

## Research Article

# Long-term D-Dimer Elevation Post-COVID-19: It's Significance in Thrombotic Complications Following Joint Replacement Surgeries

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## Abstract

**Background:** Patients recovering from COVID-19 may experience persistent elevations in D-dimer levels, increasing their risk of thrombosis. This study aimed to investigate the impact of persistent elevated D-dimer levels in patients with a history of COVID-19 on postoperative outcomes after knee and hip arthroplasty.

**Methods:** A prospective cohort study was conducted from March 2021 to September 2022 at the Military Teaching Hospital Mohammed V in Rabat. Patients scheduled for total knee or hip replacements were included. Those with a history of COVID-19 (n=75) were tested for D-dimer levels during pre-anesthetic evaluation. Patients were classified into normal (n=63) or elevated D-dimer (n=12) groups. Follow-up included monitoring for asymptomatic Deep Vein Thrombosis (DVT) six weeks after surgery.

**Results:** Among 335 patients, 75 had a history of COVID-19. Elevated D-dimer levels were associated with a higher rate of hospitalization (45.3%) and more severe COVID-19 cases (58.3%). However, preoperative D-dimer levels did not significantly impact the incidence of thromboembolic complications after joint replacement surgeries.

**Conclusion:** While patients with a history of COVID-19 may have persistent elevations in D-dimer levels, our study did not find a significant association with postoperative thromboembolic complications. Preoperative risk stratification remains important for perioperative planning, but modifications to thromboprophylaxis in these patients may not be warranted. Further research is needed to better understand the impact of COVID-19 on postoperative outcomes and identify potential risk factors for complications in this population.

**Keywords:** COVID-19; D-Dimer levels; Thromboembolic complications; Joint arthroplasty

## Introduction

D-dimer is a protein fragment that is produced when a blood clot is broken down in the body. Elevated levels of D-dimer can indicate the presence of a blood clotting disorder or an increased risk of thrombosis [1,2]. In the context of COVID-19, it has been observed that patients with severe disease are at a higher risk of developing blood clots and other coagulation abnormalities. Even after recovering from COVID-19, some patients may continue to experience persistent elevations in D-dimer levels, which could potentially increase their risk of developing blood clots [3].

In patients who are planned for arthroplasty of the knee and hip, the risk of Venousthromboembolism (VTE) is already high due to the surgical procedure itself [4-6]. However, the presence of persistent elevations in D-dimer levels in patients who have recovered from COVID-19 may further increase this risk [7]. This could have significant implications for the management of these patients, as the use of prophylactic anticoagulation therapy may need to be adjusted based on their D-dimer levels [8].

Therefore, it is important to investigate the prevalence of persistent elevations in D-dimer levels in patients who have recovered from COVID-19 and are planned for arthroplasty of the knee and hip. By identifying patients who are at a higher risk of developing VTE due to persistent elevations in D-dimer levels [9,10] appropriate prophylactic measures can be taken to minimize this risk and ensure optimal patient outcomes [11,12].

Our study aims to investigate D-dimer levels in patients who have recovered from COVID-19 and are scheduled for knee and hip arthroplasty. The primary objective of this research is to assess whether there exists a persistent elevation of D-dimer levels in these patients, which could potentially signify an increased susceptibility to Venous Thromboembolism (VTE) post-surgery. Furthermore, the study seeks to delve into the possible correlation between elevated D-dimer levels and various clinical outcomes, including the occurrence of postoperative thromboembolic complications. Ultimately, our research aims to contribute to clinical decision-making and enhance patient outcomes by identifying potential risk factors and tailoring appropriate prophylactic measures.

## Methods

**Study Design:** This is a prospective cohort study conducted at the Operating Room of the Military Hospital Mohammed V in Rabat over duration of 18 months, spanning from March 2021 to September 2022. The primary objective of the study is to assess the influence of elevated D-dimer levels in patients who have recently recovered from COVID-19 (within the last 6 months) on the outcomes of prosthetic joint surgery.

**Inclusion and Exclusion Criteria:** Patients eligible for inclusion were those scheduled for total joint prosthetic surgery, encompassing both Total Knee Replacement (TKR) and Total Hip Replacement (THR). Patients with a history of prosthetic revision or trauma were excluded from the study.

