

Venous Thromboembolic Complications in Patients with Coronavirus Diseases 2019 Infection Hospitalized in the Infectious and Tropical Diseases Department of CHNU de FANN in Dakar

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Abstract Introduction: Coronavirus Disease 2019 (COVID-19) is caused by SARS-CoV-2. High rates of venous thromboembolic disease (VTE) are reported in COVID-19, correlating with severe disease and unexplained deaths. This study aimed to characterize VTE development and associated factors in COVID-19 patients hospitalized at SMIT from January to December 2021. **Materials and methods:** We conducted a retrospective, descriptive, and analytical study of COVID-19 patients with VTE hospitalized at the SMIT, CHNU Fann, Dakar, from January to December 2021. **Results:** Among 248 hospitalized COVID-19 patients over 12 months, 12 developed VTE, a frequency of 4.84%. Patients were predominantly male (66.67%, sex ratio 1.25) with a mean age of 50.57 years (28-74). Common comorbidities included hypertension, diabetes (both 33.33%), and smoking (25%). RT-PCR was positive in 7 patients, and all 4 patients tested for D-dimer had elevated levels. All patients received corticosteroids and anticoagulation. Antiasthenic were administered in 11 patients, and antibiotics in 10. Only two patients had received a dose of COVID-19 vaccine. The average hospital stay was 10.82 days, with extremes of 1 and 25 days. Smoking was the only significant factor associated with thromboembolic complications. The case fatality rate was 33.33%. **Conclusion:** Venous thromboembolic complications are common in COVID-19, emphasizing the critical role of COVID-19 prevention. frequent in COVID-19 disease, hence the importance of prevention against COVID-19.

Keywords: COVID-19, venous thromboembolic complication, SMIT, Senegal

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1. Introduction

Coronavirus disease 2019 (COVID-19) is a new type of respiratory infectious disease caused by a virus of the Coronaviridae family, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This emerging disease is a zoonosis and have been found in COVID-19 patients with pneumonia in the city of Wuhan in China's Hubei province in December 2019. It spread rapidly, first across China, then around the world. The World Health Organization (WHO) officially declared it a public health

emergency of international concern on January 30, 2020, then a pandemic on March 11, 2020 [1].

Between the detection of the first case worldwide in late December 2020 and May 23, 2021, a cumulative total of 166,000,000 confirmed cases of COVID-19, including 3,400,000 deaths, were reported by the WHO. The countries most affected during this period were the United States, with 33,000,000 confirmed cases, including 600,000 deaths, and Italy, with 4,200,000 confirmed cases, including 127,000 deaths [2].

On March 2, 2020, Senegal confirmed its first case of COVID-19. In response to the spread of the virus, Senegal declared a nationwide state of emergency on March 23,

2020 [3].

COVID-19 is frequently complicated by a high incidence of thromboembolic events, encompassing both venous and arterial manifestations. These significant coagulation abnormalities have been consistently confirmed by observational studies and through systematic screening in various healthcare establishments [4,5,6]. Often asymptomatic, these events negatively impact patient prognosis. Additional risk factors for these complications include bed rest, advanced age, obesity and the severity of disease requiring hospitalization. Furthermore, inflammation directly linked to the virus itself plays a crucial role. This inflammation can lead to direct invasion of endothelial cells, resulting in endothelitis and a prothrombotic state, ultimately manifesting as immunothrombosis at the vascular level [4]. The high incidence of venous thrombosis during the COVID-19 epidemic quickly emerged as a major medical challenge. This was particularly significant given that a substantial number of patients were affected despite receiving well-managed prophylactic anticoagulation.

Consequently, assessing the risk of VTE and implementing effective preventive measures for high-risk patients became crucial. Numerous global studies have established COVID-19 as a recognized risk factor for VTE, particularly deep vein thrombosis (DVT) and pulmonary embolism (PE). This risk is especially pronounced in patients presenting severe forms of the disease, with reported prevalences varying from 3 to 85% depending on the methodology employed [7,8,9,10,11,12,13,14,15].

