

Frequency evaluation of gastrointestinal symptoms and liver test disorder in patients during the Covid-19 outbreak in the military unit: A single-center pilot study

Askeri birlikte Covid-19 salgını sırasında hastalarda gastrointestinal semptomların ve karaciğer test bozukluğu sıklığının değerlendirilmesi: Tek merkezli pilot çalışma

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Background and Aims: Coronavirus disease-2019 is a disease presenting with respiratory as well as gastrointestinal symptoms. In addition, the liver enzyme can be disrupted during the disease. This study aimed to investigate the extent of the military co-epidemic during the Coronavirus disease-2019 epidemic process and the frequency of gastrointestinal symptoms and liver test disorders. **Materials and Methods:** Demographic, radiological, laboratory, and clinical analysis of soldiers diagnosed with Coronavirus disease-2019 was carried out retrospectively in March, April, and May of 2020, using real-time polymerase chain reaction. **Results:** Coronavirus disease-2019 was detected in 17 (0.7%) of the 2,152 soldiers coming from different cities to perform their military services and 9 (0.4%) of the soldiers in the following days after recruitment. In addition, 1 (0.3%) of 320 senior militaries and 2 (3.6%) from 56 other soldiers who came to the unit from other units were also diagnosed with Coronavirus disease-2019. The mean age was 21.2 ± 1.8 years. In torax computed tomography, only 4 (13.7%) patients had pneumonia. At the time of diagnosis, 6.8% of the patients had gastrointestinal symptoms and 13.7% had liver enzyme disruption. None of the patients experienced respiratory failure, intensive care, and death; all the patients recovered. **Conclusion:** In the present literature, our study is the first to investigate the Coronavirus disease-2019 outbreak in the military unit in the world and the frequency of gastrointestinal symptoms and liver enzyme disruptions in these patients. Our study revealed that Coronavirus disease-2019 was milder in young populations and gastrointestinal symptoms and liver test disorder were less frequently observed. Coronavirus disease-2019 outbreak was taken under control by fast and accurate triage and suitable isolation for those with the suspected disease in environments where many people such as military units will live close together. Coronavirus disease-2019 should always be kept in mind, especially in patients with gastrointestinal symptoms, and early patient isolation prevents the spread of the epidemic in such crowded environments.

Key words: Military unit, Covid-19, pandemic, gastrointestinal symptoms, liver tests

INTRODUCTION

Coronaviruses are RNA viruses belonging to the coronavirus family and usually cause mild infections.

However, it has been observed that coronaviruses can cause high mortality in epidemics of severe acute respira-

Giriş ve Amaç: Covid-19 çoğu zaman solunum yolu semptomları ile prezente olan bir hastalık olsa da gastrointestinal semptomlar da birçok hastada görülebilmektedir. Ayrıca hastalık süresince karaciğer testlerinde değişik oranlarda bozulmalar da olabilmektedir. Çalışmamızda Covid-19 salgını sürecinde ilimizde bulunan askeri birliğin boyutunu ve hasta olanlarda gastrointestinal semptom ve karaciğer test bozukluğu sıklığını araştırmayı amaçladık. **Gereç ve Yöntem:** Mart 2020, 30 Mayıs 2020 tarihleri arası dönemde ilimizde bulunan askeri birlikte retrospektif olarak real time polimeraz zincir reaksiyonu pozitif Covid-19 tanılı askerlerin demografik, radyolojik, laboratuvar ve klinik açıdan analizi yapıldı. **Bulgular:** Askerlik görevini yapmak üzere ülkemizin değişik şehirlerinden gelen 2152 asker adayının ilk giriş muayenesi sonucu 17'sinde (%0.7), birliğe alındıktan sonra asker olanların takip eden günlerde 9'unda (%0.4) Covid-19 saptandı. Birlikte daimi bulunan 320 rütbeli askerden 1 (%0.3) kişi Covid-19 olurken başka birliklerden ilimizdeki birliğe gelen 56 askerden 2'si (%3.6) Covid-19 oldu. Hastaların yaş ortalaması 21.2 ± 1.8 idi. Toraks bilgisayarlı tomografide yalnızca 4 (%13.7) hastada pnömoni vardı. Hastaların tanı anında %6.8'inde gastrointestinal semptom, %13.7'sinde ise karaciğer test bozukluğu vardı. Hiçbir hastada solunum yetmezliği, yoğun bakıma alınma ve ölüm olmadı ve hastaların tümü komplikasyonsuz şekilde iyileşti. **Sonuç:** Çalışmamız literatürde görebildiğimiz kadarıyla Dünyada askeri ünitelerde yapılmış Covid-19 salgını ve bu hastalarda gastrointestinal semptom ve karaciğer test bozukluğu sıklığını araştıran ilk çalışma özelliği taşımaktadır. Çalışmamızda genç popülasyonda Covid-19'un daha hafif şiddette seyrettiğini, gastrointestinal semptom ve karaciğer test bozukluğunun daha az sıklıkta izlendiğini bulduk. Askeri birlik gibi çok fazla kişinin birarada yakın şekilde yaşayacağı ortamlarda yapılacak hızlı ve doğru triaj ve hastalık şüphesi olanlara uygun izolasyon ile Covid-19 salgını kontrol altına alınabilecektir. Ayrıca gastrointestinal semptomu olanlarda Covid-19 her zaman akılda tutulmalıdır ve hastaların erken izolasyonu ile bu tür ortamlarda salgının yayılması engellenebilecektir.

