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Factors Affecting Outcomes of COVID-19 Infection among Older Adults with Type 2 Diabetes: A Single Center, Cross-Sectional Study

ABSTRACT

Objective: COVID-19 infection and the factors affecting it are major concerns worldwide. This retrospective study aimed to investigate clinical, laboratory and radiological characteristics associated with disease severity and hospitalization among older adults with type 2 diabetes mellitus (T2D) with COVID-19.

Materials and methods: A retrospective case series study was conducted to review the records of older adults with T2D infected with COVID-19. Sociodemographic, COVID-19-related data, laboratory tests at the time of COVID-19 diagnosis and CT findings were collected. Bivariate and multivariate regression analysis were done to determine the predictors of the studied outcome, either hospitalization or complete recovery.

Results: A total of 343 patients' records were reviewed, with a mean age of 73.6 ± 6.4 years. Most of patients had fever and cough at the time of diagnosis and ground glass opacities was found on CT in 62.1% of patients. Hospitalized patients had higher duration of diabetes, suffered more from dyspnea, body aches and chest pain, had higher HbA1c, CRP and ferritin and lower lymphocytes and hemoglobin. Fasting plasma glucose and HbA1c positively affected the duration from onset of symptoms till resolution, while hemoglobin level negatively affected it. Logistic regression analysis revealed that duration of diabetes, HbA1c, ferritin and dyspnea were significant predictors of hospitalization.

Conclusions: Among older adults with T2D infected with COVID-19, poor glycemic control is associated with higher risk of hospitalization and longer duration till recovery of symptoms. Longer duration of diabetes, high serum ferritin and the presence of dyspnea are associated with higher risk for hospitalization among these patients. (Clin Diabetol 2023; 12; 4: 239–246)

Keywords: diabetes, COVID-19, older adults, hospitalization

Introduction

COVID-19 infection is caused by an RNA virus called severe acute respiratory syndrome coronavirus 2 which was first discovered in 2019 in China [1–3]. It spread so fast abroad, and The World Health Organization announced it as a pandemic in March 2020 [4].

Diabetes mellitus (DM) is a major health issue affecting the entire world [5]. In 2019, the International

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Diabetes Federation (IDF) declared Egypt as one of the ten countries with the highest number of patients with DM, with 9 million affected individuals [6].

DM is challenging in the era of COVID-19 pandemic. The prevalence of diabetes among ICU patients hospitalized for COVID-19 is 3 times higher, and the number of deaths is at least twice as high as in people without DM [7]. Diabetes can affect the immune responses of patients through many mechanisms that can cause poor outcomes [8].

Old age may be a risk factor for bad prognosis of COVID-19 infection and the mortality rate rises with age [9, 10]. With the underlying comorbidities, older adults are more susceptible to COVID-19 and its complications [11, 12].

The symptoms of COVID-19 infection vary from being asymptomatic to having severe illness and death [13]. High proportion of severely ill patients have one or more preexisting comorbidities such as hypertension, DM, obesity, dyslipidemia, and cardiovascular disease [14].

Diabetes shows higher prevalence among adults over 65 years compared to those under 65 years and it is expected that greater proportion of older adults with COVID-19 infection will also have DM [15]. The problems facing older adults with DM infected with COVID-19 reflect the interaction of the problems of DM, COVID-19, and problems of DM, COVID 19 and ageing [15].

Linking the state of glycemic control with COVID-19 infection progression has been suggested. First, improper glycemic state causes disturbed cytokine response and inadequate immune response [16]. Also, increased accumulation of advanced glycation end products (AGEs) leads to loss of pulmonary capacity [17]. Lastly, comorbidities such as cardiovascular diseases, overweight and hypertension are known risk factors for severe COVID-19 [18].

When older adults with DM are infected with COVID-19, the management strategy of DM may need to be modified to face the probable outcomes. With no adverse effects on respiratory systems, insulin is advised to manage severely ill individuals with COVID-19 [19].

Identifying the risk factors of COVID-19 progression and early prediction of disease course are very important as they allow preventative measures in older adults with DM to decrease the occurrence of severe outcomes.

Both DM and old age are expected to affect the outcome of COVID-19 infection and lead to hospitalization. Depending on this hypothesis the current study aims to identify the clinical, laboratory and radiological characteristics associated with disease severity and hospitalization among older adults with type 2 diabetes (T2D) infected with COVID-19.

