Review Article

A comprehensive review on herbal preservatives

Kundan Kushwah[1], Harshwardhan Dawar[2], Asish V S[3*]

[1]Professor and HOD , Department of Orthopaedics,M.G.M.M.C. and M.Y.H., Indore,India
[2]Assistant Professor, Department of Orthopaedics,M.G.M.M.C. and M.Y.H., Indore,India
[3]Senior Resident,Department of Orthopaedics,Sreegokulam medical college and Research foundation, Venjaramood, TVM, Kerala,India

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Abstract

Background: Avascular necrosis (AVN) of the hip is a progressive and disabling condition resulting from compromised blood supply to the femoral head. During the COVID-19 pandemic, increasing reports of post-COVID musculoskeletal complications have raised concern regarding a possible association between SARS-CoV-2 infection and AVN, particularly in the setting of corticosteroid use and COVID-19–related vascular injury. However, available evidence remains limited, especially from the Indian population. The present study aimed to evaluate the correlation between prior COVID-19 infection and avascular necrosis of the hip joint and to analyze demographic characteristics, disease severity, steroid exposure, and time to onset in a tertiary care setting.**Methods:** This cross-sectional observational study was conducted in the Department of Orthopaedics at a tertiary care center over one year. Sixty patients diagnosed with idiopathic AVN of the hip were included. Clinical history focusing on COVID-19 infection, steroid therapy, and symptom onset was recorded. Radiological assessment using X-ray and MRI was performed, and AVN was graded using the Ficat and Arlet classification. Data were analyzed using descriptive statistics.**Results:** The mean age of patients was 38.78 ± 10.58 years, with a male predominance of 75%. Grade 2 AVN was the most common stage (40%), followed by Grade 3 (30%) and Grade 4 (26.7%). Bilateral hip involvement was observed in 61.7% of cases. Twenty patients (33.3%) had a history of COVID-19 infection, among whom Grade 2 and Grade 3 AVN predominated. Only 35% of COVID-19–positive patients had documented steroid exposure. The mean interval between COVID-19 infection and AVN onset was 6.53 months.**Conclusion:** The study suggests a possible association between COVID-19 infection and AVN of the hip, with evidence supporting a multifactorial pathogenesis beyond steroid exposure alone. Long-term surveillance and early evaluation of hip symptoms in post-COVID patients are essential.

Keywords: COVID-19; Avascular necrosis; Hip joint; Steroid therapy; post-COVID complications.

Introduction

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), resulted in an unprecedented global health emergency and stimulated extensive scientific research aimed at understanding its pathogenesis, clinical spectrum, and long-term consequences. Although substantial progress has been made in characterizing the acute manifestations of the disease, its multisystem involvement and delayed complications continue to present significant clinical challenges [1]. The declaration of COVID-19 as a pandemic by the World Health Organization marked a critical milestone in global health, highlighting the scale and severity of its impact. In recent years, increasing attention has been directed toward post-COVID-19 syndrome, a condition characterized by persistent symptoms such as fatigue, dyspnea, malaise, neuropsychiatric disturbances, and cardiovascular complications that may persist for weeks or months after apparent recovery [2].Among the emerging but relatively under-recognized post-COVID complications is involvement of the musculoskeletal system, particularly the possible association between COVID-19 infection and avascular necrosis (AVN) of the femoral head [3]. AVN is a debilitating disorder caused by compromised blood supply to bone, leading to osteocyte death, collapse of the femoral head, and progressive joint destruction if not identified early. Traditionally, AVN has been linked to trauma, prolonged corticosteroid exposure, excessive alcohol intake, and metabolic disorders. However, recent clinical observations have raised concern regarding its development as a post-COVID sequela [4].Several mechanisms have been proposed to explain this association. The widespread use of systemic corticosteroids in hospitalized COVID-19 patients, particularly during the pandemic surge in India, has been recognized as a major contributing factor because of their established adverse effects on bone metabolism and microcirculation[5].Additionally, COVID-19-related hypercoagulability, endothelial dysfunction, microvascular thrombosis, and exaggerated inflammatory responses may further impair bone perfusion, thereby increasing susceptibility to AVN [6]. Genetic predisposition, including single nucleotide polymorphisms affecting pro-inflammatory cytokines such as IL-1β, IL-6, and IL-8, may exacerbate immune-mediated vascular injury and coagulation abnormalities, amplifying the overall risk [7]. The combined influence of corticosteroid exposure, immune dysregulation, and vascular compromise likely explains the increasing reports of AVN in post-COVID patients [8–10].

