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Blood sugar measurements in non-diabetic patients presented with COVID-19

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List of abbreviations

Abbreviations	Meanings
ACE2	Angiotensin converting enzyme2
BMI	Body Mass Index
CI	Confidence Interval
COVID-19	Coronavirus Disease 2019
CRP	C-reactive protein
CT	Computerized Tomography
CVD	Cardiovascular Disease
DKA	Diabetic Ketoacidosis
DM	Diabetes Mellitus
FPG	Fasting Plasma Glucose
Hb	Hemoglobin
HbA1c	Glycated Hemoglobin A1c
ICU	Intensive Care Unit
IFNs	Interferons
ILs	Interleukins
MCP1	Monocyte Chemo-attractant Protein 1
MERS-CoV	Middle East respiratory syndrome coronavirus
NK	Natural Killer
RBS	Random Blood Sugar
ROS	Radical Oxygen Species
RT-PCR	Reverse Transcription Polymerase Chain Reaction
SARS	Severe Acute Respiratory Syndrome
SD	Standard Deviation
SPO2	Oxygen Saturation
SPSS	Statistical Package for Social Sciences
T2DM	Type 2 Diabetes Mellitus
TNFs	Tumor Necrosis Factors
UK	United Kingdom
USA	United States of America

Abstract

Background: The new coronavirus disease 2019 (COVID-19) pandemic outbreak resulted in millions of co-morbidities and mortalities all over the world. The hyperglycemia with or without diabetes mellitus is prevalent in COVID-19 disease.

Aim of study: To identify the prevalence of hyperglycemia in COVID-19 patients and to evaluate the relationship between hyperglycemia and severity of COVID-19 disease.

Patients and methods: This study is a descriptive cross sectional study conducted in AL-Shifaa 14 Hospital in Kirkuk city-Iraq for duration of six months during the period from 1st of January till 30th of June, 2021 on convenient sample of 250 non-diabetic COVID-19 patients. The diagnosis of COVID-19 disease was confirmed by the supervisor according to clinical symptoms and signs, RT-PCR finding and CT-scan finding. The severity of COVID-19 disease was categorized by the supervisor according to Iraqi Ministry of Health guidelines.

Results: The prevalence of hyperglycemia among COVID-19 patients was (8%). The COVID-19 severity of patients was classified into; mild (27.2%), moderate (13.6%) and severe (59.2%). The means of random blood sugar and HBA1c were significantly increased among patients with severe COVID-19 disease ($p<0.001$). The significant risk factors of severe COVID-19 disease are elderly age, unemployment, marital status, clinical co-morbidity and pregnancy.

Conclusions: The prevalence of severe cases of COVID-19 disease among non-diabetic patients is high with direct link to hyperglycemia.

Keywords: COVID-19, Non-diabetic, Hyperglycemia.

Abstract

1.1. Background

New coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been one of the most important epidemics of the century threatening human health worldwide. Due to the COVID-19, more than 130 million patients have been infected, and more than 2.8 million deaths have occurred around the world[1, 2].until (2020/7/19)

Mortality and morbidity rates of COVID-19 disease increase significantly in certain population groups such as males, older adults, or patients with comorbidities. Type 2 diabetes mellitus (T2DM) is one of the most frequent comorbidities in COVID-19 patients with considerably increased mortality and morbidity rates [3]. Moreover, recent data indicate that new-onset hyperglycemia is common among hospitalized COVID-19 patients with no history of diabetes in the past. Besides, hyperglycemia

on hospital admission is a significant prognostic factor (good) for COVID-19 patients without diabetes mellitus[4, 5]. Studies from the United States, Italy, Spain, and China have consistently shown an increased risk of mortality, intensive care unit (ICU) admission, and a need for mechanical ventilation in patients with on admission hyperglycemia but no previous diagnosis of diabetes mellitus[6, 7].

Hyperglycaemia in hospitalized patients, irrespective of its cause, is associated with adverse outcomes. Hyperglycaemia could be present in patients with known or undiagnosed diabetes, or during acute illness (termed 'stress hyperglycaemia')[8]. Stress hyperglycaemia has two scenarios: patients with undiagnosed diabetes or impaired glucose tolerance, and patients who develop hyperglycaemia as a result of the severe stress and increased counterregulatory hormones[9]. Diabetes and hyperglycaemia are associated with a poor outcome (higher severity and mortality) in patients with COVID-19[10]. Admission hyperglycaemia has been observed as a predictor of radiographic imaging of SARS-CoV2, regardless of previous diabetes diagnosis [11]. Diabetes is one of the most common causes of morbidity and mortality around the world. In 2019, 463 million people had diabetes, with an expectation that this number will rise to 578 million people worldwide by 2030 and 700 million by 2045. In the top 10 countries with more cases of diabetes, Mexico ranks 6th worldwide, with 12.8 million people affected[12].

1.2. Role of diabetes in prediction of COVID-19 course

COVID-19 patients with type 2 diabetes mellitus (T2DM) and/or cardiovascular disease (CVD) are admitted more often to intensive care units (ICUs) compared to those without T2DM or CVD[13]. Older age and T2DM are both risk factors for COVID-19, but the observation that

T2DM is a disease that is frequent in advanced age, slightly confounds this association[14].The risk of developing severe COVID-19 is higher in people with DM, especially if they have other co-morbidities, thus making patients with DM an at-risk population. The worse the glycemic control, the worse the severity of infection and the greater the risk of mortality[15]. In the initial studies of COVID-19, DM appeared to be 2.26 times (95% confidence interval [CI]: 1.47-3.49) more common in patients with more severe COVID-19 compared to those with less severe infection, while at the same time the presence of DM entailed an odds ratio of 2.85 (95%CI: 1.35-6.05) of intra-hospital mortality. As already mentioned, these results were not always adjusted for age, which is a major confounding factor in the prevalence of DM. In Italy, one-third of patients who died of COVID-19 had DM (median age 80.5 years) and were predominantly male (70%). Compared with the prevalence of DM in the same population segment in Italy in 2018 (20.3%), the authors reported a relative risk of diabetes of 1.75 in patients who died from COVID-19. It is therefore necessary to emphasize the advanced age of patients with severe COVID-19, as well as their multiple comorbidities, defining them as a population particularly at risk[16].

1.3. COVID-19 disease and inflammation

COVID-19 is characterized by the excessive production of inflammatory factors, leading to an “inflammatory storm” (a combination of pro-inflammatory immunoactive molecules, such as interleukins [ILs], interferons [IFNs], chemokines and tumor necrosis factors [TNFs]) in some patients[17]. Diffuse pulmonary alveolar damage, inflammatory cell infiltration with hyaline membranes, myocardial inflammation, lymphocyte infiltration in the liver, and pancreatitis are some of the major inflammatory findings during the course of the generalized COVID-19[18].

In sharp contrast to the above, the IFN type I response is impaired in these patients[19]. For patients with severe COVID-19, this so-called cytokine storm is a potentially life- threatening event[20].

In 317 patients with laboratory-confirmed COVID-19, inflammatory responses and higher levels of IL-6 were related to disease severity[18, 21]. In patients with COVID-19, inflammatory markers such as C-reactive protein, D-dimers, ferritin, and IL-6 are increased; they have a direct effect on microvascular and macrovascular structures in patients with DM[22].

1.4. Diabetes, obesity and inflammatory similarities with COVID-19

Although T1DM is not related to obesity, the majority of patients with T2DM are overweight or obese. Resembling the inflammatory processes of COVID-19, prolonged hyperglycemia, regardless of diabetes type, can also impact immune function, whereas compromised immunological status is linked to macrovascular complications of DM[18].

Inflammation begets increased oxidative stress that can damage proteins, lipids and DNA, systemically, as well as locally, both in the liver and in muscles, the predominant organs that regulate glucose output and glucose metabolism, increasing insulin resistance. In T2DM, inflammation occurs in the pancreatic β cell (insulitis)[23]. Macrophages play a key role in β cell inflammation, along with IL-1β signaling (a core inflammatory process in the locally stressed β cell). Along with the local injury of the pancreatic cells, lipotoxicity further deteriorates pancreatic

function. Free fatty acids can also induce the local production of IL-1β- and IL-1-dependent pro-inflammatory cytokines, which target the pancreatic islets. This process also increases nitric oxide production, lowers mitochondrial ATP, causing additional β cell dysfunction, along with the release of reactive oxygen species by hypoxia and endothelial damage. TNF-α is linked to insulin resistance, obesity and islet inflammation, while IL-6 promotes islet cell apoptosis; both lead to T2DM. Obesity and DM (which often are described as "diabesity") favor a switch from (anti-inflammatory) M2 macrophage predominance to (pro-inflammatory) M1 macrophage predominance, further contributing to exaggerated inflammation. Of note, infection with respiratory syncytial virus increases the production of IFNγ, provokes natural killer (NK) cell activation and exacerbation of inflammation in muscle and adipose tissues. Moreover, NK cell activity was found to be lower in patients with DM; glycated hemoglobin A1c (A1c) levels are associated with NK cell activity[24].

