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ORIGINAL ARTICLE

Evaluation of pain in patients with COVID-19

COVID-19 hastalarında ağrı değerlendirmesi

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Summary

Objectives: A new type of coronavirus outbreak has emerged in China and caused a pandemic. World Health Organization (WHO) announced the official name of this disease 'COVID-19'. The main purpose of this study is to evaluate pain in COVID-19 patients.

Methods: Patients who were followed in the ward of an infectious diseases department because of possible or confirmed COVID-19 between May and September of 2020 were included in the study. The Turkish version of the Brief Pain Inventory (BPI) was applied. Demographic features, frequency, location, the intensity of pain, and response to analgesics were analyzed.

Results: A total of 178 participants were included in the study. Ninety-one (51.1%) of patients had pain complaints and the mean pain score (MPS) was 2.28±2.81 over 10. Fifty-nine (56.0%) of participants with pain required analgesic therapy and 41 (80.3%) of them showed ≥50% pain relief with simple analgesics. Twelve of the remaining 18 who did not get enough pain relief with simple analgesic were taking their analgesics pro re nata (PRN) rather than around the clock (ATC). Pain frequency and intensity and mean hospitalization duration (MHD) were similar between confirmed and possible cases.

Conclusion: Regarding the results, we conclude that pain is not one of the challenging symptoms and easily manageable in patients with a mild-moderate intensity of COVID-19. Our results were not enough to make a correlation between pain and the clinical course of the disease. Further studies are required for the evaluation of pain including patients in intensive care units.

Keywords: Chest pain; COVID-19; headache pain; myalgia.

Özet

Amaç: Yeni bir tip koronavirüs salgını Çin'de ortaya çıktı ve pandemik oldu. Dünya Sağlık Örgütü (DSÖ) bu hastalığın resmî adını 'COVID-19' olarak ilan etti. Bu çalışmanın ana amacı COVID-19 hastalarında ağrıyı değerlendirmektir.

Gereç ve Yöntem: 2020 yılının Mayıs ve Eylül ayları arasında muhtemel veya kesin COVID-19 tanısıyla enfeksiyon hastalıkları servisinde takip edilmiş olan toplam 178 hasta çalışmaya dahil edildi. Kısa Ağrı Envanteri'nin (BPI) Türkçe versiyonu uygulandı. Demografik özellikler, ağrının sıklığı, lokasyonu, şiddeti ve analjeziklere yanıtı analiz edildi.

Bulgular: Hastaların doksan birinde (%51.1) ağrı şikayeti vardı ve ortalama ağrı skoru (OAS) 10 uzerinden 2,28±2,81'di. Ağrısı olan hastalardan elli dokuzu (%56.0) ağrı kesiciye ihtiyac duydu ve kırk birinde (%80.3) basit ağrı kesicilerle yuzde elliden daha fazla ağrı azalması saptandı. Yeterli ağrı palyasyonu sağlanamayan on sekiz hastanın on ikisinin ağrı kesicilerini duzenli olarak almak yerine ağrı oldukca almış oldukları gozlendi. Muhtemel ve kesin vakaların ağrı frekansı, şiddeti ve hastanede kalış suresi benzerdi.

Sonuç: Sonuçlarımıza göre COVID-19 hastalarında ağrının baş edilmesi zor bir semptom olmadığı ve hafif-orta klinik şiddetteki hastalarda kolaylıkla tedavi edilebildiği kanaatine vardık. Sonuçlarımız ağrı ve hastalığın klinik seyri arasında bir bağlantı kurmak için yeterli değildi. Ağrı değerlendirmesi için yoğun bakım hastalarını içeren başka çalışmalara ihtiyaç vardır.

Anahtar sözcükler: Göğüs ağrısı; COVID-19; baş ağrısı; miyalji.