Early diagnosis of AVN is crucial, as prognosis is closely related to the stage and extent of femoral head involvement. However, overlap of symptoms with other post-COVID conditions and increased healthcare burden may delay timely diagnosis [11]. Magnetic resonance imaging remains the gold standard for early detection because of its high sensitivity and specificity [12]. Despite growing concern, existing evidence is largely limited to case reports and small retrospective studies, with limited epidemiological data from India, where steroid exposure and baseline AVN risk factors are prevalent [13]. Therefore, the

*Correspondence
Dr. Asish V S
Senior Resident, Department of Orthopaedics,Sreegokulam medical college and Research foundation, Venjaramood, TVM, Kerala, India
E-Mail: asishvs7@gmail.com

present study aims to evaluate the correlation between COVID-19 infection and avascular necrosis of the hip joint in a tertiary care setting, with the objective of identifying associated risk factors and improving understanding of its pathophysiology and clinical implications.

Material and methods

This cross-sectional observational study was conducted in the Department of Orthopaedics and Traumatology at MGM Medical College & MY Hospital, a tertiary care center in central India. The study aimed to evaluate the correlation between prior COVID-19 infection and the occurrence of avascular necrosis (AVN) of the hip joint. The study was carried out over a period of one year following approval from the Institutional Ethics Committee.

A total of 60 patients diagnosed with avascular necrosis of the hip joint were included. Patients presenting to the orthopaedic outpatient department with hip pain were screened, and those diagnosed with idiopathic AVN and fulfilling the inclusion criteria were enrolled after obtaining informed written consent. Patients with a history of trauma to the affected hip, steroid use unrelated to COVID-19 treatment, chronic alcoholism, or medical conditions known to predispose to AVN such as rheumatoid arthritis, coagulopathies, autoimmune disorders, and chronic dermatological diseases were excluded.

Data Collection and Clinical Assessment

After obtaining informed written consent, eligible patients were enrolled. A detailed clinical history was obtained for each participant, with particular emphasis on prior COVID-19 infection status. Information regarding steroid therapy administered specifically for COVID-19 treatment, including dosage and duration, was recorded. Additional parameters included duration of hospital stay for COVID-19 illness, interval between COVID-19 infection and onset of hip pain, presence of comorbid conditions, and history of substance use or addictions.

All patients underwent radiological evaluation of the affected hip joint. Plain radiographs and magnetic resonance imaging (MRI) were performed to confirm the diagnosis of avascular necrosis and assess disease extent. Imaging investigations were provided free of cost under the Ayushman Yojana scheme available at the institution.

Statistical Analysis

Collected data were entered into Microsoft Excel (version 10.0) and subsequently analyzed using IBM SPSS Statistics. Descriptive statistical analysis was performed. Continuous variables were expressed as mean ± standard deviation, while categorical variables were summarized as frequencies and percentages. Graphical representation of data was performed using bar charts, pie charts, and scatter plots where appropriate.

Results

The demographic analysis showed that the study population had a mean age of 38.78 ± 10.58 years, with the majority of patients clustered in the 31–40-year age group (27/60, 45.0%), followed by the 21–30-year group (13/60, 21.7%) and the 41–50-year group (11/60, 18.3%), while fewer patients were aged 51–60 years (8/60, 13.3%) and above 60 years (1/60, 1.7%). A clear male predominance was observed, with 45 males (75.0%) and 15 females (25.0%), resulting in a male-to-female ratio of 3:1. Regarding disease severity, Grade 2 AVN was the most frequent presentation, affecting 24 patients (40.0%), followed by Grade 3 in 18 patients (30.0%) and Grade 4 in 16 patients (26.7%), whereas Grade 1 disease was uncommon (2 patients, 3.3%). In terms of laterality, bilateral involvement was noted in 37 patients (61.7%), compared to unilateral disease in 23 patients (38.3%). Overall, the findings indicate that AVN in this cohort predominantly affected middle-aged males and was commonly detected at intermediate to advanced stages with a higher frequency of bilateral hip involvement. [Table 1]

