

ORIGINAL ARTICLE

GASTROINTESTINAL AND METABOLIC DISTURBANCES IN POST-COVID-19 DISEASE OUTCOMES

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Saif M. Hassan¹, Mohammed J. Jawad², Mahmood J. Jawad¹, Ahmed R. Abu-Raghib³, Najah R. Hadi⁴¹AL-ZAHRAWI UNIVERSITY COLLEGE, KARBALA, IRAQ²UNIVERSITY OF KARBALA, KARBALA, IRAQ³AL-NAHRAIN UNIVERSITY, BAGHDAD, IRAQ⁴UNIVERSITY OF KUFA, KUFA, IRAQ

ABSTRACT

The aim: Recognizing gastrointestinal symptoms that precede COVID-19 respiratory difficulties may be crucial for effective early detection and treatment.

Materials and methods: A total of 200 individuals with the post-covid-19 symptoms for both genders in clinical private and hospital COVID-19 verified by polymerase chain reaction were tracked until they recovered. To evaluate the duration of symptoms as a predictor of COVID-19 prognosis, we proposed a link between gastrointestinal symptoms, metabolic disturbances and disease severity. Glucose disturbances were observed in 65 percent of participants, higher D-Dimer plasma levels have been found in 77 percent of participants, and ferritin plasma levels were found in 62 percent of participants.

Results: While gastrointestinal symptoms were common, with nausea accounting for 51% of participants, an increase in appetite accounting for 76% of patients, and anal fissure accounting for 30% of participants. Both metabolic and GIT symptoms disturbances impact a large percentage of men.

Conclusions: Our conclusion was any patient with covid-19 must need to follow up for at least 1 month after recovery to notified of the post-covid symptoms especially the male gender

KEY WORDS: Covid-19, post-Covid symptoms, S. ferritin, glucose disturbance, and D-dimer

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INTRODUCTION

On 31 December 2019, the World Health Organization was alerted to a cluster of pneumonia patients in Wuhan City, China. Moreover, one week later, on 7 January 2020, Chinese authorities confirmed that they had identified a novel coronavirus as the cause of pneumonia that is related to the same family of viruses that causes "Severe Acute Respiratory Syndrome" SARS and some types of the common cold. The proposed interim name of the virus is "2019 novel coronavirus" or "2019-nCoV", after that called Coronavirus Disease 2019 (COVID-19) [1]. Most of COVID-19 cases in this locality were male from urban areas. The common onset symptoms were the fever, sore throat and dyspnea or cough. Majority of cases were isolated and treated at home. The estimated case fatality rate was within the global range (2.4%) [2]. COVID-19 is causing a lot of concern because of its respiratory symptoms. Furthermore, patients with COVID-19 sometimes develop gastroenteritis and other digestive disturbances via alteration of intestinal permeability, resulting in enterocytes dysfunction [3]. The viral load of coronavirus appeared in the feces of 54% of the infected patients [4] that's lead to intestinal barrier integrity is disrupted, and gut micro-organisms can activate innate and adaptive immune cells, causing proinflammatory cytokines to be released into the circulatory system, resulting in systemic inflammation.

Through dendritic cells, some intestinal signaling pathways can control inflammation; therefore, Immunomodulation of innate host immunity via epithelial receptor activation could be a new therapeutic strategy for eradicating SARS-CoV-2 in the early stages of infection [5]. ACE2 receptors are found in epithelium cells in the lungs, small intestine, and colon, tubular cells in the kidney, neuronal and glial cells in the brain, enterocytes, vascular endothelial cells, smooth muscle cells, and cardiomyocytes, amongst many other human cells susceptible to viral infection(6). S-protein of the virus was binding to ACE2 receptors caused down-regulation of endogenous anti-viral mediators, upregulation of NF-κB pathway, ROS and pro-apoptotic protein(7). The SARS-CoV-2 activity could cause ACE2 modifications in the gut that increase susceptibility to intestinal inflammation and diarrhea, therefore, A probable link for gut microbiota dysbiosis in this interplay is ACE2 imbalance, which is likely a crucial role for poor outcomes in COVID-19 patients with prior comorbidities(8).

THE AIM

Recognizing gastrointestinal symptoms that precede COVID-19 respiratory difficulties may be crucial for effective early detection and treatment.

