Clinical, Laboratory and Radiological Predictors of Unfavorable Hospital Admission Course for Diabetic Patients with COVID-19

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ABSTRACT

Background: Patients with diabetes mellitus infected with the new coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), are at risk of high morbidity and mortality.

Objective: Our study aimed to address the clinical, laboratory and radiological predictors of hospital admission course for patients with diabetes mellitus with COVID19 infection at the time of admission.

Patients and Methods: This was a single center, retrospective study of patients with diabetes mellitus (DM) admitted with COVID-19 infection. Patients with unfavorable admission course were compared with those of favorable course regarding patient characteristics, clinical presentation, results of laboratory investigations and chest CT severity score. Univariate and multivariate analysis associated with the unfavorable course was performed.

Results: Among 141 patients with DM admitted with COVID19, 44 patients had unfavorable course. Those with the favorable course were significantly younger (53.3±16.4) vs (67.3 ±15.8) in the unfavorable course group, multivariate analysis revealed that age more than 65, presence of hypertension, CT severity scoring, high HBA1c, AST, IL6, oxygen saturation less than 93% and low lymphocyte count were the independent predictors of the unfavorable hospital admission course.

Conclusions: Our finding suggests that old age, presence of hypertension, hypoxia at presentation, in addition to high HBA1c, AST, IL6, CT severity scoring and low lymphocyte count were significant predictors of unfavorable admission course in COVID19 patients with diabetes.

Keywords: Coronavirus, COVID19, Diabetes mellitus, Predictors, Prognosis.

INTRODUCTION

In December 2019, an outbreak of pneumonia in Wuhan city in China caused by a new coronavirus SARS-CoV-2 and the disease was named COVID-19 (coronavirus disease 2019). It has been spread quickly and pandemic was declared by WHO on March, 2020[(1,2)]. The clinical presentation of COVID-19 range from being asymptomatic to severe lower respiratory tract disease, the more severe form of the disease is more common in elderly patients and those who have comorbidities like diabetes mellitus, hypertension and cardiovascular disease [(3)].

Patients with diabetes mellitus are at risk of high morbidity and mortality from many infectious diseases, Moreover, diabetes mellitus has been associated with increased risk of death from pneumonia related complications [(4,5)]. Recent studies showed that diabetes mellitus increase mortality in patients with COVID19[(6)], and up to 20-30% of non-surviving patients with COVID-19 had preexistent diabetes mellitus[(3,7)].

To our best knowledge, very few publications can be found which address one or more of risk factors for mortality in patients with diabetes mellitus infected with COVID-19. However, it is still unknown the factors which associated with poor prognosis and mortality in the admitted diabetic patient. Our study aimed to study the clinical, laboratory and radiological predictors of hospital admission course for patients with diabetes mellitus infected with COVID19 at time of admission.

PATIENTS AND METHODS

In this retrospective study, we included all adult type 2 diabetic patients (141 patients) with laboratory-confirmed COVID-19 admitted to Zagazig University Hospital between 20 May 2020 and 20 July 2020.

A confirmed case was defined as a positive result on real time PCR assay of nasopharyngeal swab specimens for SARS-CoV-2. In our study, we aimed to identify the clinical, laboratory and radiological markers predicting the unfavorable course of the disease at the initial assessment of diabetic patients admitted to hospital for management of COVID19.

From medical records of admitted patients, we collected the data of:

- Patient characteristics at admission: age, gender, body mass index, job, smoking status, other comorbidities (hypertension, hyperlipidemia, asthma, cardiac or liver disease…..).
- Clinical presentation at admission: fever, cough, fatigue, dyspnea, diarrhea, sore throat and headache.