Table 1. Demographic and Clinical Profile of Study Participants (N = 60)

Variable	Category	Frequency (n)	Percentage (%)
Age (years)	21–30	13	21.7
	31–40	27	45.0
	41–50	11	18.3
	51–60	8	13.3
	>60	1	1.7
Gender	Male	45	75.0
	Female	15	25.0
AVN Grade (Ficat & Arlet)	Grade 1	2	3.3
	Grade 2	24	40.0
	Grade 3	18	30.0
	Grade 4	16	26.7
Laterality	Bilateral	37	61.7
	Unilateral	23	38.3

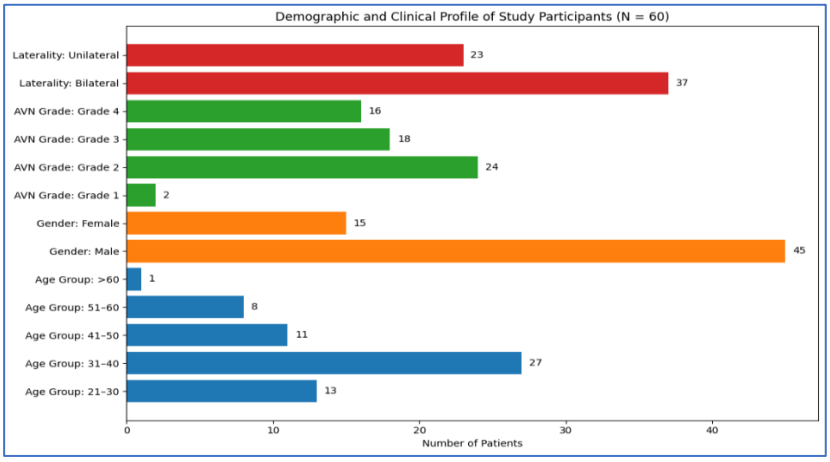


Figure 1. Demographic and Clinical Profile of Study Participants (N = 60)

Among the 60 study participants, one-third had a documented history of COVID-19 infection, with 20 patients (33.3%) being COVID-19 positive and 40 patients (66.7%) reporting no prior infection. Within the COVID-19 positive subgroup, avascular necrosis predominantly presented as moderate to advanced disease. Grade 2 and Grade 3 AVN were the most frequent, each affecting 7 patients (35.0%), while Grade 4 disease was observed in 5 patients (25.0%). Early-stage disease was uncommon, with only 1 patient (5.0%) presenting with Grade 1 AVN. Bilateral hip involvement was more frequent than unilateral disease among COVID-19 positive patients, seen in 11 cases (55.0%) compared to 9 cases (45.0%), suggesting a tendency toward more extensive joint involvement in this subgroup.

Table 2. COVID-19 Status and AVN Severity among Study Participants (N = 60)

Variable	Category	Frequency (n)	Percentage (%)
COVID-19 status	COVID-19 positive	20	33.3
	COVID-19 negative	40	66.7
AVN grade in COVID-19 positive patients (n = 20)	Grade 1	1	5.0
	Grade 2	7	35.0
	Grade 3	7	35.0
	Grade 4	5	25.0
Laterality in COVID-19 positive patients	Bilateral	11	55.0
	Unilateral	9	45.0