T2DM is a disease that often occurs and/or is related to obesity. Insulin resistance and related progression to overt diabetes are strongly associated with hypertrophy and hyperplasia of adipose cells. According to the World Obesity Federation, obesity-related conditions seem to worsen the effects of COVID-19; indeed, the Centers for Disease Control and Prevention reported that "people with heart disease and diabetes are at higher risk of COVID-19 complications" and severe obesity (body mass index of ≥ 40) entails a higher risk for severe disease or death. As previously mentioned, COVID-19 favors an inflammatory environment that may progress to a "cytokine storm" (hypersecretion of inflammatory molecules: IL-2, IL-7, granulocyte-colony stimulating factor, IFN-γ inducible protein 10, monocyte chemo-attractant protein 1 [MCP1],

macrophage inflammatory protein 1-α, and TNF-α). In an analogous fashion, obesity presents a state of low-grade inflammation, as a result of the secretion of inflammatory cytokines (TNF-α, IL-1, IL-6, IL-10), transforming growth factor-β, adipokines (leptin, resistin, adiponectin), MCP-1, C-X-C motif chemokine 5, hemostatic proteins (plasminogen activator inhibitor-1), proteins affecting blood pressure (angiotensinogen) and angiogenic molecules (vascular endothelial growth factor). Hypoxia and ischemia in adipose tissue and local endothelial damage lead to the production of reactive oxygen radicals (radical oxygen species, ROS) that affect both the microenvironment and macroenvironment of blood vessels. Hyperglycemia and DM affect various target organs, including the vasculature. Obesity (and its concomitant inflammation) enables another mechanism *via* which COVID-19 can provoke damage, which is directly related to the microvascular complications of DM [20].

1.5. COVID-19 and glucose metabolism

Hyperglycemia was observed in patients with SARS in 2003, caused by another coronavirus, closely related to COVID-19, SARS-CoV-1) possibly due to potential transient impairment of pancreatic islet cell function. Two more *coronaviridae* (’MERS-CoV’ and ‘HCoV-EMC’, causing Middle Eastern Respiratory Syndrome and human coronavirus;) attach to cells *via* dipeptidyl peptidase 4 (DPP-4, an enzyme that regulates insulin secretion)[25].

Glycemia on one hand is associated with SARS-CoV-2 replication[26]; elevated glucose levels and glycolysis increase SARS-CoV-2 replication and viral proliferation through the production of ROS (Figure 1). Notably, both T1DM and T2DM, are associated with a dysregulated immune response and increased morbidity and mortality [27]. On the other hand, in an inverse relationship, the presence of COVID-19

causes deterioration of glycemic control in already established DM. In a case series of critically ill, mostly not well-controlled patients with pre-existing T2DM (7 of 8 were on oral therapy before ICU admission), 85 to 480 units of insulin per day were needed to harness hyperglycemia[26].

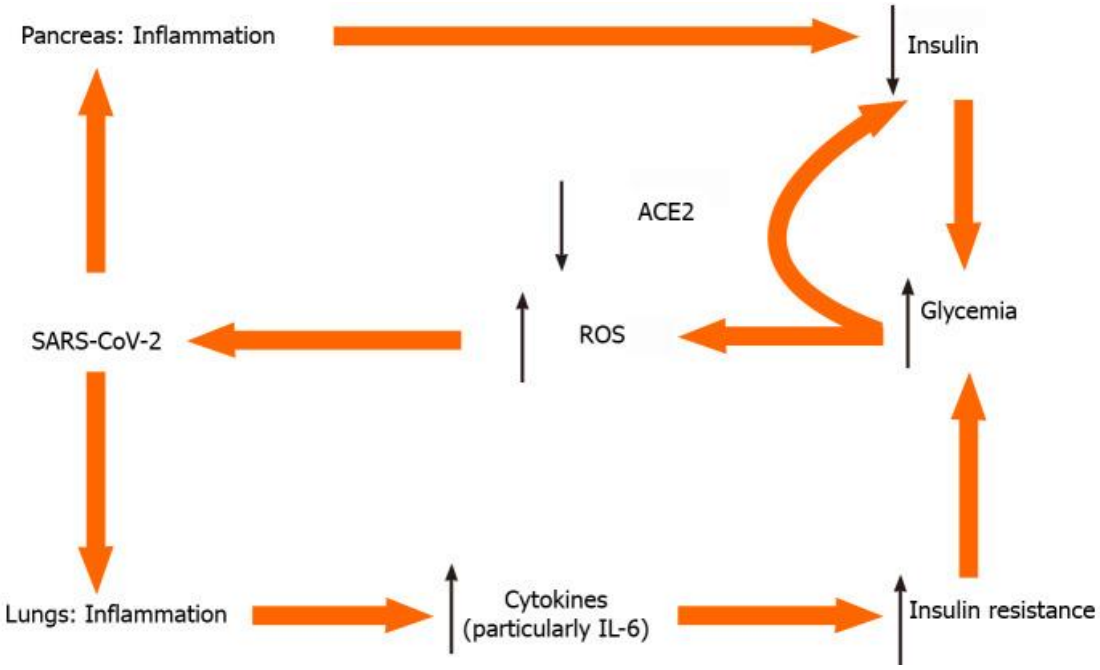

Figure 1: Selected tentative pathways for hyperglycemia in severe acute respiratory syndrome coronavirus 2 infection. ACE2: Angiotensin converting enzyme 2; IL-6: Interleukin 6; ROS: Radical oxygen species; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2 [28].

The difference in diabetic ketoacidosis (DKA) rates in COVID-19 was four times higher in Black and two times higher in Hispanic patients with T1DM *vs* White patients with T1DM (but no statistical significance

was documented). Potential explanations for these observations include the lower socioeconomic status of minority populations vis-à-vis that of the White population, the lack of appropriate nutrition and the lack of medical supervision in the use of insulin. Although DKA is a major untoward event in T1DM, the majority of DKA cases with COVID-19, were observed in T2DM patients[29].

An initial diagnosis of DM was common in patients infected with SARS-COV-2, with neither any prior history of DM, nor using glucocorticoids. This new-onset hyperglycemia was an independent predictor for mortality[30] and was attributed to the binding of SARS-COV-2 to the angiotensin converting enzyme 2 (ACE2) receptor in pancreatic islets with concomitant local damage[30, 31]. This ‘‘new-onset” hyperglycemia could be classified either as ‘‘stress-induced” hyperglycemia, as ‘‘new-onset DM” in previously unrecognized prediabetes, as hyperglycemia owing to the effects of SARS-CoV-2 to the pancreatic islets or as a result of ‘‘secondary DM”, following use of corticosteroids[30].

Quoting the definitions of the American Diabetes Association, new-onset hyperglycemia without DM is defined as fasting plasma glucose (FPG) between 5.6 mmol/L and 6.9 mmol/L (100-125 mg/dL) and/or A1c between 5.7% and 6.4%, in absence of such measurements in the past. New-onset DM is defined by either of FPG > 7.0 mmol/L (> 126 mg/dL) and/or an A1c > 6.5% and/or a random glucose > of 11.1 mmol/L (200 mg/dL). Thus, abnormal glucose measurements, in the absence of A1c > 6.5% could be expected, especially during this recent viral infection (that could not have affected the A1c levels yet). Several cases of hyperglycemia or new-onset DM in COVID-19 have been reported. As might be expected, COVID-19 has been associated with severe metabolic

complications of already preexisting DM, including DKA and hyperosmolarity, necessitating high doses of insulin for glycemic control[32].

ACE2 is expressed in the respiratory system, in the intestines, kidneys, myocardium, vasculature and pancreatic islets. SARS-CoV-2 binds to ACE2, using it as a ligand for cell entry. Interestingly, ACE2-knockout mice are more vulnerable to β cell dysfunction, a fact that could explain why infection with SARS-CoV-2 can cause hyperglycemia in humans without preexisting DM. After endocytosis of the virus complex, ACE2 expression is down regulated, acting in a dual way. On one hand this impairs pancreatic islet cells' function and causes β cell injury. On the other hand, down regulation of ACE2 Leads to unopposed angiotensin II action, which may further impair insulin secretion, by reducing blood flow and reducing insulin secretion while increasing oxidative stress in the pancreatic cell? Thus, corona viruses might damage pancreatic islets, and give rise to hyperglycemia[31].

1.6. Literatures on new-onset hyperglycemia due to COVID-19

Recently, a young 37-year-old patient with COVID-19 presented with all the clinical features of hyperglycemia and DKA, this being possibly the first case of new-onset DM secondary to COVID-19 [33]. Another case of DKA precipitated by COVID-19 in a 54-year-old patient with newly diagnosed DM was also reported [34]. Since DKA occurs as a result of insulin deficiency, such observations give rise to questions regarding the potential effect of COVID-19 in this dangerous condition [34].

