**Title page**

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

**Ali Fawzi Abd alsahib1, Doaa Faris Jabaz2 , Akeel M. Hamza3, Anwar Jasib Almzaiel4**†\*

1 Department of Internal Medicine, University of Al-Qadisiyah, College of Medicine, Al-Diywaniyah, Iraq1

2 Department of surgery, College of Medicine, University of Al-Qadisiyah, Al-Diywaniyah, Iraq2

3Al-Diwaniyiah health office, General Teaching Hospital, Al-Diywaniyah, Iraq

4†Department of Medical Chemistry, College of Medicine, University of AL-Qadisiyah, Al-Diywaniyah, Iraq

 **\*Corresponding author:** e-mail:**Vipvip128@yahoo.com**

**Anwar.almzaiel@qu.edu.iq**

**Abstract**

**Background:** COVID-19 infection manifests itself in a variety of ways, from asymptomatic/mild symptoms to death or serious illness. Coughing, shortness of breath, and fever are all common symptoms. Other symptoms include weakness, muscle discomfort, lethargy, sore throat, breathing problems, and loss of smell and/or taste. COVID-19 is diagnosed utilizing clinical indicators, CT scans or chest x-rays, serological tests, and molecular diagnostics of the viral genome using RT-PCR.

**Aim of the study:** In the current study we aimed to shed light on the duration of fever, the most important symptom of the disease, and its association with other patients’ characteristics.

**Patients and methods:** The current 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 ranging in age from 16 to 81 years. Age, gender, WBC count, lymphocyte percent, lung involvement assessed by CT-scan, duration of fever at time of presentation, and duration until fever subsides following initiation of treatment were the main variables studied in the current study, in addition to the presence of chronic medical illnesses such as diabetes mellitus, systemic hypertension, asthma, and pulmonary tuberculosis.

**Results:** The mean age of all enrolled patients was 50.38 ±16.27 years and there was no significant difference in mean age between males and females (*p* = 0.924). There was also no significant difference in mean WBC count and lymphocyte % between males and females (*p* > 0.05). Lung involvement according to CT-scan was ranging from 0 -80 % and the mean was 26.77 ±21.43 %; there was no significant difference in mean lung involvement between males and females (*p* = 0.770). The mean duration of fever at time of presentation in all enrolled patients was 6.61 ±3.60 days and it ranged from 1 to 21 days. Duration of subside of fever was ranging from 2 -25 days in all patients with a mean of 5.82 ±3.53 days; there was no significant difference in mean duration between males and females (*p* = 0.214). The duration needed for fever to subside was positively and significantly correlated to WBC count, the duration of fever at presentation and to the presence of diabetes mellitus (*p* < 0.05).

**Conclusion:** Longer duration of fever after diagnosis and treatment of COVID-19 can be predicted by high WBC count, longer duration of fever and presence of diabetes and those patients can be at high risk of severe complications and death.

**Key words:** Characteristics, Fever, COVID-19

**Introduction**

In December 2019, an epidemic of pneumonia of unknown origin broke out in Hubei Province, China, causing health care worldwide 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 rapidly detect and control the highly infected disease. The etiology of the disease has been recognized as the rare acute respiratory syndrome coronavirus 2 (SARS-CoV-2) after numerous studies, and the sickness has been dubbed "coronavirus-19" (COVID-19) by Chinese researchers (1-3). COVID-19 infection manifests itself in a variety of ways, from asymptomatic/mild symptoms to death or serious illness. Cough, shortness of breath and fever are all frequent Manifestations. Weakness, muscle pain, malaise, sore throat, respiratory difficulty, and loss of smell and/or taste are among the other features mentioned (4, 5). Clinical signs, CT scan or chest x-ray, serological tests and molecular diagnostics of the viral genome using RT-PCR are used to diagnose COVID-19. Lympopenia, thrombocytopenia leukopenia, raised inflammatory markers and 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).

According to many factors (the most crucial one being the time span from virus acquisition to the onset of symptoms), these results may be affected. Symptoms may begin to appear between two and 14 days following introduction to the virus, as the body requires time to respond to the antigenic viral attack on the body. The viral replication window is to blame for problems with COVID-19 growth and false negative results (1).

