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ORIGINAL ARTICLE

The painful joint after COVID-19 treatment: A study on joint osteonecrosis following COVID-19-related corticosteroid use

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ABSTRACT

Objectives: This study aims to evaluate the incidence of osteonecrosis (ONC), with a special focus on ONC of the femoral head (ONFH), in novel coronavirus disease 2019 (COVID-19) patients two years after the pandemic.

Patients and methods: This prospective study included COVID-19 patients who were admitted to our center between March 2020 and June 2020. A total of 472 patients (289 males, 183 females; mean age: 42.3±12.0 years; range, 18 to 60 years) were arranged in a list according to their date and time of admission and, then, divided into two groups: those not receiving corticosteroid (CS) treatment (Group 1, n=236) and those receiving CS treatment (Group 2, n=236). The patients were evaluated for joint pain based on X-rays and magnetic resonance imaging scans, and the patients were routinely followed. For each patient in Group 2, additional data regarding CS use were recorded. The possible relationship between ONC and risk factors was analyzed.

Results: Both groups were similar in terms of age and sex. Group 2 had a significantly longer hospitalization period. A significant increase in the number of painful joints was observed in Group 2. At two years, 5.1% of the patients in Group 1 complained of at least one painful joint compared to 11.9% of patients in Group 2. Eight patients from Group 2 developed ONC.

Conclusion: The incidence of ONC after CS therapy in COVID-19 patients is on the rise. At two years, 5% of patients receiving various doses of CSs may develop ONC. Residual joint pain is common even after recovering from the virus. No relationship is evident between the duration of treatment, cumulative dosage of medication, maximum one-day dosage received, and the presence of ONC.

Keywords: Corticosteroids, COVID, hip, knee, osteonecrosis.

The novel coronavirus disease 2019 (COVID-19) is often characterized by a severe acute respiratory syndrome in affected patients.[1] The majority of COVID-19 patients are asymptomatic and very few require medical treatment. On the other hand, severely ill patients are hospitalized, often requiring mechanical ventilation support.[2] A variety of agents have been attempted for the treatment of COVID-19,[3] but only corticosteroids (CSs) have been defined as life-saving in the management of COVID-19.[4]

Widespread usage of CSs has been called out since the beginning of the pandemic, arguing that an uncensored use could lead to a secondary crisis of osteonecrosis (ONC), mainly on the hip and knee joints.[5] While no incidence of large patient cohorts has yet been published, some initial reports have started to emerge regarding ONC lesions of the jaw,[6] knee joint[7] and hip.[8] A study regarding the long-term results of the severe acute respiratory syndrome (SARS) outbreak in 2003 reported ONC rates ranging between 21.1 and 57.7% in patients treated with CSs, the slight majority of which were female.[9] The symptoms appeared as early as one month after treatment with a high dosage and

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the incidence increased drastically within the first six months.[10] Osteonecrosis is most commonly encountered in the hip joint[9,11] and, considering the debilitating effects, on the quality of life in affected patients, an early diagnosis is extremely important.

Anti-apoptotic effects of thymoquinone may be a promising treatment option for early stage of ONC.[11] Cumulative and maximum dose play a role, but also underlying diseases such as diabetes and autoimmune diseases, influence the final outcome.[12] Early diagnosed patients have the possibility to undergo medical treatment[13] or surgery.[14] Due to the large number of patients who were administered CSs during the pandemic, data regarding previous SARS outbreaks and the relative urgency of early diagnosis, in the present study, we aimed to evaluate the incidence of ONC, with a special focus on ONC of the femoral head (ONFH), in COVID-19 patients two years after the pandemic.

PATIENTS AND METHODS

This single-center, prospective, longitudinal study was conducted at Ankara City Hospital, Department of Orthopedics and Traumatology between March 2020 and June 2020. Patients were arranged in a list according to their date and time of admission and, then, divided into two groups: those not receiving CS treatment (Group 1) and those receiving CS treatment (Group 2). Inclusion criteria were as follows: age between 18 and 60 years, hospitalization at our center with International Classification of Diseases, 10th Revision (ICD-10) codes related to COVID-19 (U06, U07.0, U07.1 and U07.2) for at least five days, a positive polymerase chain reaction (PCR) result confirming the COVID-19 diagnosis and no prior history of CS usage. Exclusion criteria were as follows: age >60 years, hospitalization in more than one medical center, prior usage of CS medication for any reason (e.g., rheumatoid arthritis, systemic lupus erythematosus, organ transplantation, other autoimmune diseases), a history of hypercoagulability condition (e.g., Factor V Leiden, sickle cell anemia, malignancy), and a prior diagnosis of hip-related deformities or surgeries (e.g., Perthes disease, developmental hip dysplasia, hip fracture). A power analysis with an alpha (α) error of 0.05 and a power of 90% (β error) calculated that 133 patients were required in each group.

