The Behavior of Fever in Patients Diagnosed with SARS-Cov-2 Infection Prior and at Time of Treatment Initiation

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ABSTRACT

Background: The COVID-19 infection may manifest with a range of symptoms, spanning mild or asymptomatic cases to severe illness or fatal outcomes. Typical symptoms include pyrexia, cough, and difficulty breathing. Other possible manifestations consist of fatigue, muscle aches, general discomfort, sore throat, respiratory issues, and inability to perceive smell or taste. Diagnosis of COVID-19 entails the utilization of clinical indicators, computed tomography (CT) scans or chest radiographs, serological assays, and molecular testing, such as RT-PCR to identify the virus's genetic material, by healthcare professionals.

Objective: In the present investigation, our aim was to clarify the length of pyrexia, the predominant feature of the illness, and its relation to different patient characteristics.

Subjects and Methodology: An investigation (cross-sectional) was carried out in the Province of Al-Diwaniyah, located in Iraq. A total of 99 COVID-19 cases were included in the study, consisting of 49 women and 50 men, spanning from 16 to 81 years of age. The primary variables examined in this research encompassed the patients' gender, age, lymphocyte percentage, count of leukocytes, pulmonary participation evaluated through CT imaging, length of pyrexia upon presentation, duration of fever subsiding after treatment initiation, and the existence of co-morbid conditions such as pulmonary tuberculosis, asthma, essential hypertension, and diabetes mellitus.

Results: The average age of total participants was 50.4±16.3 years, with no notable variation in age averagebetween women and men (p=0.924). Similarly, there was an absence of significant variation. in averagesof lymphocyte % and WBC count between the two genders (p>0.05). Pulmonary participation, as discerned through CT imaging, varied from 0 to 80%, with a mean of 26.77±21.43 %; notably, there existed no substantial disparity in lung participation between the female and male cohorts (p=0.770). The participants' average fever duration upon arrival was 6.6±3.6 days, varying from 1-21 days. The lengthfor high temperature to diminish ranged from 2 to 25 day, and an average of 5.82±3.53 day. There was no significant disparity in duration between women and men (p=0.214). The length of fever at presentation, the presence of diabetes mellitus, and the WBC count were all found to have a significant and positive association with the time it took for the fever to subside (p<0.05).

Conclusion: Prolonged fever following the detection and management of COVID-19 may be anticipated in individuals with elevated WBC count, extended fever duration, and a history of diabetes. Such patients are more likely to face severe consequences and mortality.

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

INTRODUCTION

The rapid transmission rate of an uncertain origin pneumonia epidemic that emerged in China's Hubei Province in December 2019 has raised global concern. 1. Suspected cases were quickly isolated, and therapeutic and diagnostic protocols were established using epidemiological and clinical information to promptly detect and treat this extremely contagious illness. Thorough investigation resulted in pinpointing the uncommon "acute respiratory syndrome coronavirus 2 (SARS-CoV-2)" as the responsible pathogen, and Chinese researchers officially named the disease "coronavirus-19" (COVID-19) (1-3). The infection gives rise to a range of symptoms, spanning from mild or asymptomatic manifestations to fatal outcomes or severe condition. Common symptoms include coughing, respiratory distress, and elevated body temperature. Furthermore, individuals have also reported experiencing weakness, muscle soreness, overall unease, a scratchy throat, difficulty breathing, and a diminished sense of smell or taste as additional symptoms (4, 5). Different techniques including clinical symptoms, CT scans, molecular analysis of the virus gene through RT-PCR, serology tests and x-rays of chest are utilized in the detection of COVID-19. 1.Frequent lab findings in subjectswith a positive RT-PCR test often consist of low lymphocyte, platelet, and white blood cell counts, increased levels of markers of inflammation and CRP, decreasedlevels of albumin, as well as compromised liver and kidney function (6-8).

