TumerNecrosis in COVID19 and Dibates

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Abstract

Background: The World Health Organization (WHO) and health authorities have devoted significant attention to understanding risk factors for coronavirus disease 19 (COVID-19) and their role in disease outcomes including tumer necrosis factor. In addition, diabetes may lead to lung dysfunction, such as decreased forced expiratory volume and forced vital capacity. Therefore, diabetes could possibly be a risk factor for covid-19. Our study aims to investigate the clinical characteristics of patients with severe covid-19 with diabetes mellitus, and the association of diabetes with the outcome in patients with severe covid-19.

Materials and Methods: This study was carried out in a period between November 2021 and March 2022, blood was taken from patients (80) with covid-19. Samples were taken from patients who were present in Al-Zahraa teaching hospital in Iraq. A total of samples were subjected to laboratory examinations including Tumor necrosis factor α using specific ELISA Kit.

Result: The result of this observational study was depending on the analysis of data from 80 COVID-19 patients. All selected sociodemographic features, disease indicators, and history of chronic disease were listed as frequencies and percentages. The mean age was 52 years old. The SPO2 for those patients was ranged from 79 to 95% with a mean equal to 90.10 ±3.48. All patients showed elevated CRP value with a mean = 83.52. More than half of the sample (52.5%) were females and near half of the (48.8%) were overweighted when calculate their BMI. The majority (92.5%) mentioned having no family history of diabetes mellitus and 95% of them have no any other diagnosed chronic disease. Near two thirds (67.5%) were prescribed steroid in the treatment regime for their COVID-19 infection. Mean difference of TNF was tested among positive Covid-19 having diabetic status, results showed that

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INTRODUCTION

The Covid 19coronavirus (Covid-19), H5N1 influenza A, H1N1 2009 and Middle East respiratory syndrome coronavirus (Covid 19) cause acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) which leads to pulmonary failure and result in fatality. These viruses were thought to infect only animals until the world witnessed a Covid 19 (COVID-19) outbreak caused by Covid-19, 2002 in Guangdong, China (1). Only a decade later, another pathogenic coronavirus, known as Middle East respiratory syndrome coronavirus (Covid 19) caused an endemic in Middle Eastern countries (2).

The incidence of type 2 diabetes mellitus (T2DM) is increasing worldwide, and diabetes is one of the leading causes of morbidity and mortality globally among chronic diseases (3). Among chronic comorbidities of COVID-19, diabetes had the second highest incidence rate (7.4%–19.0%), following hypertension (15%–30%) (4). Patients with diabetes were likely at higher risk for severe COVID-19 and mortality (5). The IL-6, ferritin, C-reaction protein, and D-dimer levels were significantly increased in patients with diabetes, suggesting that a marked inflammatory cytokine storm was associated with a more pejorative prognosis compared to patients without diabetes (6).

Diabetes has been reported as a high risk of death in two earlier coronavirus infections of SARS and the Middle East respiratory syndrome (MERS) (7). Data about the immune and inflammatory response of COVID-19 in patients with diabetes is limited at present. Increased inflammatory susceptibility and enhanced disease severity is observed in patients of COVID-19 with diabetes, which is associated with increased intensive care unit admission. The cytokine storm is often associated with dysregulation in glucose metabolism, which results in a metabolic and energetic failure (8). The hyperglycemia is thought to provide glucose to leukocytes without the support of insulin; therefore, the glucose uptake of leukocytes may not be influenced in patients with insulin resistance or insulin deficiency (9). In one study, it was investigated the incidence of abnormal glucose metabolism in COVID-19 patients and to discuss whether there are any differences in immune and inflammatory response of patients with or without diabetes (10). Accumulating evidence suggests that a subgroup of patients with severe COVID-19 might have a cytokine storm syndrome, which was proposed to play a critical role in the pathogenesis of COVID-19 (11). It was reported that the ICU patients with COVID-19 infection had higher plasma levels of TNF levels . Especially, significant increased IL-6 levels might be associated with the mortality due to the virally driven hyperinflammation(12).

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MATERIALS AND METHODS:

Samples collection

Blood was taken from patients (80) with covid-19 through a skilled and professional procedure. Samples were taken from patients who were present in Al-Zahraa teaching hospital in Iraq on patients according ethic committee.and the samples were sent to Al-Karama laboratories (virology and immunity) . A total of samples were subjected to laboratory examinations including Tumor necrosis factor α using specific kit ELISA Kit (13).