The hospitals registry was screened according to the inclusion criteria during the month of July 2020 for eligible patients. Calculating for dropouts and loss to follow-up, we decided to include the first 250 patients in each group. Demographic data and detailed data related to the medications administered during hospitalization were meticulously collected. For each patient in Group 2, the following additional information regarding CS use was recorded: total dose

	After receiving treatment for COVID-19, have you experienced any of the following symptoms in the last 6 months:	**Yes**	**No**
HIP	Pain in the anterior region of the groin/hip area		
	Pain in the groin/hip area starting without any specific movement		
	Pain in the groin/hip area while rising from a chair		
	Pain in the groin/hip area while going uphill or downhill		
	Pain in the groin/hip area while climbing stairs		
Shoulder	Pain in any of the shoulders during the night		
	Pain in any of the shoulders starting without any specific movement		
	Loss of motion in any of the shoulders		
	Crepitus onset or general weakness in any of the shoulders		
Knee	Pain in the knee starting without any specific movement or with minor trauma		
	Pain in the knee during the night		
	Pain in the knee when touching it		
	Loss of motion in any knee		

FIGURE 1. The questionnaire used for screening patients of residual joint pain after recovery from COVID-19.

of CS usage (presented as cumulative prednisolone equivalent, after conversion, in mg), maximal dose per day, total duration of treatment (days).

According to their admission date (oldest first), patients were called at intervals of six months and were asked a set of questions relating to recently occurring hip, knee and shoulder pain specifically, and other joint pain in general (Figure 1). Patients describing pain in one or more joints were invited for an outpatient visit. X-rays and magnetic resonance imaging (MRI) were obtained for the evaluation of the painful joints. Patients with painful joints were followed with routine visits every six months and routine X-rays and MRIs were taken, if pain persisted. All patients were contacted by phone up to the second year after admission.

The study was initially started with 250 patients in each group. Thirteen patients in Group 1 and 12 patients in Group 2 refused to fulfill the questionnaire or attend to routine follow-up visits at various intervals, reporting lack of actual joint pain. One patient in Group 2 died due to a job-related accident, while one patient from each group failed to show up for the scheduled MRIs. Both patients refused to further participate and reported that the pain they felt was tolerable. Finally, a total of 472 patients (289 males, 183 females; mean age: 42.3±12.0 years; range, 18 to 60 years) including 236 patients in each group completed the study (Figure 2).

Radiological evaluation

Magnetic resonance imaging and X-rays were evaluated by two experienced orthopedic surgeons. The primary focus of the study was on ONFH, while other joints were also examined for ONC lesions. Diagnosis of ONFH was confirmed by a single density "bandlike" lesion with a low rim of signal intensity surrounding the necrotic spot in T1 sequences, and/or by a "double-density sign" with an external low signal intensity rim and a high signal intensity internal rim on the T2 images (Figure 3).

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 20.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean ± standard deviation (SD) or median (min-max) for continuous variables or in number and frequency for categorical variables. Fisher chi-square test, continuity correction chi-square test, and Pearson chi-square test were used to compare categorical variables between groups. The Mann-Whitney U test was used to compare data sets that were not normally distributed, while independent samples t-test was used to compare normally distributed datasets. Univariate and multivariate logistic regression analyses were performed to identify the association between ONC and the risk factors. A p value of <0.05 was considered statistically significant.

RESULTS

Age and sex of the patients were similar between the groups. Patients receiving CSs (Group 2), on the other hand, had a significantly longer hospitalization period (8.9±3.7 days *vs.* 11.1±7.1 days). Demographic data are shown in Table I.

