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Analysis of Patients with Major Fractures with and without COVID-19 Infection

Analýza pacientů se závažnou zlomeninou s a bez infekce COVID-19

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ABSTRACT

PURPOSE OF THE STUDY

As in orthopedic trauma patients, a hyperinflammatory response due to cytokine release occurs in patients with moderate and severe COVID-19 infection. In these patients, untimely surgical intervention can create more destructive situations in the postoperative period. Our aim in this study was to investigate the effect of COVID-19, trauma and surgical intervention on acute phase reactants' levels in patients with and without COVID-19 infection.

MATERIAL AND METHODS

Twenty-four patients diagnosed with COVID-19 infection and major fractures requiring surgical treatment were evaluated retrospectively (Group 1). Twenty-four COVID-19 negative patients with similar trauma were included in the study as a control group (Group 2). These two groups were compared in terms of demographic data, time to surgery, total hospitalization time, and preoperative and postoperative acute phase reactants' [C-reactive protein (CRP), D-dimer, ferritin, fibrinogen and white blood cell (WBC)] values.

RESULTS

Time to surgery was 8.3 ± 0.7 days and the total hospital stay was 15.2 ± 0.8 days, in Group 1. These values were determined as 3.3 ± 0.4 and 6.5 ± 0.6 days, respectively for the patients in Group 2 ($p < 0.001$ and $p < 0.001$, respectively). When the acute phase reactant values studied during admission were examined, a significant difference was found between the two groups in terms of CRP, D-dimer, ferritin and WBC (p = 0009, p = 0.002, $p < 0.001$ and $p < 0.001$, respectively). In the preoperative period, a significant difference was observed between the groups in terms of CRP and ferritin (p = 0.011, $p < 0.001$, respectively). A significant difference was found only in terms of ferritin from the laboratory values studied in the postoperative period ($p < 0.001$).

DISCUSSION

To our knowledge, the present study is the first study which compares and investigates the effects of COVID-19 infection, major fracture and surgical intervention on acute phase reactants' values. Surgical treatment is generally recommended as soon as possible in daily orthopedic practice. However, in patients with asymptomatic or mildly symptomatic COVID-19 infection, it remains unclear how long surgical intervention will be delayed after admission and clinical stabilization of patients with a fracture that requires surgical fixation. In a meta-analysis, patients with COVID-19 infection accompanying hip fracture had a mortality rate of 32.6% in the early postoperative period, and the mortality risk of these patients was found to be 5.66 times higher compared to patients without COVID-19 infection. In our study, one patient (4.2%) with COVID-19 infection who underwent partial hip arthroplasty due to femoral neck fracture.

CONCLUSIONS

The follow-up and treatment of patients with COVID-19 infection with accompanying a major fracture requiring orthopedic surgery is a complex situation. We recommend that acute phase reactants such as CRP, D-dimer, erythrocyte sedimentation rate (ESR), and ferritin should be closely monitored in these patients during the period from admission to surgery, and surgical intervention should be performed while these values are in remission or decline.

Key words: COVID-19, fracture, trauma, acute phase reactants, surgical timing.

INTRODUCTION

Severe acute respiratory sydrome coronavirus 2 (SARS-CoV-2), also known as novel coronavirus or COVID-19, first appeared in China on December 31, 2019 and soon led to a pandemic that affected the whole world. Although there has been a decrease in the frequency and number of orthopedic elective surgical interventions or fractures in this period to date (14, 19), knowing little about emergency interventions for COVID-19 positive patients with orthopedic fractures confronts our orthopedic colleagues with various difficulties (1, 17). A hyperinflammatory response due to cytokine release occurs in patients with moderate and severe COVID-19 as well as in orthopedic trauma patients (6, 18). In this period, prothrombotic coagulopathy due to COVID-19 infection accompanied by increased acute phase reactants (D-dimer, CRP, ESR, ferritin, troponin) and leukocytosis may cause severe acute respiratory distress sydrome and related multiple organ failure (13). Hyperinflammatory and hypercoagulability caused by this infection in patients with COVID-19 may create higher inflammatory response in patients with a major fracture (12, 16). In these patients, as in damage-controlled orthopedics (DCO), it is necessary to be protected from destructive situations such as acute respiratory distress syndrome (ARDS) caused by a second-hit caused by an untimely surgical intervention (4, 16). Understanding the inflammatory state by evaluating the acute phase reactants in the preoperative period in COVID-19 patients accompanied by trauma can prevent undesirable complications that may occur in the postoperative period.

