 (8.8)	3 (6.7)	6 (7.3)	6 (13.6)	
	40-49	24 (14)	6 (13.3)	14 (17.1)	4 (9.1)	
	50-59	38 (22.2)	9 (20)	19 (23.2)	10 (22.7)	
	60-69	58 (33.9)	15 (33.3)	30 (36.6)	13 (29.5)	
	70-79	17 (9.9)	6 (13.3)	7 (8.5)	4 (9.1)	
	≥80	14 (8.2)	4 (8.9)	4 (4.9)	6 (13.6)	
Sex	Male	82 (48.0)	25 (55.6)	28 (34.1)	29 (65.9)	0.002
	Female	89 (52.0)	20 (44.4)	54 (65.9)	15 (34.1)	
Residence area	Urban	151 (88.3)	39 (86.7)	75 (91.5)	37 (84.1)	0.435
	Rural	20 (11.7)	6 (13.3)	7 (8.5)	7 (15.9)	
Nationality	Iranian	170 (99.4)	45 (100)	81 (98.8)	44 (100)	0.579

Table 2. The Association Between Different Groups of Severity With Comorbidities and Risk Factors

Comorbidity and Risk Factor		All Patients (n=171) No. (%)	Mild (n=45) No. (%)	Moderate (n=82) No. (%)	Severe (n=44) No. (%)	*P* Value
Hypertension	Yes	90 (52.6)	25 (55.6)	42 (51.2)	23 (52.3)	0.895
	No	81 (47.4)	20 (44.4)	40 (48.8)	21 (47.7)	
Chronic cardiac disease	Yes	49 (28.7)	12 (26.7)	26 (31.7)	11 (25)	0.688
	No	122 (71.3)	33 (73.3)	56 (63.3)	33 (75)	
Asthma	Yes	15 (8.8)	3 (6.7)	9 (11)	3 (6.8)	0.620
	No	156 (91.2)	42 (93.3)	73 (89)	42 (93.3)	
Hyperlipidemia	Yes	30 (17.5)	6 (13.3)	17 (20.7)	7 (15.9)	0.546
	No	141 (82.5)	39 (86.7)	65 (79.3)	37 (84.1)	
Chronic neurological disorder	Yes	10 (5.8)	1 (2.2)	4 (4.9)	5 (11.4)	0.162
	No	161 (94.2)	44 (97.8)	78 (95.1)	39 (88.6)	
Chronic kidney disease	Yes	18 (10.5)	3 (6.7)	7 (8.5)	8 (18.2)	0.150
	No	153 (89.5)	42 (93.3)	75 (91.5)	36 (81.8)	
Hypothyroid	Yes	4 (2.3)	1 (2.2)	2 (2.4)	1 (2.3)	0.996
	No	167 (97.7)	44 (97.8)	80 (97.6)	43 (97.7)	
Vital status	Dead	0(0.0)	0(0.0)	26(100.0)	26(100.0)	<0.001
	Discharged	45(31.0)	84(57.9)	16(11.0)	145(100.0)	

mild, moderate, and severe groups, respectively ($P=0.06$). The mean lymphocytes percentage was 23.2%, 23.6%, and 16.6% in the mild, moderate, and severe groups, respectively, which was significantly different ($P=0.005$). The mean neutrophil percentage was 67.4%, 69.6%, and 77.9% in the mild, moderate, and severe groups, respectively, which was significantly different ($P=0.004$). The mean partial thromboplastin time (PTT) was 32.4±9.2 seconds, 31.9±4.8 seconds, and 32.8±5.7 seconds in the mild, moderate, and severe groups, respectively ($P=0.86$). The mean international normalized ratio (INR) was 1.12±0.13, 1.12±0.25, and 1.53±1.21 in the mild, moderate, and severe groups, respectively, which was significantly different; in addition, it was significantly higher in the severe group ($P=0.011$). The mean ALT was 37.4±22.1 U/L, 43.2±56.3 U/L, and 76.8±13.6 U/L in the mild, moderate, and severe groups, respectively, which was not significantly different ($P=0.217$). However, AST was significantly different ($P=0.002$), so that it was 51.6±75.3 U/L, 42.3±56 U/L, and 124.2±257 U/L in the mild, moderate, and severe groups, respectively (Table 3).