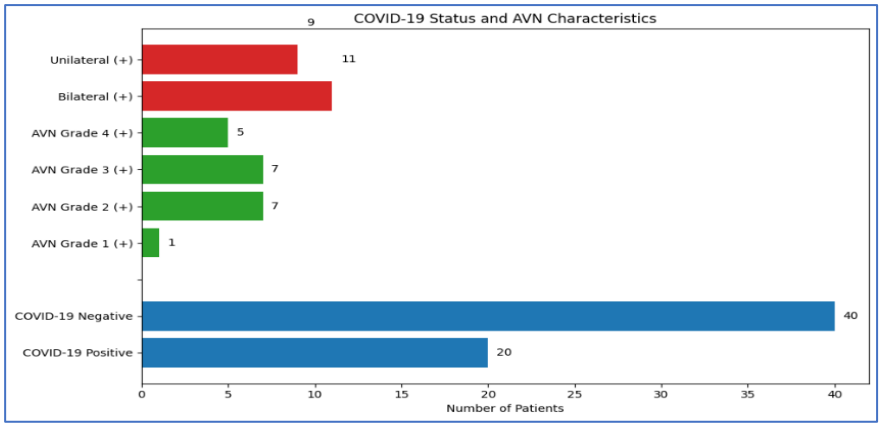


Figure 2. COVID-19 Status and AVN Severity among Study Participants (N = 60)

Analysis of steroid exposure among COVID-19 positive patients showed that the majority, 13 out of 20 patients (65.0%), did not receive systemic corticosteroid therapy. Among those who received steroids, short-duration courses were more common, with 4 patients (20.0%) receiving treatment for 14 days, while only 1 patient each (5.0%) received steroids for 5, 7, or 10 days. This indicates that AVN occurred even in patients without documented steroid exposure, suggesting the contribution of additional COVID-19-related mechanisms. Regarding the timing of disease onset, AVN manifested over a wide temporal range following COVID-19 infection. Symptom onset occurred between 2 and 6 months in 4 patients (20.0%), while the majority developed symptoms later, with 8 patients (40.0%) each experiencing onset between 6–12 months and 1–2 years after infection. These findings indicate that AVN can present as both an early and delayed complication of COVID-19, emphasizing the need for prolonged clinical surveillance in affected patients.

Table 3. Steroid Exposure and Time to AVN Onset in COVID-19 Positive Patients (n = 20)

Variable	Category	Frequency (n)	Percentage (%)
Steroid therapy duration	No steroid therapy	13	65.0
	5 days	1	5.0
	7 days	1	5.0
	10 days	1	5.0
	14 days	4	20.0
Time to AVN onset after COVID-19	2–6 months	4	20.0
	6–12 months	8	40.0
	1–2 years	8	40.0

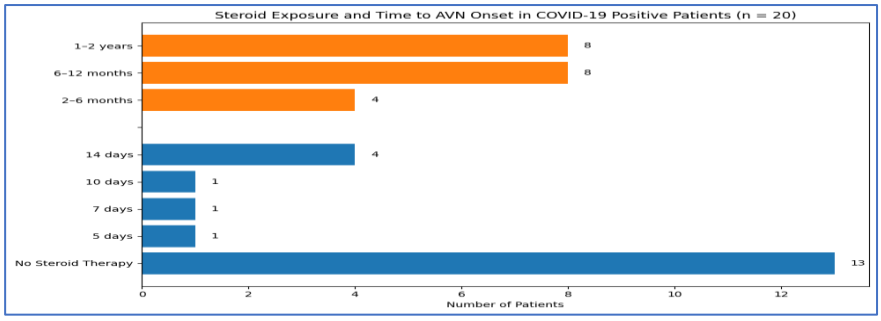
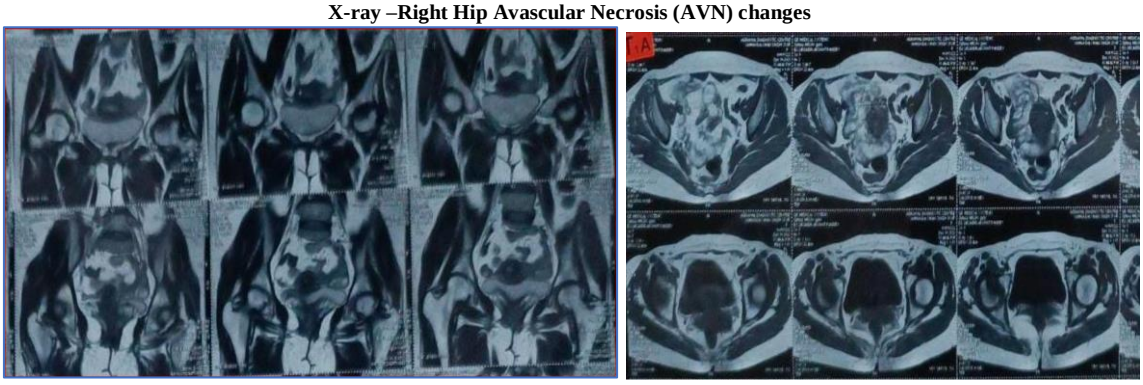