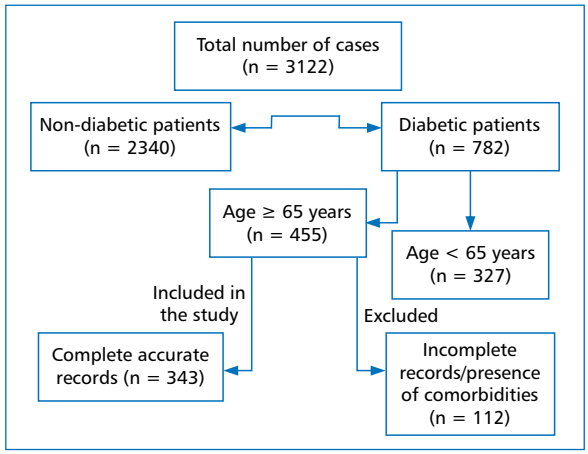

Figure 1. Flow Chart of the Reviewed Records Included in the Study

Methods

Study design and setting

A retrospective case series study design was conducted to review the electronic medical records of older adults with T2D who were examined at Alexandria University Hospitals and were diagnosed to have COVID-19 infection requiring home isolation and were followed during the isolation. Using a random sample technique, all eligible records of older adults with T2D diagnosed with COVID-19 between September 2020 and September 2021 were reviewed and included in the study (Fig. 1). Inclusion criteria included patients with T2D aged 65 years or more infected with COVID-19 and requiring home isolation, while exclusion criteria included patients with DM younger than 65 years, having advanced renal, hepatic, or cardiac diseases or suffering from any type of malignancy in addition to patients with severe COVID-19 infection requiring immediate hospitalization. The patients' medical records were reviewed in detail by three experienced physicians (M. G. Abdrabo, A. M. Mohsen and A. Y. El Feky).

The T2D status was designated based on the patient's medical history, based on the diagnostic criteria of the American diabetes association by meeting any one of the following: 1) Fasting plasma glucose level ≥ 126 mg/dL; 2) Plasma glucose level ≥ 200 mg/dL after 2 hours of a 75-g oral glucose load in a glucose tolerance test; 3) Random plasma glucose level ≥ 200 mg/dL in patients with classic symptoms of hyperglycemia; 4) Glycated hemoglobin (HbA1c) ≥ 6.5% [20].

Data collection tool

The records of patients were reviewed using a checklist formed of two sections. The first section included sociodemographic data (age, sex, and duration of diabetes). Second section included data regarding the COVID-19 infection such as presenting symptoms of COVID-19, time of onset, time to recovery, laboratory tests at time of COVID-19 diagnosis [fasting plasma glucose (FPG), determined by the glucose hexokinase method], HbA1c (determined by high-performance liquid chromatography using Tosoh automated G8 analyzer), complete blood count (CBC) results (analyzed by Sysmex XN-1000), C-reactive protein (CRP) (determined by Siemens BN ProSpec analyzer by nephelometry), D-dimer (analyzed by Sysmex CS 2100i using scattered light detection method), lactate dehydrogenase (LDH) (determined by Siemens Advia Chemistry Analyzer) and serum ferritin (analyzed by ADVIA Centaur using direct chemiluminescent immunoassay) and computed tomography (CT) scan findings.

The outcome of infection was determined either complete recovery of infection or need of hospitalization. Fifty-six studied patients (16.3%) were hospitalized and 287 patients (83.7%) had complete recovery from infection.

Ethical consideration

This study was approved by the Ethics Committee of Faculty of Medicine, Alexandria University, Egypt (IRB No.: 00012098). The study was performed in accordance with the international ethical guidelines of the Declaration of Helsinki. The privacy, anonymity and confidentiality of data were maintained.

Statistical analysis

The collected data was wrangled, coded, and analyzed using the SPSS software (Armonk, NY: IBM Corp version 25.0). The quantitative variables were expressed using mean ± SD whereas categorical data were presented in number and percentage. A chi-square test was used to estimate the difference between the categorical variables; and the patients were categorized based on the outcome of COVID-19 infection: recovery or hospitalization. Fisher exact probability was used in cases of invalid chi-square test. Independent sample t test was used to determine whether there are any statistically significant differences between the means of the studied groups. Univariate binary logistic regression model was conducted using ten variables: age, FPG, duration of diabetes, HbA1c, CRP, ferritin, lymphocytes, dyspnea body aches, and CT findings. The significant variables in the univariate logistic regression were entered into the multivariate logistic regression model to estimate the significant predictors affecting hospitalization. Odds ratios and 95% confidence intervals (OR, 95% CI) were reported. Statistical significance was considered when $p < 0.05$.