The mean BUN was 31.9±14.5 mg/dL, 35.1±24.7 mg/dL, and 64.6±55.7 mg/dL in the mild, moderate, and severe groups, respectively, which was significantly different ($P=0.001$). The mean LDH was 414.3±155.7 U/L, 466.7±285.5 U/L, and 630±324 U/L in the mild,

moderate, and severe groups, respectively, which was significantly different ($P=0.023$). The mean blood glucose was 124.84±19.60 mg/dL, 119.42±21.32 mg/dL, and 86.13±16.09 mg/dL in the mild, moderate, and severe groups, respectively ($P<0.001$). Respiration rate was 18.78+-2.81, 19.87+-7.8, and 23.33+-13.20 in the three groups of mild, moderate, and severe, respectively(*P* value=0.002). Systolic blood pressure was 124.84+-19.60, 119.42+-21.32, and 86.13+-16.09 in the three groups of mild, moderate, and severe, respectively(*P* value<0.001). O2 saturation was 96.51+-1.79, 94.84+-3.74, and 91.05+-8.35, in the three groups of mild, moderate, and severe, respectively(*P* value=0.002). There was no significant difference among the three groups in terms of vital signs heart rate and diastolic blood pressure (Table 4).

Regarding the treatments received by the three study groups, a significant difference was observed among the three groups only in terms of treatment with Lopinavir-Ritonavir ($P=0.012$). It was administered for 11.1%, 26.8%, and 38.6% of patients in the mild, moderate, and severe groups, respectively. No significant difference was observed among the groups regarding other treatments (Table 5).

Discussion

One of the main objectives of this study was to find the factors related to the prognosis and severity of COVID-19 in diabetic patients. Regarding comorbidities, there was no significant difference between mild, moderate, and severe groups of diabetic patients with COVID-19 with severity of disease.

Our results showed significant gender differences

Table 3. The Association Between Different Groups of Severity with Laboratory Tests

Lab Tests	All patients (n=171) (mean ± SD)	Mild (n=45) (mean ± SD)	Moderate (n=82) (mean ± SD)	Severe (n=44) (mea n± SD)	*P* Value
Hemoglobin(g/dl)	11.92±2.289	12.54 ±2.352	11.94±2.07	11.26±2.48	0.055
white blood cell (×10^9/L)	8.92±7.25	7.37±4.11	8.14±4.04	11.92±9.75	0.069
Lymphocyte (%)	19.80 ± 13.23	23.24 ± 12.61	23.61 ± 13.07	16.66 ± 13.19	0.005 **
Neutrophil (%)	71.26 ± 14.78	67.47 ± 14.33	69.69 ± 14.58	77.99 ± 13.74	0.004 **
Hematocrit (%)	35.52 ± 7.02	36.797 ±7.46	35.17 ± 6.97	34.88± 6.68	0.251
Platelets (×10^9/L)	238.79 ±108.2	226.97±92.69	246.98 ± 114.39	235.05±111.89	0.589
PTT (s)	32.37 ± 6.18	32.41 ± 9.27	31.98 ±4.85	32.83 ±5.71	0.864
PT (s)	15.24 ± 10.14	13.56 ± 0.7	13.46 ± 1.60	18.62 ± 16.94	0.011 *
INR	1.26 ± 0.74	1.12 ± 0.13	1.12 ± 0.25	1.53 ± 1.21	0.011 *
ALT (IU/L)	51.32 ± 85.2	37.49±22.13	43.28 ± 67.69	76.86 ± 130.66	0.217
Bilirubin (T) (µmol/L)	1.44 ± 0.7	0.83 ± .45	1.98 ± 4.33	1.11 ± 0.65	0.418
AST(IU/L)	66.45 ± 146.1	51.69 ± 75.33	42.35 ± 56.03	124.22±257.68	0.002 **
Glucose (mg/dL)	207.04±113.62	180.13± 116.64	223.9 ±109.46	199.57±117.13	0.163
BUN (mg/dL)	42.23 ± 36.67	31.99 ± 14.54	35.10 ± 24.74	64.66 ± 55.71	0.001 **
Creatinine (mg/dL)	1.46 ± 1.31	1.12 ± 0.42	1.45 ± 1.59	1.81 ± 1.26	0.009**
LDH (IU/L)	491.87±276.89	414.38 ± 155.71	466.75 ± 285.57	630.86±334.84	0.023 *
Sodium (mEq/L)	137.54 ± 6.32	137.41± 4.13	137.25 ±5.44	138.14 ± 8.96	0.609
Potassium (mEq/L)	7.78 ±35.96	5.56 ± 7.64	11.20 ±53.15	4.42 ± 0.64	0.183
FBS (mg/dL)	286.75±186.79	512.0 ± 0	283.0 ± 80.61	69.0 ± 0	0.249
Troponin	1211.6 ±7445.16	3.77 ± 4.28	3014.65± 12110.39	215.18±480.31	0.007 *

