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Characteristics of fever in patients with COVID-19 at presentation and after initiation of treatment

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ABSTRACT

Coronavirus-19 (COVID-19) infection presents in a many ways, from asymptomatic or mild symptoms to death or serious illness. Coughing, shortness of breath, and fever are the common symptoms. Other symptoms include weakness, muscle discomfort, lethargy, sore throat, breathing problems, and loss of smell and/or taste. COVID-19 is diagnosed using clinical indicators, CT scans or chest x-rays, serological tests, and molecular diagnostics of the viral genome using reverse transcription polymerase chain reaction. This study analyzes the duration of fever, the most important symptom of the disease, and its association with other patient characteristics. The cross-sectional study was conducted in Iraq's Al-Diwaniyah Province, located in the Mid-Euphrates region. The study included 99 COVID-19 cases, 50 males and 49 females aged 16–81 years. Age, gender, white blood cell (WBC) count, lymphocyte percent, lung involvement assessed by CT scan, duration of fever at the time of presentation, and duration until the fever subsides following initiation of treatment were the main variables studied, in addition to the presence of chronic medical illnesses such as diabetes mellitus, systemic hypertension, asthma, and pulmonary tuberculosis.

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The mean age of all patients was 50.38 ± 16.27 years, with no significant difference between males and females (P = 0.924). There was also no significant difference in mean WBC count and lymphocyte percent between males and females (P > 0.05). Lung involvement from CT scan ranged from 0 to 80% and the mean was 26.77 ± 21.43%, with no significant difference between males and females (P = 0.770). The mean duration of fever at the time of presentation was 6.61 ± 3.60 days and it ranged from 1 to 21 days. The duration of subsiding fever ranged between 2 and 25 days in all patients with a mean of 5.82 ± 3.53 days, with no significant difference between males and females (P = 0.214). The duration needed for the fever to subside was positively and significantly correlated to the WBC count, the duration of fever at presentation, and the presence of diabetes mellitus (P < 0.05). Longer duration of fever after diagnosis and treatment of COVID-19 can be predicted with a high WBC count. Patients with diabetes having a longer duration of fever are at high risk of developing severe complications and death.

Keywords: *characteristics; patience; clinical; Fever; COVID-19*

INTRODUCTION

In December 2019, an outbreak of pneumonia of unknown origin occurred in Hubei Province, China, causing global health concerns due to the rate of transmission. The suspects were isolated and therapeutic/diagnostic protocols based on clinical and epidemiological data of patients were established to quickly detect and control the highly infectious disease. Further studies revealed the etiology of the disease as the rare acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and was named "coronavirus-19" (COVID-19) by Chinese researchers.[1–3] COVID-19 infection presents itself in a variety of ways, from asymptomatic or mild symptoms to death or serious illness. The common symptoms include cough, shortness of breath, and fever. Weakness, muscle pain, malaise, sore throat, respiratory difficulty, and loss of smell and/or taste are among the other symptoms.[4,5] Clinical signs, CT scans or chest x-rays, serological tests, and molecular diagnostics of the viral genome using reverse transcription polymerase chain reaction (RT-PCR) are used to diagnose COVID-19. Lymphopenia, thrombocytopenia leukopenia, raised inflammatory markers and C-reactive protein CRP, reduced albumin, high cardiac biomarkers, and impaired liver and renal function are the most frequent lab findings in individuals with RT-PCR that is positive.[6–8]

The diagnostic results are affected based on many factors, primarily by the time span from virus acquisition to the onset of symptoms. Symptoms appear between 2 and 14 days after exposure to the virus, as the body requires time to respond to the antigenic viral attack on the body. This viral replication window is the period causing increased COVID-19 transmission and false negative results.[1]

There were two kinds of COVID-19 testing used during the pandemic: PCR assays for active infection and serological tests for past infection. The existence of an adequate amount of viral genome in the sample of patients and the sensitivity of the RT-PCR test are required for early identification of COVID-19 through PCR.[9,10] However, diagnostic screening methods to detect 2019-nCoV even at low virus titers must be developed. Serological

tests identify antibodies to viral proteins, such as IgG, IgM, and IgA, in those who have established an immune response due to an active or prior infection.[11] Serological testing, used in combination with PCR, improves diagnosis sensitivity/accuracy, although immunological tests do not help diagnose and screen early infection due to the window period. Antibodies to 2019-nCoV can take up to 2 weeks to appear after infection.[12] thus making it difficult to detect active viral shedding in the early stages of the infection and determine its rate of spread.

As molecular testing directly identifies viral RNA, it is more sensitive than immunological and serological testing in the diagnosis of primary infection. It can be used even during the COVID-19 incubation period for early screening (before symptom onset). Immunity tests are practical and necessary if the virus re-emerges in society for a second time. The Chinese researches showed that people with mild viral symptoms have a wide range of antibodies, while younger people have fewer antibodies and some people have no antibodies at all.[13]

This study analyzes the duration of fever, the most important symptom of the disease, and its association with other patients' characteristics.