Results

A total of 343 electronic medical records of older adult patients with T2D were reviewed in this study. The mean age was 73.6 ± 6.4 years, 51.6% (n = 177) of patients were females, and their mean duration of diabetes was 21.2 ± 8.0 years. Two hundred thirteen patients had other chronic illnesses other than DM: 85 patients were hypertensive, 23 patients had stable cardiovascular diseases, 19 patients had chronic renal impairment, 43 patients had stable liver disease, 15 patients had chronic pulmonary disease and 28 patients had other chronic illnesses. Most common COVID-19 symptoms at time of diagnosis were fever (n = 287, 83.7%), cough (n = 220, 64.1%), diarrhea (n = 114, 33.2%), anosmia (92, 26.8%) and dyspnea (n = 78, 22.2%). CT findings in the form of ground glass opacity (GGO) were found among 62.1% (n = 213) patients and the mean duration from onset to resolution of infection was 19.0 ± 7.02 days. Duration of DM was higher among hospitalized COVID-19 patients than recovered patients (23.1 ± 7.3 years compared to 20.8 ± ± 8.1 years), p = 0.05. Hospitalized COVID-19 patients suffered more from dyspnea (51.8% compared to 16.4% of recovered), $p < 0.001$, body aches (33.9% vs. 15.0%), p = 0.001 and chest pain (7.1% vs. 0.0%), p = 0.001 (Tab. 1).

The laboratory data of the older adults with T2D are illustrated in Table 2. Hospitalized COVID-19 patients with T2D had higher HbA1c than recovered patients (8.5 ± 1.0% vs. 7.1 ± 1.7%), $p < 0.001$, higher CRP level (60.1 ± 21.3 vs. 49.1 ± 27.4 mg/L), p = 0.001, lower hemoglobin (Hb) level (10.7 ± 1.6 g/dL vs. 11.3 ± 1.5 g/dL), p = 0.016, lower lymphocytes level (755.1 ± ± 273.8 cells/μL vs. 1159.7 ± 817.2 cells/μL), $p < 0.001$ and higher ferritin level (929.2 ± 218.9 vs. 421.7 ± ± 236.6 ng/mL). No significant difference was found regarding FPG, white blood cells count (WBC), LDH and D-dimer (p = 0.056, p = 0.082, 0.068 and 0.074 respectively).

In recovered non-hospitalized COVID-19 patients, the mean time till recovery was 17.2 ± 5.3 days. The duration from onset of symptoms till resolution was positively correlated with FPG (r = 0.204, p = 0.001) and HbA1c (r = 0.137, p= 0.02) and it was negatively correlated with Hb level (r = –0.162, p = 0.006) (Fig. 2).

Table 3 shows the univariate and multivariate logistic regression analysis of predictors affecting hospitalization of older adults with T2D who suf-

Table 1. Demographic and Clinical Symptoms of the Older Adults with T2D

	Total (n = 343)	Outcome resolution (n = 287)	Hospitalization (n = 56)	P#
Age [years]				
Mean ± SD	73.6 ± 6.4	73.5 ± 6.3	74.1 ± 6.7	0.544
Sex				
Male	166 (48.4%)	141 (49.1%)	25 (44.6%)	0.539
Female	177 (51.6%)	146 (50.9%)	31 (55.4%)	
Duration of diabetes [years]				
Mean ± SD	21.2 ± 8.0	20.8 ± 8.1	23.1 ± 7.3	0.05
Symptoms at diagnosis				
Ageusia (loss of taste)	21 (6.1%)	17 (5.9%)	4 (7.1%)	0.760
Cough	220 (64.1%)	190 (66.2%)	30 (53.6%)	0.071
Fever	287 (83.7%)	244 (85.0%)	43 (76.8%)	0.127
Dyspnea	76 (22.2%)	47 (16.4%)	29 (51.8%)	< 0.001*
Delirium	34 (9.9%)	25 (8.7%)	9 (16.1%)	0.092
Anosmia	92 (26.8%)	86 (30.0%)	6 (10.7%)	**0.003***
Vomiting	19 (5.5%)	14 (4.9%)	5 (8.9%)	0.212
Body aches	62 (18.1%)	43 (15.0%)	19 (33.9%)	**0.001***
Chest tightness	10 (2.9%)	10 (3.5%)	0 (0.0%)	0.377
Diarrhea	114 (33.2%)	108 (37.6%)	6 (10.7%)	**< 0.001***
Chest pain	4 (1.2%)	0 (0.0%)	4 (7.1%)	**0.001***
Abdominal pain	12 (3.5%)	12 (4.2%)	0 (0%)	0.228
CT findings (GGO)	213 (62.1%)	161 (56.1%)	52 (92.9%)	**0.001***

