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THE EFFECT OF PREEXISTING COMORBIDITIES ON CLINICAL SYMPTOMS OF SARS-COV2 INFECTION

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Abstract:

The recent novel coronavirus disease 2019 which is caused by SARS-COV2, is the midst of worldwide panic and global health concern since December, 2019. It has been spread dramatically all over the world and became an important global crisis**.** It is reported that SARS-COV2 infection, in persons with underlying comorbidities have an increasingly bad progression that often-causing death. This retrospective comparative study aims to evaluates some of comorbid conditions in correlation to severity of COVID-19. 400 COVID-19 patients have been recruited from Al-Diwaniyah teaching hospital-Iraq, from 1st of December, 2020 until the end of January, 2021. From what is known of the epidemiological data, COVID-19 patients' who have a comorbidity, such as diabetes mellitus and hypertension, are more likely to develop more severe progression of the SARS-CoV2 infection also, older patients, especially those 65 years and above who have comorbidities and are infected, are more susceptible to get wars manifestations. Patients with chronic disease should take all necessary precautions to avoid SARS CoV-2 infection and should take a good medical care.

Keywords: Critical COVID-19 symptoms , comorbidities, hypertension, diabetes, Iraqi population

INTRODUCTION

The global pandemic corona-virus-2019 disease is one of the unprecedented challenges among infectious disease in recent history, it is caused by sever acute respiratory syndrome virus 2 (SARS-COV2). It is rapidly spread all over the world and became an important public health issue. The severity of clinical outcomes differs among the infected persons, the majority of subjects that have been infected with SARS-COV2 developed mild-to-moderate symptoms and even some of them presented with asymptomatic infection. However, the probability to develop severe disease is very high especially among elderly people and those with comorbidities. Severity of COVID-19 infection and risk of death is always correlated with several underlying risk factors like: gender, age, obesity, chronic disease and other comorbidities that could affect the function of immune system causing development of severe manifestations and eventually death (Sanyaolu, 2020). The comorbidities like; cardiovascular disease, chronic lung and kidney disease, diabetes, immune compromised cases, malignancy and even obesity are the most common underlying risk factors which correlated with deteriorated clinical symptoms and critical COVID-19 (Liu K *et al*., 2020; Zhang J *et al*., 2020).

The inter-association between COVID-19 profile and diabetes mellitus has been heavily studied. Even so, the information in this field is rapidly emerged, with different reports published frequently (Drucker., *et al* 2020). Most available publications did not distinguish between the types of diabetes millitus, but mainly concentrate on Type 2-DM, due to its high prevalence. It was found that hyperglycemia affect the immune system and increase viral replication also, the synthesis and release of pro-inflammatory mediators and the oxidative stress were higher in diabetic patients compared with healthy individuals, that makes outcomes of SARS-CoV-2 infection in diabetics to be worse. High blood glucose level will increase the expression of furin and ACE-2 which may promote the entrance of virus inside the host cell. SARS-CoV2 infection mainly modulates the inflammatory and immune responses, that might cause a cytokine storm, resulting in possible lethal clinical symptoms in diabetic patients. An experimental study suggested that the ACE-2 receptor expressed in beta cells of pancreas and the SARS virus in-variably destroying these beta-cells which cause acute diabetes. The reason of hyperglycemia in diabetic patients during SARS-CoV2 may related to insulin resistance and damage of beta-cells (Jayaswal *et al*., 2021).