The purpose of this study, in which patients with a major fracture with and without SARS-CoV-2 infection were compared was to investigate the effect of COVID-19 and trauma on acute phase reactants' levels and to examine the change in these values after surgical intervention.

MATERIAL AND METHODS

After obtaining the approval of the local ethics committee patients who were admitted to the emergency department of a single tertiary care hospital between March

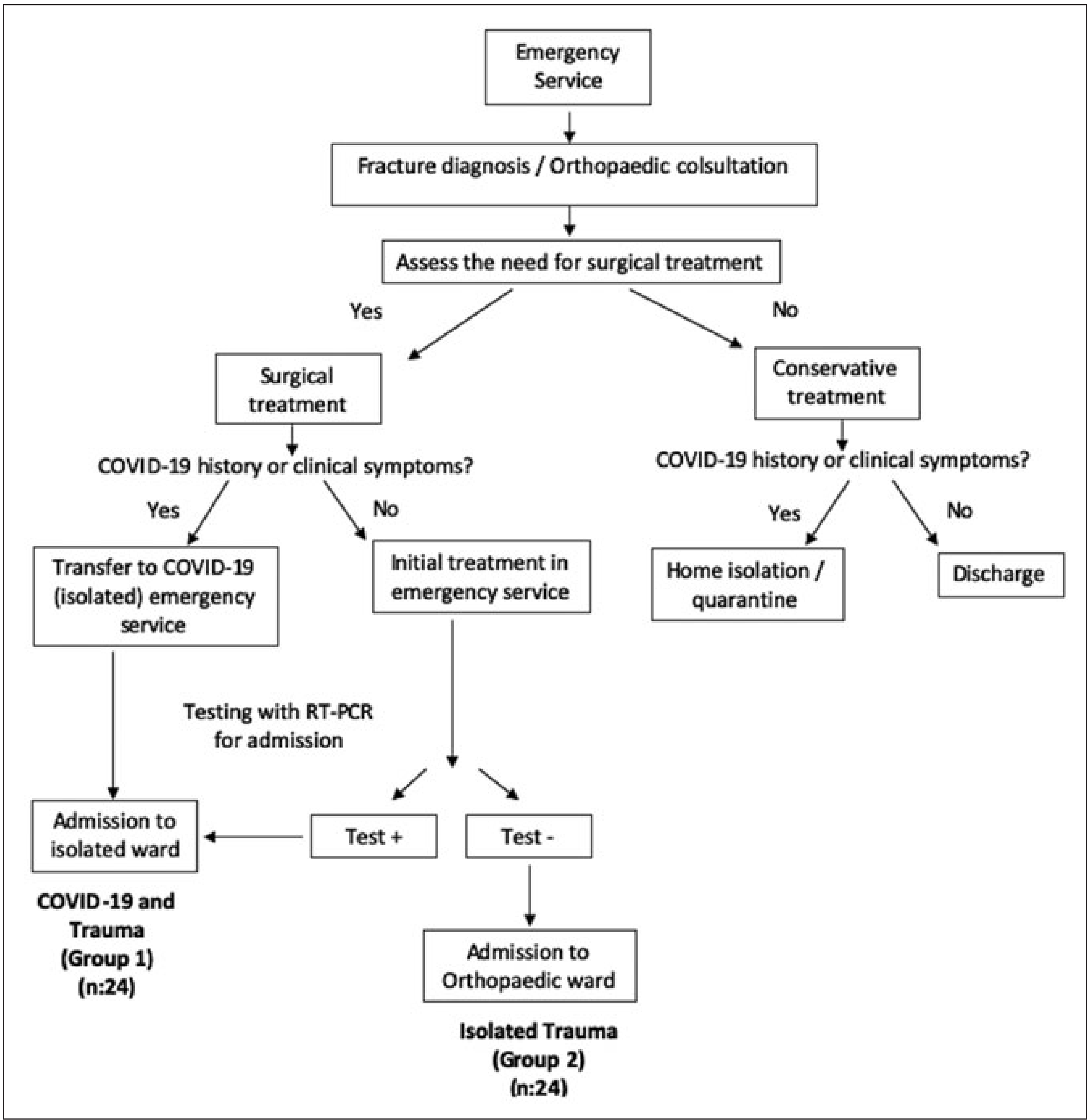

Fig. 1. Algorithm for management of trauma patients with fracture during COVID-19 pandemic.

2020 and November 2020 who had major fractures (fracture of upper or lower extremity which requires surgical treatment and pelvic-hip region fractures) were evaluated retrospectively. Conservatively treated patients were not included in the study. Those who were diagnosed with COVID-19 with a positive reverse transcriptase polymerase chain reaction (RT-PCR) test were named as "COVID-19 positive Trauma Group" (Group 1). Accordingly, a total of 27 patients were evaluated. In the preoperative period, an 82-year-old male patient with intertrochanteric femur fracture died on the 12th day of hospitalization and a 90-year-old male patient with intertorchanteric femur fracture and humeral shaft fracture died on the 11th day of hospitalization due to respiratory failure. These patients could not be treated surgically because of their infections. Conservative treatment was decided for one female patient, who was scheduled otherwise surgical treatment for proximal humerus fracture, due to severe pneumonia caused by COVID-19. The patient was discharged on the 18th day of hospitalization after treatment. These three patients were excluded from the study, and finally 24 patients were included in the study as Group 1.