In a study by Li *et al* among 658 hospitalized patients with confirmed COVID-19, 42 (6.4%) out of 658 patients presented with ketosis on admission with no obvious fever or diarrhea. Patients with

ketosis were younger (median age 47.0 years *vs* 58.0 years; $P = 0.003$) and had a greater prevalence of fatigue (31.0% *vs* 10.6%; $P < 0.001$), DM (35.7% *vs* 18.5%; $P = 0.007$) and digestive disorders (31.0% *vs* 12.0%; $P < 0.001$). According to their data, COVID-19 infection caused ketosis or ketoacidosis, and induced DKA for patients with DM. Ketosis increased the length of hospital stay and mortality, while DM increased the length of hospital stay for patients with ketosis but had no effect on their mortality[35].

It remains to be determined whether, after resolution of COVID-19 symptoms, glucose levels are restored to normal, thus remitting the initial diagnosis of DM. To provide answers to this conundrum, a global registry of patients with COVID-19-related diabetes have been established (COVIDIAB Project)[36].

1.7. Outcome in patients with new-onset hyperglycemia without DM vs. normoglycemic COVID-19

Hyperglycemia (two or more blood glucose measurements > 10 mmol/L or 180 mg/dL within any 24-h period with an A1C < 6.5%), regardless of the presence of DM, is related to an increase in COVID-19 mortality compared to normoglycemia. Hyperglycemia without DM is further related to increased need for mechanical ventilation, to need for ICU hospitalization and to mortality[37]. In the same way, complications within the first month of hospital stay were increased in hyperglycemic patients without DM resulting in higher all-cause mortality[38]. Hyperglycemia at admission (but without confirmed DM) was related to a 71% increase in mortality in 1317 patients[39, 40].

When hyperglycemia without the presence of DM was compared to known DM (new-onset and/or preexisting DM) in COVID-19 patients, a

significant increase in mortality was observed among 271 patients with new-onset hyperglycemia without DM, compared to pre-existing DM. Nevertheless, ICU admission did not seem to differ significantly[41]. Critically and non-critically ill COVID-19 patients sometimes present with higher-than-expected glycemia, even in the absence of DM. Regarding the direct association of glycemia in already admitted patients in ICU due to COVID-19 infection, hyperglycemia was noted in 20 of 36 patients. Among those, none had a prior history of DM and the incidence of hyperglycemia proved to be higher that would be expected in an ICU due to stress-induced responses[42]. In a series of 157 patients with COVID-19, a substantial number of patients with and without DM presented with hyperglycemia upon admission, while critically ill patients showed compromised insulin secretion and/or impaired sensitivity to insulin[43].

1.8. Outcome in patients with new-onset DM vs. normoglycemic COVID-19

New-onset DM (and/or DKA) has been reported to occur in 16% to 21% of COVID-19 cases [33], but the incidence of complications, need for ICU and intubation, varies among studies (n = 413), with some showing an increase and others no difference, compared to normoglycemic patients[44].

1.9. Outcome in patients with new-onset DM vs. pre-existing

The risk of all-cause death in COVID-19 patients with new-onset DM is nearly double compared to that of patients with pre-existing DM. A statistically significant association of ICU admission and/or of mortality in COVID-19 patients with new-onset DM (37%), compared to patients with pre-existing DM (20%) was noted; this association persisted

after adjustment for age and gender. Summing up the available literature, COVID-19 patients with new-onset hyperglycemia, even without a frank diagnosis of DM due to any cause (stress-induced/COVID-19-induced/pre-existing dysglycemia), show a worse course of the disease, higher rate of complications and all-cause mortality when compared to normoglycemic or patients with DM[45].

1.10. Treatment for COVID-19 and glycemia

In published reports, COVID-19 patients with hyperglycemia/secondary DM were usually treated effectively with insulin. In early reports, patients were also treated with hydroxychloroquine[40]. The hydroxychloroquine is known to increase endogenous insulin secretion [46]. Since the use of hydroxychloroquine for SARS-CoV-2 was—at least—controversial, and has been phased out, hyperglycemia may be seen more often in patients with SARS-CoV-2 (with or without DM). Possibly higher insulin dosage—than expected—may be needed. Hyperglycemia is also to be expected by the widespread use of dexamethasone in COVID-19 patients, per the newer treatment protocols[47-50].

Aim of study

To identify the prevalence of hyperglycemia in COVID-19 patients and to evaluate the relationship between hyperglycemia and severity of COVID-19 disease.

Patients & Methods

Patients

Study design & settings

A descriptive cross sectional study conducted in AL-Shifaa 14 Hospital in Kirkuk city-Iraq for duration of six months during the period from 1st of January till 30th of June, 2021.

Study population

All non-diabetic patients with positive reverse transcription polymerase chain reaction (RT-PCR) admitted to wards of AL-Shifaa 14 Hospital were the study population.

Inclusion criteria

1. Adult patients (age ≥20 years).
2. Non-diabetic.
3. Positive RT-PCR.

Exclusion criteria

1. History of diabetes mellitus.
2. Younger age.

Sampling

A convenient sample of 250 non-diabetic COVID-19 patients was selected from AL-Shifaa 14 Hospital after eligibility to inclusion and exclusion criteria.

Methods

Data Collection

The data was collected by the researcher directly from patients and filled in a prepared questionnaire. The questionnaire was designed by the researcher and supervisor. The following information was checked in every COVID-19 patient:

1. Demographic characteristics of COVID-19 patients: Age and gender.
2. Social characteristics of COVID-19 patients: Residence, occupation and marital status.
3. Clinical complaints of COVID-19 disease: Fever, cough, loss of smell, loss of taste, dyspnea and chest pain.
4. Clinical history of COVID-19 patients: Past medical & surgical history, drug history, family history, smoking history, alcohol history and pregnancy history.
5. Endocrine symptoms of COVID-19 patients.
6. Examination findings of COVID-19 patients.
7. Vital signs of COVID-19 patients.
8. PCR findings of COVID-19 patients.
9. Investigations findings of COVID-19 patients: Random blood sugar level, HbA1c level, D-dimer level and C-reactive protein level.
10. Chest CT-scan score of COVID-19 patients.

Each patient included in this study was examined by the researcher after taking full history and a sample of 5 ml of blood taken from them in order to complete the investigations. The patients referred from Al-Shifaa 14 hospital to Kirkuk General Hospital or Azadi Teaching Hospital or from private clinic to implement the chest CT-scan. The diagnosis of COVID-19 disease was confirmed by the supervisor according to clinical symptoms and signs, RT-PCR finding and CT-scan finding. The severity of COVID-19 disease was categorized by the supervisor according to

Iraqi Ministry of Health guidelines (Appendix 1). All the investigations were implemented in the Laboratory of Al-Shifaa 14 hospital. The hyperglycemia was defined as RBS>180mg/dl.[5]

The used computerized tomography scan equipment was Siemens (64 slice CT scanner-Germany). The chest CT scan score was measured by semi-quantitative CT severity scoring which categorized according chest lesions affecting lung five lobes detected by CT; 0=no involvement, one score= < 5% involvement, two scores= 5–25% involvement, three scores= 26–50% involvement, four scores= 51–75% involvement and five scores= > 75% involvement. Finally, the total chest CT scan score was the sum of affected lobes with range of 0-25 [51].

Ethical considerations

1. Approval was taken from Iraqi Board of Medical Specializations.
2. An agreement was taken from hospital authorities.
3. An oral informed consent was taken from patients enrolled in the study.

Statistical analysis

All patients' data entered using computerized statistical software; Statistical Package for Social Sciences (SPSS) version 22 was used. Descriptive statistics presented as (mean ± standard deviation) and frequencies as percentages. Multiple contingency tables conducted and appropriate statistical tests performed, Chi square test was used for

categorical variables (Fishers exact test was used when expected variable was less than 20% of total variable). One way ANOVA analysis was used between more than two means. In all statistical analysis, level of significance (p value) set at ≤ 0.05 and the result presented as tables and/or graphs.

Results

This study included 250 COVID-19 patients admitted with mean age of 52±19.2 years and range of (20-90 years); 13.6%, of patients were in age group 20-29 years, 18.4% of patients were in age group 30-39 years, 11.6% of them were in age group 40-49 years, 14% of them were in age group 50-59 years, 17.6% of them were in age group 60-69 years

and 16% of them were in age group 70-79 years and 8.8% of COVID-19 patients were in age of 80-90 years. Male COVID-19 patients were more than females with male to female ratio as 2:1. (***Table 1 and Figures 2, 3***)

Table 1: Demographic characteristics of COVID-19 patients.