Procedure of Mouse Tumor necrosis factor α (TNF) ELISA Kit

Reagent Preparation: all reagents should be brought to room temperature before use. Standard reconstitute the 120µl of the standard (32ng/ml) with 120µl of standard diluent to generate a 16ng/mlstandard stock solution. Allow the standard to sit for 15 mins with gentle agitation prior to making dilutions. Prepare duplicate standard points by serially diluting the standard stock solution (16ng/ml) 1:2 with standard diluent to produce 8ng/ml, 4ng/ml, 2ng/mland1ng/mlsolutions. Standard diluent serves as the zero standard(0 ng/ml). Any remaining solution should be frozen at -20°C and used within one month. Dilution of standard solutions suggested are as follows: In order to prepare serial dilutions from stock standard it was taken 120 ul Original Standard + 120 ul Standard diluents to prepare 16 ng/L (Standard No.5), 120 ul Standard No.5 + 150ul Standard diluents to prepare 8 ng/L (Standard No.4), 120 ul Standard No.4 + 120 ul Standard diluent to prepare 4 ng/L (Standard No.3), 120 ul Standard No.3 + 120 ul Standard diluent to prepare 2 ng/L (Standard No.2), 120 ul Standard No.2 + 120 ul Standard diluent to prepare 40 IU/L (Standard No.1).Wash buffer dilute 20ml of wash buffer concentrate 25X into deionized or distilled water to yield 500 ml of 1x Wash Buffer. If crystals have formed in the concentrate, it was mixed gently until the crystals have completely dissolved. All reagents, standard solutions and samples as instructed were prepared at room temperature. It was determined the number of strips required for the assay. It was inserted the strips in the frames for use. The unused strips should be stored at 2-8°C. It was added 50µl standard to standard well. Note: Don't add antibody to standard well because the standard solution contains biotinylated antibody. It was added 40µl sample to sample wells and then add 10µl anti-TNF antibody to sample wells, then add 50µl streptavidin-HRP to sample wells and standard wells (Not blank control well). It was removed the sealer and wash the plate 5 times with wash buffer. Soaked wells with at least 0.35 ml wash buffer for 30 seconds to 1 minute for each wash. For automated washing, it was aspirated all wells and wash 5 times with wash buffer, overfilling wells with wash buffer. Blot the plate onto paper towels or other absorbent material. It was added 50µl substrate solution A to each well and then add 50µl substrate solution B to each well. Incubate plate covered with a new sealer for 10 minutes at 37°C. It was added 50µl stop solution to each well, the blue color will change into yellow immediately. It was determined the optical density (OD value) of each well immediately using a microplate reader set to 450 nm within 10 minuets after adding the stop solution.

Statistical Analysis

Data were entered, coded, and analyzed in SPSS (statistical package for social sciences) software program version 26. Data analysis were done using different tests. Frequency and percentages were used for the description of categorical variables. The mean and standard deviation were used to describe the continuous variables. Both Chi-square and Fisher's exact test were used for the assessment of the association between categorical variables. For the differences between means in continuous variables, the independent sample t-test, one way ANOVA test were used accordingly. Spearman correlation coefficient was used to assess the presence of correlation in non-normally distributed variables. A P-value equal to or less than 0.05 was considered significant. A bar chart was also used for the graphical presentation of the data.

RESULTS

Demographic features and disease history relation to COVID-19 patients

The result of this observational study was depending on the analysis of data from 80 COVID-19 patients admitted to AL-Zahra Teaching Hospital. All selected sociodemographic features, disease indicators, and history of chronic disease were listed as frequencies and percentages in table (3-1). The mean age was 52 years old. The SPO2 for those patients was ranged from 79 to 95% with a mean equal to 90.10 ±3.48. All patients showed elevated CRP value with a mean = 83.52.

More than half of the sample (52.5%) were females and near half of the (48.8%) were overweighted when calculate their BMI. The majority (92.5%) mentioned having no family history of diabetes mellitus and 95% of them have no any other diagnosed chronic disease. Near two thirds (67.5%) were prescribed steroid in the treatment regime for their COVID-19 infection.

Table (3-1) Sociodemographic features and disease history of the studied 80 COVID-19 patients admitted to the hospital.

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Sociodemographic features	Minimum – Maximum	Mean	Standard Deviation
Age (Years)	25-90	52.10	17.71
SPO2* (%)	79-95	90.10	3.48
CRP** (mg/L)	55.11-120.56	83.52	15.63
Variables	**Categories**	**Frequency**	**Percent**
Sex	Female	42	52.5%
	Male	38	47.5%
BMI *** (kg/m2)	Under weight	3	3.8%
	Normal	30	37.5%
	Over weight	39	48.8%
	Obese	8	10.0%
Diabetes mellitus	Yes	60	75.0%
	No	20	25.0%
Family history of diabetes	Yes	6	7.5%
	No	74	92.5%
Presence of other chronic diseases	Yes	4	5.0%
	No	76	95.0%
Treatment (Steroid)	Yes	54	67.5%
	No	26	32.5%

*SPO2: Saturation of Peripheral Oxygen.