PATIENTS AND METHODS

The cross-sectional study was conducted in Iraq's Al-Diwaniyah Province, which is located in the Mid-Euphrates region. The study included 99 COVID-19 cases, 50 males and 49 females aged 16–81 years. The main variables studied were age, gender, white blood cell (WBC) count, lymphocyte percent, lung involvement assessed by CT scan, duration of fever at the time of presentation, and duration until the fever subsides following the initiation of treatment. The study also considered the presence of chronic medical illnesses, such as diabetes mellitus, systemic hypertension, asthma, and pulmonary tuberculosis.

The study was approved by the ethical committee of the College of Medicine at the University of Al-ethical Qadisiyah. All participants gave their verbal consent. The collected data was uploaded to an MS Office Excel spreadsheet and analyzed using SPSS (version 16) software. The parameters range, mean, and standard deviation presented numerical variables, while numbers and percentages represented categorical variables. Statistical tests were used, such as independent samples student *t*-test for assessing the difference in averages between males and females, the Chi-square test for determining the relationship between qualitative variables, and the Spearman correlation test for correlation among the study variables. The threshold for significance was set at $P \leq 0.05$.

RESULTS

Table 1 presents the characteristics of the patients with COVID-19 who participated in this research. The average age of all patients was 50.38 ± 16.27 years, with no significant difference between males and females ($P = 0.924$). The mean WBC count was 7075.80 ± 3659.27 × 10^9/L and it ranged from 2400 to 14,000 × 10^9/L, with no significant difference between males and females ($P = 0.761$). The mean lymphocyte percent of all patients was 27.12 ± 9.24%, and it ranged from 10 to 55%, with no significant variation between males and females ($P = 0.165$). Lung involvement according to CT scan ranged from 0 to 80% and the mean was 26.77 ± 21.43%, with no significant difference between males and females ($P = 0.770$).

The mean duration of fever at the time of presentation in all patients was 6.61 ± 3.60 days and it ranged from 1 to 21 days. The mean duration of fever at presentation in males was higher than in females, but the difference was not significant ($P = 0.086$). The duration of subsiding fever ranged from 2 to 25 days in all patients with a mean of 5.82 ± 3.53 days, with no significant difference in

TABLE 1. Characteristics of patients with COVID-19 enrolled in this study.

Characteristic	Total n = 99	Male n = 50	Female n = 49	P
Age (years)				
Mean ± SD	50.38 ± 16.27	50.54 ± 14.78	50.22 ± 17.81	0.924 NS
Range	16–81	20–81	16–75	
WBC count × 10^9/L				
Mean ± SD	7075.80 ± 3659.27	6964.00 ± 3139.33	7189.80 ± 4153.47	0.761 NS
Range	1100–20,000	2400–14,000	1100–20,000	
Lymphocyte %				
Mean ± SD	27.12 ± 9.24	25.84 ± 9.31	28.43 ± 9.09	0.165 NS
Range	10–55	10–50	14–55	
Lung involvement % (CT scan)				
Mean ± SD	26.77 ± 21.43	26.14 ± 22.45	27.41 ± 20.56	0.770 NS
Range	0–80	0–80	0–80	
Duration of fever at presentation (days)				
Mean ± SD	6.61 ± 3.60	7.22 ± 3.82	5.98 ± 3.28	0.086 NS
Range	1–21	3–21	1–15	
Prognosis (duration of fever to subside in days)				
Mean ± SD	5.82 ± 3.53	5.38 ± 3.13	6.27 ± 3.88	0.214 NS
Range	2–25	2–20	3–25	

n: number of cases; SD: standard deviation; WBC: white blood cells; CT: computed tomography; NS: not significant

TABLE 2. Chronic medical illnesses in patients with COVID-19.

Medical Illnesses	Total n = 99	Male n = 50	Female n = 49	P
Diabetes mellitus, n (%)	17 (17.2)	8 (16.0)	9 (18.4)	0.755 NS
Systemic hypertension, n (%)	20 (20.2)	8 (16.0)	12 (24.5)	0.293 NS
Asthma, n (%)	1 (1.0)	1 (2.0)	0 (0.0)	1.000 NS
Pulmonary tuberculosis, n (%)	1 (1.0)	1 (2.0)	0 (0.0)	1.000 NS

n: number of cases; NS: not significant

mean duration between males and females (P = 0.214). Table 2 displays the data on chronic medical illnesses in patients with COVID-19. There was no significant association between gender and the presence of any of the chronic illnesses (P > 0.05).