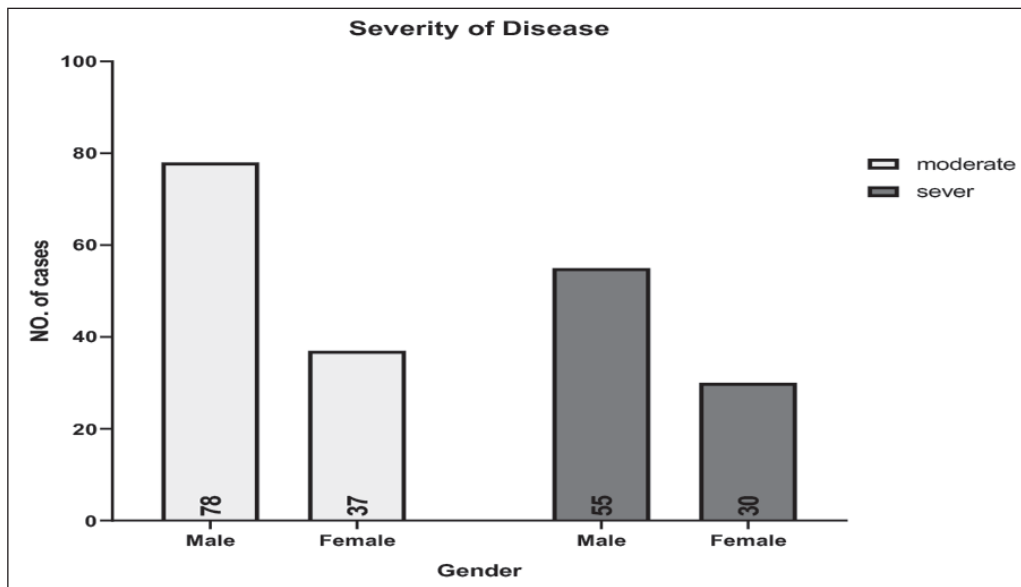


Fig. 1. The severity of disease between the genders. The male gender showed high number of cases for both moderate and sever cases

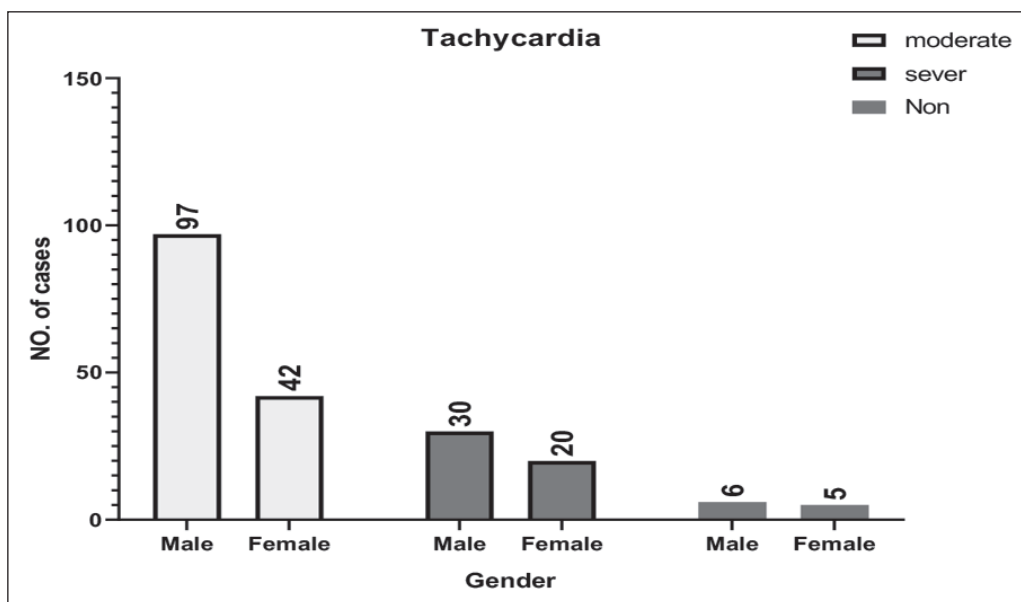


Fig. 2. The number of tachycardia cases between the genders. The male gender showed high number of cases for both moderate and sever cases

MATERIALS AND METHODS

Patients with Covid-19 were included in an online survey that ran from December 1, 2020, to April 4, 2021. The WHO recommended that all patients be diagnosed using the RT-PCR method. A total of 200 COVID-19-positive patients from various provinces in central and southern Iraq were studied (wasit, Babylon, Diwaniya, Basra, etc.). Al-Zahrawi University College's Human Research Ethics Committee gave their approval to the project. The survey included demographic questions (age, gender, education, and employment/student status), health-related questions, and questions about the risk of COVID-19, as well as changes in personal, social, and occupational functioning as a result of the pandemic.