In Senegal, all fourteen regions were affected. The regions of Dakar (66%, n=48,656 confirmed cases), Thiès (10%, n=7,823 cases,) and Diourbel (4%, n=3,291 cases) were the most impacted by the pandemic in terms of case numbers. Senegal recorded 1,968 deaths, representing a mortality rate of 2.21%, according to the Ministry of health and social action (MSAS) on December 29, 2022 [16]. It should be noted that treatment was provided free of charge, demonstrating the determination of the health authorities to eradicate this disease as quickly as possible. The country experienced three waves during the pandemic, the first between March and November 2020, the second between October 2020 and January 2021, and the third from July to September 2021. Our study was conducted during the second and third waves.

In Senegal, like many other countries, medical teams have observed a significant increase in VTE cases among COVID-19 patients, particularly those with severe forms of the disease [3].

In the light of these findings, we conducted a study in the infectious and tropical diseases department of FANN (SMIT) hospital in Dakar. Our aim was to determine the prevalence of VTE diseases and the clinical profile of COVID-19 patients hospitalized within the SMIT at Fann hospital.

2. Objectives

The specific objectives are to:

- Describe the epidemiological, clinical, paraclinical and therapeutic aspects of patients with COVID-19 hospitalized at SMIT from January to December

2021 who present a VTE complication.

- To study the evolutionary modalities and risk factors associated with VTE complications in these COVID-19 patients hospitalized at SMIT from January to December 2021

3. Study Setting

Our study took place at the Ibrahima Diop Mar Infectious and Tropical Diseases Department (SMIT) of the FANN CHNU (Figure 1). The SMIT, which has existed since 1960, is the national reference structure for the management of infectious diseases in Senegal. It has a fourfold vocation: to provide care, to participate in the theoretical and practical teaching of students, to carry out research and to share its expertise nationally and internationally. SMIT comprises a two-storey building with a capacity of 72 beds in individual cabins. The medical staff consists of 04 full professors, 05 associate professors, 01 associate lecturers, 03 hospital practitioners, 02 hospital interns, 29 doctors enrolled in the DES program. The paramedical staff consists of 14 state nurses, 09 registered nurses, 01 midwife, 10 nursing assistants, 02 social workers, 04 ward attendants, 01 general supervisor, 05 stretcher-bearers, 02 management assistants.

Organization of care activities: The department receives patients evacuated from other health facilities in Dakar or from the interior of the country, as well as inpatients or referrals from other departments of the CHNU de Fann. Outpatient consultations are carried out by doctors specializing in the field, or interns, from 8am to 2pm. On-call duty alternates between doctors and nurses.

SMIT environment: SMIT is located within the hospital, which is a national reference facility. It also includes a number of hospital services with a national vocation, such as the pneumo-physiology service, the neurology service, the Fann CTE, the gerontology / geriatrics service, psychiatry, etc., as well as diagnostic support services such as imaging, bacteriology-virology and biochemistry. This environment is conducive to multi-disciplinary collaboration in patient management and the performance of examinations such as brain CT, MRI, GeneXpert and standard blood and biochemical tests. The SMIT also works with other laboratories outside the CHNU de Fann, notably the Bio24 laboratory and the Institute Pasteur of Dakar (IPD), for biological exploration and diagnostic confirmation of COVID-19, as well as for research.

4. Patients and Methods

Study design and participants

This is a retrospective, descriptive and analytical study covering the period from January to December 2021. All adult patients hospitalized with confirmed SARS-CoV-2 infection in the DAKAR infectious and tropical diseases department according to the Senegalese guidelines were screened and with also venous thromboembolic disease following SARS-CoV-2 infection.

The diagnosis of COVID-19 was made on the basis of positive PCR and/or positive RDT.

Patients with incomplete records were not included in this study.

Data collection and entry

Data were collected using a previously tested and validated survey form. Epidemiological, demographic, clinical, biological, treatment, outcomes were collected.