Anahtar kelimeler: Askeri birim, Covid-19, pandemi, gastrointestinal belirtiler, karaciğer testleri

tory coronavirus (SARS-CoV) in 2003 and Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012 (1-3).

At the end of 2019, a deadly new coronavirus disease, which started in Wuhan City of China and then spread ra-

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pidly to the whole world, emerged. The World Health Organization called this new coronavirus disease Covid-19 and declared a pandemic on March 11, 2020. This new coronavirus species has been taxonomically called 'severe acute respiratory syndrome coronavirus (SARS-CoV-2)' by the virus committee (4).

Covid-19 can manifest itself in a wide clinical spectrum in the form of asymptomatic infection, mild upper respiratory disease, pneumonia, respiratory failure, and death (5,6). Covid-19 has increased disease severity and mortality with older ages (7).

SARS-CoV-2 causes respiratory symptoms generally and sometimes these symptoms may be accompanied by symptoms of other systems. Some of these symptoms are related to the digestive system (8-10). The disease can sometimes be presented with only digestive system symptoms without any upper or lower respiratory symptoms (11).

During Covid-19, liver enzyme is disrupted in some of the patients and generally manifests as mild and transient disorders in most of the patients. Rarely, liver enzyme levels may be very high. Besides, it has been reported in the literature that there is a significant relationship between increased disease severity and impairment of liver enzymes (5,6,12-14).

In our study, we aimed to evaluate the soldiers in the city of Bilecik who were affected by the Covid-19 outbreak concerning gastrointestinal symptom (GI) and the frequency of deterioration in liver tests.

MATERIALS and METHODS

Study Design and Participants

The study was conducted retrospectively between 10 March 2020 and 30 May 2020 at the 9th Gendarmerie Training Regiment Command in Bilecik city center, by recruiting soldiers with the diagnosis of Covid-19. Republic of Turkey Ministry of Health approval for this study was obtained (2020-05-29T10_25_55). In our study, research and publication ethics were complied.

The patients were divided into 3 groups according to the severity of the disease. Covid-19 patients with mild symptoms of respiratory disease but no signs of pneumonia in thorax computed tomography (CT), those with pneumonia in CT in addition to symptoms of respiratory disease, and those with severe respiratory failure and intensive care.

As GI symptoms, complaints of nausea, vomiting, diarrhea, and abdominal pain were questioned. Three or

more soft-lasting defecations per day were considered diarrhea. At least one of the values of aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transpeptidase, total and direct bilirubin outside the reference range is considered as liver test disorder. Patients with a history of antibiotic use, diarrhea-predominant irritable bowel syndrome, and known liver disease were excluded from the study.