DATA COLLECTION

Clinical features were documented using a yes/no questionnaire that assessed each patient about constitutional symp-

toms (fever, severity of disease), cardiovascular symptom (tachycardia), neurological symptoms (headache, loss of taste, and loss of smell), metabolic symptoms (glucose level, D-dimer, and ferritin) and GI symptoms (nausea, appetite, and anal fissure). The following WHO criteria were used to define diarrhoea in this study: three or more loose stools per day, or a higher quantity of motions than normal.

STATISTICAL ANALYSIS

The descriptive statistics of categorical variables were represented by counts and percentage, the association between age groups, place of isolation, underlying comorbidity, clinical symptoms and severity of disease was analyzed by application of One-way ANOVA test was used as appropriate at level of significance $\alpha = 0.05$. All statistical analyses were applied using SPSS 26.0 for Windows and graphs were draw by using GraphPad prism v 8.

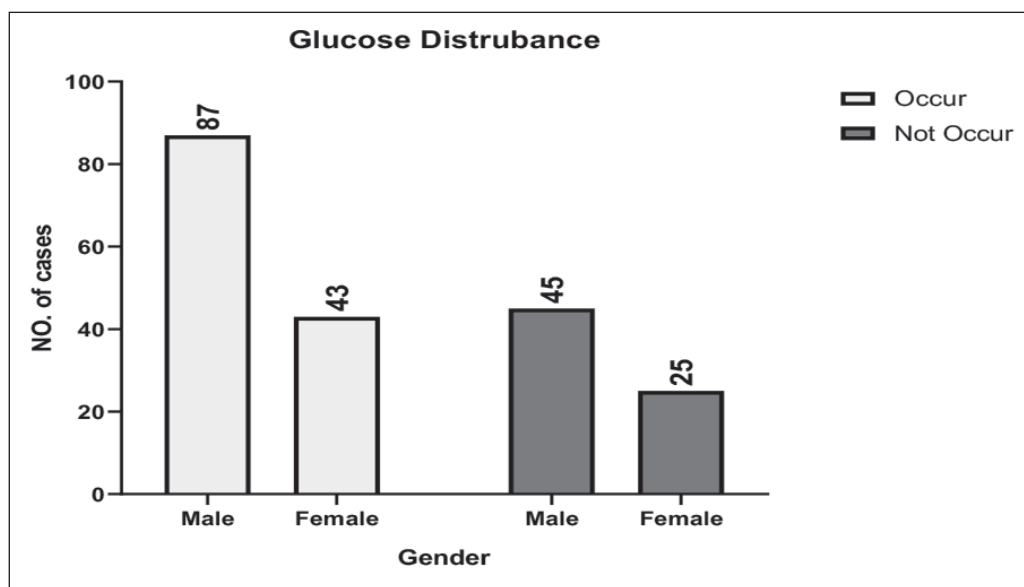


Fig. 3. The number of Glucose Disturbances cases between the genders, the male gender showed high number of cases