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Different studies have been emphasizing the importance of controlling the blood pressure in management of COVID-19 disease (Bozkurt *et al.*, 2020). It is also seen that the most predominant comorbidities that affect COVID-19 outcomes are the cardiovascular disease and hypertension, and often these patients being on ACE inhibitors and Angiotensin receptor blockers medications (Wan *et al.*, 2020). Reports is contradictory on whether these medications cause increased vulnerability or are beneficial to COVID-19 patients (Hofmann *et al.*, 2020). Several studies about SARS-COV2 infection in different countries have been found a correlation between clinical comorbidities and COVID-19 infectivity and/or severity, Biswas M et al., (2021) reported that the presence of medical condition is correlated with sever COVID-19 and increase the relative risk for severe COVID-19 for HT (FF= 1.95, 95% CI: 1.58-2.40, p < 0.0001) and for DM (RR = 1.97, 95% CI: 1.48-2.64). Also, the British Medical Journal (BMJ), (2021) depending on British CDC (2021), documented that most common sever medical illness among COVID-19 patients was cardiovascular disease (30.9%), uncomplicated DM (20.7%), respiratory diseases (17.7%), renal complication (16.2%) and asthma (14.5%). Among 18525 patients, 22.5% (n = 4161) patients being without chronic comorbidities. They concluded that elderly people, male sex, comorbidities and obesity are a risk factor for bad disease prognosis. Similarly, Ge E et al., (2021) a study from Canada noticed that existing number of comorbidities was strongly associated with severe prognosis and rate of death. This study includes 167500 subjects positively infected with SARS-COV2, about half of them (43%, n = 73378) having at least one chronic disease. The most common chronic illness was; HT (24%, n = 40154), asthma (16%, n = 26814) and DM (14.7%, n = 24662). They also noticed that individuals with mortality complication among patients with comorbidities (HR= 2.80, 95% CI: 2.35-3.34, p< 0.001). Also, Honardoost M, (2020), in his meta-analysis study revealed that among 6270 persons, 41% of them have a clinical comorbidity, mainly HT and DM (OR = 2.37, 95% CI: 1.80-3.13) and (OR= 2.61, 95% CI: 2.02-3.3), respectively. The severity of COVID-19 was higher among patients with cardiovascular disease (OR = 4.85, 95% CI: 3.11-7.57). And yet, there is no published study that opposes this finding, rather all studies emphasize the priority of people with chronic disease getting COVID-19 vaccine.

METHODOLOGY

A total of 400 patients with a positive COVID-19 were included in this study, recruited from Al-Diwaniaya Teaching Hospital- Iraq. Both gender and all age group included within study. The work was done during the period from 1st of November, 2020 to the end of February, 2021. All hospitalized COVID-19 cases with confirmed infection diagnosed by RT-PCR on the nasal/throat swab sample were included. The infected individuals with COVID-19 were divided into two groups depending on the severity of sign and symptoms; the 1st group involved 296 infected persons with mild/moderate sings, and the 2nd group contained 104 persons who had been infected with severe symptoms as shown in fig. 1. The study was corresponded with ethics of Al-Diwaniaya teaching hospital and verbal informed had been obtained from all patients participated in the study.

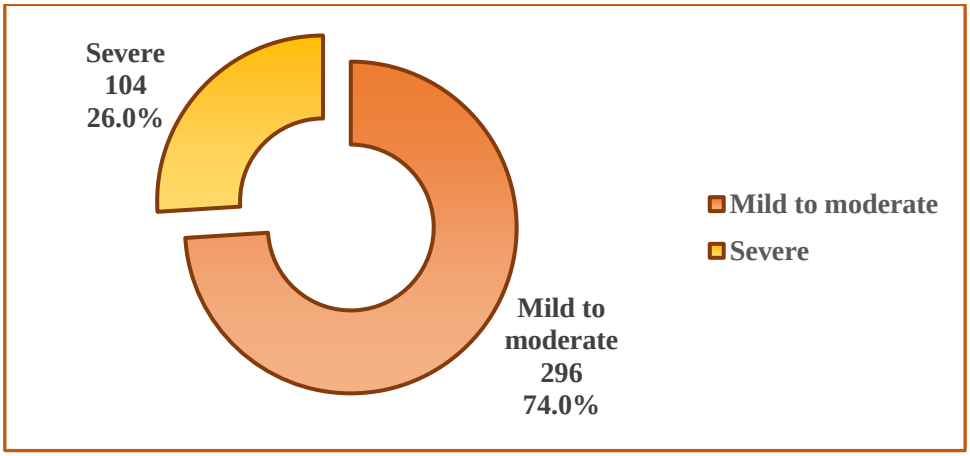

Figure 1: Frequency distribution of patients according to disease severity after combining mild and moderate cases into a single group

Definitions and measures

The clinical severity for COVID-19 was classified depending on the Iraqi Ministry of Health and Environment definitions. Milder case defined as "Patient with mile upper respiratory tract infection, and may have simple symptoms like cough, fever, headache, malaise, nasal congestion sore throat, without evidence of Hypoxia or shortness of breathing". Moderately cases

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are those presented with "mild pneumonia without signs of bad clinical complications. The severe includes patients with "acute respiratory distress, bad pneumonia, Sepsis and/or Septic shock.