#Categorical variables were tested using chi-square and Fischer exact test, while continuous variables were tested using independent t-test; *Significant
CT — computed tomography; GGO — ground glass opacities; SD — standard deviation; T2D — type 2 diabetes

Table 2. Comparison between Resolution and Hospitalization according to Laboratory Data

	Total (n = 343)	Outcome		p#
		Resolution (n = 287)	Hospitalization (n = 56)	
FPG [mg/dL]				
Mean ± SD	183.5 ± 50.9	181.9 ± 51.2	191.6 ± 48.7	0.056
HbA1c [%]				
Mean ± SD	7.3 ± 1.6	7.1 ± 1.7	8.5 ± 1.0	**<0.001**
CRP [mg/L]				
Mean ± SD	50.9 ± 26.8	49.1 ± 27.4	60.1 ± 21.3	**0.001**
Hb [g/dL]				
Mean ± SD	11.2 ± 1.5	11.3 ± 1.5	10.7 ± 1.6	0.016
WBC [cells/μL]				
Mean ± SD	9869.5 ± 10308.5	9971.7 ± 11179.3	9345.9 ± 3250.7	0.082
Lymphocytes [cells/μL]				
Mean ± SD	1093.7 ± 770.1	1159.7 ± 817.2	755.1 ± 273.8	**< 0.001***
Ferritin [ng/mL]				
Mean ± SD	504.6 ± 299.7	421.7 ± 236.6	929.2 ± 218.9	**< 0.001**

#Independent t-test was used to test significance
CRP — C-reactive protein; FPG — fasting plasma glucose; Hb — hemoglobin; HbA1c — glycated hemoglobin; WBC — white blood cells

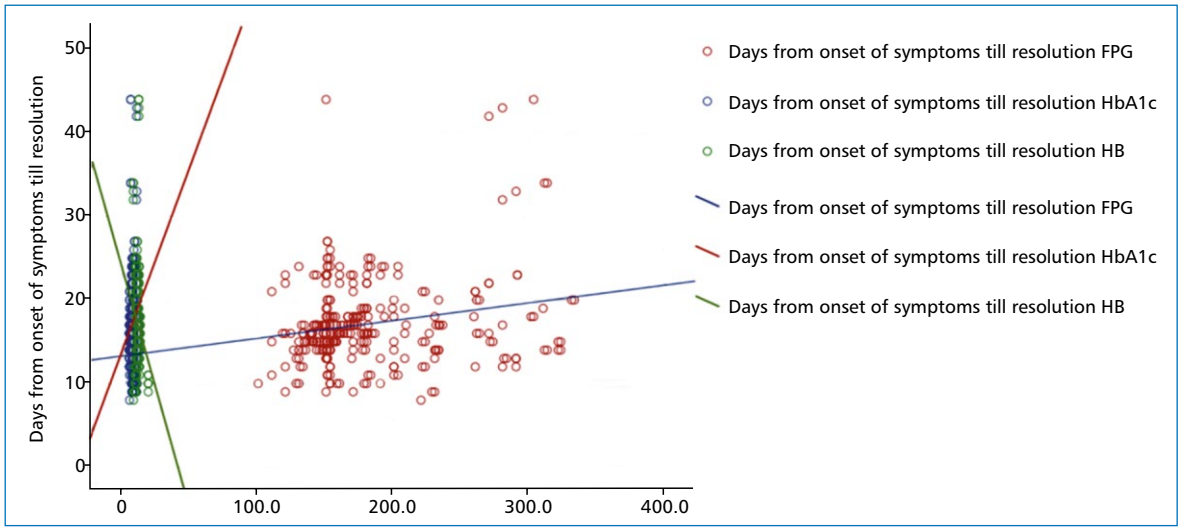

Figure 2. Scatterplot between Duration from Onset to Resolution with FPG (blue); HbA1c (red); hemoglobin (green)