Variable	No.	%
Age mean±SD (52±19.2 years)		
20-29 years	34	13.6
30-39 years	46	18.4
40-49 years	29	11.6
50-59 years	35	14.0
60-69 years	44	17.6
70-79 years	40	16.0
80-90 years	22	8.8
Total	250	100.0
Gender		
Male	168	67.2
Female	82	32.8
Total	250	100.0

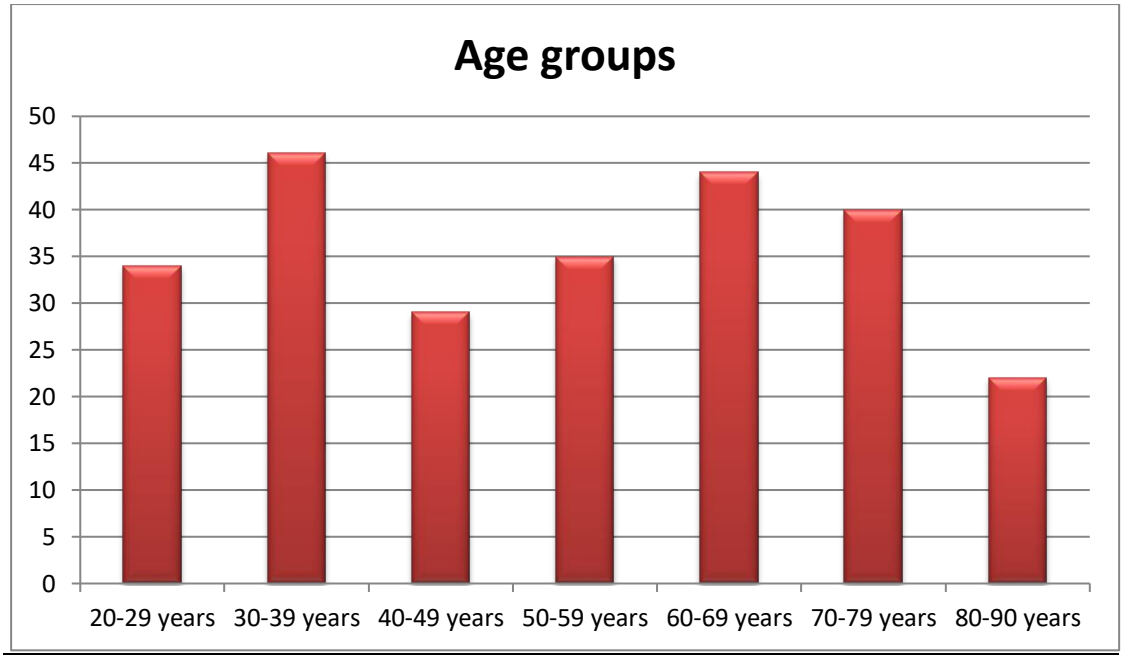

Figure 2: Age distribution of COVID-19 patients.

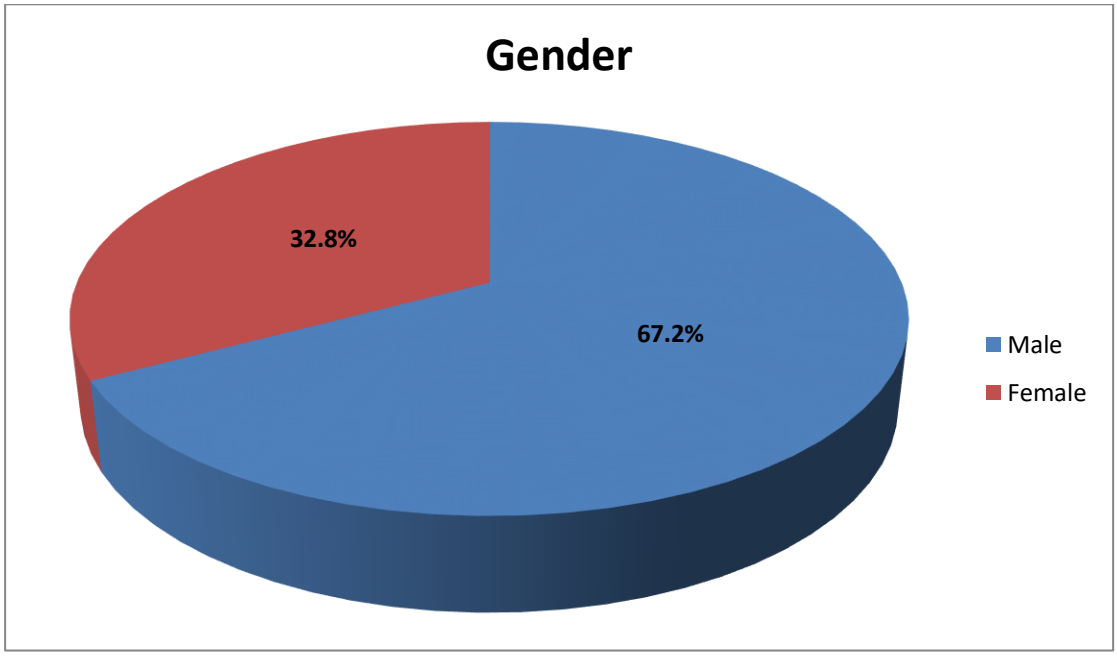

Figure 3: Gender distribution of COVID-19 patients.

Most of studied COVID-19 patients were urban residents and 4.8% of them were rural residents. The occupation of COVID-19 patients was distributed as followings; public servants (34.4%), students (4.8%), self employed (15.2%), retired (14.4%) and housewife (31.2%). Married COVID-19 patients represented 88% of them, while single patients represented 12% of them. (***Table 2***)

Table 2: Social characteristics of COVID-19 patients.

Variable	No.	%
Residence		
Urban	238	95.2
Rural	12	4.8
Total	250	100.0
Occupation		
Public servant	86	34.4
Student	12	4.8
Self employed	38	15.2
Retired	36	14.4
Housewife	78	31.2
Marital status		
Married	220	88.0
Single	30	12.0
Total	250	100.0

The common clinical complaints of patients with COVID-19 disease were cough (91.2%), fever (83.2%), dyspnea (74.4%), chest pain (66.4%), loss of smell (31.2%) and loss of taste (27.2%). (***Table 3***)

Table 3: Clinical complaints of COVID-19 disease.

Variable	No.	%
Fever		
Yes	208	83.2
No	42	16.8
Total	250	100.0
Cough		
Yes	228	91.2
No	22	8.8
Total	250	100.0
Loss of smell		
Yes	78	31.2
No	172	68.8
Total	250	100.0
Loss of taste		
Yes	68	27.2
No	182	72.8
Total	250	100.0
Dyspnea		
Yes	186	74.4
No	64	25.6
Total	250	100.0
Chest pain		
Yes	166	66.4
No	84	33.6
Total	250	100.0

The endocrine symptom of COVID-19 patients was commonly thirst (32.8%), followed by; thirst and sweating (26.4%), thirst, polyurea and sweating (3.2%), etc. (***Table 4***)

Table 4: Endocrine symptoms of COVID-19 patients.

Variable	No.	%
Endocrine symptoms		
No	86	34.4
Thirst	82	32.8
Sweating	4	1.6
Thirst and polyurea	4	1.6
Thirst, polyurea and	8	3.2
Thirst and sweating	66	26.4
Total	250	100.0

The past medical history was hypertension in 25.6% of COVID-19 patients and hypertension and thyroid in two patients. The drug history was positive for steroids and others in four patients and positive for 25.6% of patients. The family history for DM was recorded among 5.6% of COVID-19 patients and family history of others among four patients. Smoking history was present among 28.8% of COVID-19 patients, while alcohol history was recorded for four patients and pregnancy was detected in two patients only. (***Table 5***)

Table 5: Clinical history of COVID-19 patients.

Variable	No.	%
Past medical history		
No	184	73.6
Hypertension	64	25.6
Hypertension and	2	0.8
Total	250	100.0
Drugs history		
No	224	89.6
Steroids and others	4	1.6
Others	22	8.8
Total	250	100.0
Family history		
No	232	92.8
DM	14	5.6
Others	4	1.6
Total	250	100.0
Smoking history		
No	178	71.2
Yes	72	28.8
Total	250	100.0
Alcohol history		
No	246	98.4
Yes	4	1.6
Total	250	100.0
Pregnancy history		
No	248	99.2
Yes	2	0.8
Total	250	100.0

The breathing was vesicular for all patients. The added sounds were crepitation (15.2%), wheezing (4%) and wheezing and crepitation (4%). The PCR was positive for all patients. The mean measures of vital signs for COVID-19 patients were (95.5 beat/m) for pulse rate, BP (118.8/76.7 mmHg), RR (19.8 breath/m), temperature (37.7 C°) and SPO_2 (81.5%). (***Table 6***)

Table 6: Examination and PCR findings of COVID-19 patients.

Variable	No.	%
Breathing		
Vesicular	250	100.0
Total	250	100.0
Added sounds		
No	192	76.8
Wheezing	10	4.0
Crepitation	38	15.2
Wheezing and crepitation	10	4.0
Total	250	100.0
PCR		
Positive	250	100.0
Total	250	100.0
Pulse rate mean±SD (95.6±13.5 beat/m)		
Blood pressure mean±SD (118.8/76.7±11.6/7.2 mmHg)		
Respiratory rate mean±SD (19.8±5.1 breath/m)		
Temperature mean±SD (37.7±0.9 C°)		
SPO_2 mean±SD (81.5±14.4 %)		

The mean measures of investigations for COVID-19 patients were RBS (115 mg/dl), HbA1c (6.5%), CT scan chest occupancy (37.6%), CRP (48.7 mg/dl) and D-dimer (490.1 ng/ml). The hyperglycemia was detected among 8% of COVID-19 patients. (***Table 7 and Figure 4***)

Table 7: Investigations findings of COVID-19 patients.