There were two kinds of COVID-19 testing used during the pandemic: An active COVID-19 infection can be diagnosed using PCR assays, which are a type of molecular diagnostic tool. 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). Consequently, it is vital to develop diagnostic screening methods that can detect 2019-nCoV even at low virus titers in order to improve diagnostics. Antibodies to viral proteins are the other sort of serological test. Serological tests are used to identify those who have established an immune response to the virus as a result of an active or prior infection. In reaction to the virus, IgG, IgM, and IgA antibodies may be detected, as well as IgM, which is generated early on (11). Serological testing, in combination with PCR, appear to improve diagnosis sensitivity/accuracy, although immunological tests do not help diagnose and screen in early infection due to the window-period. Antibodies to 2019-nCoV can take up to two weeks to appear after infection (12).

Because of this, early testing for IgM/IgG antibody levels are unable to detect active viral shedding in the early stages of disease, and to determine whether or not a person is contagious. For example, because molecular testing directly identifies viral RNA, it is more sensitive than immunological and serological testing in the diagnosis of primary infection, and it can be used even during the COVID-19 incubation period to speed up early screening (before symptom onset). Immunity tests will be practical and necessary if the virus reappears in society for a second time. People with mild viral symptoms have a wide range of antibodies, while younger people have less antibodies and some people have no antibodies at all, according to Chinese researchers (13).

In the current study we aimed to shed light on the duration of fever, the most important symptom of the disease, and its association with other patients’ characteristics.

**Patients and methods**

The current 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 ranging in age from 16 to 81 years. Age, gender, WBC count, lymphocyte percent, lung involvement assessed by CT-scan, duration of fever at time of presentation, and duration until fever subsides following initiation of treatment were the main variables studied in the current study, in addition to the presence of chronic medical illnesses such as diabetes mellitus, systemic hypertension, asthma, and pulmonary tuberculosis.

The study was approved by the college of medicine/University of Al-ethical Qadisiyah's approval committee. All participants gave their verbal agreement. The collected data was then uploaded to an Office Excel spreadsheet and finally to SPSS (version 16) software. Range, mean, and standard deviation were used to present numerical variables. Numbers and percentages were used to represent categorical variables. The difference in averages between males and females was assessed using an independent samples student t-test. To assess the relationship between qualitative variables, the Chi-square test was performed. The correlation between the various included variables was investigated using the Spearman correlation test. The threshold for significance was set at p ≤ 0.05.

**Results**

Table 1 lists the characteristics of the patients with COVID-19 who participated in this research. The average age of all recruited patients was 50.38 ± 16.27 years, with no statistically significant difference between males and females (p = 0.924).The mean WBC count was 7075.80 ±3659.27 X109/L and it ranged from 2400 -14000 X 109/L. There was also insignificant difference in mean WBC count between males and females (*p* = 0.761). The mean lymphocyte % of all enrolled patients was 27.12 ±9.24 % and it ranged from 10 -55 %; there was no significant variation in mean lymphocyte % between males and females (*p* = 0.165). Lung involvement according to CT-scan was ranging from 0 -80 % and the mean was 26.77 ±21.43 %; there was no significant difference in mean lung involvement between males and females (*p* = 0.770).

The mean duration of fever at time of presentation in all enrolled patients was 6.61 ±3.60 days and it ranged from 1 to 21 days. The mean duration of fever at presentation of males was higher than that of females, but the difference was not significant (*p* = 0.086). Duration of subside of fever was ranging from 2 -25 days in all patients with a mean of 5.82 ±3.53 days; there was no significant difference in mean duration between males and females (*p* = 0.214). The rate of chronic medical illnesses in patients with COVID-19 is shown in table 1. There was no significant association between gender and the rate of any of these chronic illnesses (*p* > 0.05).

Correlation of prognosis (evaluated by duration required to fever to get subside) with other characteristics of patient with COVID-19 was shown in table 3. The duration needed for fever to subside was positively and significantly correlated to WBC count, the duration of fever at presentation and to the presence of diabetes mellitus (*p* < 0.05).