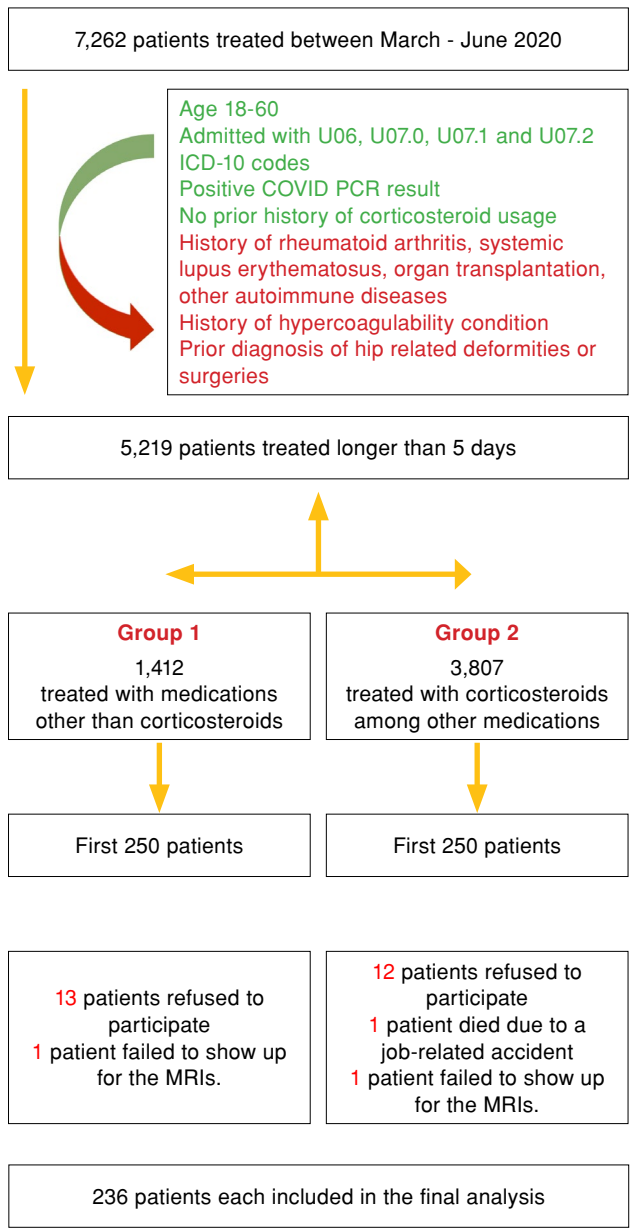


FIGURE 2. Study flowchart.

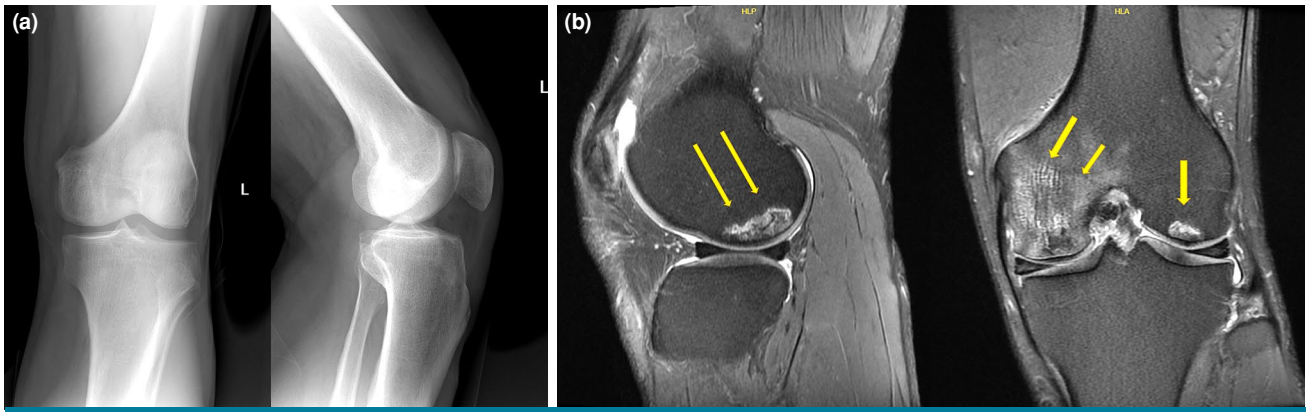


FIGURE 3. A relatively normal X-ray of a patient's knee **(a)** exhibiting clear signs of osteonecrosis of magnetic resonance imaging. The "double density sign" with an external low signal intensity rim and a high signal intensity internal rim on the T2 images (arrows) can be observed **(b)**.

The patients were administered different dosages of CSs for a mean of 6.8±4.1 (range, 1 to 27) days and the mean cumulative dosage of medication (total cumulative dosage of CS given to patients during hospitalization) used was 1,491.9±2,506.6 (range, 50 to 20,675) mg of prednisolone. Data regarding CS usage is presented on Table II.