**Diagnostic Measures:** Patients with a documented history of COVID-19 (verified as positive for SARS-CoV-2 IgG antibodies) and planned for joint replacement underwent D-dimer level assessment during their pre-anesthetic evaluation before the surgery. D-dimer levels were categorized according to the established normal laboratory range, with values <500 ng/ml considered within the normal range, and values >500 ng/ml classified as elevated. Patients displaying elevated D-dimer levels underwent preoperative lower extremity echodoppler and contrast-enhanced CT scans to detect any potential presence of thrombosis and/or pulmonary embolism. Additionally, patients with a history of COVID-19 who underwent joint replacement were monitored for asymptomatic Deep Vein Thrombosis (DVT) using a bilateral Doppler ultrasound of the lower limbs performed six weeks post-surgery.

**Statistical Analyses:** The study's sample size for this exploratory analysis was not pre-determined, but an estimated range of 50 to 200 patients with a history of COVID-19 infection was assumed to be included. Descriptive statistical methods, comprising absolute and percentage frequencies, chi-square tests for categorical data, and mean  $\pm$  standard deviation as well as t-tests for continuous data, will be employed to describe data and conduct group comparisons. Notably, fibrinogen CRP will not be analyzed due to the limited number of observations in the D-dimer group exceeding 0.5. A significance level of 0.05 has been set for all analyses.

## Results

### Characteristics of Patients with and without History of COVID-19

During the study period from March 2021 to September 2022, a total of 335 patients were scheduled for total joint replacement surgery (THA or TKA) at the Traumatology-Orthopedics Services I and II of the Mohammed V Military Hospital in Rabat. The mean age of the patients was  $65.24 \pm 10.06$  years, with 189 females and 146 males, yielding a male-to-female ratio of 0.77. The patients had an average Body Mass Index (BMI) of  $30.14 \pm 5.78$ . Out of the total patient cohort, 75 patients had confirmed COVID-19 exposure more than 2 months prior, representing a rate of 22.3%.

Regarding patients with recent COVID-19 history, 75 patients (42 females, 56%) were consecutively enrolled with a mean post-COVID-19 interval of 118 days (ranging from 68 to 142 days). Their mean age was  $64.22 \pm 10.03$  years, and comorbidities were observed in 58 patients (77.3%). The most common comorbidities included hypertension (26.6%), type 2 diabetes (16%), asthma and COPD (8%), and ischemic heart diseases (5.3%). The average BMI was  $30.24 \pm 5.89$ .

Among participants with mild COVID-19 ( $n=41$ , 54.6%), none required hospitalization or thromboprophylaxis. Among those with moderate to severe disease, 34 patients (45.3%) were hospitalized, with 7 (9%) requiring ICU admission. All hospitalized patients received heparin-based prophylaxis during their stay, and none required invasive ventilation.

Table 1 summarizes the demographic and clinical characteristics of patients, Table 2 further details the demographic and clinical features of patients with recent COVID-19 history.

### BD-dimer Levels in Patients Scheduled with a History of COVID-19

#### Elevated D-dimer Levels

D-dimer measurements conducted at an average of 118 days (with a range of 68–142 days) after the diagnosis of COVID-19

**Table 1:** Demographic and Clinical Characteristics of Patients with and without History of COVID-19.

Parameters	Total (n=335)	History of COVID-19 (n=75)	No history of COVID-19 (n=260)	P value
Mean Age	65.24 $\pm$ 10.03	64.22 $\pm$ 10.03	67.26 $\pm$ 10.27	0.0025
Male/Female	146/189	33/42	113/147	NS
BMI (kg/m <sup>2</sup> )	30.14 $\pm$ 5.78	30.16 $\pm$ 5.89	29.40 $\pm$ 4.82	NS
PTH/PTG	160/175	36/39	124/136	NS
ASA I	80 (23.8%)	17	63	NS
ASA II	193 (57.6%)	44	149	NS
ASA III	37 (11%)	14	23	NS

Note: "NS" stands for "Not Significant" and indicates that the difference is not statistically significant.