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- Measurements of vital signs (blood pressure, pulse, respiratory rate and temperature) and of oxygen saturation.
- Laboratory investigations: complete blood count (CBC) was identified by cell counter (Sysmex XN2000, Japan), liver function test, creatinine, urea, C-reactive protein (CRP), fasting blood sugar (FBS), HBA1c, 2 hours postprandial sugar (PPS), LDH were done on Cobas 6000 auto analyzer (Roche diagnostic, Germany), prothrombin time and fibrinogen were measured on blood coagulation analyzer, model CA1500 (Sysmex, Japan), interleukin 6 (IL-6) levels were analyzed by ELISA sandwich technique, using commercially available kit (Quantikine, R and D system, Inc. , Minneapolis, USA), D-dimer, sodium, potassium, arterial blood gases, ESR and real-time polymerase chain reaction (RT-PCR) for SARS-CoV-2.

Molecular detection of SARS CoV-2 (RT-PCR):

Nasopharyngeal swabs were collected for SARS-CoV-2 real time reverse transcription polymerase chain reaction. Extraction of viral RNA was performed by using QIAamp. DNA blood minikit, from QIAGEN (Switzerland). The extracted nucleic acid was reverse transcripted into cDNA, quantitative real time PCR analysis was performed using TaqMan real time PCR method. A house keeping gene (IPC) as an internal control was used for calibration. The amplification process was done by using COVID 19 primer design kit, from GENESIG, and performed on QIagen-Rotor gene Q real time PCR instrument, Germany. During the operation, the probes annealed to three target sequences: ORF1ab, nucleocapsid (N) and spike (S), two of the three genes must be positive to consider the sample as positive for COVID19.

- Initial chest CT scan finding done to all patients at admission to diagnose and evaluate the severity of the disease, CT severity score (CT-SS) was estimated.

CT protocol:

Chest CT imaging was performed on a 16-detector CT scanner (Emotion; SIEMENS, Germany). The patients were examined in supine position. CT images were then acquired during a single inspiratory breath-hold. The scan started from the lung apex to the costophrenic angles. We used the following parameters: 1.0 mm section thickness for reconstruction, 1.0 mm gap, tube voltage 120 kV, tube current 350 mAs, FOV 36.8×42.9 cm.

Chest CT image analysis:

CT scans were reviewed in thin-sections to reach a decision. The predominant patterns on CT scans were categorized as ground glass opacification (GGO), crazy-paving pattern, consolidation, and linear opacities.

Other minor signs which are not typical for Covid-19 were also observed including bronchiectasia, cavitation, pleural effusion, pericardial effusion, pneumothorax and mediastinal lymphadenopathy. The pattern of the distribution of the pulmonary lesions was evaluated as peripheral (predominantly subpleural), central and diffuse. The number of lobes involved was determined also. To determine the severity of disease, we depended on the main findings of GGO, crazy-paving pattern and consolidation. Both lungs were divided into five zones (3 right lobes and two left lobes). This included right upper lobe, right middle lobe, right lower lobe, left upper lobe, and left lower lobe.

Every lung lobe was assigned a score according to the percentage of involvement as the following:

- Score 0: corresponding to 0% involvement.
- Score 1: less than 5% involvement.
- Score 2: involvement of 5% to less than 25 %.
- Score 3: involvement of 25 % to less than 50 %.
- Score 4: involvement of 50 % to less than 75 %.
- Score 5: involvement of 75 % or more.

The summation of scores of the 5 zones resulted in a semi-quantitative evaluation for overall lung involvement (maximal CT score for both lungs was 25). For each patient the CT severity score was estimated[8].

The unfavorable course include: death during hospital admission and the need for ICU admission due to multiorgan failure or the need for mechanical ventilation during their hospital admission.

Ethical consent: An approval of the study was obtained from Zagazig University Academic and Ethical Committee.

Statistical Method

All data were analyzed using SPSS version 20 software (SPSS Inc., Chicago, IL, USA). Continuous data were expressed as the mean ± SD and median (range), and the categorical data were presented as a number (percentage). Continuous data were checked for normality by using Kolmogorov-Smirnov test. Continuous variables with or without normal distribution between favorable and unfavorable admission course were compared using student t-test and Mann–Whitney U test, respectively.