5. Definitions

- VTE [17,18] is characterized by the presence of a thrombus in a vein, impairing blood flow. It manifests itself in two (2) forms:
 - o Deep vein thrombosis (DVT), also known as phlebitis: this corresponds to the presence of a thrombus or blood clot in a deep vein, most often in the lower limbs.
 - o Pulmonary embolism (PE): characterized by the obstruction of a pulmonary artery or one of its branches by a thrombus, most often secondary to phlebitis [17,18].
- Obesity = overweight: BMI is 25 and <30 = overweight and BMI=30 is obese according to WHO
- Anemia is defined by a hemoglobin level < 13g/dl in men and < 12g/dl in women. In moderate anemia, the Hb varies between 7 and 9.9 g/dL, regardless of sex or age. Severe anemia occurs when Hb falls below 7 g/dL.
- PNN hyperleukocytosis is an abnormal increase in the total number of leukocytes, with a predominance of neutrophils >7500/mm³.
- Thrombocytopenia is defined as a platelet count below 150,000 cells/L. It has been classified as mild (100,000 to 150,000 cells/L), moderate (50,000 to 100,000 cells/L) and severe (less than 50,000 cells/L).

Statistical analysis

Data were entered using Excel. Data were analyzed using R software version 4.4.1. Graphs were obtained using Microsoft Office Excel Professional Plus 2021 for MacOs.

Quantitative variables are described in terms of effectif, mean, median, standard deviation, extremes and percentage, and qualitative variables are described in terms of effectif (absolute frequency) and percentage (relative frequency) of completed data.

In univariate analysis, a comparison was made between thromboembolic complications and other variables. The Chi2 test was used to compare proportions. The difference was statistically significant when the p-value was strictly less than 0.05. For multivariate analysis, we used the binary logistic regression method. All variables with a p value ≤0.25 were retained to model VTE.

Ethical considerations

Our study was conducted in compliance with ethical considerations. The identity of the people included was protected by anonymity with the use of a code, and access to the patient's file was strictly limited to those involved in its management. Access to the data was authorized by the head of the infectious diseases department.

6. Results

Frequency of thromboembolic disease

During the study period, a total of 248 patients were hospitalized for COVID-19 with 12 (4.84%) developing venous thromboembolism (VTE) **Characteristics of COVID-19 patients with venous thromboembolic complication.**

Among the 12 patients with a VTE complication, the mean age was 50.57 years (range: 28 – 74 years). The majority were male (8 patients, 66.67%), with a sex ratio of 2. A medical history was noted in 8 patients (66.67%). The most common comorbidities observed in COVID-19 patients with VTE were hypertension (n=4, 33.3%) and diabetes (n=4, 33.33%) Signs had been evolving for less than 14 days in most cases (n=10). Respiratory signs were noted in all patients (n=12). Respiratory signs were present in all 12 patients. Extra-respiratory signs were noted in 5 patients, including cardiovascular (n=2), neurological (n=1), digestive (n=1), and locomotor (n=1) manifestations (Table 1).

Regarding laboratory findings, 11 patients had a complete blood count (CBC), of these, six (6) presented with moderate anemia, five (5) had Hyperleukocytosis (with elevated polymorphonuclear neutrophils - PNN) and 3 patients had a normal CBC.

C-reactive protein (CRP) was performed in 11 patients, with 10 showing elevated level. D-Dimer assay was performed and found to be elevated in 4 patients. RT-PCR for COVID-19 was positive in 7 patients (Table 2).

All 12 patients received corticosteroid therapy and anticoagulation. Antiasthenic were administered to 11 patients and antibiotics to 10. Two patients had received three doses of a COVID-19 vaccine. The average hospital stay was 10.82 days, with ranging from 1 day to 25 days. Regarding patient outcomes, six patients recovered and four died. The outcome of the remaining two patients could not be determined as they were transferred to another facility.

Factors associated with VTE: In our study, only smoking (p=0.012) was significantly associated with the occurrence of thromboembolic complications (Table 4).

Table 1. Distribution of patients with COVID-19 hospitalized at SMIT from January to December 2021 with a venous thromboembolic complication according to associated risk factors

Patients	Age>45ans	Tabac	HTA	Obesity	Diabetes	Risk factors
1						0
2						0
3						0
4	Yes		Yes		Yes	3
5	Yes					1
6						0

Patients	Age>45ans	Tabac	HTA	Obesity	Diabetes	Risk factors
7	Yes		Yes			2
8	Yes	Yes	Yes			3
9	Yes	Yes			Yes	3
10					Yes	1
11	Yes		Yes		Yes	3
12	Yes	Yes		Yes		3

Table 2. Distribution of patients with thromboembolic complications according to biological characteristics