Table 3. Univariate and Multivariate Logistic Regression Analysis for the Different Parameters Affecting Hospitalization

Independent variables	Univariate		95% CI for OR		Multivariate#		95% CI for OR	
	Sig.	OR	Lower	Upper	Sig.	OR	Lower	Upper
Age [years]	0.543	1.014	0.970	1.060				
FPG [mg/dL]	0.197	1.004	0.998	1.009				
Duration of diabetes [Years]	**0.05***	1.038	1.000	1.078	**0.009***	1.137	1.033	1.252
HbA1c [%]	**< 0.001***	1.642	1.370	1.969	**< 0.001***	3.703	2.117	6.476
CRP [mg/dL]	**0.006***	1.015	1.004	1.026	0.078	0.961	0.919	1.005
Ferritin [ng/mL]	**< 0.001***	1.008	1.006	1.010	**< 0.001***	1.011	1.008	1.015
Lymphocytes [cells/μL]	**< 0.001***	0.999	0.998	0.999	0.275	0.999	0.998	1.001
Dyspnea[A]	**< 0.001***	5.485	2.979	10.097	**0.004***	6.252	1.807	22.333
Body aches[A]	**0.001***	2.914	1.535	5.333	0.061	4.305	0.937	19.788
CT Findings (GGO)A	< 0.001*	10.174	3.584	28.881	0.595	2.058	0.144	29.345

#Significant variables in univariate analysis were included in the multivariate logistic analysis; [A]ref; No; Variables adjusted in multivariable analysis were the significant variables in univariate analysis: duration of diabetes, HbA1c, CRP, ferritin, lymphocytes, dyspnea, body aches and CT findings
CI — confidence interval; CRP — C-reactive protein; CT — computed tomography; FPG — fasting plasma glucose; GGO — ground glass opacities; HbA1c — glycated hemoglobin; OR — odds ratio

fered from COVID-19. Eight significant predictors in univariate analysis were duration of diabetes (OR = 1.04, 95% CI: 1.0–1.08, p = 0.05), HbA1c (OR = 1.64, 95% CI: 1.37–1.97, p < 0.001), CRP (OR = 1.02, 95% CI: 1.004–1.03, p = 0.006), ferritin (OR = 1.008, 95% CI: 1.006–1.01, p < 0.001), lymphocytes (OR = 0.999, 95% CI: 0.998–0.999, p < 0.001), dyspnea (OR = 5.49, 95% CI: 2.98–10.097, p < 0.001), body aches (OR = 2.91, 95% CI: 1.54–5.33, p = 0.001) and CT findings (OR = 10.17, 95% CI: 3.58–28.88, p < 0.001). These eight significant variables (duration of diabetes, HbA1c, CRP, ferritin, lymphocytes, dyspnea, body aches, and CT findings) were included in the multivariate logistic regression model, but only four significant predictors were detected: duration of diabetes (OR = 1.14, 95% CI: 1.03–1.25, p = 0.009), HbA1c (OR = 3.70, 95% CI: 2.12–6.48, p < 0.001), ferritin (OR = 1.011, 95% CI: 1.008–1.015, p < 0.001) and dyspnea (OR = 6.52, 95% CI: 1.81–22.33, p = 0.004).

Discussion

In this study we attempted to assess the risk factors associated with hospitalization among older adults with T2D suffered from COVID-19 infection. Older adult patients, especially with DM, are at high risk of COVID--19-related adverse outcomes and mortality which may be linked to the comorbidities and diseases that accumulate with age and diabetes-related chronic inflammation [21].

The results of the current study showed that 16.3% of the studied cases needed hospitalization. Hospitalized patients showed significantly higher levels of HbA1C, serum ferritin, CRP and the higher incidence of GGO on CT scan compared to non-hospitalized divisions. Also, hospitalized patients had lower levels of lymphocytes and hemoglobin compared to non-hospitalized patients.