Categorized data of the two groups were compared using the Chi-square (χ^2) test. Odd ratio (OR) was used to estimate risk in univariate analysis with 95 % confidence interval. If interval contain 1, the P value of test statistics was non-significant. A Stepwise logistic regression analysis was performed to assess the influence of various risk factors on hospital admission course in multivariate model. P-value of less than 0.05 was considered as statistically

significant. P < 0.001 was considered highly statistically significant and P > 0.05 was considered non-statistically significant.

RESULTS

A total of 141 patients with diabetes mellitus confirmed with COVID-19 were included in the study. In terms of the outcome, 17 patients died during hospital admission, 22 patients were mechanically ventilated during hospital admission, 5 patients were admitted to ICU due to multiorgan failure, the remaining 97 patients had favorable admission course. Those with the favorable course were significantly younger compared to the unfavorable course group. Those who experienced unfavorable hospital admission courses had significantly higher BMI and a higher prevalence of hypertension, hyperlipidemia and chronic pulmonary disease (Table 1).

Table (1): Baseline characteristics of the study population.

	Favorable course (n=97)	**Unfavorable course (n=44)**	**p- value**
Age (years) Mean±SD	53.3±16.4	67.3 ±15.8	<0.001
Gender, N (%) -Male -Female	 51 (52.57%) 46 (47.42%)	 21 (47.7%) 23 (52.27%)	>0.05
BMI (kg/m2) Mean±SD	29.6±2.45	34.6±3.71	<0.05
Smoking N (%)	21 (21.65%)	9 (20.45%)	>0.05
Hypertension N (%)	46 (47.42%)	32 (72.72%)	<0.005
Chronic lung disease N(%)	23 (23.7%)	16 (36.36%)	<0.05
Hyperlipidemia N (%)	38 (39.17%)	26 (59.1%)	<0.005

Fever and cough were the most common presenting symptoms of both groups, yet those with unfavorable course were more likely to present with shortness of breath, tachycardia and tachypnea at admission. Oxygen saturation at presentation was significantly lower in the unfavorable course group compared to favorable course. The baseline concentration of LDH, CRP, IL6, FBS, HBA1c, urea, creatinine, total WBCs count, neutrophil count, ALT, AST, fibrinogen and prothrombin time were significantly higher the in unfavorable course group, while lymphocyte and eosinophil counts were significantly lower compared to favorable course group. There were significant differences between the CT severity scoring between favorable course group and unfavorable course group. More than 90% of patients with unfavorable hospital admission course had an affection of four or five lobes at initial CT scan in contrast to only 46.3% of favorable course group who were presented by four or more lobe affection (Table 2). Figures (1, 2) showed CT scan and CT severity score for two patients with favorable and unfavorable course respectively.

Table (2): Clinical laboratory and radiological parameters of the diabetic patients at admission.