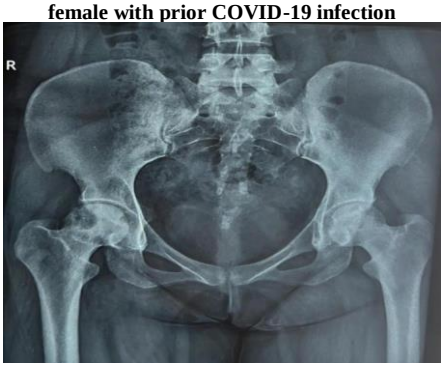
Figure 3. Steroid Exposure and Time to AVN Onset in COVID-19 Positive Patients (n = 20)

X-ray –Right Hip Avascular Necrosis (AVN) changes

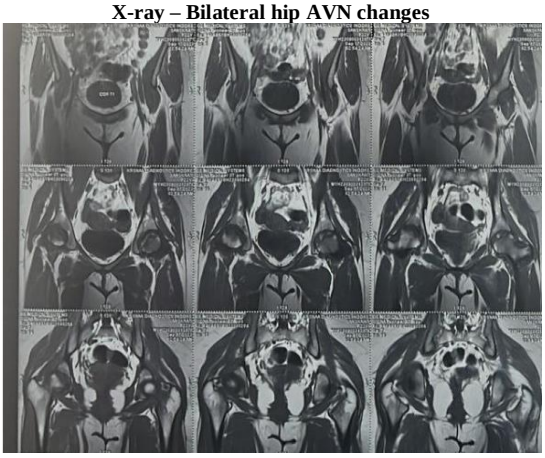


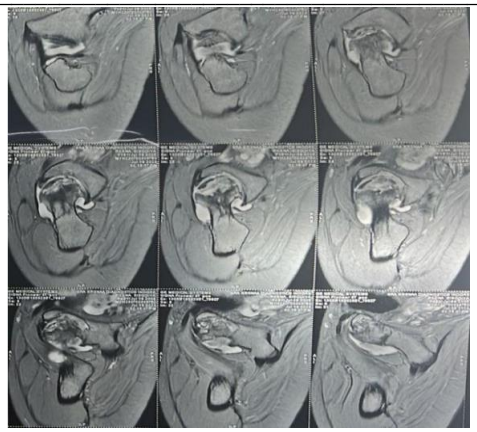
MRI-AVN right hip FICAT ARLET Stage 3

Figure 4. Figure. Radiological images showing Stage III avascular necrosis of the right hip (Ficat–Arlet classification) in a 41-year-old female with prior COVID-19 infection