Data regarding number of painful joints and signs of ONC on MRI are presented in detail in Table III. The results showed a significant increase in the number of painful joints on the first- and second-year visit, after an apparently similar six-month period.

The most frequently affected joint was clearly the hip, with two patients in Group 1 and eight in Group 2 developing ONC at the end of the study period. Data are presented in Table IV. Only one patient in Group 2 was treated with a hip replacement

TABLE I
Demographic and clinical data of patients

	Group 1 Control (n=236)					Group 2 Corticosteroid (n=236)					
	n	%	Mean±SD	Median	Min-Max	n	%	Mean±SD	Median	Min-Max	*p*
Age (year)			42.8±12.2	45	18-60			41.7±11.8	43	20-60	0.293*
Sex											0.052+
Male	133	56.4				156	66.1				
Female	103	43.6				79	33.5				
Total days of hospitalization			8.9±3.7	8	5-22			11.1±7.1	10	5-76	**0.000***
Occupation											**0.005+**
Unemployed	76	32.2				51	21.6				
Freelancer	29	12.3				46	19.5				
Doctor	9	3.8				9	3.8				
Engineer	3	1.3				0	0.0				
Governmental employee	21	8.9				43	18.2				
Nurse	8	3.4				3	1.3				
Pharmacist	1	0.4				1	0.4				
Retired	24	10.2				15	6.4				
Military personnel	8	3.4				8	3.4				
Student	14	5.9				9	3.8				
Teacher	7	3.0				13	5.5				
Manual labor worker	36	15.3				38	16.1				
Smoking											**0.006+**
Yes	72	30.5				46	19.5				
No	164	69.5				190	80.5				
Alcohol											**0.000+**
Yes	36	15.3				0	0.0				
No	200	84.7				236	100				

SD: Standard deviation; * Mann-Whitney U test; + Pearson chi-square.

TABLE II
Data regarding corticosteroid use of Group 2. The dosages are presented in mg of prednisone equivalent

	Group 2 Corticosteroid (n=236)		
	Mean±SD	Median	Min-Max
Total days of hospitalization	11.1±7.1	10	5-76
Total days of corticosteroid therapy	6.8±4.1	6	1-27
Cumulative dosage of corticosteroid received	1491.9±2506.6	437.5	50-20675
Maximum one-day dosage received	542.0±949.8	100	25-5000

SD: Standard deviation.

(52 months after hospitalization), since his affected hip joint degenerated in a quick manner (Figure 4). Knee ONC was also managed with a decompression of the necrotic site and injected with a bone marrow aspirate concentrate (data not shown here).

A regression analysis was performed to explore the relationship between CS usage and overall presence of ONC. Univariate and multivariate analyses failed to find a significant relationship between duration of treatment, cumulative dosage

TABLE III
Comparative data between the two groups with regards to joint pain and osteonecrosis presence

		Group 1 Control (n=236)		Group 2 Corticosteroid (n=236)		
		n	%	n	%	*p**
6 months	Number of painful joints					0.104
	0	224	94.9	215	91.1	
	1	12	5.1	21	8.9	
	2	0	0.0	0	0.0	
	Signs of osteonecrosis on MRI+					NA
	Yes	0	0.0	0	0.0	
	No	12	100	21	100	
1 year	Number of painful joints					**0.035**
	0	224	94.9	209	88.6	
	1	12	5.1	26	11.0	
	2	0	0.0	1	0.4	
	Signs of osteonecrosis on MRI+					**0.032**
	Yes	0	0.0	8	29.6	
	No	12	100	19	70.4	
1.5 years	Number of painful joints					**0.010**
	0	224	94.9	206	87.3	
	1	12	5.1	28	11.9	
	2	0	0.0	2	0.8	
	Signs of osteonecrosis on MRI+					**0.032**
	Yes	0	0.0	10	33.3	
	No	12	100	20	66.7	
2 years	Number of painful joints					**0.010**
	0	224	94.9	206	87.3	
	1	12	5.1	28	11.9	
	2	0	0.0	2	0.8	
	Signs of osteonecrosis on MRI+					**0.030**
	Yes	2	16.6	12	40.0	
	No	10	83.4	18	60.0	

Magnetic resonance imaging; * Pearson chi-square; + Percentage of osteonecrosis in painful joints only.

TABLE IV
Comparative data of primary endpoint between the study groups

	Group 1 Control (n=236)		Group 2 Corticosteroid (n=236)		
	n	%	n	%	*p*
Overall presence of osteonecrosis					**0.007**
Yes	2	0.8	12	5.1	
No	234	99.2	224	94.9	
Joint with osteonecrosis					0.334
Hip	2	100	8	66.6	
Knee	0	0	4	33.4	

* Pearson chi-square.