	Favorable course (n=97)	**Unfavorable course (n=44)**	**p- value**
Clinical presentation at admission N(%)			
Fever	76 (78.35 %)	35 (79.54%)	>0.05
Cough	50 (51.54%)	23 (52.27%)	>0.05
Dyspnea	46 (47.42%)	28 (63.63%)	< 0.001
Diarrhea	8 (8.24%)	5 (11.36%)	>0.05
Headache	19 (19.58%)	8 (18.2%)	>0.05
Fatigue	66 (68%)	31 (70.45%)	>0.05
Mean arterial blood pressure (mmHg)	93 (86–107)	95 (85–107)	>0.05
Heart rate (bpm)	81 (73-95)	89 (74 -102)	< 0.05
Respiratory rate (rpm)	19 (16-22)	22 (18- 29)	< 0.05
O_2 saturation %	0.95 (0.94-0.97)	0.90 (0.86-0.95)	< 0.001
IL6 (pg/mL)	14.6 (8.3-25.9)	32.1 (16.3-75.1)	< 0.001
FBS (mg/dL)	178 (149-213)	203 (158-327)	< 0.001
HBA1c %	7.8 (6.5-10.3)	9.3 (6.9-12.7)	< 0.001
CRP (mg/l)	10.72 (5.23, 19.94)	67.61 (25.59- 121.36)	< 0.001
ESR (mm/hr)	47.0 (22.2–67.6)	53.0 (33.3–78.3)	>0.05
LDH (U/L)	439 (373.2–579.6)	588 (406.2–748.3)	0.008
Creatinine (mg/dl)	1.21 (0.72-1.45)	1.76(0.69-3.45)	0.01
Urea (mg/dl)	23.2 (13.42- 39.35)	37.36 (21.5, 56.5)	0.02
D-dimer (ug/mL)	2.25 (0.78, 6.25)	3.28 (0.68, 8.43)	>0.05
WBC count (10^9/L)	4.92 (3.95-7.23)	7.14 (4.21-9.92)	0.01
Lymphocyte count (10^9/L)	2.16 (1.04-3.08)	0.96 (0.58-1.45)	< 0.001
Neutrophils count (10^9/L)	2.43 (1.95-3.70)	6.32 (2.35-9.35)	< 0.05
Eosinophil count ((10^9/L)	1.32 (0.27- 2.90)	0.21 (0-0.43)	< 0.05
Hemoglobin (g/dl)	11.9 (11.2–15.0)	12.3 (11.–16.1)	>0.05
Albumin (g/dL)	3.82(3.25-4.27)	3.96(3.33-4.29)	>0.05
ALT (U/L)	32.4 (17.6- 45.4)	45.2 (26.3- 63.4)	< 0.05
AST (U/L)	36.5 (28.4- 59.3)	62.3 (34.2- 91.2)	< 0.01
Total bilirubin (mg/dL)	0.92 (0.72-1.23)	1.11 (0.83, 1.42)	>0.05
Fibrinogen (g/L)	3.7 (3.2 - 4.28)	4.55 (3.25- 5.15)	< 0.05
Prothrombin time (seconds)	12.4 (11.4–12.9)	13.2 (11.6–14.8)	0.009
Sodium (mmol/L)	138.3(135.2-144.9)	139.2(134.4- 143.7)	>0.05
Potassium (mmol/L)	3.9 (3.65- 4.36)	3.61 (3.34.4.23)	>0.05
CT severity score (CT-SS)			
Mean±SD	7.62±2.66	14.43±2.69	<0.001
Minimum	3	10	
Maximum	13	19	
Number of lobes affection			
1 lobe	0	0	
2 lobes	3 (3.09%)	0	< 0.001
3 lobes	37 (38.14%)	4 (9.09%)	< 0.001
4 lobes	36 (37.11%)	14 (31.8%)	>0.05
5 lobes	9 (9.27%)	26 (59.09%)	< 0.001