Variable	Mean	SD
RBS (mg/dl)	115	41.7
HbA1c (%)	6.5	1.1
D-dimer level (ng/ml)	490.1	613.1
C-reactive protein (mg/dl)	48.7	46.7
CT scan chest (%)	37.6	25.8
Total	250	100.0

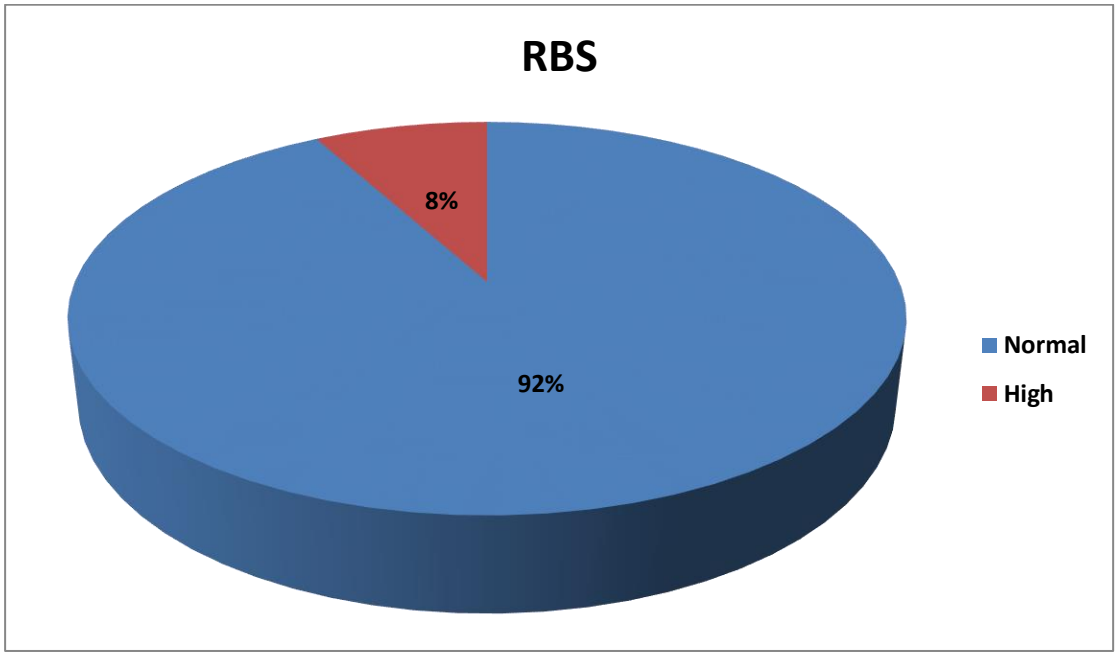

Figure 4: Prevalence of hyperglycemia among COVID-19 patients.

The COVID-19 severity of patients was classified into; mild (27.2%), moderate (13.6%) and severe (59.2%). (***Table 8 and Figure 5***)

Table 8: COVID-19 severity distribution.

Variable	No.	%
COVID-19 severity		
Mild	68	27.2
Moderate	34	13.6
Severe	148	59.2
Total	250	100.0

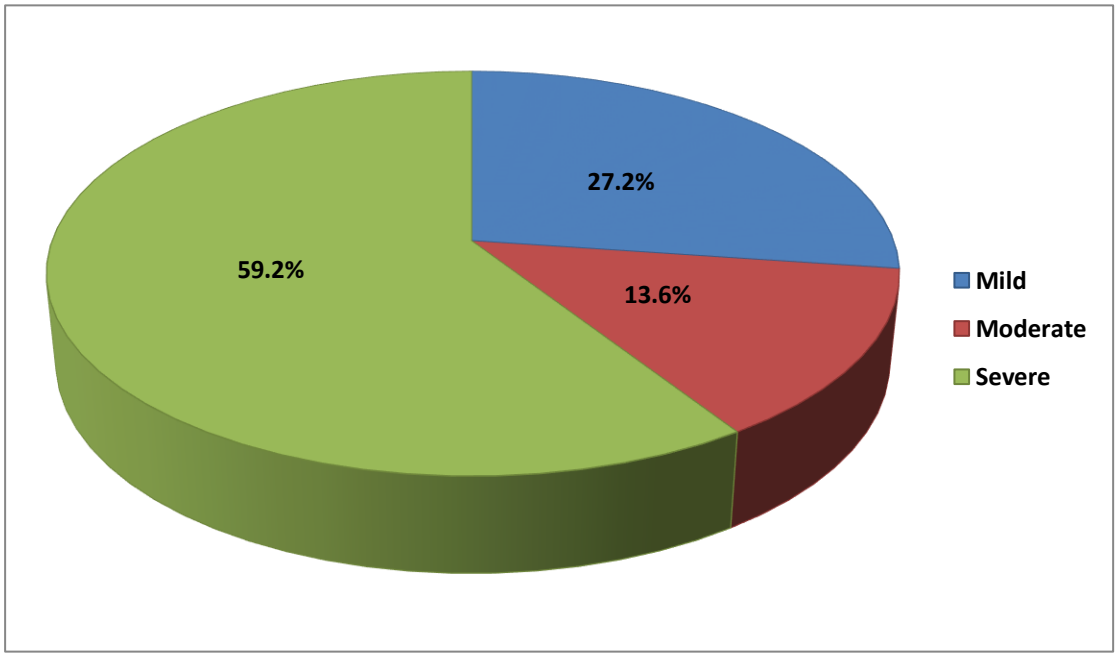

Figure 5: COVID-19 severity.

There was a highly significant association between increased age of patients and COVID-19 severity (p<0.001), 100% of patients with age of 80-90 years had severe COVID-19 disease. No significant differences were observed between patients with different COVID-19 severity regarding gender (p=0.5). (***Table 9***)

Table 9: Distribution of demographic characteristics according to COVID-19 severity.

Variable	COVID-19 severity						P
	Mild		Moderate		Severe		
	No.	%	No.	%	No.	%	
Age							<0.001* S
20-29 years	26	76.5	6	17.6	2	5.9	
30-39 years	22	47.8	8	17.4	16	34.8	
40-49 years	8	27.6	6	20.7	15	51.7	
50-59 years	6	17.1	6	17.1	23	65.7	
60-69 years	4	9.1	6	13.6	34	77.3	
70-79 years	2	5.0	2	5.0	36	90.0	
80-90 years	0	-	0	-	22	100.0	
Gender							0.5* NS
Male	42	25.0	24	14.3	102	60.7	
Female	26	31.7	10	12.2	46	56.1	

** Chi square test, NS=Not significant, S=Significant*.

No significant differences were observed between patients with different COVID-19 severity regarding residence (p=0.1). There was a highly significant association between unemployed patients (retired and housewives) and COVID-19 severity (p<0.001). A highly significant association was observed between married patients and COVID-19 severity (p<0.001). (***Table 10 and Figure 6***)

Table 10: Distribution of social characteristics according to COVID-19 severity.

Variable	COVID-19 severity						P
	Mild		Moderate		Severe		
	No.	%	No.	%	No.	%	
Residence							0.1* NS
Urban	66	27.7	34	14.3	138	58.0	
Rural	2	16.7	0	-	10	83.3	
Occupation							<0.001* S
Public servant	42	48.8	10	11.6	34	39.5	
Student	8	66.7	4	33.3	0	-	
Self employed	8	21.1	6	15.8	24	63.2	
Retired	2	5.6	4	11.1	30	83.3	
Housewife	8	10.3	10	12.8	60	76.9	
Marital status							<0.001** S
Married	48	21.8	28	12.7	144	65.5	
Single	20	66.7	6	20.0	4	13.3	