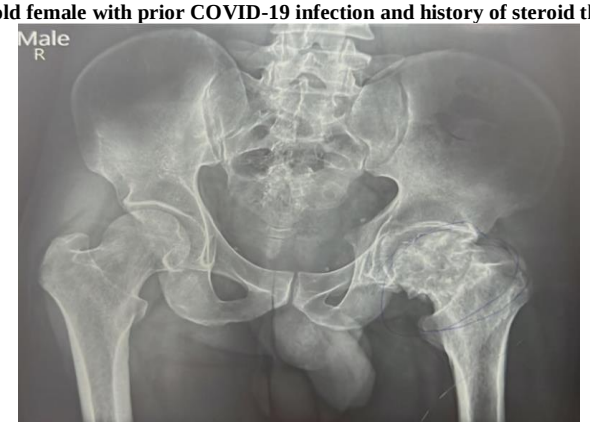
X-ray – Bilateral hip AVN changes



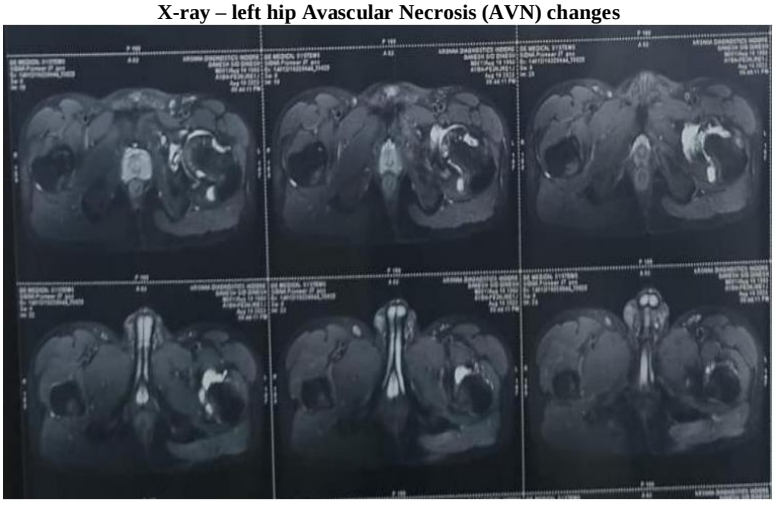


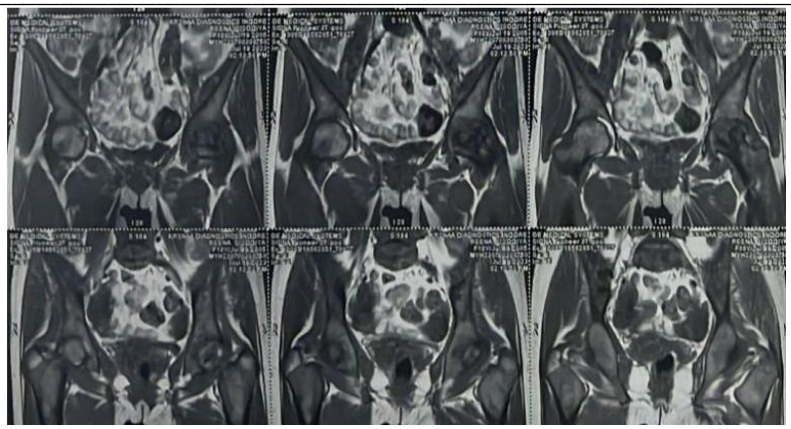
MRI-Bilateral Avascular Necrosis (AVN)of hip joint FICAT ARLET grade 3

Figure 5. Radiological images demonstrating bilateral Stage III avascular necrosis of the hip joints (Ficat–Arlet classification) in a 22-year-old female with prior COVID-19 infection and history of steroid therapy



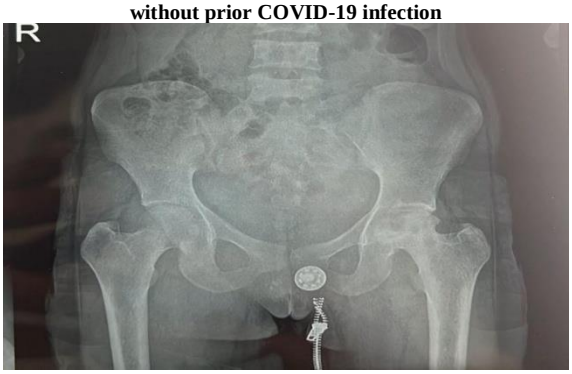
X-ray – left hip Avascular Necrosis (AVN) changes