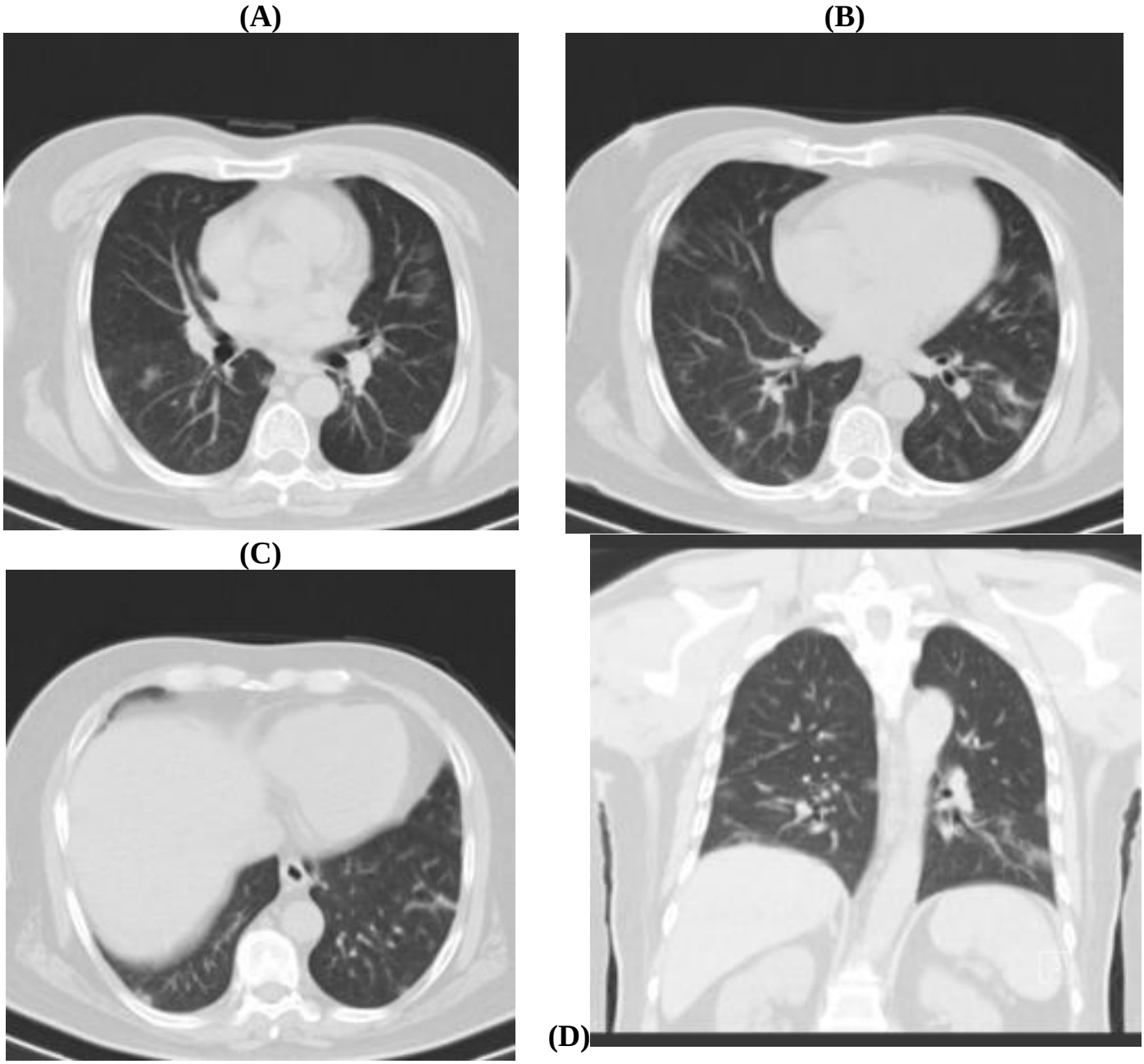

Figure (1): (A, B, C axial and D coronal): Male patient 50 y. Unenhanced chest CT scan shows bilateral and peripheral distribution of ground-glass opacities more dominant in the lower lobes. CT-SS was 7. The patient showed favorable course.