Table 1. Analysis of the effect of categorical variables

	Group 1 (n:24)	Group 2 (n: 24)	p value
Gender (female/male)	9/15	12/12	0.281
Fracture side (right/left)	14/10	11/13	0.282
Comorbid disease(present/absent)	11/13	9/15	0.385
ASA (1/2/3/4)	4/7/13/0	2/15/6/1	0.067
Region of the fracture (upper extremity/pelvic region/lower extremity)	1/15/8	3/11/10	0.399
Upper extremity			
humerus intercondylar	1	1	
elbow fracture dislocation	–	1	
both bone forearm	–	1	
Pelvic region			
sacrum	1	–	
acetabulum	1	–	
fermoral neck	4	1	
intertrochanteric	9	8	
Lower extremity			
femur shaft	–	1	
distal femur	–	2	
tibia plateu	1	3	
tibia shaft	3	3	
trimalleolar	2	–	
bimalleolar	1	–	
talus	1	–	
calcaneus	–	1	

Twenty four patients who were admitted to the hospital with similar fractures and who had not a COVID-19 infection at the same time period were evaluated retrospectively and named as "Group 2" (Fig. 1).

During the preoperative period, the laboratory values used in the follow-up of the disease during the COVID-19 treatment and evaluated periodically were recorded. CRP, D-dimer, ferritin, fibrinogen and WBC values of the patients were examined. Additionally, the values studied in the postoperative period were analyzed in order to evaluate the effect of surgical intervention on these acute phase values. Two groups were compared in terms of demographic data, time to surgery, total hospitalization time, and preoperative and postoperative laboratory values. All of the blood samples were studied in the same machines (Roche cobas 8000, Roche Diagnostics, Rotkreuz, Switzerland used for biochemical testings, Mindray BC-6800 Analyzer, Shenzhen, China used for hematology controls, Siemens BN™ II system used for CRP analysis).