**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 X109/L** |  |  |  |  |
| Mean ±SD | 7075.80 ±3659.27 | 6964.00 ±3139.33 | 7189.80 ±4153.47 | 0.761 NS |
| Range | 1100 -20000 | 2400 -14000 | 1100 -20000 |
| **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 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:** The rate of chronic medical illnesses in patients with COVID-19

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Characteristic** | **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

**Table 3:** Correlation of prognosis (evaluated by duration required to fever to get subside) with other characteristics of patient with COVID-19

|  |  |
| --- | --- |
| **Characteristic** | **Prognosis (duration of fever subside)** |
| ***r*** | ***p*** |
| Age (years) | 0.094 | 0.356 |
| Gender | 0.126 | 0.214 |
| WBC count X109/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

**Discussion**

The mean age of all enrolled patients in the current trial was 50.38 ± 16.27 years, with no significant difference in mean age between males and females. Indeed, it has been documented that the disease can affect any age even children; however, the disease is mostly mild or asymptomatic (14, 15) and this explains why our patients are mostly adults as the severity of the disease increases with age in addition the study was made in medical department; therefore, patients were 16 years or older.

In this study, WBC count ranged between 2400 -14000 X 109/L indicating that some patients had leukopenia, there was no significant difference in mean WBC count between males and girls, and some had normal counts while others had leukocytosis. In addition, some patients had normal lymphocyte %, other had low % and yet others had high % and the difference between males and females was insignificant. This finding indicates that relying on WBC count in the diagnosis of COVID-19 may be misleading because of inconsistency of WBC count and lymphocyte %. However, it has been stated that higher WBC count at admission and low lymphocyte % at admission can be predictors of poor prognosis and higher mortality rate (16, 17).

In the current study, lung involvement according to CT-scan was ranging from 0 -80 % and the mean was 26.77 ±21.43 %; between boys and females, there was no significant difference in lung involvement.

Early detection and diagnosis are critical, especially for false-negative RT-PCR tests, but CT is also useful in monitoring the clinical course and determining the disease severity because of the low sensitivity of real-time reverse transcription polymerase chain reaction (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" pattern, "reversed halo" sign, and enlarged vessels. Other viral pneumonias, such as influenza, parainfluenza, adenovirus, respiratory syncytial virus, rhinovirus, and human metapneumovirus, have CT results comparable to those of COVID-19. Some differences and parallels can be found in the CT results for COVID-19 when compared to those for severe acute respiratory syndrome (SARS) (18).

 In the current study, the mean duration of fever at time of presentation in all enrolled patients was 6.61 ±3.60 days and it ranged from 1 to 21 days. The mean duration of fever at presentation of males was higher than that of 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 the hospitalization term(20). The lack of fever at the time of first screening does not rule out COVID-19 infection, despite the fact that fever is the most prevalent symptom in COVID-19 patients. In COVID-19 patients, the average duration of fever was ten days. (95 confidential intervals [CIs]: 8–11 days), according to Chen et al. 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). 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) COVID-19 patients who did not get ICU treatment had a lower mortality rate(21).

The emergence of a fever early in the viral phase of COVID-19 is most likely a symptom of the body's immune response to viral replication in order 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, which is characterized by a persistent fever, exacerbates the sickness(22). Fever might be unhelpful in circumstances where significant inflammation has set in. In this study, the duration of subside of fever was ranging from 2 -25 days in all patients with a mean of 5.82 ±3.53 days; there was no significant difference in mean duration between males and females and the main predictors of duration required to fever in order to subside were WBC count, the duration of fever at presentation and to the presence of diabetes mellitus. It has been shown that the 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 diabetic patients should be closely monitored and treated promptly to prevent life threatening complications as early as possible to reduce mortality rate in such risky population.

**Conclusion:** Longer duration of fever after diagnosis and treatment of COVID-19 can be predicted by high WBC count, longer duration of fever and presence of diabetes and those patients are at a high risk of developing serious complications and dying.

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