Various factors can influence the results, but the timing from viral exposure to symptom onset is the most critical. The human body necessitates a certain amount of time in order to react to virus invasion,

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and signs may happen anywhere from 2 days to 2weeks after being exposed to the virus. The viral replication period plays a key role in limiting the transmission of COVID-19 and leading to inaccurate negative test outcomes (1).

During the pandemic, two types of COVID-19 tests have been developed: PCR tests are used as a molecular diagnostic tool that detects an active COVID-19 infection by analyzing viral genetic material. Detecting COVID-19 promptly through PCR relies on the existence of an adequate quantity of virus genetic material in the sample and the sensitive capacity of the RT-PCR test (9, 10). Therefore, it is essential to have improved diagnostic screening techniques capable of identifying the 2019-nCoV even when viral levels are minimal. Another type of diagnostic test is serologybased, which rely on antibody to virus protein. Serologyassays can detect subjects who have produced an adaptive immunity reaction to viral particles as a result of a recent or past infection. Antibody like IgA, IgG, and IgM, as well as early-formed IgM in response to the virus, may be present (11). The combination of serological testing and PCR seems to enhance the sensitivity and accuracy of diagnosis. However, it is important to note that immunological tests are not effective in diagnosing and screening early infections due to the window-period. It may take up to two weeks for antibodies to 2019-nCoV to become detectable after infection (12).

Consequently, in the initial phase of illness, early IgM/IgG antibody tests are incapable of identifying active viral shedding or determining if an individual is contagious. Conversely, molecular tests, which directly detect viral RNA, exhibit higher sensitivity compared to immunological and serological testing for diagnosing primary infection. Moreover, these tests can expedite early screening, even amidst the COVID-19 period of incubation, prior to the onset of symptoms. If the virus resurfaces for a second time in the community, immunity tests will benecessary and mandatory. Researchers from China have noted diverse immunity reaction results, including broad spectrum of antibodies in individuals with mild viral manifestation, lower levels of antibodies in younger individuals, and the absence of antibodies in certain individuals (13).

Our aim in this study was to determine the length of time that fever persists, as it is the main indicator of the illness, and examine its relationship with different patient attributes.

PATIENTS AND METHODOLOGY

A recent investigation was carried out in Al-Diwaniyah governorate, located in of Iraq. The research focused on 99 COVID-19 patients, with 50 males and 49 females having an age range between 16 and 81 years. The study analyzed variousvariables such as patient gender, age, lymphocyte %, WBC count, pulmonaryenrollment detected through CT-scan, length of high temperature upon admission, time for fever to decrease after treatment, and the presence of chronic medical conditions like pulmonary tuberculosis, asthma, essential hypertension and diabetes mellitus.

The approval for the research was granted by the ethicscommittee at the College of Medicine, Al-Qadisiyah University. Written consent was obtained from all participants.

The data collected was transferred to an Office Excel spreadsheet and subsequently imported into SPSS software (version 16). Numeric variables were displayed as a range, mean, and standard deviation, while categorical variables were presented as the number and percentage. The disparity in averages among males and females was evaluated through the application of an independent samples t-test. The association among qualitative variables was evaluated using a chi-square test. To examine the correlation among the variables included, a correlation test (Spearman) was employed. The significance level was established at a threshold of $p \leq 0.05$.

RESULTS

Table 1 displays the attributes of the patients included in this study who were diagnosed with COVID-19. The mean age of the entire cohort of participants was recorded at 50.38 ±16.27 years, with no significant variation observed in the mean age between the male and female groups (p=0.924).The mean white blood cell count was recorded as 7075.80 ±3659.27 X109/L, exhibiting a range of 2400 -14000 X 109/L. Likewise, there existed no notable disparity in the mean WBC count observed between the male and female subjects (p=0.761). An average lymphocyte proportion of 27.12±9.24 % was detected across all participants, with values spanning from 10 -55%. Remarkably, a substantial fluctuation in the mean lymphocyte percentage between genders was not observed (p=0.165). The degree of pulmonary involvement, as ascertained through CT-scan evaluations, varied from 0-80 %, with a mean of 26.77±21.43%. Moreover, no significant dissimilarity in the mean lung involvement was noted between male and female individuals (p=0.770).