Patients	CRP	Creatinine level	Blood ionogram	TP-INR	D-Dimers	Intermediate RT-PCR
1	normal	normal	Hyponatremia hypochloremia	normal	not done	positif
2	high	normal	normal	low	high	positif
3	high	normal	normal	normal	high	no
4	high	normal	normal	high	not done	positif
5	high	normal	normal	low	not done	no
6	high	normal	normal	normal	high	positif
7	high	normal	normal	normal	not done	negatif
8	high	high	Hyponatremia, Hyperkalemia	low	high	not done
9	not done	not done	not done	not done	not done	not done
10	high	normal	normal	normal	not done	positif
11	high	high	normal	normal	not done	positif
12	high	high	Hypernatremia	low	not done	positif

Table 3. Distribution of patients with thromboembolic complications according to antibiotic treatment used

Antibiotic	Effectif (N=10)
Azithromycin + Ceftriaxone	3
Azithromycin	2
Azithromycin + Ceftriaxone + Amoxicillin- clavulanic acid	1
Ceftriaxone	1
Azithromycin + Amoxicillin- clavulanic acid	1
Ceftriaxone + Amoxicillin + clavulanic acid	1
Amoxicillin- clavulanic acid	1

Table 4. Factors associated with thromboembolic complications

Variables	Thromboembolic complications		Total	p-value
	No (N=62)	Yes (N=12)		
Age				0,15
<45	13 (72,22%)	5 (27,78%)	18 (100%)	
>45	49 (87,50%)	7 (12,50%)	56 (100%)	
Gender				0,8
F	26 (86,67%)	4 (13,33%)	30 (100%)	
M	36 (81,82%)	8 (18,18%)	44 (100%)	
RT-PCR				>0,9
no	16 (84,21%)	3 (15,79%)	19 (100%)	
yes	45 (83,33%)	9 (16,67%)	54 (100%)	
Risk factors				
Diabete	13 (76,47%)	4 (23,53%)	17 (100%)	0,5
Obesity	3 (75%)	1 (25%)	4 (100%)	0,5
Dyslipidemia	1 (100%)	0 (0%)	1 (100%)	>0,9
kidney failure chronic	0 (0%)	1 (100%)	1 (100%)	0,2
HTA	16 (80%)	4 (20%)	20 (100%)	0,7
Heart disease	6 (85,71%)	1 (14,29%)	7 (100%)	>0,9
AVC	2 (100%)	0 (0%)	2 (100%)	>0,9
Smoking	1 (25%)	3 (75%)	4 (100%)	0,012

7. Discussion

Frequency of venous thromboembolic complications

The frequency of VTE complications in COVID-19 patients in our study was 4.84% (n=12). This figure is notably lower than those reported by other studies. For instance, research by Klok et al., Lodigiani et al. and

Poissy et al. [7,12,19] showed significantly higher frequencies of 31%, 27% and 25% respectively. Similarly, in the study carried out at Zhongnan Hospital in Wuhan, China, during the period from January to May 2020, revealed that approximately 25% of the 191 included patients developed thromboembolic events, mainly pulmonary embolisms particularly in mechanically ventilated patients (almost 30% thrombosis) [10].

Furthermore, a retrospective observational study conducted at New York's Presbyterian Hospital, involving 1,000 hospitalized for COVID-19 patients, showed that 30% of intensive care patients developed deep vein thrombosis (DVT) or pulmonary embolism (PE), despite systematic anticoagulant prophylaxis. Among these 70% of thrombosis cases 70% were pulmonary embolisms [11]. Similarly, a study conducted at Milan's San Raffaele Hospital revealed that 30% of COVID-19 patients in intensive care developed thromboembolic complications, mainly pulmonary embolism (PE) for 70%, and 15% suffered DVT, despite the systematic administration of anticoagulant prophylaxis [12].

In Africa, a retrospective study carried out in the military hospitals of Libreville and Akanda in Gabon observed that among 167 patients admitted with SARS-CoV-2 infection, thromboembolic manifestations were presented in 18 cases, i.e. around 10.8% of cases [13]. Several factors could explain the discrepancy in frequency observed in our study. A major contributing factor is early management with preventive anticoagulation administered to a large portion of our cohort (72.98%). Furthermore, the limited number of patients included in our study might have reduced statistical power, thus influencing the observed prevalence. Additionally, the reality of limited technical diagnostic capabilities for VTE in our setting could potentially lead to an underestimation of the true frequency. In contrast, the study by Bouaziz et al., [20] reported a lower frequency of VTE events (1.84%, n=33) among 1,790 hospitalized for COVID-19 patients.