Procedures

At the end of March 2020, 2152 soldier candidates came to the 9th Gendarmerie Provincial Regiment Command in Bilecik city center to perform their military service from different cities of our country. All soldiers were questioned for symptoms that could be compatible with Covid-19, such as sore throat, runny nose, sneezing, muscle aches, fatigue, fever, cough, and shortness of breath before being recruited to the military unit.

At the first entrance, 108 candidate soldiers had some symptoms, and these were isolated in a separate room in the Ertugrulgazi male dormitory in our city without being included in the military unit. 2044 candidate soldiers were recruited to the military unit. Of the 2177 soldiers who applied to the unit doctor with different symptoms within the following days after being taken to the military unit, 151 of them had symptoms that could be compatible with Covid-19. These soldiers were taken to the isolation in the dormitory. One of the 320 military personnel, who worked together permanently, was insulated after symptoms occurred in senior military.

In addition, 56 soldiers from other troops who came to the unit in our province to complete the rest of their military service were insulated in a separate area within the union. Nasopharyngeal swab was taken from all of the soldiers who were insulated in the dormitory.

Nasopharyngeal swabs were sent to Bursa City Hospital Microbiology Laboratory with a cold chain in the virocult. Here, the SARS-CoV-2 viral genome was investigated using the RT-qPCR kit (99.4% sensitivity, 99.0% specificity).

Thorax CT was performed in the Radiology Department of Bilecik State Hospital for patients who had positive RT-PCR results. Later, these patients were transferred to the Halime Hatun girls dormitory, which was temporarily turned into a hospital in our city. Nasopharyngeal swabs were taken from the soldiers who were still in isolation in the dormitory of male students, whose first test was negative, and for the second and sometimes the third time.

The positive ones were also transferred to the Halime Hatun girls dormitory. All patients with positive PCR results received oseltamivir for 5 days and also hydroxychloroquine therapy by the recommendations of the Republic of Turkey Ministry of Health Sciences Board. Also, azithromycin treatment was added to those with pneumonia. Control PCR was taken 48 hours after the treatment was completed.

The negative results were sent back to the male dormitory and kept in quarantine for 14 more days in separate rooms. Those who did not have any complaints after the quarantine was sent to the military unit, including soldiers. The RT-PCR results of the patients were checked again from the Public Health Management System site. The accuracy of the results was confirmed.

After the patients were admitted to the girls' dormitory, venous blood was collected in the morning of the following day after at least 8 hours of fasting before treatment was started. Total blood count, glucose, urea, creatinine, sodium, potassium, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), total and direct bilirubin, C-reactive protein (CRP), lactate dehydrogenase (LDH), D-dimer, fibrinogen, and ferritin parameters have been studied with appropriate transport.

The medical history of the patients was examined from the hospital information system. For those who had shortcomings in their stories, the 9th Provincial Gendarmerie Regiment Command was interviewed with the doctor of the unit. The doctor of the troops contacted the soldiers who had recovered and were doing his military service, questioned the presence of GI symptoms before the diagnosis of Covid-19, and reported it to us.

Outcome Data and Statistical Analysis

In our study, we collected and analyzed the demographic, clinical, laboratory, and radiological findings, GI symptoms, and clinical results of the patients. Statistical

analysis was carried out by using SPSS software (version 22.0, SPSS Inc, Chicago, IL, US). Continuous variables were expressed as median while categorical variables are shown as a percentage (%).

RESULTS

In the first examination and the following period, Covid-19 was detected in a total of 26 (1.2%) of 2152 soldiers who have recently joined the union, 1 (0.3%) of 320 senior military working together, and 2 (3.6%) of 56 soldiers from other units (Table 1). The youngest of the patients was 19, the oldest was 26 years old, and the mean age was 21.2 ± 1.8 , and all of the patients were male. The most common symptom in patients was sore throat (75%). In thorax, CT taken at the beginning of the disease, 4 (13.7%) patients had pneumonia while 25 (86.3%) patients did not. None of the patients with pneumonia worsened in the clinic during follow-up and all were discharged with healing.