Introduction

The year 2020 has become one of the darkest years for the public health of human civilization because of the worldwide outbreak of a viral disease. A new type of severe acute respiratory syndrome coronavirus (SARS-CoV-2) has emerged in Hubei province, Wuhan, China, and immediately became a global health concern.[1] The WHO announced that the official name of the 2019 novel coronavirus is 'Corona Virus Disease-19' (COVID-19). On January 30, 2020,

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COVID-19 was registered as the sixth Public Health Emergency of International Concern (PHEIC) by the World Health Organization (WHO), which was officially declared as a pandemic on March 11, 2020.[1,2]

The main clinical symptoms of COVID-19 patients are fever (88.5%), cough (68.6%), myalgia or fatigue (35.8%), expectoration (28.2%), and dyspnea (21.9%). Minor symptoms include headache or dizziness (12.1%), diarrhea (4.8%), nausea, and vomiting (3.9%).[2]

Acute respiratory distress syndrome (ARDS) is reported to be the most common complication of COVID-19.[1,3,4] Other severe or fatal complications include pneumonia, type I respiratory failure, sepsis, metabolic acidosis, septic shock, arrhythmia, acute cardiac injury, heart failure, acute kidney injury, bleeding, or hypoxic encephalopathy.[5–7] Clinical manifestations can range from being mild to severe and patients can present as either symptomatic or asymptomatic, but most COVID-19 cases are symptomatic with a moderate case-fatality rate.[1,4,8] Pain is one of the clinical manifestations of COVID-19. Myalgia, headache, sore throat, thoracic pain are amongst the types of pain observed in COVID-19 patients.[1,9] In a systematic review including 3600 patients, Fu et al.[4] reported the prevalence of myalgia, chest pain, headache, and sore throat as 28.5%, 14.9%, 14.0%, and 12.3%, respectively. Studies reported headache prevalence between 11–34% in COVID-19 patients.[5,10–12] However, no enough articles are evaluating the pain profiles and treatment results of pain in COVID-19 patients.

In this study, our purpose is to reveal the frequency, intensity, localization of pain. We also assessed the response to the analgesics. Furthermore, we inspected the relationship between pain presence and the severity of the disease. For this aim, we designed a study including patients who are followed in the ward of an infectious diseases department of a university hospital due to confirmed or possible COVID-19 and we evaluated their status of pain using the Brief Pain Inventory (BPI).

The Brief Pain Inventory (BPI) was developed to provide a quick and easy means of measuring pain intensity and the extent to which pain interferes in the lives of the pain sufferers.[13] It was developed by Cleeland et al.[14,15] Validation and reliability of the Turkish version of the BPI have been shown in several studies.[16,17]

Material and Methods

This study was performed in the ward of the infectious diseases department of Ondokuz Mayıs University Hospital, Samsun, Turkey. Approval of the institutional ethics committee and approval from the Turkish Ministry of Health were obtained before the study. A total of 178 hospitalized patients because of possible or confirmed COVID-19 were included in the study. While diagnosing the possible or confirmed COVID-19, the definition in the guideline of the Turkish Ministry of Health was considered (Table 1). The collection of specimen procedures were performed according to the guidelines of the Turkish Ministry of Health. Firstly, an oropharyngeal swab was taken and with the same stick, also nasopharyngeal swab was taken. Real-time reverse transcriptase-polymerase chain reaction (PCR) test that is specific for COVID-19 was applied for the laboratory confirmation of the disease.

Patients with <90% oxygen saturation in room air or <94% oxygen saturation with oxygen support were transferred to the ICU. Patients with respiration rates higher than 30 per minute were also transferred to the ICU. Patients who have no fever, cough, or dyspnea for at least 48 hours were discharged and advised for following the measures.

For the evaluation of the pain profile of the patients, the Turkish version of the Brief Pain Inventory (BPI) was used. The BPI questionnaire was applied in the ward by the physicians of the infectious diseases department personally. Patients in the intensive care unit were not included in the study. Demographic data and the frequency of accompanying diseases noted. The rate of confirmed cases' mean hospitalization duration (days), the frequency of intensive care requirement, frequency of pain, localization of pain, severity of pain, the requirement of analgesics, and the types of administered analgesics were recorded. Response rates to the analgesics were also noted. A response with ≥ 50% pain relief was defined as 'satisfactory'. The frequency and intensity of pain between PCR positive and PCR negative cases were compared. The frequency and intensity of pain be-