The mean duration of fever at initial presentation among all participants was 6.61±3.60 days, ranging from 1 to 21 days. A slightly lengthier average fever period was observed in males compared to females, although this disparity did not reach statistical significance (p=0.086). The duration of fever resolution varied from 2 to 25 days for all patients, with an average of 5.82±3.53 days. No notable discrepancy in average fever duration was found between male and female patients (p=0.214). Chronic medical conditions prevalence among COVID-19 patients is presented in Table 1. No substantial relationship was noted between gender and the prevalence of any of these chronic conditions (p>0.05).

Table 3 demonstrated a correlation between the prognosis of COVID-19 patients, as measured by the time it took for their fever to subside, and various patient characteristics. The duration required for fever to subside was found to have a positive and significant correlation with the patient's white blood cell count, the existence of diabetes mellitus and the length of time they had a fever upon presentation (p<0.05).

Table 1. Features of subjects with COVID-19 who were recruited for this research investigation

Characteristic	Female n = 49	Male n = 50	Total n = 99	p
Age (years)				
Mean ±SD	50.22 ±17.81	50.54 ±14.78	50.38 ±16.27	0.924 NS
Range	16 -75	20 -81	16 -81	
Lung involvement % (CT-scan)				
Mean ±SD	27.41 ±20.56	26.14 ±22.45	26.77 ±21.43	0.770 NS
Range	0 -80	0 -80	0 -80	
Duration of fever at presentation (days)				
Mean ±SD	5.98 ±3.28	7.22 ±3.82	6.61 ±3.60	0.086 NS
Range	1 -15	3 -21	1 -21	
Prognosis (duration of fever subside in days)				
Mean ±SD	6.27 ±3.88	5.38 ±3.13	5.82 ±3.53	0.214 NS
Range	3 -25	2 -20	2 -25	
WBC count X109/L				
Mean ±SD	7189.80 ±4153.47	6964.00 ±3139.33	7075.80 ±3659.27	0.761 NS
Range	1100 -20000	2400 -14000	1100 -20000	
Lymphocyte %				
Mean ±SD	28.43 ±9.09	25.84 ±9.31	27.12 ±9.24	0.165 NS
Range	14 -55	10 -50	10 -55	

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

Table 2. The frequency of co-morbid medical conditions in individuals afflicted with COVID-19.

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

n: number of cases; **NS**: not significant

Table 3. Correlation between the prognosis, as assessed by the duration needed for fever to subside, and various patient characteristics in individuals with COVID-19

Characteristic	Prognosis (duration of fever subside)	
	r	*p*
Age (years)	0.094	0.356
Gender	0.126	0.214
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
WBC count $X10^9$/L	0.488	< 0.001 **
Lymphocyte	0.142	0.162

: significant at $p \leq 0.01$; *: significant at $p \leq 0.05$; **CT: computed tomography; **WBC**: white blood cells; ***r***: correlation coefficient

DISCUSSION

The mean age of all the individuals who took part in this research was 50.4±16.3 years. Interestingly, there was no significant variation in the average age between women and men. It is widely acknowledged that the illness can affect people of all ages, even children. However, it is worth mentioning that the disease tends to be milder or asymptomatic in most cases (14, 15). This elucidates why the majority of our patients were adults, as the disease severity tends to increase with age. Furthermore, it is important to note that the research was practiced in a medical ward, hence the inclusion criteria required patients to be 16 years or more.