**Table 2:** Demographic and Clinical Parameters of Patients with Recent History of COVID-19.

Parameters	Total (n=75)
Demographic and Clinical Parameters	
Age	64.22±10.03
Gender: Male/Female (%)	33/42
Comorbidities	
Hypertension (HTA)	26.6%
Diabetes	16%
Chronic Obstructive Pulmonary Disease (BPCO)	8%
Ischemic Heart Disease	5.3%
BMI (kg/m <sup>2</sup> )	30.24±5.89
Mean Scheduling Delay	118(68–142)
Hospitalization - n (%)	34(45.3%)
ICU Hospitalization	7(9%)
Mild Form	41(54.6%)
Severe Form	7(9.3%)
Moderate Form	27(36%)
Thromboprophylaxis	34(45.3%)

This table presents the demographic and clinical characteristics of patients with a recent history of COVID-19 who were included in the study. It outlines their age, gender distribution, underlying comorbidities, Body Mass Index (BMI), mean scheduling delay, rates of hospitalization, and forms of COVID-19 severity. Additionally, it highlights the utilization of thromboprophylaxis among these patients.

**Table 3:** D-dimer Levels in Patients with History of COVID-19.

D-dimer Levels	<500 ng/ml	500-1500 ng/ml	>1500 ng/ml
Patients (n)	63(84%)	7(9.3%)	5(6.6%)

This table presents the distribution of D-dimer levels among patients with a history of COVID-19. It demonstrates that the majority (84%) of patients had D-dimer levels below 500 ng/ml, while a smaller proportion exhibited elevated levels in the ranges of 500-1500 ng/ml (9.3%) and greater than 1500 ng/ml (6.6%) revealed elevated D-dimer levels (>500 ng/ml) in 16% (12/75) of the patients. Among them, 5 individuals (6.6%) had D-dimer levels exceeding 1500 ng/ml, while 62 patients (84%) had levels below 500 ng/ml Table 3.

### Comparison of Patients Based on Their D-dimer Levels

A comprehensive comparison between patients with elevated D-dimer levels and those with normal levels. The analysis includes parameters such as age, gender distribution, BMI, hospitalization rates, form severity, anticoagulant treatment, CRP levels, and abnormal chest X-ray findings. The data reveals that elevated D-dimer levels were significantly more frequent in patients who had experienced severe SARS-CoV2 infections necessitating hospitalization, compared to those with milder forms. Moreover, patients with elevated D-dimer levels displayed higher instances of abnormal lung radiography, elevated CRP levels, and earlier consultations in the anesthesia clinic. Importantly, both groups were found to be similar in terms of age, gender, and comorbidities (Table 4).

**Table 4:** Comparison of Characteristics between Patients with Elevated and Normal D-dimer Levels.

Parameters	Total (n=75)	D-dimers in Normal (n=63)	Elevated D-dimers (n=12)	p value
Age	64.22±10.03	63.40±8.50	65.32±7.08	NS
Gender: Male/Female (%)	33/42	27/36	6/6	NS
BMI (kg/m <sup>2</sup> )	30.24±5.89	29.84±6.39	31.06±4.89	NS
Hospitalization - n (%)	34(45.3%)	22(30%)	12(16%)	0.0020
Asymptomatic/Benign Form		41(54.6%)		0.0001
Moderate Form		27(36%)		
Severe Form			7(58.3%)	
Anticoagulant Treatment	44	32	12(16%)	0.0026
Parameters During Recovery Examination				
CRP (mg/l)	11(10.5–11.7)	10.9(10.5–11.7)	11.1(10.5–11.7)	
Abnormal Chest X-ray (%)	6(9%)	1(15.8%)	5(41.6%)	0.0021

**Table 5:** Incidences of persistent elevations post COVID in the literature.

Authors	Country	Year	Patients with Prior COVID-19	% Persistently Elevated D-dimers
Townsend [24]	Ireland	2021	150	25.3%
Folkman [31]	Sweden	2022	126	12%
Meisinger [26]	Germany	2022	350	15%
Kalaivani [32]	India	2022	(206 ICU)	42.7%
Mandal [33]	UK	2021	384	30.1%
Lehmann [23]	Austria	2021	129	15%
Weinberge [34]	USA	2023	313	19.4%
Our Study	Morocco	2023	75	16%

### Preoperative and Postoperative Evaluations in Patients with Elevated D-dimer Levels:

**Preoperative Evaluations:** Preoperatively, an echodoppler of the lower extremities and a contrast-enhanced tomography were performed on the 12 patients with elevated D-dimer levels to rule out the presence of thrombosis and/or pulmonary embolism. These patients underwent surgery under the same conditions as the 63 patients without elevated D-dimer levels.