** Fishers exact test, **Chi-square test, NS=Not significant, S=Significant.*

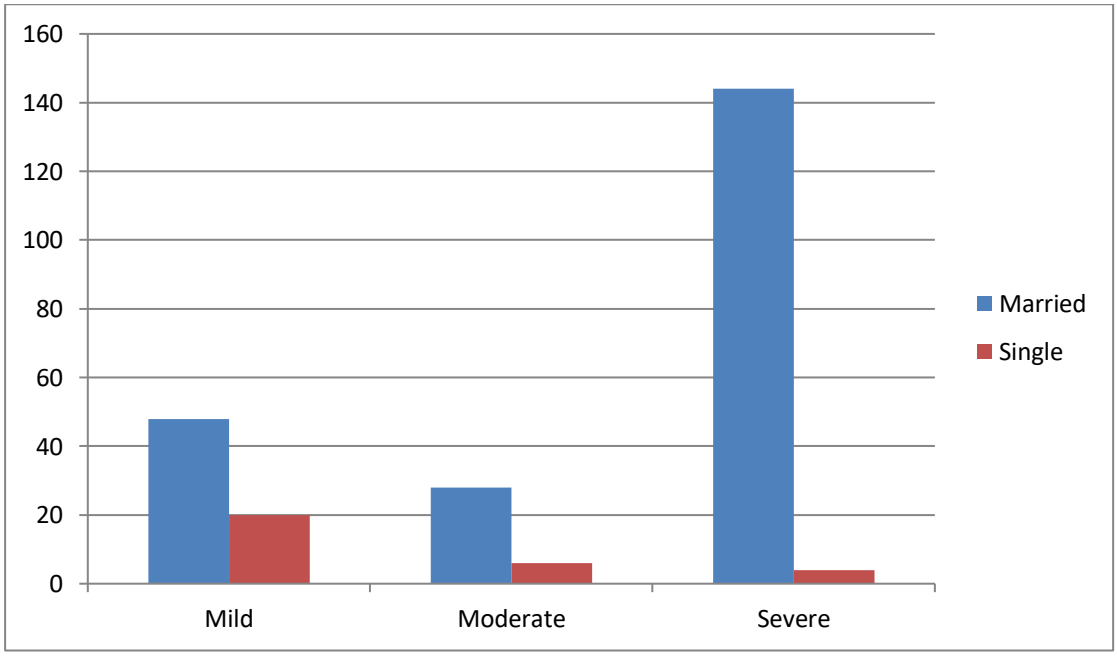

Figure 6: Distribution of marital status according to COVID-19 severity.

No significant differences were observed between patients with different COVID-19 severity regarding cough complaint (p=0.1). There was a significant association between fever, loss of smell and loss of taste with mild COVID-19 severity (p=0.01, p=0.004 and p=0.01, respectively). A highly significant association was observed between dyspnea and chest pain with severe COVID-19 severity (p<0.001). (***Table 11 and Figure 7***)

Table 11: Distribution of clinical complaints according to COVID-19 severity.

Variable	COVID-19 severity						P
	Mild		Moderate		Severe		
	No.	%	No.	%	No.	%	
Fever							0.01*S
Yes	64	30.8	28	13.5	116	55.8	
No	4	9.5	6	14.3	32	76.2	
Cough							0.06* NS
Yes	66	28.9	32	14.0	130	57.0	
No	2	9.1	2	9.1	18	81.8	
Loss of smell							0.004* S
Yes	32	41.0	8	10.3	38	48.7	
No	36	20.9	26	15.1	110	64.0	
Loss of taste							0.01* S
Yes	28	41.2	8	11.8	32	47.1	
No	40	22.0	26	14.3	116	63.7	
Dyspnea							<0.001*S
Yes	14	7.5	28	15.1	144	77.4	
No	54	84.4	6	9.4	4	6.3	
Chest pain							<0.001*S
Yes	18	10.8	24	14.5	124	74.7	
No	50	59.5	10	11.9	24	28.6	

** Chi-square test, NS=Not significant, S=Significant.*

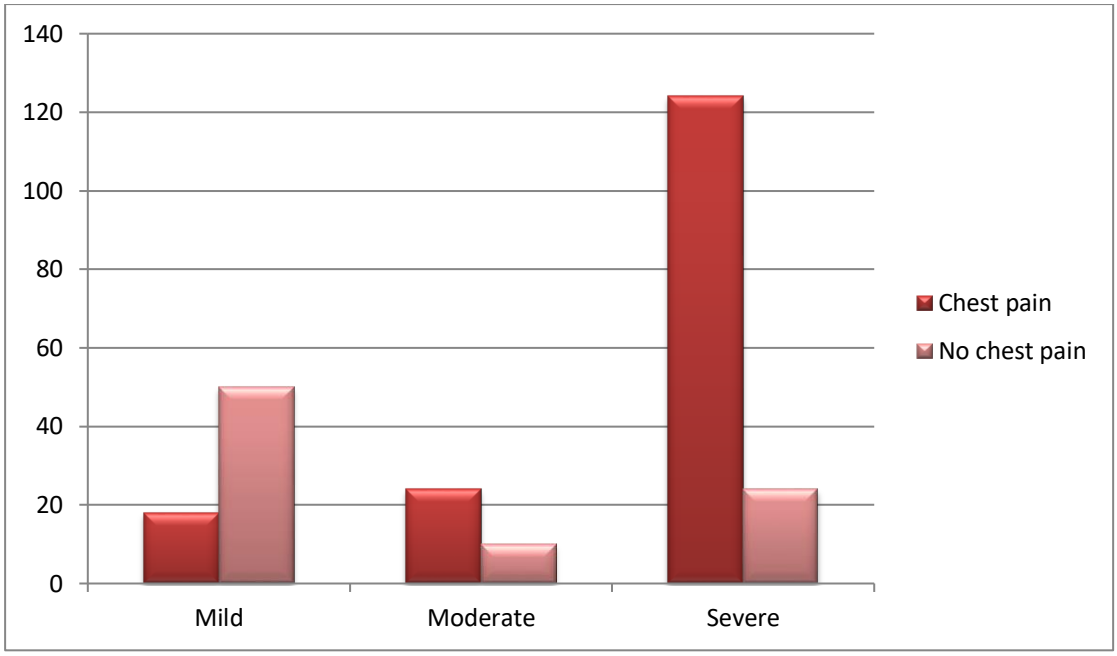

Figure 7: Distribution of chest pain according to COVID-19 severity.

There was a highly significant association between sweating and severe COVID-19 disease (p<0.001). (***Table 12***)

Table 12: Distribution of endocrine symptoms according to COVID-19 severity.

Variable	COVID-19 severity						P
	Mild		Moderate		Severe		
	No.	%	No.	%	No.	%	
Endocrine symptoms							<0.001*S
No	40	46.5	10	11.6	36	41.9	
Thirst	16	19.5	10	12.2	56	68.3	
Sweating	0	-	0	-	4	100.0	
Thirst and polyurea	4	100.0	0	-	0	-	
Thirst, polyurea and sweating	2	25.0	2	25.0	4	50.0	
Thirst and sweating	6	9.1	12	18.2	48	72.7	

** Fishers exact test, S=Significant.*

There was a significant association between positive past medical history like HT and thyroid diseases and COVID-19 severity (p=0.002). A highly significant association was observed between positive drugs history and COVID-19 severity (p<0.001). No significant differences were observed between patients with different COVID-19 severity regarding family history (p=0.08), smoking (p=0.2) and alcohol history (p=0.5). There was a significant association between positive pregnancy and moderate COVID-19 severity (p=0.002). (***Table 13***)

Table 13: Distribution of clinical history according to COVID-19 severity.

Variable	COVID-19 severity						P
	Mild		Moderate		Severe		
	No.	%	No.	%	No.	%	
Past medical history							0.002*S
No	62	33.7	26	14.1	96	52.2	
HT	6	9.4	8	12.5	50	78.1	
HT and thyroid	0	-	0	-	2	100.0	
Drugs history							<0.001*S
No	68	30.4	34	15.2	122	54.5	
Steroids and others	0	-	0	-	4	100.0	
Others	0	-	0	-	22	100.0	
Family history							0.08* NS
No	64	27.6	30	12.9	138	59.5	
DM	2	14.3	2	14.3	10	71.4	
Others	2	50.0	2	50.0	0	-	
Smoking history							0.2** NS
No	48	27.0	28	15.7	102	57.3	
Yes	20	27.8	6	8.3	46	63.9	
Alcohol history							0.5* NS
No	66	26.8	34	13.8	146	59.3	
Yes	2	50.0	0	-	2	50.0	
Pregnancy							0.002*S
No	68	27.4	32	12.9	148	59.7	
Yes	0	-	2	100.0	0	-	

** Fishers exact test, **Chi-square test, NS=Not significant, S=Significant*.

A highly significant association was observed between sounds of wheezing and crepitation with severe COVID-19 disease (p<0.001). (***Table 14***)

Table 14: Distribution of examination findings according to COVID-19 severity.

Variable	COVID-19 severity						P
	Mild		Moderate		Severe		
	No.	%	No.	%	No.	%	
Added sounds							<0.001*S
No	68	35.4	28	14.6	96	50.0	
Wheezing	0	-	0	-	10	100.0	
Crepitation	0	-	6	15.8	32	84.2	
Wheezing and crepitation	0	-	0	-	10	100.0	

** Fishers exact test, S=Significant*.

No significant differences were observed between patients with different COVID-19 severity regarding blood pressure (p=0.4). Means of pulse rate and respiratory rate were significantly increased among patients with severe COVID-19 disease (p=0.002, p<0.001, respectively). Mean temperature was significantly higher among patients with moderate COVID-19 disease (p=0.02). The mean SPO_2 was significantly lower among patients with severe COVID-19 disease (p=0.001). (***Table 15 and Figure 8***)

Table 15: Distribution of investigations measures according to COVID-19 severity.