Statistical analysis

Statistical package for Social Sciences version 24 (IBM SPSS Corp, Armonk, NY, USA) was used for the statistical analysis. The Shapiro-Wilk test was used to evaluate the normality of groups. For the normally distributed continuous data, t or ANOVA tests were used according to the group number. If the distribution of data was not normal, Mann-Whitney U or Kruskal-Wallis tests were used according to the group number to compare the groups. Categorical data was analyzed by using Fisher exact or chi-squared tests. A p value below than 0.05 was accepted as statistically significant.

RESULTS

No statistically significant difference was found between the patient groups in terms of gender, fracture site, side, comorbid diseases (as diabetes mellitus, hypertension, coronary artery disease, chronic renal failure, asthma, chronic obstructive pulmonary disease) and American Society of Anesthesiologist (ASA) scores (Table 1).

In Group 1, time to surgery was 8.3 ± 0.7 days and the total hospital stay was 15.2 ± 0.8 days. In Group 2, these values were determined as 3.3 ± 0.4 and 6.5 ± 0.6 days, respectively. There was a statistically significant difference between two groups ($p < 0.001$ and $p < 0.001$, respectively). There was no significant difference between the two groups in terms of mean age ($p = 0.861$). When the acute phase reactant values studied during admission were examined, a significant difference was found between the two groups in terms of CRP, D-dimer, ferritin and WBC ($p = 0.009$, $p = 0.002$, $p < 0.001$ and p <0 .001, respectively) (Table 2).

In the preoperative period, a significant difference was observed between the groups in terms of CRP and ferritin values ($p = 0.011$, $p < 0.001$, respectively). A significant difference was found only in terms of ferritin from the laboratory values studied in the postoperative

Table 2. Analysis of the effect of continuous variables

	Group 1 (n:24) [mean±std. dev. (min–max)]	Group 2 (n:24) [mean±std. dev. (min–max)]	p value
Age (years)	59.1 ± 5.1 (18–92)	61.7 ± 4.4 (20–102)	0.861
Hospitalization time (days)	15.2 ± 0.8 (7–22)	6.5 ± 0.6 (4–15)	< 0.001
Time to surgery (days)	8.3 ± 0.7 (2–16)	3.3 ± 0.4 (1–10)	< 0.001
Admission			
CRP (mg/L)	48.9 ± 10.8 (3.1–193)	16.1 ± 3.8 (3.1–74)	0.009
D-dimer (mg/mL)	3.5 ± 0.9 (0.2–14.8)	8.1 ± 1.9 (1.2–34.4)	0.002
ferritin (ng/mL)	385.8 ± 78.2 (6–1982)	101.8 ± 20.4 (9.9–402.8)	< 0.001
fibrinogen (ng/mL)	434.2 ± 34.8 (186–797)	360.8 ± 23.5 (158–608)	0.155
WBC (mcl)	8.0 ± 0.6 (4.4–13.4)	12.5 ± 0.6 (5.5–18.7)	< 0.001
Preoperative			
CRP (mg/L)	39.2 ± 7.4 (6.4–168)	70.3 ± 10.0 (13.1–189)	0.011
D-dimer (mg/mL)	3.4 ± 0.8 (0.5–14.2)	3.3 ± 0.9 (0.6–21.6)	0.773
ferritin (ng/mL)	361.3 ± 31.9 (48–708)	187.5 ± 40.0 (14.8–776.8)	< 0.001
fibrinogen (ng/mL)	497.8 ± 35.7 (188–820)	491.9 ± 28.4 (190–818)	0.154
WBC (mcl)	8.4 ± 0.6 (4.0–14.6)	10.3 ± 0.3 (7.1–13.5)	0.115
Postoperative			
CRP (mg/L)	87.4 ± 12.4 (13–269)	97.9 ± 10.5 (19.2–208)	0.409
D-dimer (mg/mL)	5.3 ± 1.4 (0.7–30.3)	4.9 ± 0.9 (0.5–15.3)	0.726
ferritin (ng/mL)	575.5 ± 67.9 (194–1632)	290.1 ± 56.2 (37.3–999.4)	< 0.001
fibrinogen (ng/mL)	540.3 ± 35.7 (134–881)	572.2 ± 28.5 (272–888)	0.302
WBC (mcl)	10.3 ± 0.7 (4.5–16.1)	11.9 ± 0.5 (8.7–19.2)	0.059

CRP: C-reactive protein, WBC: white blood cell

period ($p < 0.001$). In the preoperative period, the CRP value of Group 2 was found to be higher. However, considering that the average time to surgery for Group 2 was 3.3 ± 0.4 days, it was observed that this value was similar for both groups when compared with the preoperative 3-6 days interval values of group 1 (Table 3).