*P value<0.05, **P value<0.01

Table 4. The Association between Different Groups of Severity With Vital Signs and O2 Saturation

Sign	All patients (n=171) (mean ± SD)	Mild (n=45) (mean ± SD)	Moderate (n=82) (mean ± SD)	Severe (n=44) (mea n± SD)	*P* Value
Temperature (°C)	37.24 ±1.01	37.16 ± 0.74	37.15 ± 0.74	37.52 ± 1.58	0.137
Heart rate (beats/minute)	87.62±17.21	91.42 ± 16.21	85.68 ± 16.81	87.28 ±18.83	0.199
Respiration rate (breaths/minute)	20.40 ± 8.74	18.78 ± 2.81	19.87 ± 7.89	23.33 ± 13.20	0.002**
Systolic blood pressure (mm Hg)	112.28 ±25.15	124.84 ±19.60	119.42 ±21.32	86.13±16.09	<0.001***
Diastolic blood pressure (mm Hg)	75.75±14.61	75.8 ±10.98	75.46 ± 15.06	76.28 ±17.41	0.928
O2 saturation (%)	94.37 ± 5.32	96.51 ± 1.79	94.84 ± 3.74	91.05 ± 8.35	0.008**

*P value<0.05, **P value <0.01, *** P value <0.001.

Table 5. The Association between Different Groups of Severity With Medications and Treatment Methods

Variables		All Patients (n=171) No. (%)	Mild (n=45) No. (%)	Moderate (n=82) No. (%)	Severe (n=44) No. (%)	*P* Value
Any antibiotics	Yes	155 (90.6)	40 (88.9)	76 (92.7)	39 (88.6)	0.679
	No	16 (9.4)	5 (11.1)	6 (7.3)	5 (11.4)	
Hydroxychloroquine	Yes	121 (70.8)	29 (64.4)	65 (79.3)	27 (61.4)	0.060
	No	50 (29.2)	16 (35.6)	17 (20.7)	17 (38.6)	
Oseltamivir	Yes	44 (25.7)	14 (31.1)	19 (23.2)	11 (25)	0.614
	No	127 (74.3)	31 (68.9)	63 (76.8)	33 (75)	
Lopinavir-Ritonavir	Yes	44 (25.7)	5 (11.1)	22 (26.8)	17 (38.6)	0.012 *
	No	127 (74.3)	40 (88.9)	60 (73.2)	27 (61.4)	
Ribavirin	Yes	3 (1.8)	-	3 (3.7)	-	0.191
	No	168 (98.2)	45 (100)	79 (96.3)	44 (100)	
Atazanavir	Yes	4 (2.3)	1 (2.2)	2 (2.4)	1 (2.3)	0.996
	No	167 (97.7)	44 (97.8)	80 (97.6)	43 (97.7)	
Neuraminidase Inhibitor	Yes	-	-	-	-	-
	No	171 (100)	45 (100)	82 (100)	44 (100)	
Daclatasvir and Sofosbuvir	Yes	-	-	-	-	-
	No	171 (100)	45 (100)	82 (100)	44 (100)	
Interferon Beta	Yes	1 (0.6)	1 (2.2)	-	-	0.245
	No	170 (99.4)	44 (97.8)	82 (100)	44 (100)	
Albumin	Yes	1 (0.6)	-	-	1 (2.3)	0.234
	No	170 (99.4)	45 (100)	82 (100)	43 (97.7)	
Interferon alpha	Yes	3 (1.8)	-	2 (2.4)	1 (2.3)	0.578
	No	168 (98.2)	45 (100)	80 (97.6)	43 (97.7)	
IVIG	Yes	2 (1.2)	1 (2.2)	-	1 (2.3)	0.394
	No	169 (98.8)	44 (97.8)	82 (100)	43 (97.7)	
Corticosteroid	Yes	18 (10.5)	5 (11.5)	7 (8.5)	6 (13.6)	0.666
	No	153 (89.5)	40 (88.9)	75 (91.5)	38 (86.4)	
Remdesivir	Yes	-	-	-	-	-
	No	171 (100)	45 (100)	82 (100)	44 (100)	
Plasmapheresis	Yes	-	-	-	-	-
	No	171 (100)	45 (100)	82 (100)	44 (100)	
Oxygen Saturation	<93%	3(7.3)	20(48.8)	18(43.9)	41(100)	<0.001
	>=93%	42(34.1)	61(49.6)	20(16.3)	123(100)	

