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## Heterotopic Ossification after Severe COVID-19 Pneumonia: Radiological Findings in the Current Literature

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### ABSTRACT

Heterotopic ossification is the aberrant formation of extraskeletal bone in muscle and soft tissues. Its many causes include joint arthroplasty, traumatic or neurologic injury, burns and rare genetic disorders. In non-genetic forms, an inciting event causes inflammatory cell-mediated interactions to convert progenitor cells to osteogenic precursor cells which can form new bone over the span of weeks to months. There is an intriguing association between severe COVID-19 pneumonia and heterotopic ossification. In September 2020, a case series on two Dutch patients documented the development of ectopic bone in the hips, shoulders and elbows after severe COVID-19 pneumonia requiring prolonged mechanical ventilation in the intensive care unit. In the following two months, six more patients presented similarly. More cases have been identified since the original reports. This paper seeks to explore the work published in this interim and provide updates on radiological findings.

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### Keywords

Heterotopic ossification; COVID-19; Musculoskeletal; Radiology

## Abbreviations

HO: Heterotopic Ossification; MSK: Musculoskeletal; IQR: Interquartile Range; HTN: Hypertension; HLD: Hyperlipidemia; T2DM: Type 2 Diabetes Mellitus; COPD: Chronic Obstructive Pulmonary Disease; GERD: Gastroesophageal Reflux Disease; LOS: Length of Stay; ICU: Intensive Care Unit; PT: Physical Therapy; NSAID: Non-Steroidal Anti-Inflammatory Drug; ESR: Erythrocyte Sedimentation Rate; CRP: C-Reactive Protein; CK: Creatine Kinase; ALT: Alanine Transaminase; AST: Aspartate Transferase; LFT: Liver Function Test; PSA: Pseudomonas Aeruginosa; VAP: Ventilator Associated Pneumonia; ACE2: Angiotensin Converting Enzyme 2; LUMC: Loyola University Medical Center.

## Introduction

At the time of this review, there have been 761 million cases of COVID-19 infection and over 6 million attributed deaths worldwide. Though its hallmark pulmonary pathology garners the most concern and study, COVID-19 is a multi-system disease with a myriad of extrapulmonary manifestations. Musculoskeletal manifestations though common are relatively under reported, perhaps owing to the severity and acuity of effects on other systems, nonspecificity of findings and insidious onset. The majority of patients infected with COVID-19 experienced some form of

MSK symptom. Fatigue and myalgia are reported most frequently in the acute period. A meta-analysis of the long-term effects of COVID-19 found that four out of five infected patients experience at least one lasting symptom and joint pain accounts for one out of five cases [1]. Some patients can develop myalgias, myositis, myonecrosis and rhabdomyolysis [2]. Others develop autoimmune conditions including reactive post-viral arthritis, rheumatoid arthritis, systemic lupus erythematosus and seronegative spondyloarthropathies. A small subset of COVID-19 patients who become critically ill may develop heterotopic ossification [3].

## Material and Methods

We searched the PubMed database for literature describing heterotopic ossification after COVID-19 infection. The search terms or keywords used were, COVID-19 or heterotopic ossification. We limited the search to human subjects and to English language only. Case reports, case series, retrospective studies, letters and commentaries were included. English abstracts attached to non-english papers were included. Two authors independently screened the results from this initial search. We found 16 articles reporting heterotopic ossification in 41 patients after severe COVID-19. The two authors extracted data using a standardized checklist of author, type of study, pa-

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tient age and gender, comorbidities, length of hospitalization, use and length of mechanical ventilation and use of prone positioning. We also retrieved the time to discovery of, location of and treatment of heterotopic ossification. Finally, we obtained laboratory markers including serum alkaline phosphatase, creatinine kinase, liver transaminase levels and calcium. Missing data points were indicated with 'N/A'.

In addition, we identified an additional patient from our institution whose imaging in 2021 was most consistent with heterotopic bone formation after severe COVID-19 infection. Data for this patient was included in the last row of the tables below. Briefly, this 51-year-old male with a past medical history of hypertension, hyperlipidemia, type 2 diabetes mellitus and asthma contracted COVID-19 likely from exposure to a sick family member. Despite treatment with remdesivir, COVID-19 convalescent plasma, tocilizumab and dexamethasone, patient deteriorated and required intubation 15 days after presentation and tracheostomy 24 days later. Patient was mechanically ventilated for 141 days, with intermittent prone positioning. Heterotopic ossification was noted incidentally about his bilateral hips at day 153 and about his bilateral shoulders at day 158. Due to numerous complications, his total hospitalization length was 222 days. This patient was lost to follow-up after discharge.