Table 1. Definitions of the possible case and the confirmed case regarding the guidelines of the Turkish Ministry of Health

	Possible case
A	• Fever or at least one of the signs or symptoms of acute respiratory tract disease (cough, dyspnea) AND • No other possible explanation of the clinical situation, and • Personal or one of relatives' history of existence in foreign countries in the last 14 days before the symptoms begin
	Or
B	• Fever or at least one of the signs or symptoms of acute respiratory tract disease (cough, dyspnea) AND • Close contact with a confirmed COVID-19 case in the last 14 days before the symptoms begin
	Or
C	• Fever or at least one of the signs or symptoms of acute respiratory tract disease (cough, dyspnea) AND • Necessity of hospitalization (SARI)* AND • Lack of otherwise explanation of the clinical condition
	Or
D	•Existence of sudden onset fever accompanied by cough or dyspnea without rhinorrhea
	Confirmed case
	• Detection of SARS-CoV-2 by molecular techniques in the cases that conform to the description

*: SARI (Severe Acute Respiratory Infections): Hospitalization indication due to fever, cough, and dyspnea, tachypnea, hypoxemia, hypotension, diffuse radiological findings in lung or alteration of consciousness in a patient who has acute respiratory tract infection that emerged in the last 14 days.

tween genders were assessed. Hospitalization duration between confirmed and possible cases was compared. Hospitalization duration between patients with and without pain was also compared.

Statistical Package for the Social Sciences 15.0 (SPSS 15.0) program was used for the statistical analysis of the study data. Parametric data were presented as means±standard deviations (SD) categoric data were presented as numbers and percentages. The Shapiro–Wilk test was used to analyze normal distribution assumptions of quantitative outcomes. The Student's t-test was used for the comparison of the parametric data between groups and the Mann-Whitney U test was used for the comparison of the non-parametric data between groups. A Chi-square test was used for the comparison of the census data. P values less than 0.05 were considered as 'statistically significant'.

Results

A total of 178 patients were included in the study. While 81 (45.5%) of them were confirmed COVID-19 cases, 97 (55.5%) have negative PCR test results. 81 (45.5%) of the participants were female and 97 (55.5%) were male. The mean age of the participants was 44.7±14.53 years. 102 (57.3%) of the patients were working in a job or students. 76 (42.7%) were neither working in a job nor students. When we assess the pre-existing health problems, we observed that 74 (41.5%) of the patients had no previous health problems. 24 (13.4%) have cardio-vascular, 11 (6.1%) have pulmonary disease history. 5 (2.8%) of the patients were diabetic, 5 have neurologic diseases. 56 (31.4%) of the patients have more than one of these systemic problems. The mean hospitalization duration was 6.02±5.58 days. During the hospitalization period, an ICU requirement emerged in 7 of the patients and one of them, who was 75 years old with multiple pre-existing health problems, died. In 2 of these 7 patients, acute myocardial infarction was the reason for the transfer to ICU.

Pain due to COVID-19 was observed in 91 (51.1%) of the patients. 87 (48.9%) of the participants did not report pain complaints (Fig. 1). It is observed that the frequency of pain was significantly higher in females. While the number of patients with pain was 50 (61.7%) in females, it was 35 (35.7%) in males (p=0.005) (Fig. 2). Additionally, the mean pain scores of females were significantly higher than males (3.14±3.02 vs. 1.59±2.44. p=0.001). Sixty-two (34.8%) of participants reported general myalgia, 38 (21.3%) reported headache, 20 (11.2%) reported chest pain and 20 (11.2%) reported sore throat (Table 2). The mean pain score of the patients was 2.28±2.81 over 10 points. The mean pain score of the patients who reported pain was 4.83±2.10. 59 (64.8%) of the 91 pa-