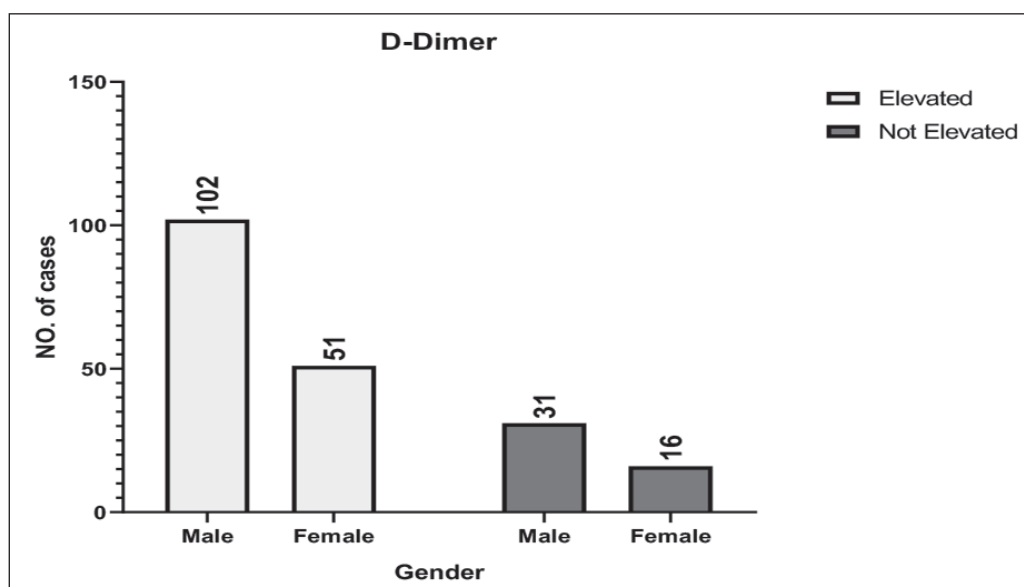


Fig. 4. The number of elevated of D-Dimer plasma level cases between the genders, the male gender showed high number of cases

RESULTS

GENDER

A total of 200 COVID-19 patients were included in the present study; 133 patients were considered male gender (66.5%) cases and 67 female gender cases (33.5%). See table (I)

Of the COVID-19 patients, 57.5% had moderate manifestations of disease, 68% of them was noticed for male and 32% for female gender while 42.5 had sever manifestations, 55% for male and 30% for female. In addition to cardiovascular symptom (tachycardia), in male gender were high as compared with female gender (70.5% vs 24%). Also, the moderate and sever cases in male gender were high as compared with female gender (69% vs. 31%, 63% vs. 37%), tables (II-III) and figures (1-2).

METABOLIC CHANGE

Glucose Disturbances was reported in 130 (64.5%) of COVID-19 patients, whereas only 70 (35.5%) of patients

withoutit ($p = 0.05$). However, the male gender was higher percent than female gender (68% vs. 32%), table (IV) and figure (3). A higher plasma D-Dimer level was recorded in most patients about 76.5% while those not suffer from that about 23.5%. However, the male gender was higher percent than female gender (67% vs. 33%) table (V) and figure (4) ($p = 0.05$). Ferritin was significantly correlated not only with disease severity but also with the duration of symptoms. As demonstrated in (Table VI) and (figure 5) we noticed that patient who suffered from elevated of ferritin plasma level about 62% while those not suffer from that about 38%. However, the male gender was higher percent than female gender (66% vs 34%).

GIT CHANGE

We noticed that patient who suffered from nausea about 51% while those not suffer from that about 49%. However, the male gender was higher percent than female gender

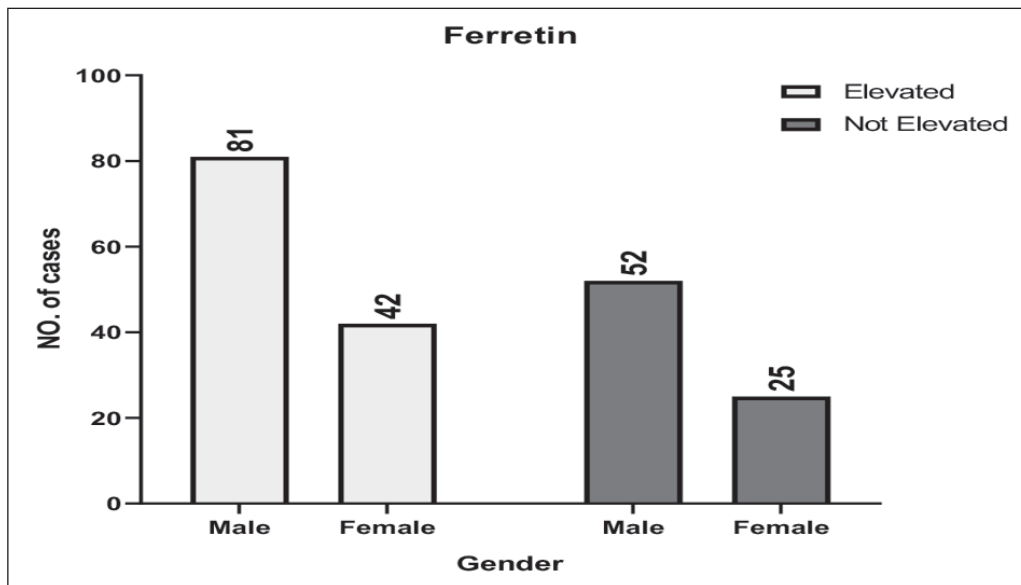


Fig. 5. The number of elevated of ferritin plasma level cases between the genders, the male gender showed high number of cases