## Results

A few clarifications must be offered before the data is presented:

1. The papers by de l'Escalopier et al. [4] and Mezghani

et al. [5] share an author and possibly share patients. Whether patients are duplicated in our analysis is unknown. Patient data could not be shared.

2. The paper by Stoiria et al. primarily reported medians [6]. The median age in their study was 71 years (IQR 67-74). The median duration of mechanical ventilation was 29 days (IQR 25-45) and the median duration of total hospitalization was 53 days (IQR 43-58). In 9 of 10 patients, prone positioning was performed and the median time of prone positioning was 12 days (IQR 7-16). Seven patients had arterial hypertension, 4 had cardiovascular disease and 3 had type 2 diabetes mellitus. Six were treated with steroids. The median maximal CRP seen in the ten patients was 352 mg/L (IQR 331-377) and median maximal creatine kinase was 820 U/L (IQR 262-1114). While the medians were not included in our data analysis, individual data points were included.

Among cases reporting age, the mean patient age was 51.9 years. Among cases reporting sex, 23 of 28 patients were male (82.1%). Commonly reported comorbidities included hypertension (n=18), type 2 diabetes mellitus (n=6), and cardiovascular disease (n=4). Chronic obstructive pulmonary disease (n=3), atrial fibrillation (n=2), and obesity (n=2) were less common (Table 1).

Among eight cases reporting the length of stay, the median was 75 days. Among ten cases reporting mechanical ventilation, the median length of time was 34.5 days. Twenty cases described prone positioning (Table 2).

**Table 1.** Characteristics of included studies and patients.

Journal	Publication type	Patient age	Sex	Comorbidities	Reference
Radiol Case Rep	Case Series	51	F	HTN, T2DM	[7]
		43	F	HTN	-
QJM	Commentary	52	M	N/A	[8]
Bone	Case Report	55	M	None	[9]
Clin Microbiol Infect	Letter to the Editor	4 patients; see clarification 1			[4]
BJR Case Rep	Case Review	68	M	N/A	[10]
IOSR-JDMS	Case Report	18	M	None	[11]
R I Med J	Case Report	23	F	Recently post-partum	[12]
Ann Phys Rehabil Med	Letter to the Editor	64	M	HTN, atrial fibrillation, cervical myelopathy	[13]
		73	M	HTN, COPD	
		74	M	HTN, COPD	
		39	M	Schizophrenia, bipolar disorder, alcohol use disorder	

Eur J Radiol	Letter to the Editor	10 patients; see clarification 1			[5]
Trauma Care	Case Report	20	M	Obesity	[14]
Acta Orthop Belg	Case Report	74	M	HTN, COPD	[15]
Clin Microbiol Infect	Letter to the Editor	10 patients of which 2 are female and 8 are male; see clarification 2			[6]
Int J Case Rep Orthop	Case Report	62	M	HTN, paroxysmal atrial fibrillation	[16]
Arch Phys Med Rehabil	Case Report	59	M	T2DM, HTN, GERD, recurrent pulmonary emboli, obesity	[17]
Turk J Phys Med Rehab	Case Report	45	M	HTN	[18]
Oxf Med	Case Report	63	M	HTN, obesity	[19]
N/A	N/A	51	M	HTN, HLD, T2DM, asthma	New LUMC patient

**Table 2.** Characteristics of hospitalization.

Hospital LOS in days	Ventilator	Ventilator time in days	Prone positioning	Reference
47	Yes	N/A	Yes	[7]
33	Yes	N/A	Yes	-
N/A	Yes	N/A	Yes	[8]
67	Yes	N/A	N/A	[9]
Not described				[4]
N/A	Yes	N/A	N/A	[10]
N/A	Yes	9	Yes	[11]
81	Yes	N/A	N/A	[12]
N/A	Yes	26	Yes	[13]
N/A	Yes	27	Yes	
N/A	Yes	30	Yes	
N/A	Yes	28	Yes	
Not described				[5]
90	Yes	69	N/A	[14]
N/A	Yes	27	Yes	[15]
All patients were mechanically ventilated and 9 of 10 patients were put in prone position; other characteristics not described.				[6]
N/A	N/A	N/A	N/A	[16]
69	Yes	43	N/A	[17]
N/A	Yes	55	Yes	[18]
134	Yes	N/A	N/A	[19]
222	Yes	141	Yes	New LUMC patient