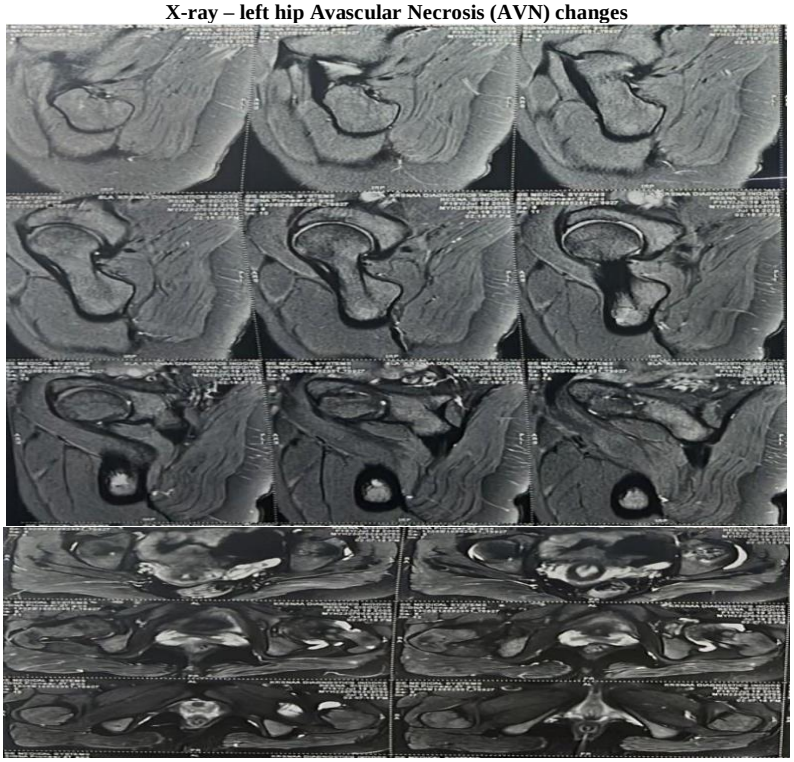


MRI- Avascular Necrosis (AVN) left hip FICAT ARLET grade 4

Figure 6. Radiological images showing Stage IV avascular necrosis of the left hip (Ficat–Arlet classification) in a 30-year-old male without prior COVID-19 infection



X-ray – left hip Avascular Necrosis (AVN) changes



MRI- Avascular Necrosis (AVN) left hip FICAT ARLET grade 4

Figure 7. Radiological images demonstrating Stage IV avascular necrosis of the left hip joint (Ficat–Arlet classification) in a 40-year-old female without prior COVID-19 infection or comorbid illness

DISCUSSION

Avascular necrosis (AVN) of the hip is a progressive and disabling condition caused by impaired blood supply to the femoral head, leading to bone death, joint pain, and long-term functional limitation. During the COVID-19 pandemic, concern has grown regarding a possible association between SARS-CoV-2 infection and AVN, particularly in relation to corticosteroid use and COVID-19–related vascular injury. Although reports of post-COVID AVN are increasing, existing evidence is largely limited to case reports and small retrospective studies. In India, where corticosteroids were widely used and baseline AVN risk factors are common, epidemiological data remain limited. This study was therefore conducted to assess the relationship between COVID-19 infection and AVN of the hip in a tertiary care setting.In the present study, the mean age of patients was 38.78 years, with a clear male predominance (75%). Most cases occurred in the 31–40-year age group, followed by the 21–30 and 41–50-year groups, indicating that AVN primarily affects young and middle-aged adults. These findings align with previous studies. Asaad SK et al. (2023) [9] reported a similar mean age of 38.65 ± 6.1 years with 70.6% male patients, while Agarwala SR et al. (2021) [14] observed AVN predominantly in males aged 36–39 years following COVID-19. Migliorini F et al. (2024) [15] also noted male predominance (74%) in a large cohort. Although Jha AK et al. (2024) [3] reported a higher mean age, they highlighted the significant impact of AVN in younger individuals. Overall, these findings support the tendency of AVN to affect males during their productive years, possibly influenced by hormonal, occupational, and lifestyle factors.