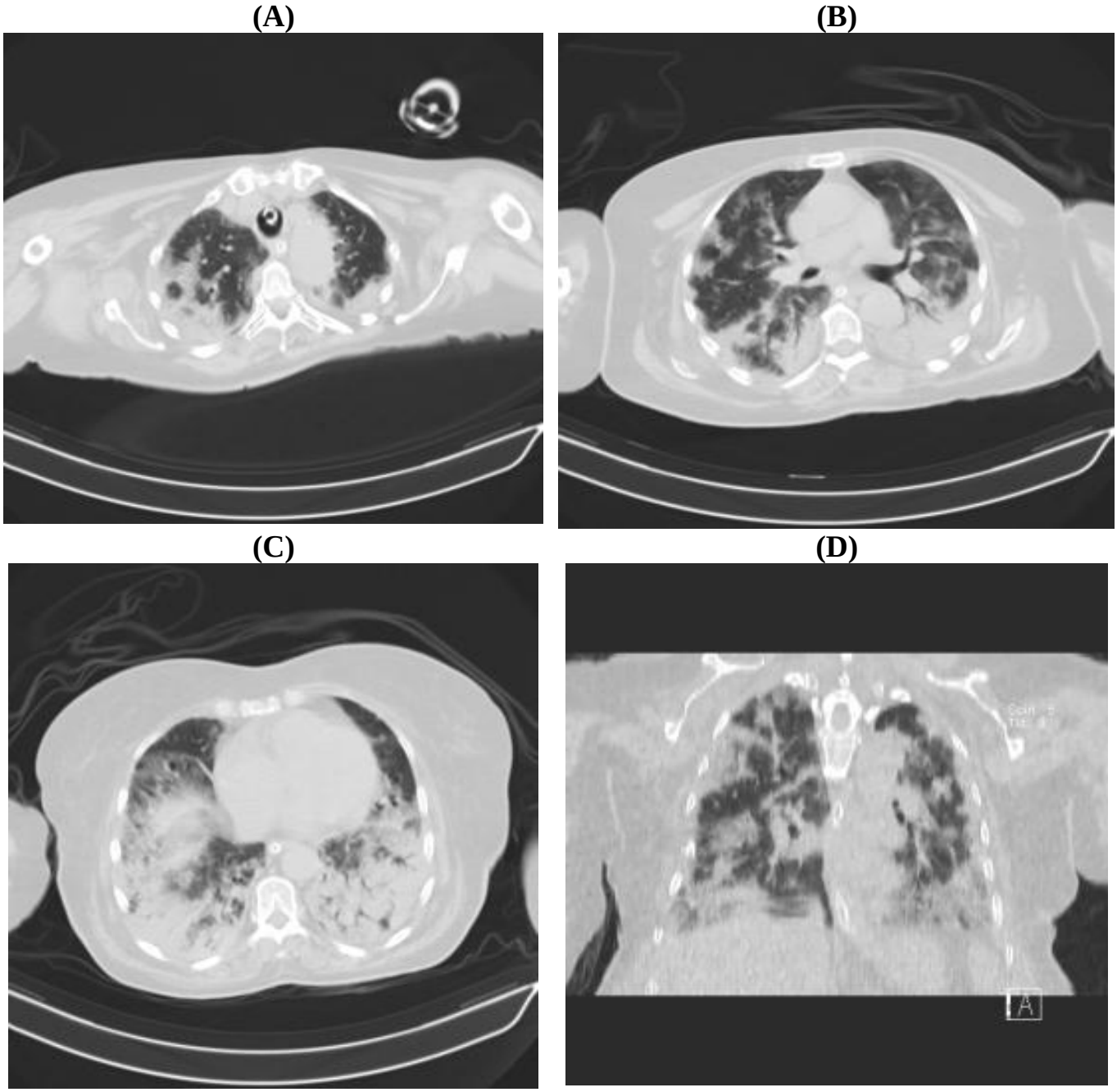

Figure (2): (A, B, C axial and D coronal): Female patient 62 y. Unenhanced chest CT scan shows bilateral and peripheral distribution of ground-glass opacities more dominant in the lower lobes and mounting to consolidation. Endotracheal tube is seen. CT-SS was 21. The patient showed unfavorable course and died.

Univariate analysis (Table 3) revealed significant increase in the risk of unfavorable admission course in patients older than 65, hypertensive, BMI more than 30, hypoxia with SPO_2 less than 93%, lymphopenia, higher HBA1C, WBCs count, IL6, ALT, AST, prothrombin time, creatinine and CT severity scoring. Based on stepwise multivariate logistic regression analysis (Table 4), age more than 65, presence of hypertension, high CT severity scoring, high HBA1c, AST, IL6, oxygen saturation less than 93% and low lymphocyte count were the independent predictors of unfavorable hospital admission course.