Statistical methods

The SPSS version 20 was used for multivariate nominal logistic regression with Likelihood ratio tests to identify factors independently predicting disease severity and mortality. In univariate analysis, categorical parameters underwent Fisher's exact test while continuous numerical parameters underwent Student's T-test. The chi-square test was performed on partial two-by-two contingency tables. The "*p*" value considered significant if its value was <0.05.

RESULTS

Baseline demographic characteristics of patients

This retrospective comparative study has been including 400 patients whom have been infected with SARS-COV2 (300 males and 100 females), 12 patients under 20 years of age, 168 patients between 21 and 40 years, 180 patients between 41 and 60 years and 40 patients above 60 years as it is illustrated in fig.2.

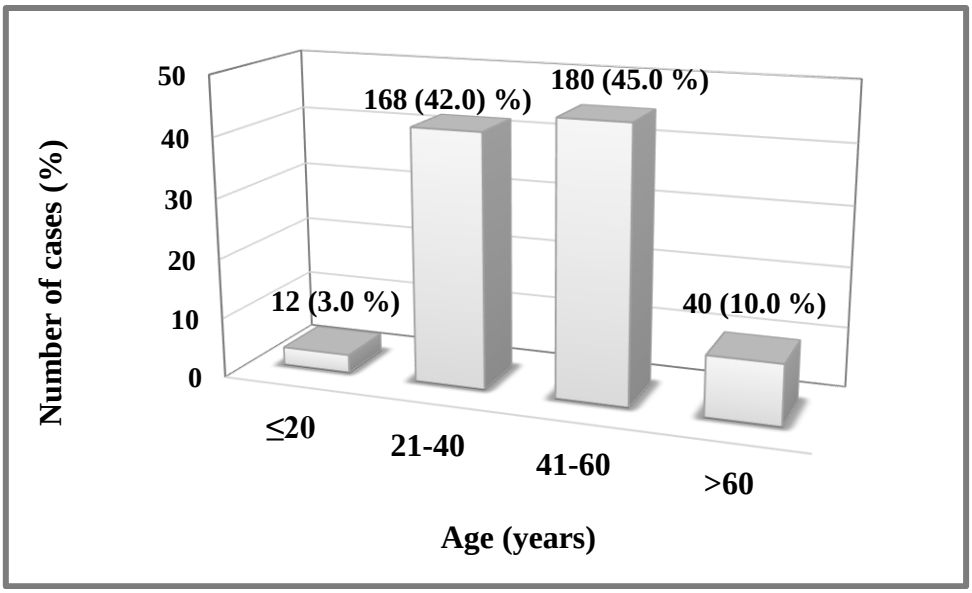

Figure 2: Histogram showing the frequency distribution of patients with SARS-COV2 infection according to age

The mean age of all individuals was 42.26 ±13.54 years with wide range of age variation from 10 to 66. Regarding the severity of SARS-COV2 infection, there was no significant difference in mean age between the mild/moderate group and the severe disease group a mean of 41.34 ±13.16 years versus 44.88 ±14.50 years, respectively (p = 0.2530). However, patients over 60 years of age were more frequently seen in severe disease group than in mild/moderate group (19.2 % *vs.* 6.8 %), respectively. Statistical wise the level of significance was very close to 0.05 (p = 0.068) as in table (1). With respect to gender, the study included 300 males and 100 females with a male to female ratio of three to one. Linked with severity of infection, the females were more frequently seen in the severe disease category than in mild to moderate group (38.5 % *vs.* 20.3 %), respectively.