Regarding disease severity, Grade 2 AVN was the most common stage in the present study (40%), followed by Grade 3 (30%) and Grade 4 (26.7%), with early-stage disease being relatively uncommon. Bilateral hip involvement was noted in 61.7% of patients, indicating a predominantly systemic process rather than localized pathology. Comparable findings have been reported in earlier studies. Asaad SK et al. (2023) [9] observed bilateral involvement in 82.3% of cases, whereas Petrusevska-Marinkovic et al. (2024) [8] highlighted the advantage of early-stage detection in their cases. Conversely, Choudhari P et al. (2020) [16] reported a higher prevalence of unilateral disease. Such variations may reflect differences in patient characteristics, timing of diagnosis, and underlying risk factors. The high rate of bilateral involvement in the present study emphasizes the need for routine bilateral hip evaluation in patients suspected of AVN.In this cohort, 33.3% of patients had a documented history of COVID-19 infection, and among them, Grade 2 and Grade 3 AVN were the most common presentations, suggesting an association between COVID-19 and moderate to severe disease. Several mechanisms may explain this link, including COVID-19–induced endothelial dysfunction, hypercoagulability, microvascular thrombosis, and heightened inflammatory responses, all of which can impair femoral head perfusion. Petrusevska-Marinkovic et al. (2024) [8] emphasized the role of microcirculatory disturbances in post-COVID AVN, while Jha AK et al. (2024) [3] highlighted the combined effects of steroid exposure and microembolism formation. Agarwala SR et al. (2021) [14] reported AVN onset within a mean of 58 days after COVID-19, suggesting accelerated disease progression. In contrast, the present study observed a longer mean interval of 6.53 months, indicating that AVN may also manifest as a delayed post-COVID complication.Steroid therapy is a recognized risk factor for avascular necrosis; however, in the present study, only 35% of COVID-19–positive patients had documented steroid exposure, suggesting that steroid use alone does not fully account for AVN development. This finding supports the role of COVID-19–related vascular and inflammatory mechanisms as independent contributors to disease pathogenesis. Petrusevska-Marinkovic et al. (2024) [8] noted that even moderate prednisolone-equivalent doses may increase AVN risk, while Asaad SK et al. (2023) [9] reported AVN following short-duration steroid therapy. Additionally, studies by Zhao et al. (2013) [17] and McKee MD et al. (2001) [18] demonstrated that AVN can develop months to years after steroid exposure, complicating causal attribution. Overall, these observations emphasize the multifactorial nature of AVN in post-COVID patients.

With respect to timing, most patients in the present study developed AVN between 6–12 months and 1–2 years after COVID-19 infection. Earlier onset has been reported by Agarwala SR et al. (2021) [14] and Petrusevska-Marinkovic et al. (2024) [8], indicating considerable variability in disease progression. This wide temporal range underscores the need for prolonged musculoskeletal surveillance in post-COVID patients, particularly those presenting with persistent or unexplained hip pain.

Although this study provides valuable insights, it is limited by a small sample size, single-center design, incomplete data on steroid dosage and cumulative exposure, lack of extended follow-up, and absence of inferential statistical analysis. Nevertheless, the findings add to the growing evidence linking COVID-19 infection with avascular necrosis of the hip and emphasize the importance of early recognition, long-term monitoring, and larger multicentric studies to clarify underlying mechanisms and improve patient outcomes.

Conclusion

Although the COVID-19 pandemic has primarily been viewed through the lens of acute infection, this study highlights its important long-term musculoskeletal implications, particularly the potential association between COVID-19 and avascular necrosis of the hip joint. The findings demonstrate that AVN predominantly affects middle-aged males, often presents at moderate to advanced stages, and frequently involves both hips. A considerable proportion of patients had a prior history of COVID-19, and the occurrence of AVN even in the absence of steroid therapy suggests that COVID-19-related inflammatory and microvascular mechanisms may play a contributory role beyond steroid exposure alone. The variable and often delayed onset of AVN following COVID-19 infection underscores the need for sustained clinical vigilance and early imaging in patients presenting with persistent hip pain. Overall, these observations emphasize the importance of long-term follow-up, early diagnosis, and a high index of suspicion for AVN in post-COVID patients, while also highlighting the need for larger, multicentric studies to further clarify underlying mechanisms and guide preventive and therapeutic strategies.

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