Table (3): Risk estimation for possible risk factors for unfavorable outcome among diabetics.

	OR	95% CI			p
Age > 65 year	2.91	1.62	-	4.72	< 0.001
Male sex	1.19	0.78	-	1.24	>0.05
BMI more than 30	1.72	1.21	-	2.37	0.009
Hypertension	3.77	2.61	-	4.73	< 0.001
Chronic lung disease	1.12	1.03	-	1.33	<0.05
hyperlipidemia	1.05	0.96	-	1.11	>0.05
SPO_2 less than 93%	0.93	0.91	-	0.96	< 0.001
HBA1c level	2.41	1.9	-	3.62	< 0.001
WBC count (10^9/L)	1.34	1.1	-	1.78	0.01
Lymphocyte count (10^9/L)	0.47	0.12	-	0.79	< 0.001
Prothrombin time (seconds)	1.21	1.01	-	1.31	<0.05
IL6 (pg/mL)	1.68	1.43	-	2.12	< 0.001
CRP (mg/l)	1.03	0.89	-	1.34	>0.05
LDH (U/L)	1.09	0.78	-	1.37	>0.05
ALT (U/L)	1.29	1.12	-	1.63	0.02
AST (U/L)	1.43	1.32	-	1.71	< 0.001
Creatinine (mg/dl)	1.12	1.01	-	1.22	<0.05
eosinophil count (10^9/L)	1.02	0.89	-	1.19	>0.05
CT severity score	1.81	1.12	-	3.04	< 0.001

Table (4): Multivariate logistic regression analysis for possible risk factors as predictors of unfavorable outcome among diabetics.

	OR	95% CI			p
Age > 65 year	1.92	1.32	-	3.22	<0.05
BMI more than30	1.17	0.98	-	1.27	>0.05
Hypertension	1.98	1.62	-	3.11	< 0.001
Chronic lung disease	1.03	0.98	-	1.14	>0.05
SPO2less than 93%	0.95	0.93	-	0.98	< 0.001
HBA1c level	2.21	1.86	-	3.71	< 0.001
WBC count (10^9/L)	1.18	0.95	-	1.33	>0.05
Lymphocyte count (10^9/L)	0.63	0.24	-	0.87	0.01
Prothrombin time (seconds)	1.09	0.96	-	1.13	>0.05
IL6 (pg/mL)	1.82	1.53	-	2.47	< 0.001
CRP (mg/l)	0.98	0.87	-	1.16	>0.05
LDH (U/L)	1.05	0.82	-	1.19	>0.05
ALT (U/L)	1.03	0.91	-	1.15	>0.05
AST (U/L)	1.13	1.02	-	1.29	< 0.001
Creatinine (mg/dl)	1.02	0.96	-	1.09	>0.05
CT severity score	1.75	1.23	-	2.48	< 0.001

DISCUSSION

In the present study, we compared the characteristics of patients with diabetes mellitus infected with COVID-19 who had unfavorable hospital admission course with those who has sound admission course and we analyzed the risk factors that predict the worse admission course for the patients. Our study showed that the independent risk factors associated with increased in-hospital mortality, ICU admission due to multiorgan failure or mechanical ventilation were the level of HBA1c, underlying hypertension, age more than 65 years, CT severity scoring, oxygen saturation less than 93, lymphopenia and high IL6, AST at time of admission.

In our study, the patients with the unfavorable course were significantly older, had higher BMI had many comorbidities like hypertension, hyperlipidemia, chronic pulmonary disease than the other group. Recent studies have demonstrated older age as a risk factor for mortality in patients infected with COVID-19 [3, 9, 10]. The age dependent defects in humeral and cellular immune function and the amplified inflammatory cytokines production may cause a poor immune response to viral replication [11]. Likewise, the unfavorable prognosis of elderly patients with diabetes

may be due to the association of many comorbidities, and the poor glycemic control.