However, our result is comparable to that reported by Porfida et al. (5.5%) [21] in patients hospitalized outside the intensive care unit, suggesting a possible similar profile for this patient category.

Socio-demographic data for COVID-9 patients with thromboembolic complications.

The sociodemographic findings of our study revealed that patients who developed VTE had a mean age of 50.57 years. This is notably younger compared to other European studies, such as those by Klok and al. [7] and Lodigiani and al. [12], where the mean ages were 62.5 and 63 years respectively. This difference could be attributed to variations in the demographic characteristics of the countries where these studies were conducted. The male predominance observed in our study (66.67%) aligns with the findings of Klok et al. [7] and Lodigiani and al. [12], who reported rates of 60% and 63% respectively, suggesting that men may indeed be more susceptible to develop VTE Complication in the context of COVID-19, considering that male sex is a well-established, non-modifiable cardiovascular risk factor.

Comorbidities and lifestyle

Our study found that arterial hypertension (33.3%) and diabetes (33.33%) were the most common comorbidities among COVID-19 patients who developed VTE. These findings are consistent with other significant studies. For instance, Klok and al [7], reported hypertension in 45% and diabetes in 20%, of their VTE cohort, while Lodigiani and al. [12], found hypertension in 40% and diabetes in 30%. Similarly, Argenziano et al. [11] also noted the prevalence of hypertension (45%) and diabetes (35%) in their patient population. These similarities across studies

consistently confirm that hypertension and diabetes are frequently associated risk factors for VTE in patients with COVID-19. However, the prevalence of obesity in our cohort was 8.33% which is lower than reported in previous studies, such as 25% by Klok and al. [7] and 35% by Lodigiani and al. [12]. This difference might be attributed to the generally higher proportions of obese people in the populations where those in America and Europe studies were conducted. Furthermore, the proportion of smoking patients in our study was 25%, which aligns closely with the 20% reported by Klok and al., [7]. This consistency further underscores the established association between smoking and an increased risk of VTE in COVID-19 patients. Overall, our findings demonstrate several key similarities with previously conducted research regarding the comorbidity and lifestyle profiles of COVID-19 patients experiencing VTE.

Biological data

In our study, D-dimer levels were elevated in 33.3% of patients. The researchers observed that D-dimer levels were well above normal thresholds, particularly in patients with severe disease [8,9,10]. Furthermore, elevated levels of D-dimer and fibrinogen, markers of hypercoagulability, were observed in these patients, inducing an exacerbated state of abnormal coagulability and hence the onset of VTE complications [12]. This result is lower than the studies by Lodigiani and al. and Poissy and al. [12,19], who reported rates of 80% and 85% respectively. In our context, this can be explained by the limited accessibility to certain biological tests, including D-dimer assays for our patient. Furthermore, the proportion of smoking patients in our study was 25%, which is close to that of the Klok and al. study [7], which reported 20% of smokers, underlining the association between smoking and the increased risk of VTE in COVID-19 patients. There are several similarities between our study and those previously carried out. It's important to note that while D-dimer elevation is not specific for VTE diagnosis, its levels can be correlated with the clinical probability and age of patients. Indeed, D-dimer levels have been independently associated with an increased risk of severe disease, thrombosis, acute renal failure, and all-cause mortality in COVID-19 patients, regardless of previously identified risk factors [21]. This finding reinforces the understanding that COVID-19 is a coagulopathic disease, with D-dimers serving as a direct link between the infection and adverse outcomes. Regarding other biological markers, our results align with the concept of thrombo-inflammation, a key feature of severe COVID-19. We observed a non-specific biological inflammatory syndrome correlated with VTE, evidenced by elevated C-reactive protein (CRP) in 83.3% of patients with VTE, neutrophilic hyperleukocytosis in 58.3%, and moderate anemia in 41.6%. These inflammatory markers are consistent with the prothrombotic state observed in COVID-19.