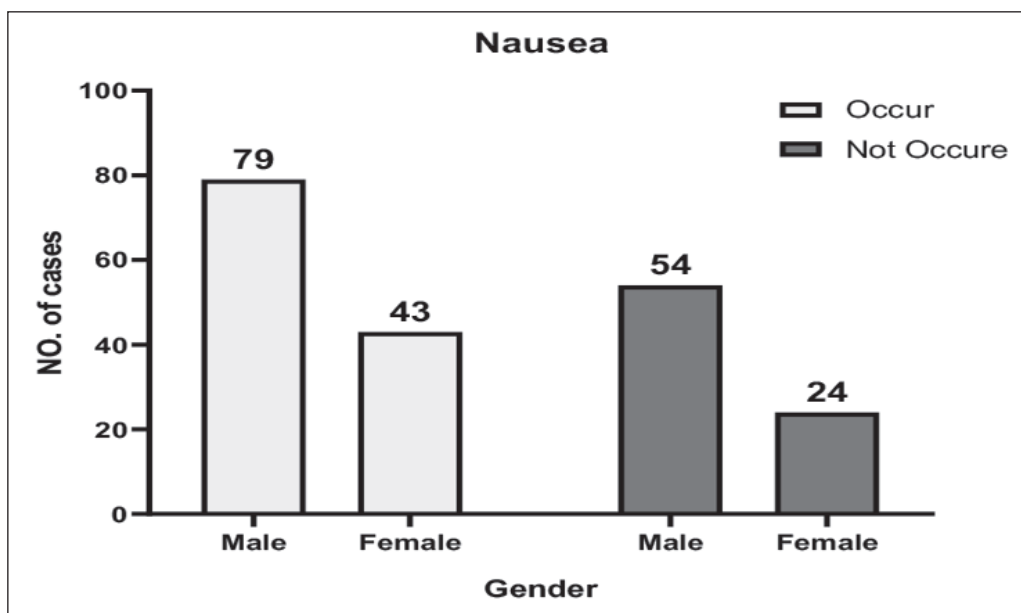


Fig. 6. The number of nausea cases between the genders. The male gender showed high number of cases

(65% vs. 35%), see table (VII) and figure (6). Table (VIII) and figure (7) show that the appetite in about 74% of total patients while those not suffer from that about 24%. However, the male gender was higher percent than female gender (70% vs. 30%), Moreover, Anal fissure in about 38% of total patients. However, 38% of them with moderate symptoms and about 10% with mild one while those not suffer from that about 62%. Also, we noticed that the male gender was higher percent for both mild and moderate than female gender (68% vs 32%, 63% vs. 38%), see table (IX) and figure (8).

DISCUSSION

According to our result, we noticed that the number of infected with covid 19 was more in male than female in gender, that's maybe due to of genetic, hormonal, and immunological differences between the two genders. The biological differ-

ences in the immune systems between men and women exist which may impact our ability to fight infection including SARS-2-CoV-2. Generally, females are more resistant to infections than men, and this is possibly mediated by several factors including sex hormones and high expression of coronavirus receptors (ACE 2) in men but also lifestyle, such as higher levels of drinking among men as compared to women. Additionally, women have a more responsible attitude toward the Covid-19 pandemic than men. This may reversibly affect the undertaking of preventive measures such as frequent hand washing, wearing of face mask, and stay at home orders [9]. There is increasing evidence that sex and sex hormones affect many components of the circulating as well as tissue-based RAAS including ACE2 [10]. Down regulation of angiotensin II receptor type 1 (AT1R) by estrogens, and regulation of renin activity by estrogens have been described and reviewed elsewhere [11]. The impact of sex steroid hormones on the T-helper 1/T-helper 2 cytokine balance is associated with the