**CRP:C-

Reactive Protein.

***BMI: Body Mass Index.

Mean difference in TNF among positive Covid-19 with diabetes

In this study mean difference of TNF was tested among positive Covid-19 having diabetic status, results showed that TNF was higher in non diabetic status (p=0.220), table (3-2).

Table (3-2) Mean difference in T.N.F. value among patients

COVID-19 patients		TNF* value		P-value (independent sample t-test)
		Mean	Standard Deviation	
Diabetes status	Yes	16.75	23.05	0.220
	No	27.90	37.32	

*Tumor Necrosis Factor-α.

Discussion

After the emergence of a novel coronavirus (Severe Acute Respiratory Syndrome-CoronaVirus-2 [SARS-CoV-2]) in China, a pandemic has spread worldwide, clinical manifestations of SARS-CoV-2 infection have been designated as COVID-19. The epidemic that originated in the Hubei province in China spread to over 60 countries, with western Europe and the US being particularly severely affected by COVID-19 (14). Data from China and Italy suggest a case-fatality of 2.3% in patients with COVID-19, with more than 50% of the fatalities occurring in patients 50 years of age or older (15).

In current study the mean age was 52 years, these outcomes were agreed with Grasselli, Zangrillo et al. (2020) showed that largest reported series from Northern Italy, case-fatality in patients 64 years or older was 36% compared with 15% in younger patients (16). Goujon, Natale et al. (2020) figures also revealed that more cases are notified among patients aged from 55 years old, and higher numbers of positive cases are reported among aged from 15 to 55 years and above 80 (17). On the other hand early in the pandemic, before interventions were widely implemented, contacts concentrated among individuals of similar age were the highest among school-aged children, between children and their parents. However, with the advent of nonpharmaceutical interventions, these contact patterns changed substantially. By mid-August 2020, although schools reopening facilitated transmission, the resurgence in the United States was largely driven by adults 20 to 49 years of age (18). Data from China showed that infants and school-aged children and teens had almost no contact to similarly aged children and teens in the first weeks after stay-at-home orders and reduced contact intensities with older individuals (19).

More than half of the sample (52.5%) were females in this study these data were in consistence with Bai et al., (2022) recorded that factors that were found to be associated with a higher risk of developing "long COVID" syndrome were female gender. Individuals affected by SARS-CoV-2 infection with the aforementioned features should be early identified and involved in follow-up programmes(20). In addition a high rate of early phase of disease has been reported in covid19, this could turn out in a more favourable outcome in women, but might play a role as well in perpetuating disease manifestations. Furthermore, we might hypothesise that women are in general more attentive to their body and related distress (21). But our outcomes were disagreed with Abate and Mekonnen (2020) as socio-demographic characteristics among 392 study participants, 387 (98.5%) participated in the study. Out of the 387 participants, 203 (52.5%) were males (22). Sixty studies were included in the review and data from 46 studies (n = 141,550) were available for meta-analysis.

A majority (58%) of papers reported men to have higher intentions to get vaccinated against COVID-19. Meta-analytic calculations showed that significantly fewer women stated that they would get vaccinated than men, OR 1.41 (95% CI 1.28 to 1.55). This effect was evident in several countries, and the difference was bigger in samples of health care workers than in unspecified general population samples (23).

Near half of the (48.8%) were over weighted when calculate their BMI in current study, these information were consistence with the WHO estimated that the global prevalence of obesity had increased nearly 3-times from 1975 to 2016, in 2016, 39% of adults were reported as overweight; on the other hand, 13% were obese (24). In the context of the COVID-19 pandemic, obese people are more susceptible to the worse outcome of COVID-19 symptoms, however, the rate of overweight during the pandemic (34.9%) is remarkably similar to the previous studies, where 38.8% and 37.3% of the participants increased their body weight on an average of 2.6 kg between 1 to 3 kg, respectively. In contrast with overweight situations, the prevalence of underweight (0.3%) and normal (4.1%) status have lessened during the COVID-19 pandemic (25, 26).