The results demonstrated that poor glycemic control is an independent risk factor for hospitalization. Some previous studies demonstrated the relation between poor glycemic control and severity of COVID-19 outcomes. One study showed that among patients with DM, adjusted for age, sex, and diabetes duration and type, those with worse glycemic control were more likely to developed fatal or critical care unit-treated COVID-19 [22]. A meta-analysis by Prattichizzo et al. [23] reported that HbA1c was linearly associated with an increased COVID-19 mortality or worsening. Another multicenter cohort study showed that among patients with type 2 DM and COVID-19, the risk of hospitalization increased with incrementally higher HbA1c levels [24].

This may be related to number of risk factors that are associated with DM, including obesity, increased inflammatory markers, hypercoagulable state and complications of DM such as cardiovascular disease and renal impairment [25].

Longer duration of DM prior to COVID-19 infection was found to be an independent risk factor for hospitalization. This finding may be explained by higher probability of DM complications accompanying longer duration of DM.

Despite the fact that many studies reported that increased age is considered a risk factor for poor COVID-19 outcomes [9–11], our study did not show any significant age difference between hospitalized and non-hospitalized patients, which may be explained by the fact that all the included patients in our study were older adults whose ages were 65 years or higher and there was no significant variability in the age to allow comparison between different age groups.

Increased inflammatory response is a main feature of COVID-19 especially in those who develop severe illness. Studies demonstrated that multiple immune cells and inflammatory mediators are involved in the disease process [26, 27]. In the current study, univariate regression analysis showed higher CRP and ferritin levels were associated with higher risk for hospitalization. However, in multivariate logistic regression analysis only serum ferritin was associated with higher risk for hospitalization.

CRP is an acute phase inflammatory protein produced by the liver that may be elevated in several conditions, such as inflammation, cardiovascular disease, and infection [28]. Ferritin is described as an acute phase reactant, as well as a mediator in severe COVID-19 infection and it can be considered as an active participant in the "cytokine storm" that characterizes severe COVID-19 infection [29, 30].

A previous meta-analysis including 13 studies reported that an elevated CRP was associated with severe COVID-19 infection and the need for ICU admission and that higher serum ferritin levels were independently associated with ARDS, severe COVID-19 infection and mortality [31]. Similar to our study, a previous study reported that ferritin levels tend to increase with disease severity [32]. Another study by Devang et al. [33] reported that ferritin can predict mortality in severe COVID-19 patients.

Our results showed that hospitalized patients had lower hemoglobin levels and lymphocytic counts compared to non-hospitalized patients. Univariate regression analysis showed that lower lymphocytic count was associated with higher risk for hospitalization. However, no association was reported in multivariate analysis. Moreover, lower hemoglobin levels were correlated with longer duration till recovery in non-hospitalized patients.

A previous study showed that anemia and increased neutrophil-to-lymphocyte ratio at the time of hospital admission could be predictors for severe COVID-19 infection requiring ICU admission [34]. Another study using data derived from Korean nationwide longitudinal cohort reported that lymphopenia and its severity levels may serve as reliable predictive factors for COVID-19 clinical outcomes including mortality, need for intensive care, and oxygen requirements and that lymphopenia at the initial presentation of COVID-19 infection is associated with poor prognosis [35].

Interestingly, our results showed that the clinical picture of the patients at the time of diagnosis may predict the risk of hospitalization. In our study, hospitalized patients complained more from dyspnea, bone aches and chest pain compared to non-hospitalized patients and the presence of dyspnea at diagnosis was found to be a risk factor for hospitalization. On the other hand, non-hospitalized patients had higher incidence of anosmia and diarrhea.

Limitations

Our study has some limitations. First, the study was a single-center, retrospective, and observational study. Second, obesity has been demonstrated to play

a significant influence on COVID-19 outcomes. However, weight data were not available for all patients. Third, due to the retrospective study design, not all the laboratory tests were done to all patients, including those for insulin, C-peptide and IL-6. Therefore, their roles in predicting disease progression might be underestimated.

Conclusions

COVID-19 infection represents a great challenge in older adults with T2D. Poor glycemic control, assessed by HbA1c levels, is associated with higher risk of hospitalization and longer duration till recovery of symptoms. Moreover, longer duration of diabetes, high serum ferritin and the presence of dyspnea are associated with higher risk of hospitalization among these patients.

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Conflict of interest

None declared.

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