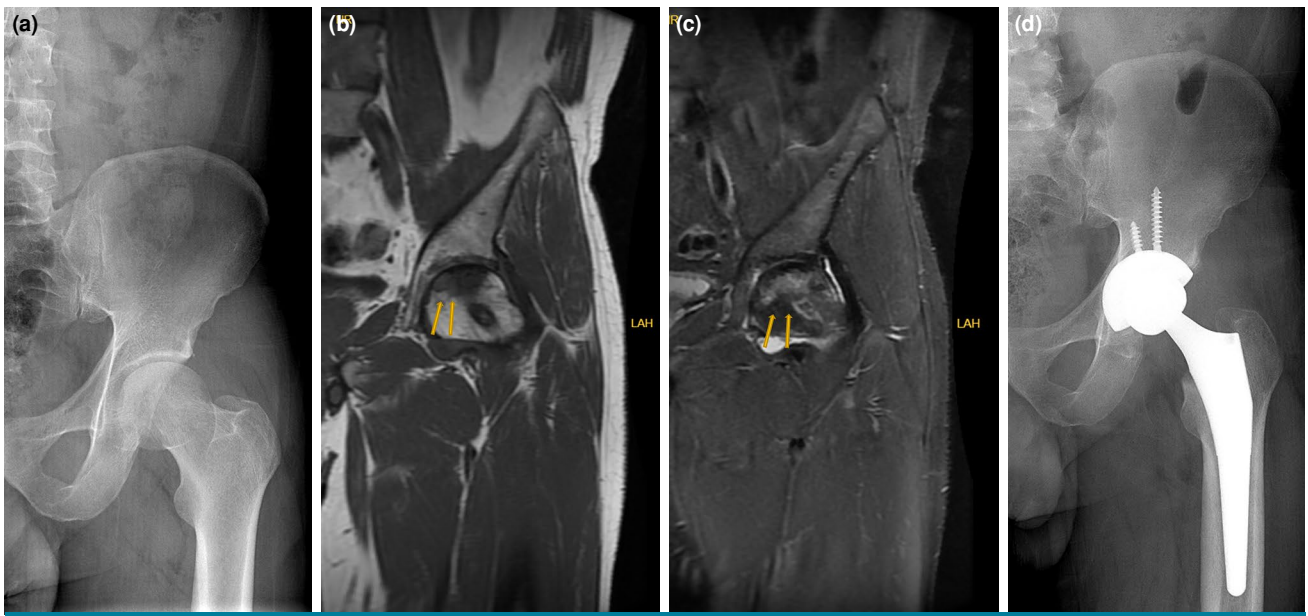


FIGURE 4. (a) Radiological analysis of a 38-years-old female patient with normal X-ray views. **(b, c)** After a failed bilateral core decompression procedure and constant pain, the osteonecrotic lesion did not resolve and **(d)** the patient was eventually treated with a hip replacement.

of the medication, and the presence of ONC (Table V).

DISCUSSION

The current study found that more than 5% of patients receiving prednisone for an average of 6.8 days developed ONC in the hip or knee joints. At two years, 11.9% of patients who received CSs had at least a residual painful joint. Duration of treatment, cumulative dosage of the medication, and maximum one-day dosage received were not correlated with the presence of ONC.

Corticosteroids have been the most effective and widely used drug type in the treatment of SARS.[15] The greatest risk of using CSs in the first place, particularly from an orthopedic perspective, is the development of joint ONC and reports from the SARS outbreak of a prevalence of up to 57.7%, should come as no surprise.[16] The results of our study which included 236 consecutive patients hospitalized and treated for COVID-19, showed a 5% incidence of ONC. This is consistent with the results reported by Assouline-Dayan et al.,[17] but is much lower compared to the study of Zhao et al.[10]

Motomura et al.[18] showed a correlation between the maximum daily dose of CSs and ONFH, while Massardo et al.[19] reported that a dose of prednisone greater than 40 mg/day was positively correlated

TABLE V
Univariate and multivariate logistic regression analysis for overall osteonecrosis presence in patients treated with corticosteroids