When the preoperative laboratory values of the patients in Group 1 were examined within the group, it was observed that the CRP and ferritin values tended to rise and then decrease within days, and that there was a general increase in D-dimer, fibrinogen and WBC values (Fig. 2).

When these values were evaluated statistically, the change in CRP, D-dimer, ferritin and fibrinogen values was not found to be significant, while the difference in the value of WBC was statistically significant (Table 3).

DISCUSSION

To our knowledge, the present study is the first study which compares and investigates the effects of COVID-19 infection, major fracture and surgical intervention on acute phase reactants' values. Perhaps the most difficult issue for orthopedic surgeons during the COVID-19 pandemic is deciding when to perform surgical intervention for fractures that occur after trauma in patients infected with COVID-19. Given the high mortality of COVID-19 patients, surgical treatment for patients with both

Table 3. Analysis of preoperative laboratory variables in Group 1 patients

	Days between 0–3	Days between 3–6	Days between 6–9	Days up to 10	P value
CRP (mg/L)	48.9 ± 10.8 (3.11–193)	67.1 ± 12.9 (8.6–168)	54.3 ± 13.8 (6.4–191)	36.4 ± 9.4 (9.0–78.3)	0.502
D-Dimer (mg/mL)	3.5 ± 0.9 (0.2–14.8)	3.1 ± 0.6 (0.5–13.2)	5.4 ± 1.8 (1.3–29.3)	6.0 ± 1.6 (2.0–14.2)	0.056
Ferritin (ng/mL)	385.8 ± 78.3 (6.0–1982)	539.1 ± 119.6 (41.0–2000)	437.5 ± 79.8 (48.0–1197)	417.8 ± 54.3 (209–708)	0.653
Fibrinogen (ng/mL)	434.3 ± 34.8 (186–797)	459.3 ± 42.8 (114–788)	562.4 ± 57.1 (208–912)	580.6 ± 46.0 (361–820)	0.086
WBC (mcl)	8.0 ± 0.6 (4.4–13.4)	7.4 ± 0.6 (4.2–13.4)	9.6 ± 0.6 (5.2–14.1)	9.8 ± 1.2 (4.0–14.6)	0.039

CRP: C-reactive protein, WBC: white blood cell

Fig. 2. Changes in preoperative laboratory values of patients who are in Group 1. The X-axis shows the average days until surgery.

fractures and COVID-19 infection should be planned carefully.

The stress caused by occurrence of fracture or surgical treatment can trigger a number of inflammatory factors, and these factors are known to increase the likelihood of pulmonary conditions such as pneumonia (21). The body's initial response to the trauma is considered as the first hit in the "double-hit" hypothesis. It is known that immunological responses to COVID-19 infection are an inflammatory process characterized by the increase of proinflammatory cytokines such as IL-2, IL-6 and TNF-α (8). With the effect of the increased systemic inflammatory response in COVID-19 infection, the "first hit" effect created by trauma may increase even more. Therefore, this inflammatory response triggered by the COVID-19 infection may cause a "second-hit" effect (12). Moreover, systemic inflammation from this COVID-19 infection is thought to cause endothelial dysfunction and then predispose microangiopathy and microthrombi (7). These conditions may appear as thromboembolic events characterized by clinically increased D-dimer levels, increased fibrinogen and fibrin degradation products. These patients should be protected from destructive conditions such as acute respiratory distress syndrome (ARDS) caused by an untimely surgical intervention, just like polytrauma patients (4, 16).