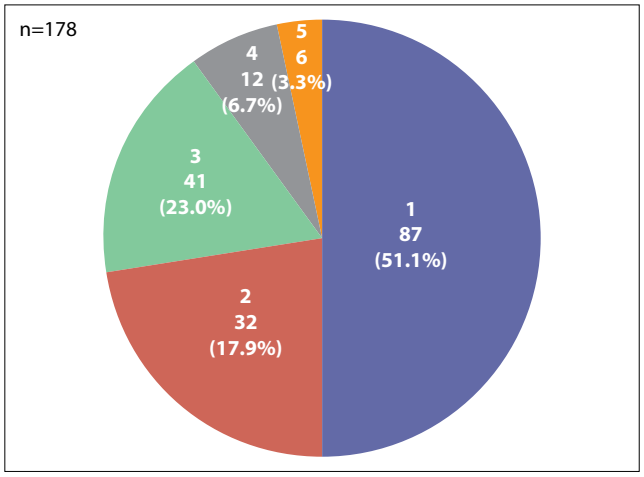

Figure 1. Frequency of pain and response to analgesics of the patients. 1: Patients without pain. 2: Patients with pain but do not demand analgesics. 3: Patients with pain and get a satisfactory result with simple analgesics. 4: Patients who do not get enough pain relief with simple analgesics but use their drug pro re nata. 5: Patients without satisfactory pain relief despite taking analgesics according to a clockwork schedule.

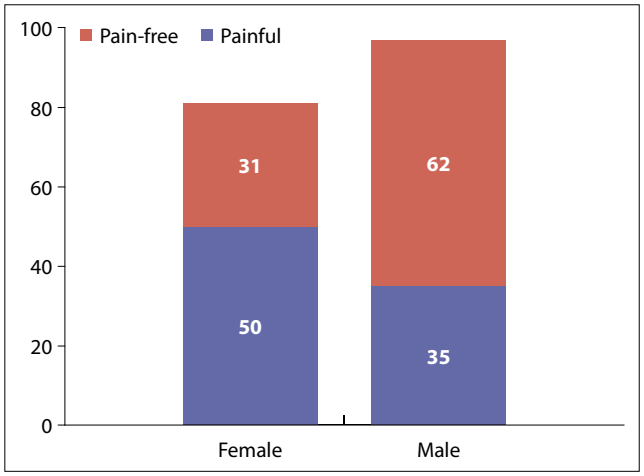

Figure 2. Pain frequency in females and males.

tients with pain required analgesics. Patients received only simple analgesics (paracetamol or NSAIDs). 41 of these 59 patients have reported 50% or more pain relief. 42 (84%) of the participants who require analgesic drugs were taking their analgesic PRN rather than the clockwork schedule. We observed that 12 of the 18 individuals who do not get enough pain relief were taking their analgesics PRN. Regular consumption of simple analgesics was not effective enough only in 6 (3.3%) of 178 COVID-19 patients.

We did not observe statistical significance in terms of the frequency of pain existence between confirmed cases and possible cases. 41(50.6%) of the confirmed cases and 50 (51.5%) of the possible cases reported pain (p=0.97). Mean pain scores of the patients with pain complaints were similar between

Table 2. Frequency of locations of pain

Location of pain	n	%
Myalgia	62	34.8
Headache	38	21.3
Chest pain	20	11.2
Sore throat	20	11.2
Total number of participants	178	

confirmed and possible cases. It was 2.27±2.25 in confirmed cases and 2.30±2.13 in possible cases (p=0.919). There was also no significant difference in terms of hospitalization durations. Mean hospitalization durations of confirmed cases and possible cases were 6.00±2.22 and 6.01±7.38 days, respectively (p=0.81). The mean hospitalization duration of patients with pre-existing diseases was slightly higher than the ones without pre-existing diseases but there was no statistical significance (8.53±9.50 vs. 5.74±2.18 days, p=0.201). We also did not find a significant difference in terms of pain frequency and pain scores between the patients with and without pre-existing health problems. While 38 (51%) of patients without pre-existing problems have pain, 53 (50.9%) of patients with pre-existing diseases have pain (p=0.729). Mean pain scores of patients with and without pre-existing health problems were 2.24±1.79 and 2.44±2.35, respectively (p=0.535).