Although fever and cough were common presenting symptoms in both groups, yet dyspnea tachypnea, tachycardia and low oxygen saturation were significant common presentations in the unfavorable course group. Our results showed that the presence of hypoxia at the time of admission was an independable predictive factor for the unfavorable course. Hypoxia at presentation should alert that the patient might benefit from early hospital admission, close monitoring, oxygen therapy to improve prognosis and decrease mortality.

Previous studies showed that DM increased the risk of mortality in patients infected by COVID-19 [6,12,13]. Moreover, the degree of DM control is an important predictor of the hospital admission course as showed by our study. Our results showed that a high HBA1c level is an independent risk factor for poor prognosis of admitted patients infected with COVID-19. **Guo *et al.*** [6] stated that hyperglycemia increases the risk of excessive inflammatory response and release of enzymes responsible for tissue damage.

In this study, we compared the laboratory characteristics of patients with favorable and unfavorable hospital admission course at admission. IL 6 was significantly higher in the unfavorable group. In quantifying the risk of poor clinical outcomes, we showed that high IL6 at the time of admission increases the odds of unfavorable hospital admission course significantly. This result support the concept of cytokine storm resulted from the release of inflammatory factors during COVID-19 infection plays a critical role in the progression to severe form of the disease[14].

In our study, lymphopenia and eosinopenia were more significantly reported in patients with unfavorable course group in contrast to neutropenia, which was more common in favorable course group. Multivariate analysis revealed that lymphopenia at presentation is an independent predictor of unfavorable admission course, this finding was in concordance with previous study stated that lymphopenia increases the risk of mortality in diabetic patients infected with COVID19[10]. Severe form of infection with COVID19 is associated with the destruction of lymphocytes, cytokine storm and defect in cellular immune response[15], which play roles in the evolution of acute respiratory distress syndrome.

Based on our finding, serum AST and ALT were significantly higher in the unfavorable course group, moreover, multivariate analysis revealed that high AST level at admission was an independent risk predictor for unfavorable hospital admission course, this may support the concept of infection of liver cells with COVID-19[16] and hypoxia associated liver cell injury in critically ill patients infected with COVID19[17].

Depending on chest radiographs, there were large numbers of false negative results due to lack of early abnormalities**.** Chest CT with thin-section is more sensitive than chest radiography, showing abnormal changes in the lung parenchyma in early stages of disease[18,19], so chest CT has become an important diagnostic tool during the pandemic of COVID-19[20]**.**

In this study, we used a semi-quantitative scoring method using the amount of lung affection of the 3 right lobes and 2 left lobes to represent the degree of lung affection. We found that the CT-SS was significantly higher in cases with the unfavorable course when compared to cases with the favorable course; also the number of lobes affection is higher in cases with the unfavorable course when compared to cases with the favorable course. This is in agreement with **Yang *et al.*** [8]**,** who reported that CT-SS with significantly higher in severe cases of COVID-19 than in mild cases.

Early recognition of patients at risk of poor prognosis during initial assessment helps to allocate the resources to improve the prognosis, monitoring process and mortality reduction of those at risk especially during COVID1-19 outbreak with limited resources.

To our knowledge, this is the first study to investigate the predictors either clinical laboratory or radiological for the course of hospital admission for patients with DM and COVID19, yet some limitation of the study related to the retrospective nature of the study and relatively small number of patients. Further multicenter studies with inclusion of a large number of patients should be performed in the future to clarify all predictors of the unfavorable course of COVID19 in different groups of patients.

CONCLUSIONS

Our findings suggest that significant predictors of unfavorable admission course in COVID19 patients with diabetes were old age, presence of hypertension, hypoxia at presentation, in addition to high HBA1c, AST, IL6, CT severity scoring and low lymphocyte.

Competing interests: The authors declare that they have no competing interests.
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