Table (1): Mean age and frequency distribution regarding age and gender of SARS-COV2 patients among mild/moderate and severe clinical disease

	Mild/moderate ***n*** **= 296**	**Severe** ***n*** **= 104**	**Total** ***n*** **= 400**	***p***
Age (years)				
Mean ±SD	41.34 ±13.16	44.88 ±14.50	42.26 ±13.54	0.253 I NS
Range	10- 66	20- 64	10- 66	

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≤ 20, *n* (%)	8 (2.7 %)	4 (3.8 %)	12 (3.0 %)	0.769 C NS
21-40, *n* (%)	132 (44.6 %)	36 (34.6 %)	168 (42.0 %)	0.375 C NS
41-60, *n* (%)	136 (45.9 %)	44 (42.3 %)	180 (45.0 %)	0.748 C NS
> 60, *n* (%)	20 (6.8 %)	20 (19.2 %)	40 (10.0 %)	0.068 C NS
Gender				
Male, *n* (%)	236 (79.7 %)	64 (61.5 %)	300 (75.0 %)	0.065 C NS
Female, *n* (%)	60 (20.3 %)	40 (38.5 %)	100 (25.0 %)	

n: number of cases, SD: standard deviation, I: independent samples *t*-test, C: chi-square test, NS:

The Frequency Distribution of Patients According to Clinical and Medical History

The rate of chronic disorders such as DM and HT had shown a significant association with sever clinical outcomes as it is illustrated in table (2). Diabetes mellitus was seen in 44 patients (11.0 %), it was more frequently associated with severe group than with mild/ moderate group in a highly significant manner (p < 0.001, 34.6 0% *vs.* 2.70 %), respectively. On the other hand, hypertension was seen in 32 patients (8.0 %) and showed highly momentous association with the severe group rather than with mild/moderate group (p = 0.004, 23.10 % *vs.* 2.70 %), respectively. Both tuberculosis and hyperthyroidism were recorded in 4 cases and were not convincing associated with any group (p = 1.000, p = 0.260), respectively. Removal of parathyroid glands was also seen in four cases and there was no significant association reported with any group (p = 0.260). Regarding drug allergy, it was documented in 8 cases and it was also not significantly associated with any group (p = 1.000).

Table (2): Distribution of patients according to chronic disease and medications

Characteristic	**Mild/moderate *n* = 74**	**Severe *n* = 26**	**Total *n* = 100**	***p***
Diabetes mellitus, *n* (%)	8 (2.7 %)	36 (34.6 %)	44(11%)	< 0.001 C HS
Hypertension, *n* (%)	8 (2.7 %)	24 (23.1 %)	32 (8.0%)	0.004 C HS
Tuberculosis, *n* (%)	4 (1.4 %)	0 (0.0 %)	4 (1.0%)	1.000 F HS
Hyperthyroidism, *n* (%)	0 (0.0%)	4 (3.8 %)	4 (1.0%)	0.260 F NS
Thyroid gland removal *n* (%)	0 (0.0 %)	4 (3.8 %)	4 (1.0%)	0.260 F NS
Drug allergy, *n* (%)	4 (1.4 %)	4 (3.8 %)	8 (2.0%)	1.000 C NS

n: number of cases, **F**: Fischer exact test, **C**: chi-square test, **NS**: not significant at $p > 0.05$

DISSCISION

The results here in table 2 demonstrate the effect of DM and HT and their significant association with severity of clinical manifestations of COVID-19 (p <0.001, p = 0.004), respectively. Diabetes mellitus has been regarded as one of the risk factors for predisposition of SARS-CoV2 infection, on the other hand COVID-19 disease was found to increase the risk of mortality in diabetic patients (Guo *et al.*, 2020). Some of the suggested mechanisms to explain this situation will be discussed in the context of the text. During early phase of SARS-CoV 2 infection the high blood glucose level in diabetic patients is not considered as a dependent risk factor for sever COVID-19 (Zhang *et al.*, 2021). Rather than the high blood glucose level will be associated with severe pancreatic issues that can consequently lead to complicate the pancreatic condition (Scheen *et al.*, 2020). Another explanation regarding DM and its