**Evaluations in Patients with Elevated D-dimer Levels:** Six weeks after the surgery, a bilateral Doppler ultrasound of the lower extremities was conducted in all 75 patients as part of a surveillance protocol to exclude asymptomatic Deep Vein Thrombosis (DVT). There was no difference between the patients with elevated D-dimer levels and those with normal levels regarding the performance of the Doppler ultrasound. Notably, 11 patients in the normal D-dimer group missed this examination. These patients missed the ultrasound due to organizational reasons, such as limited access to ultrasound in their follow-up location, time constraints for conducting an ultrasound, or patient preference against undergoing additional tests at the hospital.

### Discussion

#### Post-COVID-19 Syndrome and Complications

The Post-COVID syndrome, termed Long COVID, refers to persistent symptoms lasting over three weeks after initial COVID-19 symptoms. Long COVID is categorized as subacute and chronic, and factors like severity of initial symptoms, ICU care, and lung function anomalies influence its occurrence [13]. Various factors including pre-existing lung disease, high BMI, advanced age, and racial minority status contribute to this condition. Complications like late-onset Guillain-Barré syndrome, opsoclonus-myoclonus syndrome, acute transverse myelitis, and cerebrovascular disorders, including ischemic stroke and cerebral vasculitis, have been reported post-COVID-19 [14].

## Timing of Scheduled Surgeries after COVID-19

Surgical procedures are classified based on urgency as urgent, semi-urgent, essential, and optional. The decision depends on factors like severity, comorbidities, patient's physical condition, infection risk, disease progression, and surgical complexity [15]. Anesthesia must consider the clinical phases of COVID-19: acute, subacute/symptomatic, chronic/post-COVID, and resolved. Severity scales help classify patients' COVID-19 status for surgical decision-making [16,17].

Patients with persistent symptoms, particularly cardiopulmonary complications, are at higher risk of adverse pre-operative outcomes. Delaying or canceling scheduled surgery can lead to complications in 50% of cases. Recommendations suggest postponing surgery during the infectious period.

**Considerations for Surgery:** Several initiatives aim to address this issue. For instance, the COVID Surg Collaborative study showed higher mortality rates in patients with recent COVID-19 diagnoses. Patients with cardiopulmonary involvement show the highest pre-operative complications. Thromboembolic risk is elevated, especially in high-risk patients [18].

Specialized evaluations and multidisciplinary pre-operative care are crucial. Factors like hospital resources, healthcare workforce availability, and protective equipment also impact surgical decisions.

Different societies have proposed scores or scales to guide surgical decision-making. Post-COVID-19 patients can undergo surgery after certain intervals, depending on their recovery status. Pre-rehabilitation might be necessary in some cases [19].

### Preoperative Assessment and Investigations in Post-COVID-19 Patients

Currently, there are no standardized guidelines for preoperative evaluation in these patients. An Oregon-based multidisciplinary team has devised a protocol stratifying patients based on surgery type and clinical status. Common recommended tests include ECG, metabolic panel, complete blood count, and D-dimers [20]. **Symptomatic patients scheduled for minor surgery** and all major surgery patients are suggested to undergo BNP and NT-PRO-BNP testing. If abnormal and cardiac decline is suspected, further tests like echocardiograms are advised. A survey involving 154 anesthesiologists revealed consensus on optimizing comorbidity management and reassessing physical condition prior to surgery. Commonly recommended tests included chest X-rays, ECGs, and coagulation profiles. Lung function assessments such as arterial blood gases, high-resolution CT scans, or pulmonary function tests are suggested for patients with significant hypoxemia, cardiac symptoms during COVID-19, major abdominal, vascular, cardiac, or thoracic surgeries, and elderly patients [21].