Variable	COVID-19 severity			P
	Mild Mean±SD	Moderate Mean±SD	Severe Mean±SD	
Pulse rate	91.2±9.8	93.7±10.4	98±15	0.002* S
BP (mmHg)	118/76±12/5	121/77±9/4	118/76±11/8	0.4* NS
RR (breath/m)	14.6±3	17.1±2.4	22.8±3.8	<0.001* S
Temperature (C°)	37.8±0.4	37.9±0.6	37.5±1.1	0.02* S
SPO_2 (%)	81.3±23.2	89.5±2.5	79.6±9.1	0.001* S

** One-way ANOVA analysis, NS=Not significant, S=Significant*.

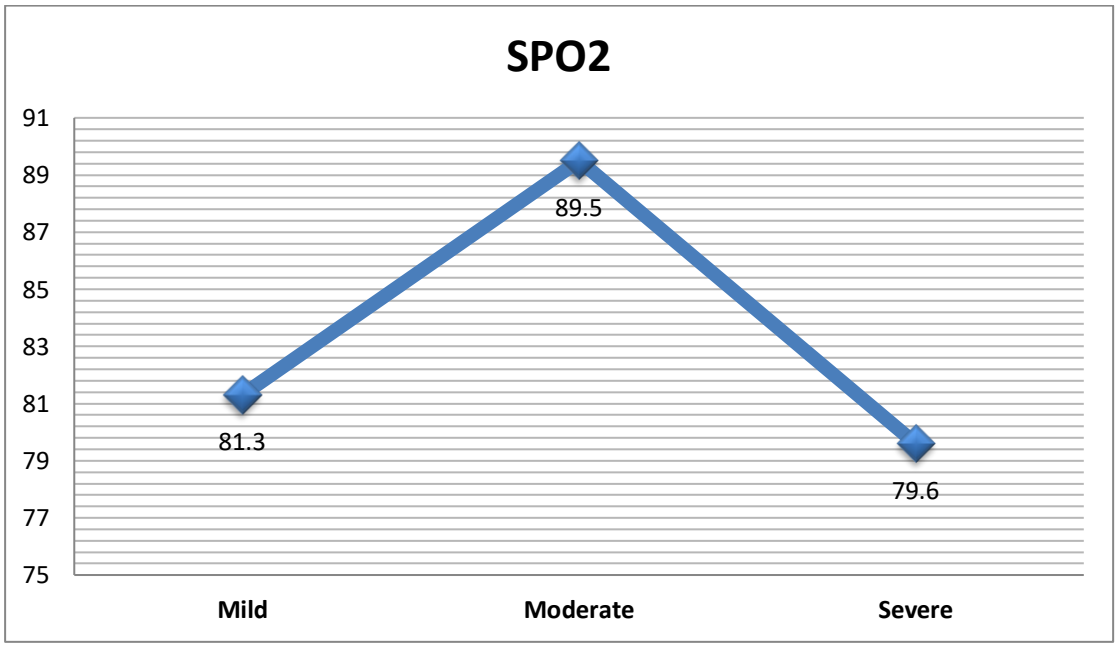

Figure 8: Distribution of SPO_2 according to COVID-19 severity.

Means of RBS and HbA1c were significantly increased among patients with severe COVID-19 disease (p<0.001). Means of CT scan chest occupancy, CRP and D-dimer levels were significantly increased among patients with severe COVID-19 disease (p<0.001). (***Table 16 and Figure 9***)

Table 16: Distribution of investigations measures according to COVID-19 severity.

Variable	COVID-19 severity			P
	Mild	Moderate	Severe	
	Mean±SD	Mean±SD	Mean±SD	
RBS (mg/dl)	100.8±15.4	118.1±13.2	129.3±74	<0.001* S
HbA1c (%)	5.3±0.2	5.8±0.2	7±1.1	<0.001* S
D-dimer level	222.2±198.1	661±1186	573.9±505.8	<0.001* S
CRP (mg/dl)	15.5±11.3	60±67	61.3±43.9	<0.001* S
CT scan chest	14.7±19.6	31.9±24.9	49.3±20.5	<0.001* S

** One-way ANOVA analysis, NS=Not significant, S=Significant*.

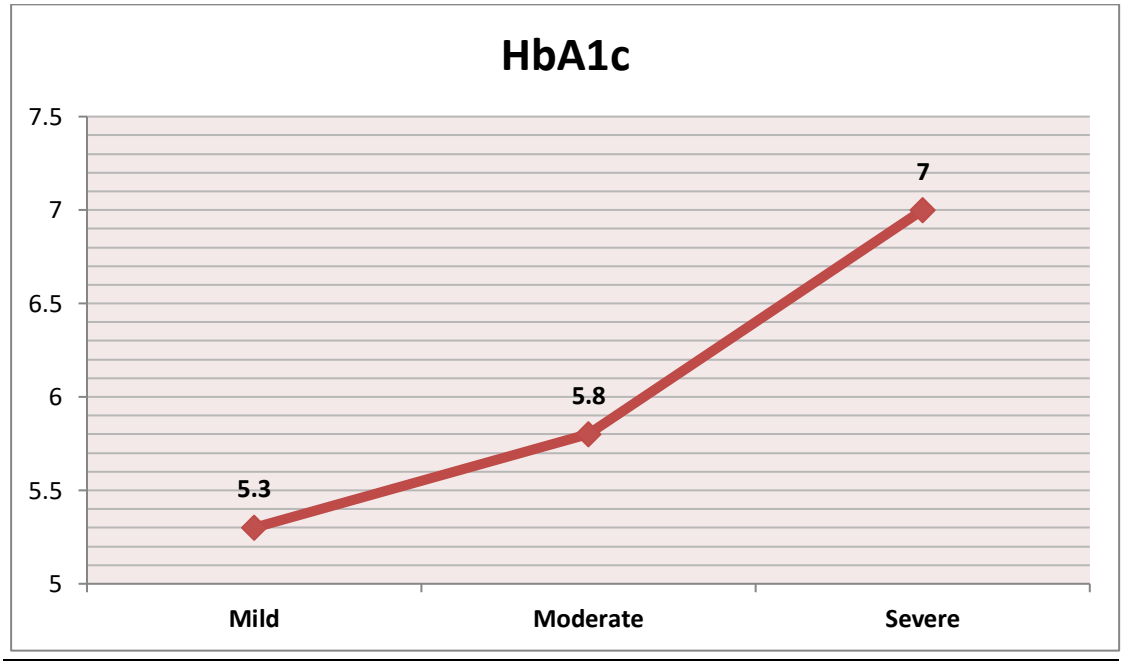

Figure 9: Distribution of HbA1c according to COVID-19 severity.

A significant association was observed between high blood sugar level and severe COVID-19 disease (p=0.01). (***Table 17 and Figure 10***)

Table 17: Distribution of blood sugar level according to COVID-19 severity.

Variable	COVID-19 severity						P
	Mild		Moderate		Severe		
	No.	%	No.	%	No.	%	
Blood sugar							0.01*S
Normal	68	29.6	30	13.0	132	57.4	
High	0	-	4	20.0	16	80.0	

** Chi-square test, S=Significant.*

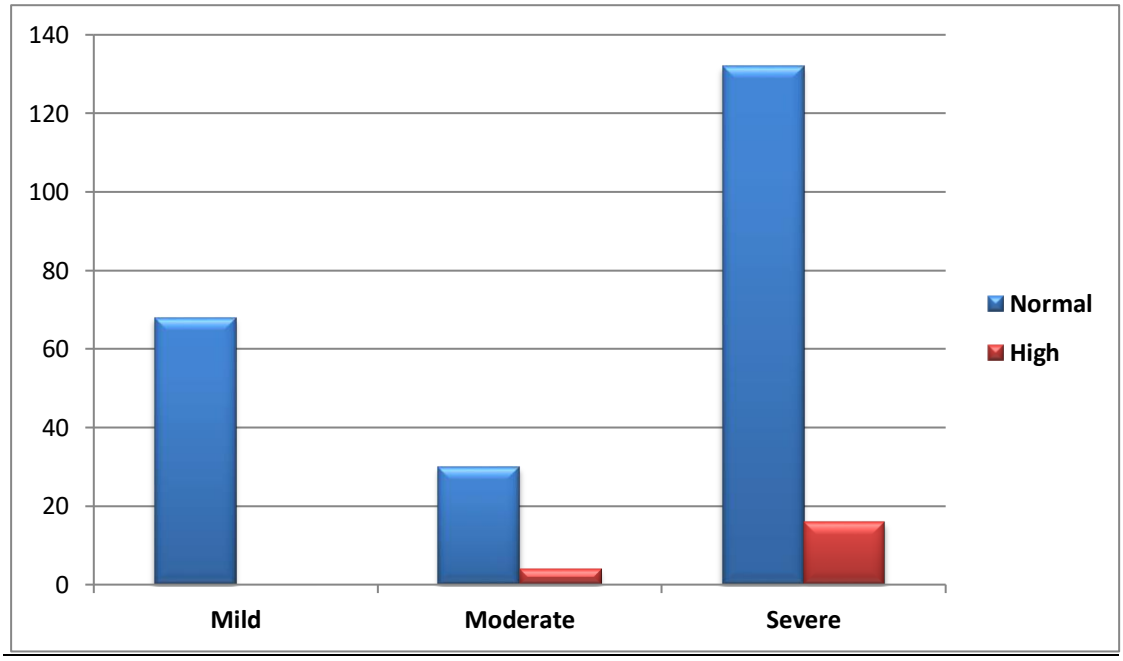

Figure 10: Distribution of blood sugar level according to COVID-19 severity.