Radiological data

In our study, thoracic angio-CT performed in 33.33% of COVID-19 patients with VTE. These scans revealed bilateral ground-glass opacities in all patients. We observed a direct relationship: the greater the degree of

radiological involvement the higher the risk of developing venous thromboembolic complications.

Our findings align with existing literature. For instance, the study by Mahsouli et al. [23] reported ground-glass opacities in 87% of patients, with bilateral involvement in 80% of cases among those who developed VTE during COVID-19 hospitalization.

Similarly, Leonard et al. [24] found a 30% prevalence of VTE in COVID-19 patients undergoing thoracic angio-CT. These results are in line with previous studies, which highlight the relationship between lung damage leading to severe forms of COVID-19 and the occurrence of VTE in these patients.

Therapeutic data

In our study, the therapeutic management of COVID-19 patients relied mainly on preventive anticoagulation, administered on admission in 72.98% of patients, which may explain the relatively low incidence of VTE (4.84%). According to the study by Planquette and al. [25], preventive anticoagulation was administered to 133 patients hospitalized for COVID-19, and 28% developed VTE. Similarly, Klok and al [3] found a 31% incidence of VTE despite systematic thromboprophylaxis of patients hospitalized for COVID-19. Patell and al. [26] found a 4.8% incidence of VTE in 214 patients who had received preventive anticoagulation. Curative anticoagulation, on the other hand, was initiated as soon as VTE was suspected, taking into account the patient's clinical profile. So, it is important to improve awareness and to prescribe an optimal thromboprophylaxis during the prevention, control and treatment of COVID-19 infection. Obviously, the prevention and control of COVID-19 infection is still the most important, but the prevention and an optimal management of vascular complications can significantly modify the prognosis and reduce the mortality. Thromboprophylaxis is required in all ICU patients, choosing mainly LMWH with longer polysaccharide chains less eliminated by kidney route such as tinzaparin or dalteparin, which can be used even in cases of creatinine clearance between 20 and 30mL/min.28–30 Nevertheless, VTE can occur despite well-conducted thromboprophylaxis [27].

Adjuvant treatment, antibiotic therapy was prescribed in 83.3% of patients (n=10). Azithromycin, ceftriaxone and amoxicillin-clavulanic acid were the main ATGTs prescribed, helping to control infectious complications that could worsen the overall inflammatory state. In addition, corticosteroid therapy was administered to all 12 patients with VTE, to reduce excessive inflammation in the patients and lower the risk of mortality.

Evolution

The mean hospital stay was 10.82 days, with extremes of 1 and 25 days. Klok and al. [5] found a median ICU stay of 7 days shorter than ours. We also noted a 50% cure rate (n=6) and 33.33% death rate (n=4). Studies published by the WHO on July 15, 2021 also found a low overall mortality rate (2.6%) [17]. In addition, thromboembolic complications contributed to increased mortality, reaching around 30-40% in patients with pulmonary embolism, compared with 12-15% in those without thrombosis [10].

The incidence of these complications was associated with higher mortality, with death rates reaching 40% in patients with pulmonary embolisms, compared with 10-15% in those without thromboembolic events [12].

The 33.33% mortality rate found in our study may be explained by the fact that our population was essentially made up of patients with VTE complications, i.e. severe cases with a guarded prognosis likely to die.

Factors associated with VTE

In our study, **smoking** was the only factor associated with VTE in patients with COVID-19 at SMIT during the period under review. Other authors have found age to be a risk factor for VTE [7], as well as D-dimer level [19].

Limitations of the study:

Our study has some limitations. First, due to the retrospective study design. We were confronted with a number of constraints:

- low number of VTE cases;
- incomplete data;
- lack of reference regarding the outcome of transferred patients.

Conclusion: Venous thromboembolic disease (VTED) in patients with COVID-19 is a frequent complication in the hospital setting, and is particularly life-threatening in patients with COVID-19. It is recommended to assess the risk of VTE, to take effective preventive measures for patients at high risk, to pay attention to VTE occurrence in asymptomatic patients or PE in patients with clinical manifestations of sudden deterioration of oxygenation, respiratory distress, or hypotension

Authors' Contributions

NFNG, NL, EY, and MS designed the study; NL and MF, collected and analyzed data, and wrote the first draft of the manuscript. All authors reviewed and commented on the manuscript and approved the final its version.

Competing Interests

We declare no competing interests.

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