TABLE 3. Correlation of prognosis (duration for fever to subside) with other characteristics of patients with COVID-19.

Characteristics	Prognosis (Duration for Fever to Subside)	
	r	P
Age (years)	0.094	0.356
Gender	0.126	0.214
WBC count × 10^9/L	0.488	<0.001**
Lymphocyte	0.142	0.162
CT scan	0.544	<0.001**
Duration of fever at presentation (days)	0.236	0.019*
Diabetes mellitus	0.245	0.015*
Systemic hypertension	0.134	0.188
Asthma	−0.024	0.817
Pulmonary tuberculosis	−0.024	0.817

*r: correlation coefficient; WBC: white blood cells; CT: computed tomography; *significant at P ≤ 0.05; **significant at P ≤ 0.01*

Table 3 shows the correlation of prognosis (duration required for fever to subside) with other illnesses in patients with COVID-19. The duration needed for the fever to subside was positively and significantly correlated to WBC count, the duration of fever at presentation, and the presence of diabetes mellitus ($P < 0.05$).

DISCUSSION

The mean age of all patients was 50.38 ± 16.27 years, with no significant difference between males and females. The disease can affect any age, even children; but it is mostly mild or asymptomatic.[14,15] The patients are mainly adults as the severity of the disease increases with age. Further, the study was conducted in a medical department, so the patients were 16 years or older.

The WBC count ranged between 2400 and 14,000 × 10^9/L indicating that some patients had leukopenia, while some had normal counts or leukocytosis, with no significant difference between males and females. Some patients had normal lymphocyte percent, some had low percent, and others had high percent, with no significant difference between males and females. Thus, relying on WBC count alone in the diagnosis of COVID-19 may be misleading because of the inconsistency of WBC count and lymphocyte percent. However, higher WBC count and low lymphocyte percent at the time of admission are predictors of poor prognosis and higher mortality rates.[16,17]

Lung involvement according to CT scan ranged from 0 to 80% and the mean was 26.77 ± 21.43%, with no significant difference in lung involvement, between males and females.

CT scan is used for early detection and diagnosis of the infection, monitoring the clinical course, and determining the disease severity because of the low sensitivity of real-time RT-PCR. Ground glass opacities with or without consolidation in the posterior and peripheral lung are CT markers of COVID-19, although later observations include consolidations, linear opacities, "crazy-paving" patterns, "reversed halo" sign, and enlarged vessels. Other types of viral pneumonia, such as influenza, parainfluenza, adenovirus, respiratory syncytial virus, rhinovirus, and human metapneumovirus, and severe acute respiratory syndrome have CT results comparable to those of COVID-19.[18]

The mean duration of fever at the time of presentation in all patients was 6.61 ± 3.60 days and it ranged from 1 to 21 days. The mean duration of fever at presentation was higher in males than in females, but the difference was not significant. Adrenergic stimulation pathways are involved in fever, which is a cytokine-mediated physiological response that promotes innate as well as adaptive immunity.[19] According to Guan et al., fever was reported in 42.8% of COVID-19 patients at the time of admission and 88.7% of COVID-19 patients during hospitalization.[20] Although fever is the most prevalent

symptom in COVID-19 patients, the lack of fever at the time of first screening does not rule out the infection. In COVID-19 patients, the average duration of fever was 10 days (95 confidence intervals [CIs]: 8–11 days). The PCR negativity of the upper respiratory sample coincided with the resolution of the fever; radiological and clinical recovery took 11 days (95 CIs: 10–12 days). The COVID-19 patients who were admitted to the intensive care unit (ICU) were more likely to develop a fever that lasted longer (31 days vs. 9 days following onset of symptoms, respectively, P 0.0001), while the COVID-19 patients who were not in ICU treatment had a lower mortality rate.[21]

Fever during the early viral phase of COVID-19 shows the body's response to viral replication to improve immunity. If the viral infection does not clear up, a virally produced state of dysregulated inflammation known as "cytokine storm" or "secondary hemophagolymphocytosis," characterized by a persistent fever, exacerbates the sickness.[22] Fever might be unhelpful in circumstances where significant inflammation has set in. The duration for the subsiding fever ranged between 2 and 25 days with a mean of 5.82 ± 3.53 days, with no significant difference between males and females. The main predictors of the duration for subsiding fever are the WBC count, the duration of fever at presentation, and the presence of diabetes mellitus. Longer duration of fever may be associated with poor prognosis and higher rate of complications and mortality. Thus, patients with high WBC count, longer duration of fever, and diabetes should be closely monitored and treated promptly to prevent life-threatening complications and reduce mortality rate.

CONCLUSION

Longer duration of fever after diagnosis and treatment of COVID-19 can be predicted by high WBC count. The patients with diabetes having such longer duration of fever are at a high risk of developing serious complications and dying.

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