When the patients diagnosed with Covid-19 were evaluated in terms of GI symptoms, 1 (3.4%) patient had vomiting, and 1 (3.4%) patient had diarrhea. GI symptoms were presented with respiratory symptoms in both patients.

In the patient who suffered from diarrhea, who also have a sore throat symptom, symptoms began to appear about 3 days before Covid-19 diagnosis. Diarrhea was in the form of watery defecation 4-5 times a day. The patient did not have abdominal pain and fever. In stool microscopic examination, there was no leukocyte and erythrocyte and there was no growth in stool culture, diarrhea ended spontaneously 3 days after hospitalization. The patient with nausea started complaining 2 days before the diagnosis of Covid-19, and he had a sore throat and fever. His nausea was stopped two days after hospitalization. There was no pneumonia sign on thorax CT in both patients. The patient with nausea had high CRP while the patient with diarrhea had leukocytosis. AST,

Table 1. Covid-19 status in the military unit

	Total	Covid-19 Preliminary Diagnosis	EMD Isolation	Covid-19 Definitive Diagnosis
First examination	2152	108	108	17
Outpatient examination	2177	151	151	10
Soldiers isolated together	56	2	2	2
Total	4385	261	261	29

EMD: Ertugrulgazi Male Dormitory.

ALT, GGT, total bilirubin, direct bilirubin, D-dimer, ferritin, fibrinogen, and LDH parameters were within the normal reference range for both patients. When patients were evaluated regarding liver tests, 4 (13.7%) patients had at least one liver enzyme disruption.

While there was a slight increase in the values of patients with impairment in liver tests, values were higher in one patient compared to the values of other patients (AST: 103 U/dl, ALT: 246 U/dl, GGT: 86 U/dl). The inflammatory markers of this patient were normal and there was no pneumonia on thorax CT. Five days after, this patient's liver tests were within the normal range. One patient with impaired liver tests had pneumonia on thorax CT, while the other three did not have pneumonia. All parameters were within the normal range, except that one of the patients with elevated liver tests had mild CRP elevation. Bilirubin levels did not fall outside the normal range in any of the patients. Laboratory parameters of the patients are given in Table 2.

DISCUSSION

One of the main findings of our study was Covid-19 has milder severity in the young population. Our second finding was that; the GI symptoms frequency and liver test disorder were not common in the young population.

Covid-19 is a disease whose severity and mortality increase with age, and it is mostly mild in young people. Studies have shown that patients over the age of 60 are approximately 4 times more mortality than those under the age of 60 (5.2%, 1.4% respectively.) (7). The mildness of the disease than the elderly seems likely to be related to a better immune system in young population. Age-related defects in the function of T and B lymphocytes may lead to a deficiency in the control of SARS-CoV-2 replication and longer pro-inflammatory responses, potentially leading to a worse outcome (15). Also, the fact that the respiratory defense mechanisms and secretion clearance is better in young people and the absence of chronic diseases may be related to this situation.

In addition to respiratory symptoms, GI symptoms frequently occur in coronavirus infections. In two recent coronavirus outbreaks (SARS 2002, MERS 2012), respiratory tract symptoms are often accompanied by GI symptoms (16-18). Although the mechanism of SARS-CoV-2 causing GI symptoms is unclear, angiotensin-converting enzyme-2 (ACE-2) is a binding receptor for SARS-CoV-2, and ACE-2 is also present at large numbers in the digestive system. It is thought that SARS-CoV-2 bind to the ACE-2 receptor in the digestive system and cause symptoms such as nausea, vomiting and diarrhea (19,20).