In terms of COVID-19 diagnostic tests, RT-PCR positivity within three months of surgery is not indicative of ongoing infectivity, whereas testing beyond that window is recommended. Patient safety and surgical team protection are important considerations, though with limited high-quality evidence. Surgical urgency, local resources, and potential outcomes from delaying surgery are vital components in decision-making [22].

### The Significance of Elevated D-Dimer Levels in Post-Discharge COVID-19 Patients

D-dimer values have been shown to hold clinical importance

in the acute phase of infection, and emerging evidence suggests their long-term prognostic relevance. Patients, especially those with severe forms of COVID-19, may exhibit persistently elevated D-dimer levels long after recovery and hospital discharge. These elevated levels are associated with increased mortality risk [23,24].

Several studies are cited to support this perspective. For instance, Atalay et al. followed 222 SARS-CoV-2 patients for up to 12 months, finding that higher D-dimer values were linked to nearly 60% higher one-year mortality risk [25]. Other studies also reveal the persistence of elevated D-dimer values in recovered COVID-19 patients, particularly those with severe respiratory disease and inflammation [26].

Clinical trials have explored adjusting anticoagulant treatment based on D-dimer values. Results from these trials suggest that such adjustments can lead to reduced mortality rates. However, determining optimal thresholds for D-dimer values in COVID-19 diagnosis and management remains challenging due to varying levels in different populations and a lack of standardized measurement methods [27].

While different guidelines offer varied recommendations regarding the use of D-dimer measurements for COVID-19, there is consensus on their potential clinical utility. The evidence indicates that elevated D-dimer levels are frequently observed in COVID-19 patients, predicting disease severity, thrombotic events, and even post-discharge outcomes [28]. Adjusting anticoagulant treatment based on D-dimer values has shown promise in improving patient outcomes. However, further research is needed to determine the exact diagnostic and prognostic thresholds and to standardize measurement methods for optimal clinical.

### Incidences of Persistent Elevations Post COVID in the Literature

Initial studies from Wuhan, China, indicated that elevated D-dimer levels were associated with Disseminated Intravascular Coagulation (DIC) in COVID-19 patients [29]. However, recent studies from Europe and North America suggest that overt DIC is rare among COVID-19 patients receiving prophylactic Low Molecular Weight Heparin (LMWH) doses. Nevertheless, elevated D-dimer levels remain consistently observed, even among patients receiving anticoagulation treatment [30].

Evidence has emerged of persistent symptoms following acute SARS-CoV-2 infection, termed "long COVID," which is characterized by symptoms lasting for weeks to months. While fatigue, shortness of breath, and reduced exercise tolerance are common, the underlying mechanisms for these persistent symptoms remain unknown. Given the role of coagulation activation, fibrinolysis, and microvascular pulmonary immunothrombosis in acute COVID-19 pathogenesis, it's been hypothesized that similar mechanisms might be significant in long COVID.

Liam Townsend [24] conducted a study to explore this hypothesis, examining clinical parameters and coagulation/inflammation biomarkers in convalescent COVID-19 patients. Increased D-dimer levels (>500 ng/ml) were observed in 25.3% of patients up to 4 months after SARS-CoV-2 infection. Similar studies in other countries (Sweden, Germany, Austria, India, the UK, USA, and Morocco) have reported varying rates of persistently elevated D-dimer levels ranging from 12% to 42.7% [23,24,26,31-34].

*The data from these studies are summarized in the table below, indicating the authors, countries, years, number of patients with prior COVID-19, and the percentage of patients with persistently elevated D-dimer levels.*

### **Characteristics of Patients with Prior COVID-19 and Persistently Elevated D-dimers**

The study found that patients who experienced severe COVID-19 infections requiring hospitalization had significantly higher occurrences of elevated D-dimer levels compared to those with a milder form of the disease. This observation is consistent with existing literature (Towensend ref). Furthermore, the study noted that patients with high D-dimer levels exhibited more lung abnormalities in chest X-rays, higher CRP levels, and were more frequently seen in early anesthesia consultations. However, in terms of age, gender ratio, and comorbidities, both groups were similar.