The most commonly utilized modalities were radiography and computed tomography. The average time to discovering heterotopic ossification was unclear; various groups reported time elapsed from non-standardized clinical turning points such as diagnosis of infection, admission, transfer to an intensive care setting, intubation, extubation, or discharge. The most frequently reported location for heterotopic ossification was in the hips. Heterotopic bone formed in 37 hips (44.0%). Other common sites included the shoulders (n=15, 17.9%), knees (n=8, 9.5%) and elbows (n=5, 6.0%). Involvement of the ankle (n=2, 2.4%), intercostal muscle (n=1, 1.2%) and isolated quadriceps femoris and iliopsoas muscle (n=1, 1.2%) was rare. Treatment commonly consisted of physical therapy (n=9), corticosteroid use (n=8), surgical excision (n=6) and NSAID use (n=5) (Table 3).

The laboratory values were chosen based on relevance to heterotopic ossification that develops secondary to noninfectious etiologies [20]. There was high variability in reporting laboratory values. Comparison and interpretation were difficult; not every paper specified reference ranges or time elapsed from the beginning of the infection to the appearance of an abnormal laboratory value. The most commonly reported value was serum alkaline phosphatase (n=10). The concentration was either within normal limits or elevated; two cases reflected a rise of alkaline phosphatase 3-4 weeks after infection. The next most commonly reported value was serum calcium (n=6); low concentrations were primarily reported. A few cases showed ESR, CRP, CK, LFTs and serum phosphate either within normal limits or elevated (Table 4).

**Table 3.** Imaging modality, time to HO discovery, location and treatment.

Imaging modality	Time to HO discovery	HO location	HO treatment	Reference
Radiographs, CT	4 months after discharge	Bilateral shoulders	PT, surgical excision	[7]
Radiographs	5 months after discharge	Right shoulder	PT, steroids	-
N/A	N/A	Bilateral hip (Brooker grade III-IV) and shoulder (Brooker grade III)	N/A	[8]
Radiographs, CT	9 weeks after infection	Bilateral shoulders, elbows, hips, knees and ankles	Hydrotherapy, ibandronate, kinesiology, PT, vitamin D	[9]
N/A	N/A	Hip	Surgical resection	[4]
N/A	N/A	Hip	Surgical resection	
N/A	N/A	Hip	Surgical resection	
N/A	N/A	Elbow	Surgical resection	
MR	2 months after infection	Left hip	Steroids	[10]
Radiographs, CT, MR	4 weeks after infection	Bilateral hips (Brooker grade IV)	Ibandronate, NSAIDs	[11]
Radiographs, CT	38 days and "several weeks" of admission	Left distal thigh/knee, vastus medialis	NSAIDs, PT	[12]
Radiographs, bone scintigraphy, CT	39 days after extubation	Bilateral hips	N/A	[13]
Radiographs, bone scintigraphy, CT	40 days after extubation	Anterior and medial compartments of the left hip	N/A	
Radiographs, bone scintigraphy, CT	41 days after extubation	Anterior and deep compartments of the left hip	N/A	
Radiographs, bone scintigraphy	30 days after admission to ICU	Bilateral shoulders	N/A	

CT	N/A	Hip	N/A	[5]
CT	N/A	Knee	N/A	
CT	N/A	Hip	N/A	
CT	N/A	Bilateral knees and hips	N/A	
CT	N/A	Bilateral knees	N/A	
CT	N/A	Bilateral hips	N/A	
CT	N/A	Bilateral hips	N/A	
CT	N/A	Bilateral hips	N/A	
CT	N/A	Bilateral hips	N/A	
CT	N/A	Bilateral hips	N/A	
Radiographs, CT	49 days after intubation	Left hip (Brooker grade III)	N/A	[14]
Radiographs, CT	10 days after extubation	Left hip	NSAIDs, PT	[15]
CT	N/A	N/A	Steroids	[6]
CT	N/A	N/A	Steroids	
CT	N/A	N/A	Steroids	
CT	N/A	N/A	Steroids	
CT	N/A	N/A	Steroids	
CT	N/A	N/A	Steroids	
CT	N/A	N/A	N/A	
CT	N/A	N/A	N/A	
CT	N/A	N/A	N/A	
CT	N/A	N/A	N/A	
Radiographs, CT, MRI	N/A	Anterolateral and posterior compartments of the bilateral hips	Celecoxib, PT, surgical resection	[16]
Radiographs	day 103 from admission	Bilateral hips (grade III on right, grade II on left)	Pain regimen without NSAIDs, PT	[17]
Radiographs	9 weeks after admission	Bilateral shoulders, elbows, hips	Indomethacin, PT	[18]
CT	5 months after admission	Bilateral intercostal muscles and bilateral shoulders	N/A	[19]
Radiographs, CT, MRI	5 months after infection	Bilateral shoulders and hips	PT	New LUMC patient