Surgical treatment is generally recommended as soon as possible in elderly and debilitated patients especially with a hip fracture. This approach not only speeds up fracture healing and facilitates mobilization, but also reduces various complications such as pneumonia and deep vein thrombosis and pulmonary embolism (15). However, since complications such as acute respiratory distress syndrome (ARDS) can develop rapidly in patients with asymptomatic or mildly symptomatic COVID-19 infection, it remains unclear how long surgical intervention will be delayed after admission and clinical stabilization of patients with a fracture that requires surgical fixation (2).

Mi et al. reported that four of the COVID-19 patients with various fractures died and severe pneumonia developed in three. Accordingly, they stated that the development of COVID-19 pneumonia in patients with fractures could cause serious adverse effects and increased mortality (11). In a meta-analysis, patients with COVID-19 infection accompanying hip fracture had a mortality rate of 32.6 % in the early postoperative period, and the mortality risk of these patients was found to be 5.66 times higher compared to patients without COVID-19 infection (20). In our study, one patient (4.2 %) with COVID-19 infection who underwent partial hip arthroplasty due to femoral neck fracture died on the 10th postoperative day because of respiratory failure. In the control group, no death was detected in the early postoperative period.

In a recent study evaluating 145 patients who underwent delayed surgery versus nonoperative treatment for hip fractures accompanied by COVID-19, they found that fewer major complications developed in patients who underwent delayed surgery, and that surgical intervention reduced pain, increased mobilization and achieved better functional results in the next period (10). Similarly, with the recommendation of infectious diseases specialists, we postponed the surgery of fractures in patients with COVID-19 infection group until better clinical status were achieved.

The general aim in orthopedic surgery is early fixation of existing fractures and thus early mobilization. In our study, while the mean time to surgery in Group 1 was 8.3 ± 0.7 days, this value was found to be 3.3 ± 0.4 days for the patients who were in Group 2. The reason for prolonged time to surgery in group 1 was the required medical treatment that patients received due to COVID-19 infection. Considering the low mortality rate of our study, we believe that it would be more appropriate to perform the surgical intervention in fracture patients with COVID-19 infection in the period when the patient's clinical findings or laboratory are in remission,