	Univariate logistic regression			Multivariate logistic regression analysis			
	HR	95% CI	*p*		HR	95% CI	*p*
Total days of hospitalization	1.02	0.97-1.09	0.343	Total days of hospitalization	0.98	0.89-1.08	0.790
Total days of corticosteroid therapy	1.09	0.97-1.21	0.120	Total days of corticosteroid therapy	1.13	0.96-1.34	0.135
Cumulative dosage of corticosteroid received	1.00	1.00-1.00	0.783	Cumulative dosage of corticosteroid received	1.00	0.99-1.00	0.547
Maximum one-day dosage received	1.00	0.99-1.00	0.711	Maximum one-day dosage received	1.00	0.99-1.00	0.976

HR: Hazard ratios; CI: Confidence intervals.

with ONC. Total cumulative dosage also plays a role. Zhao et al.[10] concluded that physicians should avoid using dosages >10 g of methylprednisolone (or equivalents) and possibly allow for "treatment holidays", since the risk of ONFH increased by a ratio of 1.29 for every 10 days of treatment. In contrast to the literature, this study found no direct relationship between the duration of treatment, overall dosage of the medication, maximum one-day dosage received and the presence of ONC.

Although early diagnosis is of utmost importance, the onset of symptoms may take time to develop. Several studies have described various times to onset, from three weeks after the last CS dosage intake[20] and up to 24 months.[21] General consensus is that between 6 and 12 months after moderate-to-high CS usage, physicians should be vigilant for the possibility of ONFH development and always consider the possibility within the first three years.[17] At 48 months, 28 patients who received different dosages of CS treatment complained of at least one painful joint, but ONC was spotted in only 12 of them. Due to the fact that symptomatic onset may come later that radiological onset, many authors recommend routine screening with X-rays and MRIs.[16,22] Zhao et al.[23] suggested that MRIs be taken at intervals of 3, 6, and 12 months after steroid administration, but not within the first months, since it has been shown to lead to false negativity.[22] Whether MRI screening should become a routine imaging modality after CS treatment is still a matter of debate.

Hofmann et al.[24] proposed that the SARS virus was in, itself, an independent factor for the occurrence of ONFH and the new COVID-19 virus might also have the same effect. Furthermore, the ensuing strong systemic inflammatory response leads to a large number of inflammatory mediators being released, some of which cause vasoconstriction, one of the accepted mechanisms of bone ONC.[25] Li et al.[26] reported that differences in susceptibility levels of patients exist and that patients suffering from the same disease and being treated with the same CS regimen do not show the same rate of complication. Consistent with the literature, a minority of patients not receiving CS therapy developed ONC in our control cohort.

Nonetheless, this study has certain limitations, and the results should be interpreted accordingly. First, we used telephone calls to screen for symptoms, while it is known that clinical complaints appear later than radiological signs. We attempted to overcome this issue by keeping in touch with the

patients every six months, trying not to miss any ongoing or newly appearing painful ONC process. The study could have been more effective, if we had screened all included patients with sequential MRIs, which would have surely detected earlier ONC processed; however, we lacked the appropriate funding for such a study design. Second, the study used a non-validated questionnaire to scan for overall joint pain in eligible patients. The questionnaire was used as a tool to standardize the questions asked to patients, although no scores or related values were used in the analysis. While we excluded patients with possible confounding factors such as diabetes, hypercoagulability, or organ transplantation, we did not screen for blood results. Vitamin D and cholesterol values, for instance, have been shown to correlate with ONC in previous studies.[25] We attempted to overcome this by excluding patients with previously known comorbidities based on previously used ICD codes, registry data, and questioning.

Despite these shortcomings, this is the first study to report on the incidence of ONC after a two-year period of CS treatment due to COVID-19. The main strength of this study is the creation of a control group and the relatively large sample size. The results of this study should not, though, refrain healthcare providers from using CSs in critically ill patients. They have been proven to have a life-saving effect, and that is more important than a possible future joint replacement.

In conclusion, the incidence of ONC after CS therapy in COVID-19 patients is on the rise. At two years, 5% of patients receiving various doses of CSs may develop ONC. Residual joint pain is common even after recovering from the virus. No relationship is evident between the duration of treatment, cumulative dosage of medication, maximum one-day dosage received, and the presence of ONC. Further studies are warranted to draw more reliable conclusions on this subject.

Ethics Committee Approval: The study protocol was approved by the Ankara City Hospital Clinical Research Ethics Committee (date: 20.01.2021, no: E1/1429/2020). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Idea/concept, analysis and/or interpretation, critical review, materials: A.F., E.V.; Design, literature review: Y.E., K.K.; Control/supervision: A.F., K.K.; Data collection and/or processing, writing the article, references and fundings: B.S.S., Y.K.

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