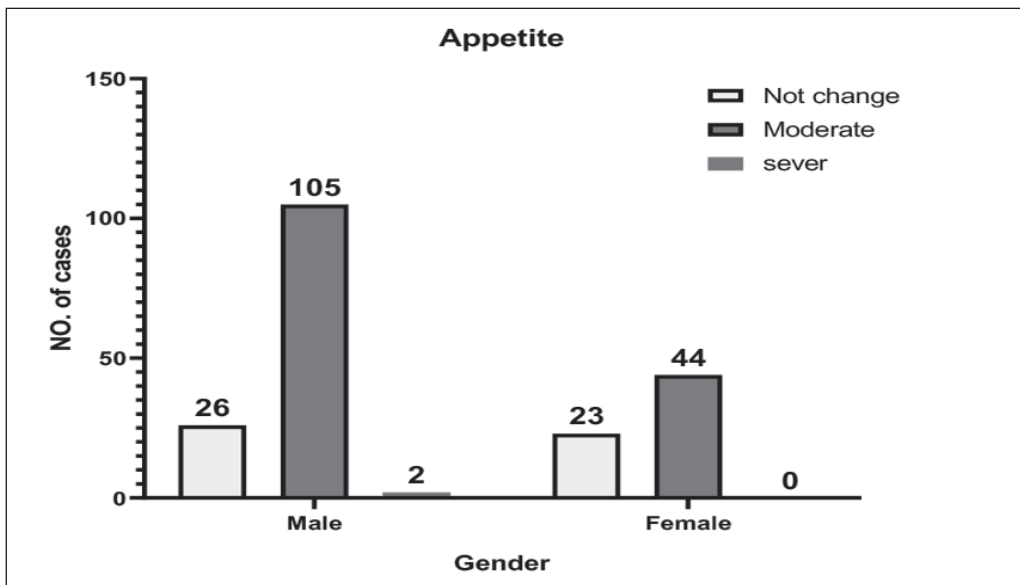


Fig. 7. The number of increase appetite cases between the genders. The male gender showed high number of cases.

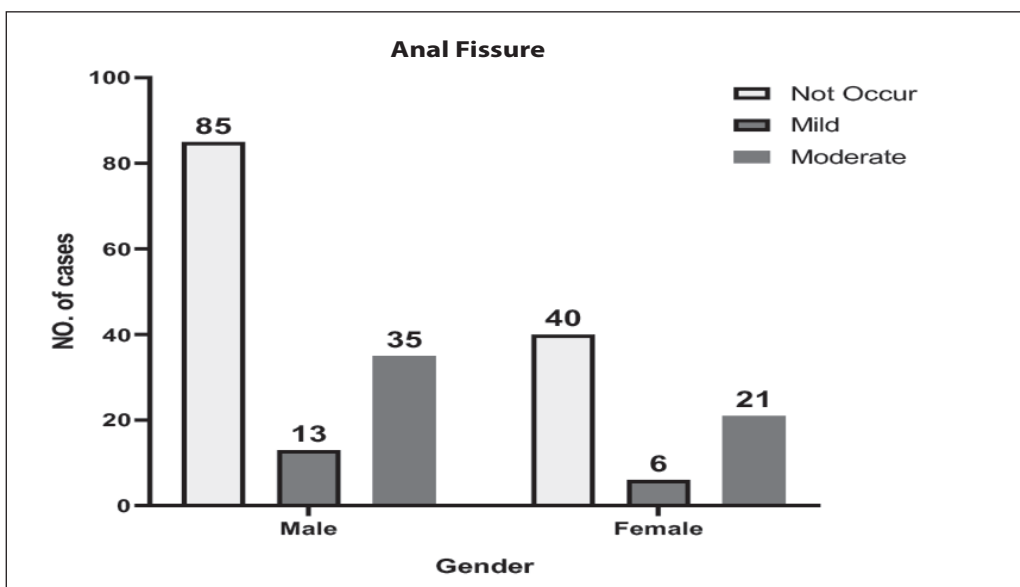


Fig. 8. The number of anal fissure cases between the genders. The male gender showed high number of cases

severity of most infectious diseases in males [12]. There are many factors related to the host, virus, and environment that may address the complexity of the COVID-19 clinical phenotype. The exact influence of host factors, specifically, genetic makeup, has remained mostly unknown. Since a strong protective immune response is essential to eliminate the virus before its progression to more severe stages, the host's good general health state is undoubtedly critical. As such, people of any age, especially older adults with comorbidities such as chronic bronchitis, diabetes, hypertension, cardiovascular disease, lung and liver diseases, chronic kidney disease, and chronic obstructive pulmonary disease (COPD) may experience more severe disease. Moreover, conditions and treatments that compromise the immune system, such as cancer treatment, bone marrow or organ transplantation, and prolonged use of corticosteroids, may also contribute to a higher risk of the disease, more severe outcomes, and even death [13]. There is emerging evidence that some people who develop long Covid have similar symptoms to people with a