In this investigation, the WBC count varied from 2400 to 14000 X 109/L, showing that certain patients exhibited leukopenia, some had a normal count, and others had leukocytosis. There was no notable distinction in the average WBC count between males and females. Furthermore, some patients had a normal lymphocyte %, while others had a low % or a high %. The gender-based variance in lymphocyte % was insignificant. These results suggest that using WBC count alone for diagnosing COVID-19 could be misleading due to the inconsistency in lymphocyte % and WBC count. Nevertheless, it has been suggested that a higher WBC count and lower lymphocyte % upon admission could serve as indicators of a poor prognosis and increased death rate (16, 17).

In the present investigation, pulmonary involvement based on CT-scan ranged from 0-80 % with a mean of 26.77±21.43 %; there was no notable distinction in mean pulmonary involvement between men and women. Chest computed tomography (CT) is essential for early detection and diagnosis, especially in cases where real-time reverse transcription polymerase chain reaction (RT-PCR) tests yield false negative results, due to the low sensitivity of RT-PCR. Additionally, CT scans are important for monitoring the clinical progression and assessing the severity of the disease. The characteristic CT features of COVID-19 include bilateral ground glass opacities associated with or with no consolidation in the peripheral and posterior lung regions, while consolidations, linear opacities, "crazy-paving" formations, enlargement of vesselsand "reversed halo" mark are the most frequently observed findings in later stages. The CT manifestations of COVID-19 bear resemblance to those of various other conditions, such as viral pneumonia induced by parainfluenza viruses influenza viruses, rhinovirus, adenovirus, and respiratory syncytial virus, human metapneumovirus, and other viruses. Upon comparing the CT findings of COVID-19 with those of severe acute respiratory syndrome, both differences and similarities are evident (18).

In the present study, the average length of fever upon arrival for all participants was 6.61±3.60 days, ranging from 1 to 21 days. Although the averagelength of high temperature upon presentation was greater in men compared to women, this difference did not reach statistical significance. Fever is a complex physiological response mediated by cytokines, involving adrenergic stimulation pathways and promoting both innate and adaptive immune reaction (19). Guan et al (20) reported that fever was present in 42.8 percent of COVID-19 patients upon admission and in 88.7 percent of COVID-19 patients during their hospitalization. Despite fever being the most frequentsign in COVID-19 subjects, the lack of high temperature during initial screening does not exclude the potential for a COVID-19 infection. According to Chen et al., the average length of fever in COVID-19 subjects was 10 days (with a 95% confidence interval of 8-11 days).

The resolution of high temperature coincided with the negative PCR results of sample obtained from upper airways, while radiological and clinical recovery took approximately11 days (with a 95% confidence interval of 10-12 days). It was observed that COVID-19 patients who received intensive critical care (ICU) had a longer duration of fever (31 days compared to 9 days following the onset of symptoms, respectively, $p = 0.0001$) compared to those who did not receive ICU care (21).

The initial onset of fever in COVID-19 during the viral stage of the disease is probably an indication of the body's immunityreaction to the multiplication of the virus, aiming to enhance immunity. In cases where the viral infection persists, the illness is aggravated by a condition called secondary hemophagolymphocytosisor “cytokine storm”, which is caused by viral influence and results in uncontrolled inflammation and persistent fever (22).Fever may not be beneficial in cases where there is significant inflammation. Based on this study, the length of time it took for the fever to subside varied from 2 to 25 days for all patients, with an average of 5.82 ± 3.53 days. The average duration did not differ significantly between women and men. The primary factors that affected the duration of fever subsiding were the white blood cell count, the presence of diabetes mellitus and the duration of fever when initially observed.Research has indicated that an extended period of fever could potentially be associated with an unfavorable outlook, heightened complexities, and elevated fatality percentages. As a result, individuals exhibiting elevated levels of white blood cells, diabetes mellitus, and prolonged fever duration necessitate vigilant observation and immediate intervention to avert critical complications and diminish mortality rates within this at-risk demographic.

CONCLUSION

Prolonged fever following the diagnosis and treatment of COVID-19 may be anticipated in individuals with elevated WBC count, extended fever duration, and a history of diabetes. Such patients are more likely to face severe complications and mortality.

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