Discussion

Earlier literatures of COVID-19 disease recognized the role of diabetes mellitus in the inflammatory response of disease development. Thereafter, the hyperglycemia, regardless of insulin resistance or diabetes mellitus, showed many adverse effects on the course and outcome of

COVID-19 disease. On other hand, the effect of COVID-19 inflammation of the pancreatic β cells lead to newly diagnosed diabetes mellitus [52].

Present study showed that prevalence of hyperglycemia among studied COVID-19 non-diabetic patients was (8%). In Iraq, a study carried out by Sami and Wais reported that hyperglycemia prevalence of 8.4% among diabetic patients is accompanied with severe course of COVID-19 disease required intensive care admission [53]. The prevalence rate of hyperglycemia in our study is lower than prevalence of (14%) reported by Haymana et al [54] nationwide retrospective cohort study on 12,817 non-diabetic patients. Our study prevalence is also lower than results of Zhang et al [55] study in China which reported that (12.5%) of non-diabetic patients had hyperglycemia. Another study carried out in USA by Mamtani et al [56] on 403 COVID-19 patients, showed that (20.6%) of patients with no history of diabetes had hyperglycemia. This low prevalence of hyperglycemia among COVID-19 patients in our study might be attributed to differences in sample size and inclusion criteria between different studies in addition to differences in severity of COVID-19 disease between those studies. However, our study finding is consistent with reports of recent Iraqi study conducted by Al-Kuraishi et al [52] which documented that the corona virus is infecting causing damage to pancreas and inhibiting insulin secretion and development of hyperglycemia among non-diabetic patients. Hyperglycemia relation to inflammation status of COVID-19 is clear among diabetic and non-diabetic patients especially if the patients were obese or pre-diabetic. There is a bidirectional relationship between chronic inflammation and hyperglycemia. Additionally, the hyperglycemia in ill-patients resulted from stress-induced insulin resistance and stimulated glucose production. The changes in immune system like cytokines and chemokines changes,

leukocytic changes and elevated apoptosis rates mainly among obese and diabetic patients referring to the role of inflammation in hyperglycemia development [57, 58]. However, the high blood sugar level is accompanied with insulin resistance and increased inflammatory cytokines levels especially in acute infections such as COVID-19 disease [59, 60]. A recent Chinese study [61] reported that blood glucose control for COVID-19 patients lead to reduction of serum levels of inflammatory markers, increased C-reactive protein and lactic dehyrogenase sensitivity. Another recent Chinese study on 174 confirmed COVID-19 patients stated that inflammatory markers levels were highly increased among diabetic patients as compared to non-diabetic and lead to poorer prognosis [62]. Mirzaei et al [63] study in Iran reported that patients with chronic viral infection, pneumonia, lung inflammation and short hospitalization were at high risk of hyperglycemia and insulin resistance. The hyperglycemia leads to stimulation of oxidative stress, lowering the immune system function, impairment of endothelial function, apoptosis stimulation and lowering the antioxidant. It also leads to decrease the intracellular bactericidal activity, stimulation of inflammation and maximizing the risk of lung disorders, cardiovascular diseases, renal failure and mortality [63].

In current study, 59.2% of COVID-19 cases were severe. This finding is higher than results of Abbas et al [64] prospective study in Iraq which reported that (37.7%) of COVID-19 hospitalized cases in Baghdad center were severe and critically ill patients. This high severity proportion might be due to fact that our center is receiving most of cases in Kirkuk province, while in Baghdad (Capital) many centers are available.

The current study found a significant association was observed between high blood sugar level and severe COVID-19 disease (p=0.01). This finding is in agreement with many literatures such as Sachdeva et

al[65] study in India and Kapoor et al [66] study in USA which reported that hyperglycemia among patients with COVID-19 diseases is related to severe course of the disease and poor outcomes. A recent interventional study carried out in Southern Iraq by Al-Ibrahimi and Nihad [67] revealed that the in-hospital mortality of COVID-19 patients was reduced after their treatment with Metformin. In our study, the mean HbA1c level was significantly increased among patients with severe COVID-19 disease ($p<0.001$). This finding coincides with results of Wang et al [68] retrospective study in China which found that increased HbA1c level was directly linked to inflammation, low oxygen saturation, hypercoagulability and mortality in COVID-19 patients.

The present study showed a highly significant association between increased age of patients and COVID-19 severity ($p<0.001$). This finding is consistent with results of Al-Hijaj et al [69] record-based observational study in Iraq which found that advancing in age increasing severity of COVID-19 disease. Our study found a highly significant association between unemployed patients and COVID-19 severity ($p<0.001$). This finding is inconsistent with results of Mutambudzi et al [70] study in UK which stated that essential workers are at high risk of severe COVID-19 disease. This inconsistency might be attributed to effect of elderly age not the occupation as most of unemployed patients in our study were older in age. Our study also showed a highly significant association between married patients and COVID-19 severity ($p<0.001$). This finding is similar to results of Nkire et al [71] study in Canada which reported that marital status had an effect on severity and outcome of COVID-19 diseases as stress and social behavior had impact on health in general.

The current study found that fever, loss of smell and loss of taste were associated with mild COVID-19 cases, while dyspnea and chest

pain were associated with severe COVID-19 cases. These findings are in agreement with results of Nabavi et al [72] study in Iran which revealed that COVID-19 symptoms with oxygen saturation and CT scan are helpful in prediction of the disease severity. Our study found a significant association between positive past medical history like HT and thyroid diseases and COVID-19 severity (p=0.002). Consistently, Fathi et al[73] systematic review and meta-analysis study reported that clinical co-morbidity is regarded as the common risk factor for severity and mortality of COVID-19 disease. In present study, there was a significant association between positive pregnancy and moderate COVID-19 severity (p=0.002). Similarly, Adhikari et al [74] study in USA revealed that most of pregnant women with COVID-19 diseases developed mild to moderate illness.

The endocrinal symptoms like sweating were significantly related to severe COVID-19 disease (p<0.001). This finding coincides with results of Zhang et al [75] study in China which reported the night sweats as first symptom of COVID-19 pneumonia and severe form of disease. Our study also showed highly significant association was observed between sounds of wheezing and crepitation with severe COVID-19 disease (p<0.001). Wang et al [76] study in China documented that the added sounds are indicators of pulmonary pathological changes and severity of COVID-19 disease. In current study, means of pulse rate and respiratory rate were significantly increased among patients with severe COVID-19 disease. These findings are in agreement with results of many studies like Junarta et al [77] study in USA and Miller et al [78] study in Australia. The mean SPO_2 was significantly lower among patients with severe COVID-19 disease (p=0.001). This finding is consistent with results of Gul et al [79] study in USA. Our study revealed that mean SPO_2 was significantly

lower among patients with severe COVID-19 disease (p=0.001). This finding is consistent with results of Mejía et al [80] study in Peru which reported that low oxygenation among COVID-19 patients predicts the mortality. The current study found that means of CRP and D-dimer levels were significantly increased among patients with severe COVID-19 disease (p<0.001). These findings are in agreement with results of Ullah et al [81] study in USA which found that high levels of CRP and D-dimer levels among hospitalized COVID-19 patients are predictable of mortality. In present study, mean chest CT scan score was significantly higher among severe COVID-19 cases (p<0.001). This finding is consistent with results of Hafez study [82] in Egypt which reported that assessing chest CT scan score is essential in detecting severity of COVID-19 disease.

Conclusions & Recommendations

Conclusions

- The prevalence of severe cases of COVID-19 disease among non-diabetic patients is high.
- High blood sugar and hemoglobin A1c levels among patients with COVID-19 disease are predictable of severity of illness.

- The significant risk factors of severe COVID-19 disease are elderly age, unemployment, marital status, clinical co-morbidity and pregnancy.
- The common clinical symptoms and signs predictive for severe COVID-19 disease are dyspnea, chest pain, sweats, sounds of wheezing and crepitation, high pulse rate, high respiratory rate and low oxygenation of blood.
- Increased levels of D-dimer and C-reactive protein levels with increased of computerized tomography scores are predictive for severe cases of COVID-19 disease.

Recommendations

❖ Encouraging physicians to routinely monitor the blood sugar and hemoglobin A1c levels for non-diabetic patients with COVID-19 disease.

- ❖ Emphasis on hyperglycemia control in non-diabetic severe cases of COVID-19 disease should be taken in consideration to prevent complications.
- ❖ Further national multi-centers studies on prevalence of hyperglycemia among non-diabetic patients with COVID-19 disease must be supported.

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