Table 2. Laboratory parameters of patients diagnosed with Covid-19

	Minimum	Maximum	Mean ± SD
Age (year)	19	26	21.2 ± 1.84
AST (U/L)	16	103	31.7 ± 18
ALT (U/L)	12	246	37.4 ± 45
GGT (U/L)	19	86	34 ± 16.4
LDH (U/L)	122	380	186.7 ± 59.2
T. bilirubin (mg/dl)	0.43	0.98	0.7 ± 0.16
D. bilirubin (mg/dl)	0.08	0.44	0.25 ± 0.11
CRP (mg/L)	0.5	72.8	6.5 ± 16.2
D-dimer	122	845	211.5 ± 142.2
WBC (/mm ³)	4830	11530	7924.8 ± 2046.7
Neutrophile (/mm ³)	1550	8500	4889.6 ± 1808
Lymphocyte (/mm ³)	1290	4390	2263.2 ± 660.7
Monocyte (/mm ³)	300	950	567.2 ± 149.6
Ferritin (ng /ml)	44.3	164.3	125.4 ± 23.8
Fibrinogen (mg /dl)	166	440	247.12 ± 63.07

AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, GGT: Gamma glutamyl transpeptidase, LDH: Lactate dehydrogenase, T. bilirubin: Total bilirubin, D. bilirubin: Direct bilirubin, CRP: C-reactive protein, WBC: White blood cell.

In our study, GI symptoms were present in 6.8% of patients at the time of admission. In a study, which 206 patients were evaluated in the literature, diarrhea was observed in 32.5% of the patients and the average age of the patients was 62.5 (21).

In another study, 204 patients with an average age of 52.9 years, 38 (18.6%) patients had GI symptoms such as diarrhea, vomiting, and abdominal pain (10). In the study in which 651 patients were evaluated, 11.4% of the patients had GI symptoms and the mean age of those with GI symptoms was 46.1 (22). As seen in these studies, the frequency of GI symptoms decreases as the age decreases. The cause of fewer GI symptoms in young people is not fully known. The better condition of both the immune system and the respiratory barrier systems in young people may decrease the load of SARS-CoV-2 in the GI tract and prevent GI symptoms. However, larger studies are needed to compare young people with older individuals, examining the SARS-CoV-2 genome burden in feces and its relationship to symptoms.

Similar to lung tissue, there is ACE-2 receptor expression in liver tissue. Especially in cholangiocytes, ACE-2 expression is evident and is 20 times higher than hepatocytes (59.7%, 2.6% respectively.) It has also been found that ACE-2 in cholangiocytes is expressed at levels comparable to that in pulmonary cells. Although cholangiocytes have many important functions in the liver, such as regeneration and immune response, it is not known whether the disorder in liver tests is due to direct liver inflammation or systemic inflammation by SARS-CoV-2 that binds to the ACE-2 receptor (23,24).

In our study, in the first biochemical study performed to patients, 13.7% of the patients had impairment in liver tests. In a study by Chen et al., 43.4% of patients had liver test disorder. Liver tests were significantly impaired in one patient and were significantly higher with levels

which are ALT 7590 U/L, AST 1445 U/L (5).

In another study, 37% of patients had impaired liver tests (6). The mean ages of these three studies were 55, 59.7, and 49 years, respectively. In another study, the average age of which was lower (41 years) compared to these studies, a lower rate (%16) of liver test disorders was detected (14). In addition, in a meta-analysis of 3024 diseases conducted in China where 21 studies were analyzed, there was a significant relationship between disease severity and liver enzymes disruption (12).

According to the literature, as the age decreases in Covid-19, fewer liver test disorders are observed. As the age decreases, the severity of the disease decreases relatively, and to investigate whether the defect in liver tests is due to inflammation or systemic inflammation caused by SARS-CoV-2 that binds to ACE-2 large-scale experimental studies are needed.

The first limitation of our study was that it a retrospective study due to the risk of transmission. In addition, due to the low number of patients, the comparative statistical analysis could not be made between the patients with and without GI symptoms or liver test disorders.

As far as we can see in the literature, our study is the first study to investigate the Covid-19 outbreak in the military unit in the world and the frequency of GI symptoms and liver test disorders in these patients. Fast and accurate triage and proper isolation of those with suspected disease may prevent the spread of the Covid-19 epidemic in such settings, where many people, such as military units, have to live together and close together. In addition, it should be kept in mind that patients with GI symptoms during triage may also have Covid-19 and these patients should be isolated.

Conflict of interest: *The authors declare that there are no conflicts of interest.*

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