We did not find a correlation between the presence of pain and hospitalization days. The mean duration of hospitalization was 6.08±4.54 days in patients with pain. It was 5.97±7.75 days in patients without pain (p=0.60). We observed that number of hospitalization days of the patients with more than one pre-existing disease was 6.04±6.45 while it was 6.01±2.74 for the patients without or one pre-existing health problem (p=0.94). There was no significant difference regarding the frequency of pain complaint or mean pain scores of the pain patients between the patients with more than one accompanying systemic health problems and the remaining patients. The number of individuals with pain in patients with more than one disease and the remaining patients were 28 (50.0%) and 63 (51.6%), respectively (p=0.97). Surprisingly, pain scores were slightly lower in patients with more than one pre-existing disease but there was no significant difference (2.08±1.70 vs. 2.32±2.24, p=0.205).

Discussion

Initially, it should be considered that this study was conducted in the standard ward of an infectious diseases department, rather than ICU settings. Only 7 of the 178 participants required ICU admission during the study. Therefore, participants of this study were not patients with a severe intensity of the disease. The frequency and severity of pain complaints may be higher in patients who are followed in ICU.

This study was conducted between May and August of 2020. Regarding the recommendations of the Turkish Ministry of Health, particularly at the beginning of the outbreak in Turkey (the first COVID-19 case was announced in the middle of March), all cases either possible or confirmed were followed in the hospital to prevent the spread of the outbreak. Thus, our study population may consist of less severe patients with some who have no indication of hospitalization in normal conditions. The frequency and severity of pain could be higher otherwise.

Similar to other studies on COVID-19 population of males were higher than females in our study. Additionally, the population of individuals who work in a job or go to school was higher than the individuals who do not work or study. These results were as we estimated because it is more possible for a person who has an active daily life and contacts with several people every day to exposure to the virus.

The rate of confirmed cases seemed to be low (45.5%) but we conclude this does not mean that only 45.5% of the participants are COVID-19 and the remaining part is mistakenly included in the study. The most common laboratory technique in use for the SARS-CoV-2 is nucleic acid amplification test (NAAT) via real-time reverse-transcription polymerase chain reaction (RT-PCR).[18] It is known that the laboratory confirmation of COVID-19 is a challenge. Bio-Speedy COVID-19 RT-qPCR® test kit that is used in Turkey detects the Orf1ab/ N gene of the virus and has 99% specificity, but the specificity of the laboratory results tremendously depend on the body part where the specimen is collected from.† In a comprehensive study including 1070 specimens collected from 205 patients, Wang et al.[19] reported the positivity rates of bronchoalveolar lavage fluid specimens 93%, followed by sputum 72%, nasal swabs 63%, fibro bronchoscope brush biopsy 46%, pharyngeal swabs 32%, feces 29%, and blood 1%. Another factor that diminishes the specificity of the PCR results is the intensity of the disease. It is suggested that the rate of a positive result is higher in patients with the serious disease than patients with mild disease intensity.[20–22] In our study collection of specimens, procedures were performed according to the guidelines of the Turkish Ministry of Health. Hereunder, an oropharyngeal swab was taken firstly and with the same stick, a nasopharyngeal swab was taken.

Depending on our results, we can suggest that pain is not one of the challenging symptoms in patients with mild or moderate severity of COVID-19. Regarding our results, only half of the patients have pain complaints, and the mean pain score was not high (2.3 over 10). Furthermore, more than a quarter of the patients with pain did not require analgesics, and 69.4% of the patients who need analgesics got enough pain relief despite they took only simple analgesics (Fig. 1). These results reflect that pain treatment in COVID-19 is basic and simple. Additionally, we observed that many of the patients who did not get enough pain relief took their drugs PRN rather than ATC. Patients who do not get enough pain relief with simple analgesics by PRN use of the drug should take their analgesics according to the ATC schedule. We suggest that for the patients who do not get enough pain relief with simple analgesics like paracetamol or NSAIDs despite proper and regular administration of the medicine, a combination of weak opioids (e.g. codeine, tramadol) can be useful and should be considered.

One of the aims of this study was to investigate the effect of pain on the clinical severity of the disease. For this purpose, we used two parameters: First was the difference between patients with and without pain in terms of ICU requirement and the second one is the difference between patients with and without pain in terms of hospitalization durations. The mean duration of hospitalization was similar in patients with pain and patients without pain. Only 7 of the participants required ICU admission and we had not enough numbers to analyze this parameter. Remarkably, acute myocardial infarction was the cause for ICU admission for 2 of these

†: https://bioeksen.com.tr/tr/covid-19-rt-qpcr-tespit-kiti

7 patients. According to the results of this study, we cannot suggest that pain has worsening effects on the clinical course of the COVID-19.