**Table 4.** Relevant labs.

<b>Alkaline phosphatase</b>	<b>Serum calcium</b>	<b>ESR</b>	<b>CRP</b>	<b>Creatine kinase</b>	<b>ALT/AST</b>	<b>Serum phosphate</b>	<b>Reference</b>
148 U/L (30-110 U/L), 20 days after infection	7.3 mg/dL (8.9-10.3 mg/dL), 20 days after infection	N/A	Elevated throughout but maximally 30.1 mg/dL (0.0-1.0 mg/dL), 22 days after infection	968 U/L (35-200 U/L), 24 days after infection	AST: 97 U/L (5-46 U/L) and ALT: 14 (7-35 U/L), 23 days after infection	Within normal range	[7]
Within normal range for 4 weeks for four weeks after infection, then discontinued trending	7.7 mg/dL (8.9-10.3 mg/dL), 24 days after infection	107 mm (0-20 mm), 10 days after infection	Elevated throughout but maximally 26.4 mg/dL (0.0-1.0 mg/dL), 8 days after infection	2199 U/L (35-200 U/L), 15 days after infection	AST: 93 U/L (5-46 U/L) and ALT: 70 U/L (7-35 U/L), 25 days after infection	5.8 mg/dL (2.5-4.7 mg/dL), 14 days after infection	
Not described							[8]
111 UI/L (40-130 UI/L)	Decreased	Within normal range	Within normal range	N/A	Within normal range	N/A	[9]
Not described							[4]
Not described							[10]
Within normal range for a month after infection followed by a steep rise to 363 U/L	Low-normal or below normal range all throughout, with maximum dip corresponding to peaks of other reported labs	N/A	N/A	Elevated in the first month, then increased	Elevated in the first month, then increased	N/A	[11]

Not described							[12]
200 UI/L (38-126 UI/L)	N/A	N/A	N/A	N/A	N/A	N/A	[13]
126 UI/L (38-126 UI/L)	N/A	N/A	N/A	N/A	N/A	N/A	
105 UI/L (38-126 UI/L)	N/A	N/A	N/A	N/A	N/A	N/A	
200 UI/L (38-126 UI/L)	N/A	N/A	N/A	N/A	N/A	N/A	
Not described							[5]
N/A	N/A	N/A	Elevated after two weeks corresponding with a new PSA VAP	N/A	N/A	N/A	[14]
Not described							[15]
Not described							[6]
Not described							[16]
Not described							[17]
Elevated to 291 IU/L	Normal, 9.3 mEq/L	N/A	N/A	N/A	N/A	N/A	[18]
Not described							[19]
147 U/L (30-110U/L), 61 days after infection	8.1 (8.9-10.3mg/dL), 54 days after infection	N/A	N/A	Within normal range	N/A	N/A	New LUMC patient



## Discussion

There were several key findings in this literature review on post-COVID-19 heterotopic ossification. Firstly, post-COVID-19 heterotopic ossification was reported more frequently in a subset of patients. The majority of cases involved middle-aged or elderly men with comorbidities. Men are known to experience higher rates of death in COVID-19 possibly related to an altered immune response due to hormonal signaling [21]. Furthermore, the immune response is generally hampered with increasing age. Another possible explanation for the increased incidence is a difference in Angiotensin Converting Enzyme 2 (ACE2) activity. ACE2 plays an anti-inflammatory role in response to COVID-19 [21]. Elderly men have lower circulating levels of ACE2, which may make them more susceptible to severe forms of COVID-19 and associated complications in comparison to their female and/or younger counterparts. ACE2 may also have a role in some common comorbidities that predispose patients to severe COVID-19 infection. Several patients had hypertension and type 2 diabetes mellitus. ACE2 activity appears to be inversely proportional to blood pressure and body mass index [21]. Hypertensive patients with low ACE2 may therefore be predisposed to more severe cases of COVID-19 infection. Diabetes appears to have a bidirectional relationship with COVID-19, where infection can lead to hyperglycemia and hyperglycemia can cause increased glycosylation of ACE2, inflammation and endothelial dysfunction, setting the stage for a severe clinical course [22].