*P value<0.05, **P value<0.01.

among study groups, so that male gender was significantly correlated with the severity of COVID-19 in patients with diabetes ($P=0.002$). In a study by Price-Haywood et al, female gender was associated with reduced hospital admissions (16). Although the exact mechanism for the effect of gender on COVID-19 has not yet been determined, differences in immune system or lifestyles of men and women can be considered as possible mechanisms (17,18). This difference may also be due to differences between males and females in the activity or expression of the ACE2 receptor, which binds to the SARS-COV-2 virus (19). However, our results showed that in addition to COVID-19 patients with no underlying diseases, the gender factor can also affect the severity and prognosis of the disease in diabetic patients.

Our results regarding lymphocyte count showed significantly lower lymphocyte count in the severe group than that in the moderate and mild groups ($P=0.001$). Cariou et al reported an inverse relationship between lymphocyte count ($10^3/mm^3$) and intubation and 7-day death in patients with diabetes and COVID-19 (20). The findings of Price-Haywood et al also showed a 1.33-fold increase in the risk of in-hospital death among patients with decreased lymphocyte counts (16). The results of a meta-analysis by Fu et al also showed a higher rate of reduced lymphocyte count in patients with severe

COVID-19 compared to non-severe cases (81.5 vs. 59.6) (21). Other studies have reported similar evidence of an association between decreased lymphocyte count and disease severity and mortality (22).

However, these results were the opposite for the neutrophil count, and the increase in neutrophil count in diabetic patients was associated with an increase in disease severity ($P=0.013$). Henry et al reported similar results about the association between increased neutrophil count in patients with severe COVID-19 (22). Other studies on changes in neutrophil and lymphocyte counts in patients with COVID-19 also suggest neutrophil to lymphocyte ratio as a prognostic factor for disease severity (23,24). According to our results, lymphocyte count and neutrophil count can be used as a relative measure for the recovery of COVID-19 patients regardless of the underlying disease of diabetes.

Our study on prothrombin time (PT) showed that it was significantly higher in the severe and mild groups than that in the moderate group, and it was higher than normal range in the severe group ($P=0019$). Our results in this case are in line with other studies on the correlation of disease severity and increased PT (22). Klok et al also proposed PT as an independent factor affecting thrombotic complications in critically ill patients with COVID-19 (25). In a study by Huang et al, patients who needed ICU care had higher PT at admission than other patients (26).

Our results regarding the INR showed an increase in the severe group compared to other groups ($P=0.011$). Shahriarirad et al reported an increase in INR in patients with both severe and non-severe COVID-19, though they did not compare the groups (27). Carlino et al compared groups of patients requiring and not requiring intensive care unit (ICU) and reported similar results regarding a significant increase in INR in those needing ICU (28). These changes in patients' PT, INR, and coagulopathy may be due to changes in the level of inflammatory factors (29).

We also showed a significant difference in AST levels between different groups ($P=0.002$). These results showed a higher level of AST in the severe group ($P=0.020$). A meta-analysis study by Zarifian et al showed increased levels of AST in 22.8% of patients with COVID-19 (30). Cariou et al reported a relationship between increased AST level in patients with COVID-19 at admission and their intubation (OR=2.23) (20). Other studies have reported an increase in the risk of death by 1.28 with an increase in AST (16). In line with these findings, meta-analytical studies have also confirmed the increase in liver enzymes associated with increased disease severity and mortality in patients with COVID-19 (31,32).