condition known as postural orthostatic tachycardia syndrome (PoTs). This condition can cause dizziness when moving to an upright position and can be triggered by infections. The most common symptoms are feeling lightheaded, palpitations and fatigue. PoTs happen because your body's ways of avoiding a drop-in blood pressure when you stand up aren't working properly [14]. When you move to an upright position the supply of blood to your heart and brain drops and your heart starts beating faster to compensate. COVID-19 can cause lung complications such as pneumonia and, in the most severe cases, acute respiratory distress syndrome, or ARDS. Sepsis, another possible complication of COVID-19, can also cause lasting harm to the lungs and other organs. Lung injury may result in breathing difficulties that might take months to improve so decrease oxygenation and palpitation or tachycardia may occur [15]. There are three scenarios that could explain why someone may be diagnosed with Type 2 diabetes after surviving a bout with COVID-19. The person has the disease, but it hasn't yet been diagnosed, the

person may have prediabetes, and the acute inflammation and/or steroid treatment finally pushed them into having diabetes. For example, the acute stressor increased their insulin resistance enough that the relative deficiency of insulin production was revealed, and glucose went above the normal

level [16]. The person may have been genetically at risk with mild stressors such as being overweight (not obese) and mildly but not completely sedentary. But then the combination of the insulin resistance from the acute infection and the high-dose steroids used to treat COVID-19 were such that a significant increase in production of insulin was required to keep glucose normal, and the pancreas just wasn't able to increase its output to that level [17]. In our study all the severe cases have glucose level disturbance and all of them receiving high dose of steroid, some of them temporarily and most of them continuously. D-dimer is a product of cross-linked fibrin; it is considered a sensitive biomarker to rule out venous

Table I. The total and percentage of genders that participate in the study

Gender	Frequency	Percent
male	133	66.5
female	67	33.5
Total	200	100.0

Table II. Severity of disease between male and female gender. Only 85 patients had severe symptoms while those had moderate symptoms were 115. The male gender had higher percentage of cases for both moderate and severe than female gender ($p < 0.05$)

Severity	Male	Female	Total	Percent
Moderate	78 (68%)	37 (32%)	115	57.5
Sever	55 (65%)	30 (35%)	85	42.5
Total	133	67	200	100.0

Table III. The occurrence of tachycardia between the genders

Severity	Male	Female	Total	Percent
Non	6 (55%)	5 (45%)	11	5.5
Moderate	97 (69%)	42 (31%)	141	70.5
Sever	30 (63%)	20 (37%)	48	24.0
Total	133	67	200	100.0

Table IV. The occurrence of Glucose Disturbances between the different genders

Occurrence	Male	Female	Frequency	Percent
Occur	88 (68%)	42 (32%)	130	64.5
Not Occur	45 (64%)	25 (36%)	70	35.5
Total	133	67	200	100.0

Table V. The occurrence of elevated of D-Dimer plasma level between the different genders

Occurrence	Male	Female	Frequency	Percent
Elevated	102 (67%)	51 (33%)	153	76.5
Not Elevated	31 (66%)	16 (34%)	47	23.5
Total	133	67	200	100.0

Table VI. The occurrence of elevated of ferritin plasma level between the different genders

Occurrence	Male	Female	Frequency	Percent
Elevated	81 (66%)	42 (34%)	123	62.0
Not Elevated	52 (68%)	25 (32%)	77	38.0
Total	133	67	200	100.0

Table VII. The occurrence of nausea between the different genders

Occurrence	Male	Female	Frequency	Percent
Occur	79 (65%)	43 (21%)	122	51.0
Not Occur	54 (69%)	24 (31%)	78	49.0
Total	133	67	200	100.0

Table VIII. The occurrence of elevated of appetite between the different gender

Occurrence	Male	Female	Frequency	Percent
Not change	26	23	49	24.5
Moderate	105 (70%)	44 (30%)	149	74.5
Sever	2	0	2	1
Total	133	67	200	100.0