In our study, the frequency and intensity of pain were higher in females. This result was similar to our expectations before the study. Pain concept between genders is a well-studied issue and current literature shows that pain is more frequently reported by women than men.[23–25] This difference can depend on two mechanisms: Biological or psychological. Biologically, it is suggested that sex hormones have effects on nociception and anti-nociception. Although estradiol and progesterone's effects on pain sensitivity are relatively complex (both exert pro-nociceptive and antinociceptive effects on pain), testosterone appears to be more antinociceptive and protective.[23,26,27] Psychologically, pain coping strategies have been found to differ between women and men. While men tend to use behavioral distraction and problem-focused tactics to manage pain, women tend to use a range of coping techniques including social support, positive self-statements, emotion-focused techniques, cognitive reinterpretation, and attentional focus.[23,28–30] On the psychological aspects of pain perception, catastrophizing that have negative effects have been found higher in females, and self-efficacy that have positive effects have been found higher in females.[31–36]

Regarding the locations of pain, our results were consistent with previous studies on the symptoms of COVID-19. Our results for myalgia, headache, chest pain and sore throat were similar to other studies. In the early periods of the outbreak, in their systematic meta-analysis, Fu et al.[4] reported 28% prevalence of myalgia, 14% chest pain, 14% headache, and 12% sore throat. In another systematic meta-analysis on the clinical characteristics of COVID-19, Zhu et al.[37] reported 33% muscle pain, 35.7% chest tightness, 15.4% headache, 13.1% sore throat, and 4.4% abdominal pain. Interestingly, none of our patients reported abdominal pain. We contribute this can be the result of the altered perception of the pain of the participants. Possibly, other symptoms such as cough, fever, dyspnea, or the dominant pain location shadowed the less intense painful body region or patients did not mind abdominal pain to report.

We observed good performance of simple analgesic (paracetamol and NSAIDs) in our study. Only a small portion of the patients did not get enough pain relief despite the regular use of simple analgesics. Speculation on ibuprofen has emerged in the early phases of the outbreak that ibuprofen worsens the course of the disease. The claim that ibuprofen is unsafe for use in individuals with COVID-19 symptoms was raised in the early stages of the COVID-19 outbreak, following the observation that SARS-CoV-2 binds to its target cell through ACE2 in the lung.[38] In contrast to this hypothesis, in their retrospective cohort study including 403 COVID-19 patients, Rinott et al.[39] showed that ibuprofen use was not associated with worse clinical outcomes, compared with paracetamol or no antipyretic. Furthermore, after a short while of the allegations on ibuprofen and NSAIDs, WHO announced a scientific brief indicating that there is no evidence supporting the use of NSAIDs is associated with negative outcomes in COVID-19 patients.‡

As mentioned above, only a small portion of COVID-19 patients with mild-moderate disease intensity did not get enough pain relief with simple analgesics. According to our experience on pain medicine, we suggest that weak opioids like codeine and tramadol can be useful for these patients but we cannot support our suggestion with the results of this study because this was an observational study depending on a questionnaire and we did not manipulate or direct the physicians of the infectious disease department to use any specific kind of analgesics for any participants in the study.

In conclusion, regarding the results of our study, we suggest that pain is not one of the challenging symptoms in COVID-19 patients who have mild or moderate severity of the disease. Most of the patients get pain relief with basic analgesic therapy. We suggest that codeine or tramadol combination with simple analgesics should be considered for the remaining part of the patients who do not get pain relief with simple analgesics. Our results are not enough to make a correlation between the presence of pain complaints and the intensity of the clinical condition. Further studies about pain including the patients with severe clinical states of COVID-19 are necessary.

‡: https://www.who.int/publications/i/item/the-use-of-non-steroidal-anti-inflammatory-drugs-(nsaids)-in-patients-with-covid-19.

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