Secondly, post-COVID-19 heterotopic ossification shares many characteristics with heterotopic bone formation secondary to other etiologies. For example, parallels in hospital courses can be drawn between patients who develop heterotopic ossification after COVID-19 infection and after neurogenic insults like spinal cord or traumatic brain injuries. Common to both etiologies of heterotopic ossification, the hip is the most commonly involved site. Less common sites include the elbow, shoulder and knee. The distal extremities are the least involved [23]. Other interesting similarities are the period of time elapsed before heterotopic bone is discovered and laboratory trends. Following a spinal cord or traumatic brain injury, the average time to discovery of heterotopic ossification is two months, with a range of two weeks to one year [23]. Our cases followed a similar general timeframe; among the cases with exact dates given, no heterotopic bone formation was identified sooner than four weeks or later than six months after infection. This is a point worthy of further exploration considering the body's immunological response to COVID-19 infection. In brief, the activation of the complement system and upregulation of various

cytokines, growth factors and bone morphogenic proteins can cause mesenchymal stem cells to differentiate into osteoblasts. One of the osteoblasts many critical roles is to secrete alkaline phosphatase. It is an enzyme that functions in alkaline environments to cleave inorganic phosphate from various substrates and redirect the molecule toward mineralization. Elevated alkaline phosphatase can indicate increased osteoblast activity. A previous study evaluating laboratory and radiological trends in 35 patients with heterotopic bone formation revealed a rise in serum alkaline phosphatase after inciting injury to abnormally elevated levels by 3-4 weeks and peak levels by 10 weeks, with positive radiographs by 4.5 weeks [24]. Two of the cases in our review demonstrated abnormal serum alkaline phosphatase by 3-4 weeks and the shortest lag time from infection to positive radiographs was 4 weeks. Our findings mirror previously published data for other causes of heterotopic ossification.

Thirdly, the same treatments and prophylactics used in other forms of heterotopic ossification are being applied to post-COVID-19 heterotopic ossification. Since immobilization is theorized to contribute to the pathogenesis of heterotopic ossification, physical therapy is often considered to be essential to the treatment of heterotopic ossification. Despite this notion, there is currently no evidence that supports movement therapies in the prevention and treatment of heterotopic ossification. Some reports suggest aggressive exercise therapy actually increases the risk for developing heterotopic ossification. Nonetheless, physical therapy is widely accessible, inexpensive and non-invasive, and therefore may remain a practical treatment option [25,26]. Steroids can reduce pain. Surgical resection is the only definitive treatment for heterotopic ossification. It is usually considered in severe cases that cause significant functional impairment or that fail conservative therapy. Some Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and radiation therapy may be beneficial as prophylaxis, reducing heterotopic bone formation after total hip arthroplasties, traumatic fractures and spinal cord injuries [27-29]. It is thought that NSAIDs achieve this by suppressing the migration and proliferation of inducible mesenchymal cells and that radiation therapy works by inhibiting the differentiation of mesenchymal stem cells into osteogenic pathways [30,31].

Given their overlapping clinical presentations, we explored risk factors for neurogenic heterotopic ossification that might help explain what triggers heterotopic bone formation in severe COVID-19 infections. There is some evidence for prolonged immobilization, muscle denervation, duration of sedation, mechanical ventilation-induced respiratory alkalosis and autonomic dysregulation contributing to the development of neu-



rogenic heterotopic ossification [32]. Patients with severe COVID-19 courses are often exposed to the same risk factors; they can often undergo lengthy stays in intensive care units, spending a variable amount of time immobilized, sedated and mechanically ventilated. Some literature on post-COVID-19 heterotopic ossification already alludes to the involvement of these same risk factors [7,11,13,14,18].

## Conclusion

There are many limitations to this review, most of which stem from the issue of an incomplete and small data set. We attempted to contact lead authors and gather more information; however, that was by and large unsuccessful. As previously mentioned, whether duplicate patients exist in our data set is also unknown. We also were not able to include medians published in previous works in our counts as the data distribution was unclear and obtaining an estimate was not appropriate for our ends. For any adequately powered study on this phenomenon to exist in the future, more cases must be discovered and shared. To bypass some of the pitfalls we discovered, we advise future groups to consider providing raw data as a supplementary document, creating a clear timeline from infection to lab abnormalities and positive radiographic findings and continuing to report biomarkers of bone metabolism. Herein, we present radiographic findings and pertinent clinical information reported to date in post-COVID-19 heterotopic ossification. Awareness about this uncommon phenomenon can enhance patient care. Continued research can aim to reveal its pathophysiology and response to targeted therapies.

## Declaration of Competing Interest

The authors declare that there is no conflict of interest associated with the manuscript.

## Declaration of Generative AI in Scientific Writing

No AI was utilized in this manuscript.

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