The majority (92.5%) mentioned having no family history of diabetes mellitus in present study, our results were agreed with Farag, Hassanin et al. (2021) as the goal of the study was to determine the frequency of newly diagnosed diabetes mellitus (DM) and its different types among COVID-19 patients, and to check the glycemic control in diabetic cases for three months. After excluding known cases of DM, 570 patients with confirmed COVID-19 were studied. All participants were classified as non-diabetic or newly discovered diabetic, DM patients without family history were highly prevalent (27). As compared to non-diabetic patients, the newly diagnosed diabetic patients had significantly older age (57.7 ± 11.4, vs. 46.4 ± 10, p < 0.001), higher BMI (32 ± 9 vs. 25 ± 4.5, p < 0.001), and positive family history of diabetes (44.2% vs. 4.5%,
p < 0.001) (28).

While Alvarado-Vasquez (2021) recorded that in previous evidence has shown the presence of relation in healthy subjects with a family history of type 2 diabetes (FH-DM2), it was hypothesized that an FH-DM2 should be considered an important risk factor, since the individuals with this background develop an early endothelial dysfunction, which would increase the susceptibility and severity of infection and damage to the endothelium, in the patient infected with the SARS-CoV-2, additionally Mantovani, Byrne et al. (2020) mentioned the same results (29, 30).

The majority 95% of patients have no any other diagnosed chronic disease in this study, these were compatible with Altuntas, Yilmaz et al. (2021) the average age of the patients studied were 61.4 years. While the average symptom duration was 8.2 days; total hospitalization period was 13.1 days. The average length of stay of patients (n = 75) who were sent to intensive care unit was 10.1. The common chronic diseases were most common among patients and the most one was hypertension with 47.2%, heart disease (27.5%) (31). Although the virus infects individuals of all ages; it is known that people at an older age and with concomitant chronic diseases have more severe symptoms. Studies show that among the the increasing number of cases mostly affected populations are people with previously known chronic diseases (32).

Near two thirds (67.5%) were prescribed steroid in the treatment regime for their COVID-19 infection, the role of various corticosteroids in the management of COVID-19 is evolving. Following an initial lack of evidence, the relatively novel data, supporting the survival benefit to severe and critical COVID-19 patients, is of limited scale, using of these drugs were 97.8% (33), steroids halt the production of cytokines and thereby have a potent anti-inflammatory effect, therefore their using was exceeded 99% in all cases (34), their use is not confined to the intensive care unit (ICU) patients; the use of steroids in non-ICU COVID-19 patients resulted in a reduced transfer to ICU, lower intubation rates and a decrease in mortality our finding were agreed these studies (35). Our finding were agreed with these studies.

Hyperglycemia and insulin resistance promote the increased synthesis of glycosylation end products (AGEs) and pro-inflammatory cytokines, oxidative stress, and stimulating the production of adhesion molecules that mediate tissue inflammation. This inflammatory process could be the underlying mechanism that contributes to increased infection susceptibility and poorer outcomes in diabetic patients (36). Although diabetes is related to decreased glucose availability in tissues that depend on insulin for glucose absorption, prolonged or random rises in blood glucose levels cause damage and dysfunction in tissues that do not rely on insulin for glucose uptake. In terms of clinical manifestations, this injury causes neuropathy, nephropathy, ataractogenesis, retinopathy, and an

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elevated risk of cardiovascular disease, notably atherosclerosis. The mechanisms of the secondary complications of diabetes are not well understood, but metabolic abnormalities such as increased levels of inflammatory cytokines, osmotic and oxidative stress, altered protein kinase C (PKC) activity, and non-enzymatic glycation of proteins are considered important causative factors are contributing to tissue ninjury and dysfunction associated with long-term diabetes. Collectively, these changes result in dysregulated cell growth and apoptosis, several non-diabetic patients developed hyperglycemia during covid19 infection and correlated with the severity of covid 19 infection in diabetic patients such as TNF-alpha levels as prognosis factors in circulations of diabetes mellitus patients with COVID19 and predisposing patients with severe infection (37).

Current data were consistence with Brenner, Ungaro et al. (2020) and with Feldmann, Maini et al. (2020) (38) as increasing age, comorbidities, and corticosteroids are associated with severe COVID-19 among patients, although a causal relationship cannot be definitively established. Notably, tumor necrosis factor antagonists do not appear to be associated with COVID-19 with DM (39). But current data were not as the same with Han et al. (2021) as ANOVA test showed a significant cant high p-value of 0.0005 for TNF, correlated with hyperglycemia in none diabetic patients during COVID19 infection, TNF alpha can be an excellent predictive test for the development of diabetes mellitus in none diabetic COVID 19 patients and predicts severe stages of COVID19 infection (40). the results were not corresponded with the study of Hussain A et al. (2020) (36).

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