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association with sever prognosis of COVID-19 it might be that the high glucose may serves as a fuel to the virus. Once the virus enters the host cell it will trigger the immune cells to produce pro-inflammatory cytokine. Higher glucose level means a successful replication of virus inside the cell, by the time the virally infected cell will produce a high toxic product causing lung tissue damage such as; reactive oxygen species (ROS), also the virus will reduce the T- cell capability of killing to kill the virus itself. Diabetes if not well controlled, can results in a fatal complication due to elevated glucose level that also could increase the titer of ACE2 receptor on immune cells like monocyte and macrophage which facilitate the viral entrance into these cells that supposed to help in virus killing. Observational studies indicate that COVID-19 is associated with an increased risk of diabetic ketoacidosis and hyperglycemia, since dysregulation of ACE2 pathway may cause alteration in glucose metabolism (Rubino F *et al*., 2020; Alkundi A *et al.,* 2020). Also the variable and fluctuation in level of some biomarkers like: D-dimer, alkaline phosphatase (ALP), C-reactive protein (CRP), blood urea nitrogen (BUN), alanine aminotransferase and lactate dehydrogenase (LDH) were reported in a diabetic infected patient and were considered an important factors correlated with the higher blood glucose level in diabetic patients (Zhu *et al*., 2020; Li X *et al*., 2020). Several researchers reported that there was a tangible difference between diabetic and non diabetic patients infected with SARS-CoV2A (Li H *et al*., 2020). Current analysis done by Yang *et al*., (2020) revealed that diabetic patients had a higher risk of sever COVID-19 (79%) compared to non-diabetics infected patients. Yan et al., (2020) found that, of 258 hospitalized COVID-19 patients, 63 of them were with diabetes found to be more likely to develop critical disease conditions.

The hypertension it has been gained popularity among physicians and researchers due to its highly representation among patients with COVID-19 disease (Schiffrin *et al*., 2020). Almost all available evidence suggests that pre-existence of HT and cardiovascular illness has been linked with bad prognosis. The exact reason is not well known and the suggested mechanism that links the pre-existence of hypertension and COVID-19 are not fully assessed yet, but it could be related to imbalance of RAS. The normal activation of RAS (ACE/Ang II/AT_1R) pathway in parallel with non-traditional (ACE2/Ang 1-7/Mas) pathway down regulation was suggested to be the underlying factors that leads to severe COVID-19 outcome in hypertension (Vieira *et al*., 2021; Lanza *et al*., 2020). In addition, hypertension is seeming to be associated with endothelial cells dysfunction and elevated level of pro-inflammatory cytokine, which involves higher levels of Ang II, cytokines like interleukin-6 and tumor necrosis factor-α, in addition to other chemokines Therefore, RAS imbalance that favors the pro-inflammatory state is supposed to be the main axis in pathophysiological mechanisms of COVID-19 (Costa *et al*., 2020). This dysregulation is might be due to the anti-hypertensive medications that taken by the hypertensive patients, specially angiotensin blocker and ACE inhibitor, these drugs lead to upregulation of ACE2 receptors that used by virus to enter the host cell and increase the infectivity rate. At the same time, the dysregulation of ACE2 expression in HT patients with SARS-COV2 will cause un-efficient immune response and uncontrolled release of proinflammatory cytokines which assumed to cause a more severe outcomes and then leads to development of cytokine storm (Olbei M *et al*., 2020). Several studies and reports have been examined the prevalence of hypertension coincidence with COVID-19 infection: Wu C et al., (2020) have been noticed that the mortality rate of SARS-COV2 is elevated up to 49% in presence of hypertension. another meta-analysis study of 2552 cases of COVID-19 suggested that the hypertension may a clinical predictor for sever SARS-CoV infection mainly in people over 60 years of age (Lippi G *et al*., 2020). Also, a retrospective cohort study from China, includes191 confirmed COVID-19 patients reveals an apparent high mortality in patients with hypertension, 48% versus 23% of survivors (Zhou *et al*., 2020).

CONCLUSIONS

Both diabetes millitus and hypertension have a serious impact on susceptibility and/or severity of COVID-19. The severity of disease mainly affected by the status of blood glucose level. Regarding the hypertension, the types of anti-hypertensive medications may have a role.

RECOMMENDATIONS

People with diabetes mellitus and hypertension should be aware and careful to avoid SARS-CoV 2 infection, since COVID-19 can increase blood glucose levels and the high blood pressure can cause severe complications. The patients with these comorbidities should check their glucose level more frequently than previously and should control their blood pressure by continuing to take their medications as prescribed under medical supervision.

ACNKOWLEGMENT

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