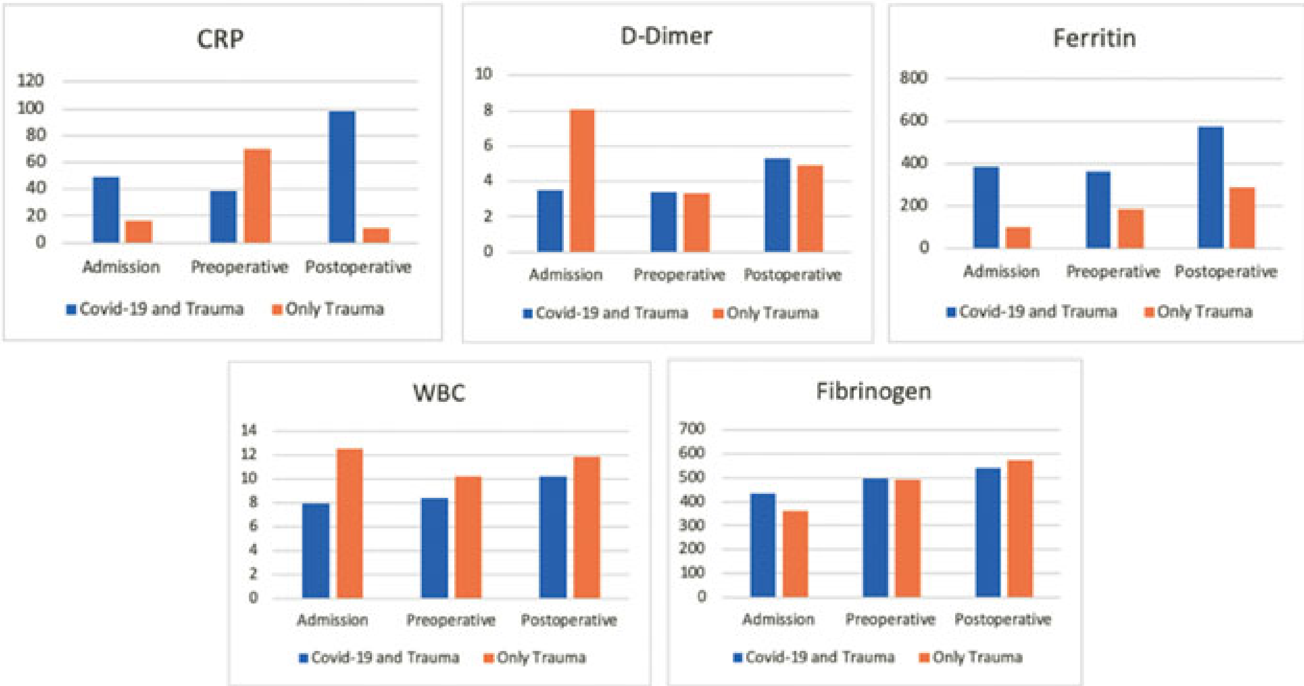

Fig. 3. The difference of laboratory values according to the periods between the two groups.

rather than early surgery. Similarly, Meng et al. in their study, where they reported the average time from injury to surgery as 8.7 ± 3.4 days, stated that this delay occurred due to COVID-19 screening and treatment to obtain appropriate and acceptable clinical results (9). However, in a study in which 13 patients accompanied by COVID-19 infection were treated with surgical intervention, the authors reported an average of 2.3 ± 1.5 days until the surgical intervention, and only one patient died because of COVID-19 pneumonia in the postoperative period, and the remaining 12 patients were discharged (3).

In our study, we determined that the preoperative CRP and WBC values of the Group 2 patients were higher than the Group 1, and the D-dimer and fibrinogen values were similar in both groups (Figure 3). We think that this is due to the fact that the average time until surgery is shorter in Group 2 patients compared to Group 1.

When the values of Group 1 patients at the preoperative period were evaluated, it was seen that these values increased in the early period with the effect of trauma and disease, and enter the phase of decreasing or plateau in the following days (Fig. 2). In an inflammatory disease characterized by the increase of immunological responses and proinflammatory cytokines such as COVID-19 infection, we think that the follow-up of acute phase reactants in the preoperative period is important for intervention in trauma patients. Similarly, Kaidi et al. reported that they had to terminate the surgical intervention due to the critical course of the patient's condition due to COVID-19 infection in their case report. They also suggested that when deciding on the optimal surgical timing in patients with COVID-19 infection, the resolution should be followed using inflammatory markers and attention should be paid to the surgical interventions planned to be performed on the 7^{th}–10^{th} days of COVID-19 symptoms (5).

Since the symptoms of fever, shortness of breath and cough of COVID-19 infection are similar to the atelectasis, pulmonary edema and pulmonary embolism which are usually seen after surgery, COVID-19 infection may complicate the postoperative picture in these patients (3). Increase in leukocytosis, anemia, D-dimer, CRP, ESR, ferritin and troponin are observed in patients in the postoperative period, it should not be forgotten that there may be difficulties in diagnosing the complications that occur in trauma patients accompanied by COVID-19 infection.

The present study has several limitations. The most important one is its' retrospective design. The limited number of included patients is another drawback. Since interleukin 6 is one of the best indicators of inflammation, it would have been very useful if it was used in the study.

CONCLUSIONS

As a conclusion; the follow-up and treatment of COVID-19 infection accompanying major fracture patients requiring orthopedic surgery is a complex situation. We recommend that acute phase reactants such as CRP, D-dimer, ESR, and ferritin should be closely monitored in these patients during the period from admission to surgery, and surgical intervention should be performed while these values are in remission or decline. It should be kept in mind that acute phase reactants used in the follow-up of COVID-19 infection in the postoperative period may increase due to surgical trauma. Whether this increase is due to surgical intervention or the progression of COVID-19 infection should be checked with close clinical follow-ups.

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