We found the increase in BUN to be significantly associated with increased disease severity ($P=0.001$). In line with our results, Zhou et al showed an increase in BUN levels associated with severe and critical COVID-19 (33). They also showed an increase in BUN in patients requiring invasive mechanical ventilation compared to patients with non-invasive ventilation (34). Besides, we observed a significant association between increased creatinine and COVID-19 severity ($P=0.009$). Zhou et al also reported an increase in creatinine in patients with severe COVID-19 in line with our results (33). These results, together with the results of a study by Thomas et al, which showed an increase in creatinine and BUN levels with an increase in inflammatory factors in patients with COVID-19, suggest renal damage through immune mechanisms in patients with COVID-19 (30). However, the exact mechanism of kidney damage remains unclear and requires further study. The results of a meta-analysis by Oyelade et al also showed an 83.93% increase in COVID-19 severity in patients with chronic kidney disease (35). These results, along with the increase in BUN and creatinine in patients with COVID-19, highlight the importance of patient care to prevent kidney damage and further care for patients with kidney diseases.

Furthermore, LDH was also significantly associated with an increase in COVID-19 severity in patients with diabetes ($P=0.013$). Another study reported the association of increased LDH in patients with diabetes and COVID-19 at admission with the rate of intubation and 7-day death (20). The results of a meta-analysis on patients with COVID-19 in Wuhan also support our findings in this regard (21). Contrary to the heterogeneity of the studies included in the meta-analysis and the fact that it covered few areas, the prevalence of 62.7% increased LDH in critically ill patients compared to 28.1% in non-critical patients mentioned in that study can confirm our results (21).

Our results also showed a significant increase in troponin with the increase in COVID-19 severity ($P=0.002$). The results of a meta-analysis by Wu et al, similar to our results, showed that troponin levels were associated with the severity of COVID-19 (36). Zheng et al also suggested troponin as a prognostic factor for worse cases of COVID-19 severity (37). Increased troponin, which is a marker for cardiac injury in patients with COVID-19, was also associated with disease severity and mortality (38, 39). Cardiac injury in patients with COVID-19 can be the result of various factors such as the effects of cytokine storm and immune response, hypoxia and supply and demand imbalance, coagulopathy, and direct virus damage to heart cells via the ACE2 receptor on the surface of these cells (40, 41). In general, troponin is a marker for heart damage, and can also predict the condition of patients with COVID-19; thus, we recommend more care in patients with increased troponin as a prognostic factor for these patients.

In our study, the increase in respiratory rate per minute was significantly associated with COVID-19 severity in patients with diabetes ($P=0.002$). Our results also showed a significant reduction in O2 saturation associated with

COVID-19 severity in patients with diabetes ($P=0.008$). In line with our study, Carlino et al showed increased respiratory rate and decreased O2 saturation in patients with COVID-19 admitted to the ICU (28). Respiratory rate and O2 saturation have been suggested in other studies as factors in the diagnosis of respiratory distress and COVID-19 severity (42, 43). Since severe pneumonia in patients with COVID-19 can lead to lung injury, respiratory rate and O2 saturation are important factors in determining respiratory distress (44). Similar to other studies, our results indicated that respiratory rate and O2 saturation are associated with the severity of COVID-19, suggesting further care for these patients.

We also examined other aspects of patients' laboratory factors and drug regimens, which did not reach significant levels due to low statistical power and small sample size (Tables 3 and 5). Failure to evaluate control measures in diabetic patients before hospitalization due to COVID-19 was the main limitation of our study.

Although our results are fairly similar to the results of other studies on patients with COVID-19 without underlying diseases, our study specifically examined patients with diabetes and COVID-19. Since these findings represent a small portion of the community, they can be generalized to the larger general population and be used to make decisions to treat patients with diabetes and COVID-19.

Conclusion

There was a significant association between disease severity and BUN, creatinine, AST, LDH, and troponin levels in diabetic patients with COVID-19. There was no significant association between different groups of severity and comorbidities.

Conflict of Interest Disclosures

The authors have no conflict of interests.

Acknowledgements

This work was supported by Clinical Research Development Center of Hormozgan University of Medical Sciences, Bandar-Abbas, Iran. We are sincerely thankful to the counsellors in the center and Tayyebeh Zareii in Clinical Research Development Center of Shahid Mohammadi Hospital.

Ethical Statement

This study used the COVID-19 registry (RCovidRH) information which has been registered on Hormozgan University of Medical Sciences and ethically approved with the code HUMS. REC.1398.482. and the grant number of 980464.

Author's Contributions

HRS and MKJ contributed in conception, design, and statistical analysis. Other authors contributed in data collection and manuscript drafting. MKJ supervised the study. All authors approved the final version of the manuscript.

Funding/Support

Clinical Research Development Center of Hormozgan University of Medical Sciences, Bandar-Abbas, Iran funded this study.

Informed Consent

All patients signed an informed consent letter.

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