Meisinger [26] discovered that individuals with elevated D-dimer levels were significantly older and more often married than those within the reference range. Additionally, subjects with elevated D-dimer levels were more likely to have a history of hypertension, venous thromboembolism, and chronic venous insufficiency.

Towensend [24] observed that increased D-dimer levels (>500 ng/ml) were found in 25.3% of patients up to 4 months after SARS-CoV-2 infection. Univariate analysis revealed that elevated D-dimer levels during convalescence were more frequent among hospitalized COVID-19 patients and those over 50 years old. However, substantial interindividual variability in D-dimer levels during convalescence was observed, even among hospitalized patients. For instance, D-dimer levels had returned to normal in 10 out of 16 (62.5%) patients who required intensive care support. Interestingly, they found that 29% of patients with elevated D-dimers had been managed exclusively on an outpatient basis during their illness. In contrast, other coagulation markers (prothrombin time, activated partial thromboplastin time, fibrinogen, and platelet count) and inflammation markers (C-reactive protein, interleukin-6, sCD25) had returned to normal in over 90% of convalescent patients.

Lehmann [23] also reported that elevated D-dimer levels were significantly more frequent among patients with severe SARS-CoV-2 infections requiring hospitalization compared to those with a milder form of the disease. Patients with persistently elevated D-dimers had significantly lower average pO<sub>2</sub> and an increased alveolar-arterial oxygen gradient. Inflammatory markers, such as CRP, were higher in patients with elevated D-dimer levels.

In summary, patients who experienced severe COVID-19 infections requiring hospitalization had a higher prevalence of persistently elevated D-dimer levels. These elevated levels were associated with lung abnormalities, higher CRP levels, and more severe respiratory impairments. The interindividual variability in D-dimer levels during convalescence underscores the complexity of the post-COVID-19 phase. While other coagulation and inflammation markers normalized, D-dimer levels remained elevated in a significant proportion of patients.

Elevated levels are linked to prolonged COVID-19 and are an independent marker of poor prognosis. They are more common in patients hospitalized for severe disease. However, the mechanisms of this elevation remain unclear.

These elevated levels are associated with long-term thromboembolic complications, requiring individualized monitoring and prophylaxis.

Persistently high D-dimer levels after COVID-19 carry the risk of long-term thromboembolic complications. Trials are evaluating different doses of heparin and other treatments. Research is needed to elucidate the mechanisms of this possible increased thromboembolic risk in COVID-19 patients undergoing orthopedic surgery. Although COVID-19 may increase this risk, there is no evidence to suggest that previous infection amplifies this risk. Prophylaxis should not be changed, but research is needed.

The study has limitations, with a restricted sample size and the need for confirmation. It highlights the importance of considering the risks of VTE and bleeding when choosing anticoagulants in COVID-19 patients undergoing orthopedic procedures.

### **Conclusion**

With the rise in joint replacement surgeries, considering COVID-19's influence on postoperative outcomes is crucial. Prior research has highlighted elevated complication rates in COVID-19 positive patients post-surgery. Our study, specifically focusing on asymptomatic resolved COVID-19 cases with persistent high D-Dimer levels, did not reveal a significant impact on thromboembolic complications in joint replacement surgeries. Nevertheless, preoperative risk assessment remains vital for effective perioperative planning and complication prevention. Healthcare professionals must stay attentive to potential risk factors for all joint surgery patients, including those with a COVID-19 history, to ensure optimal results. Further research is needed to comprehend COVID-19's effect on postoperative outcomes and identify potential complications' risk factors in this group.

### **Author Statement**

#### **Conflict of Interest Statement**

No authors have competing interests.

#### **Ethical Approval**

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

#### **Author Contributions**

EL JELLOULI Wiam, ABOU ELALAA Khalil: Conception, patient enrolment, data collection, and interpretation. All authors contributed to literature review, final draft writing, and critical revision. All the authors have participated sufficiently in this work, take public responsibility for the content, and have made substantial contributions to this research.

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