Table IX. The occurrence of anal fissure between the different genders

	Male	Female	Frequency	Percent	
Valid					
	Not Occur	85	40	125	62.5
	Mild	13 (68%)	6 (32%)	19	9.5
	Moderate	35 (63%)	21(38%)	56	28.0
	Total	133	67	200	100

thromboembolism. Abnormal coagulation function, including elevated D-dimer, has been demonstrated to be more common in deceased patients with COVID-19, and increasing odds of in-hospital death was associated with D-dimer greater than 1 µg/m [18]. D-dimer assays are commonly used in clinical practice to exclude a diagnosis of deep vein thrombosis or pulmonary embolism, and elevated D-dimer indicates increased risk of abnormal blood clotting. Elevated levels of D-dimer were also found to be related with higher mortality rate of community-acquired pneumonia. Augmented activity of urokinase could cause hyperfibrinolysis, by increasing cleavage of plasminogen into the active plasmin, and finally led to diffuse alveolar damage and acute lung injury, in a mouse model of SARS-CoV disease [19]. In our study, the level of coagulation function parameter, D-dimer, was found elevated in patients with severe COVID-19. Presumably, the severity of COVID-19 might also be associated with coagulation dysfunction. Recent studies documenting the laboratory changes of patients with confirmed COVID-19 have noted that elevated D-dimer might be associated with the disease progression of COVID-19. The level of D-dimer in patients with COVID-19 admitted to the ICU was reported to significantly increase. Clinical attention to venous thromboembolism risk should particularly be paid to those patients with severe COVID-19, who were often bedridden and presented with abnormal coagulation function. Rapid deterioration was observed in cases with significantly increased D-dimer during the disease progression [20]. Ferritin is a key mediator of immune dysregulation, especially under extreme hyperferritinemia, via direct immune-suppressive and pro-inflammatory effects, contributing to the cytokine storm. Ferritin is able to activate macrophages (macrococytes), a type of white blood cell in the immune system [21]. When they are activated, they begin to secrete cytokines. This is a class of signaling molecules that mediate and regulate immunity. When it is secreted in high concentrations, a so-called 'cytokine storm' develops, which can be fatal for half of patients, especially the elderly. It has been reported that fatal outcomes by COVID-19 are accompanied by cytokine storm syndrome, thereby it has been suggested that disease severity is dependent of the cytokine storm syndrome, it was found

that individuals with severe and very severe COVID-19 exhibited increased serum ferritin level [22]. In agreement with this, another study revealed that in patients who died by COVID-19, ferritin levels were high upon hospital admission and throughout the hospital stay. Therefore, it was concluded that serum ferritin levels were closely related to the severity of COVID-19. According to our result, we found the occurrence of nausea was about 50% of cases; however, most of them occur in male gender than in female one. The earliest clinical indication of COVID-19 in some patients is nausea/vomiting, which is frequently missed. It is now known that SARS-CoV-2 can infect not just the lungs but also the gastrointestinal tract. The angiotensin-converting enzyme 2 (ACE2) host receptor, which acts as an infection gateway, has been discovered to be abundantly expressed in the gastrointestinal epithelium and duodenal [23]. We found the occurrence of increasing appetite and anal fissure was most of them occurring in male gender than in female one. In the context of SARS-CoV-2 infection, post-COVID syndrome is becoming more widely recognized as a new clinical entity. The post-COVID syndrome is defined by symptoms that last longer than three weeks after the diagnosis of COVID-19. Its prevalence ranges from 10% to 35%; however, rates as high as 85% have been documented among patients who have previously been hospitalized [24].

CONCLUSIONS

We conclude that any patient with covid-19 where is male or female must need to follow up for at least 1 month after recovery due to there are GIT and metabolic disturbances that may be led to series evens, therefore, we must be notified of the post-covid symptoms especially the male gender

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ORCID and contributorship:

Saif M. Hassan: 0000-0003-4655-8045 ^{A-F}

Mohammed J. Jawad: 0000-0002-6096-945X ^{A-F}

Mahmood J. Jawad: 0000-0001-6542-7230 ^{A-F}

Ahmed R. Abu-Raghif: 0000-0003-4514-3892 ^{A-F}

Najah R. Hadi: 0000-0001-9084-591X ^{A-F}

Conflict of interest:

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CORRESPONDING AUTHOR

Najah R. Hadi

University of Kufa

29CG+62H, Kufa, Iraq

e-mail: drnajahhadi@yahoo.com

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