



Clinical Research

Thrombosis of Medium-Sized and Large Arteries During Covid-19 Infection: Results of the COVIVASC Study

Raphael Coscas,^{1,2} Maxime Dubosq,^{1,2} Johanna Charton,^{1,2} Salma El Batti,³ Julien Gaudric,⁴ Fabien Koskas,⁴ Laurent Chiche,⁴ Thibault Couture,⁴ Jean-Michel Davaine,⁴ Yves Castier,⁵ Pierre Cerceau,⁵ Mostafa EL Hajjam,⁶ Patricia Samb,^{7,8} Alain Beauchet,^{7,8} Lamiae Grimaldi,^{7,8} Isabelle Javerliat,^{1,2} Olivier Goeau-Brissonniere,^{1,2} Jean-Marc Alsac,³ Ilaria Onorati,⁹ Emmanuel Martinod,⁹ Pascal Desgranges,^{10,11} Joseph Touma,^{10,11} Frédéric Cochenec,^{10,11} Quentin Pellenc,⁵ Pierre Julia,³ and Marc Coggia,^{1,2} Boulogne-Billancourt, Villejuif, Paris, Bobigny, and Créteil, France

Background: COVID-19 infection is associated not only with venous thromboses but also with arterial thromboses (COV-ATs) in relation with an endothelial dysfunction, a coagulopathy and rhythm disorders. The incidence, the topography, and the prognosis of COV-ATs remain poorly known. The objective of this study was to report the overall experience of the Greater Paris University Hospitals (Assistance Publique - Hôpitaux de Paris, AP-HP) during the first pandemic wave of COVID-19 infection.

Methods: After approval by the ethics committee, a study using the AP-HP clinical data warehouse was carried out between March and May 2020. Overall, 124,609 patients had a polymerase chain reaction for COVID-19 in our hospitals, of which 25,345 were positive. From 20,710 exploitable stays, patients tested positive for COVID who presented an episode of acute COV-AT (except coronary and intracranial arteries) were selected on the basis of the French medical classification for clinical procedures codes. The data are presented as absolute values with percentages and/or means with standard deviation.

Results: Over the studied period, 60 patients (aged 71±14 years, 42 men) presented a COV-AT at the time of their hospitalization, an incidence of 0.2%. The arterial complication occurred 3±7 days

¹Department of Vascular Surgery, Ambroise Paré University Hospital, Assistance Publique-Hôpitaux de Paris, 92104 Boulogne-Billancourt, France.

²UMR 1018, Inserm-Paris11 - CESP, Versailles Saint-Quentin-en-Yvelines University, Paris-Saclay University, Paul Brousse Hospital, 94807 Villejuif, France.

³Department of Cardiovascular Surgery, Hôpital Européen Georges Pompidou, Assistance Publique-Hôpitaux de Paris, 75015 Paris, France.

⁴Department of Vascular and Endovascular Surgery—Tertiary Aortic Center, Pitié-Salpêtrière University Hospital, Assistance Publique-Hôpitaux de Paris and Sorbonne Médecine Universités, 75013 Paris, France.

⁵Department of Vascular Surgery, Bichat Hospital, Assistance Publique-Hôpitaux de Paris, Paris, France and Paris-Diderot University, Paris, France.

⁶Department of Radiology, Ambroise Paré University Hospital, Assistance Publique-Hôpitaux de Paris, 92104 Boulogne-Billancourt, France.

⁷Clinical Research Unit, Ambroise Paré University Hospital, Assistance Publique-Hôpitaux de Paris, Boulogne-Billancourt, France.

⁸University of Versailles Saint-Quentin en Yvelines, Paris-Saclay University, Paris, France.

⁹Department of Thoracic and Vascular Surgery, Hôpitaux Universitaires Paris Seine-Saint-Denis, Hôpital Avicenne, Assistance Publique-Hôpitaux de Paris, and Université Paris 13, Sorbonne Paris Cité, UFR Santé, Médecine et Biologie Humaine, Bobigny, France.

¹⁰Department of Vascular Surgery, Henri Mondor University Hospital, Assistance Publique-Hôpitaux de Paris, Créteil, France.

¹¹Paris-Est Créteil Faculty of Medicine, Créteil, France.

Correspondence to: Raphaël Coscas, Department of Vascular Surgery, Ambroise Paré University Hospital, 9 avenue Charles de Gaulle, 92104 Boulogne Cedex, France; E-mail: rcoscas@gmail.com

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after the COVID infection and was inaugural in 30% of the cases ($n = 18$). The sites of COV-AT were the lower extremities ($n = 35\%$, 58%), the abdominal aorta ($n = 10\%$, 17%), the thoracic aorta ($n = 7\%$, 12%), the upper limbs ($n = 7\%$, 12%), the cerebral arteries ($n = 7\%$, 12%), the digestive arteries ($n = 6\%$, 10%), the renal arteries ($n = 2\%$, 3%), and the ophthalmic artery ($n = 1\%$, 2%). Multiple COV-ATs were observed in 13 patients (22%). At the time of diagnosis, 20 (33%) patients were in intensive care, including six (10%) patients who were intubated. On computed tomography angiography, COVID lesions were classified as moderate and severe in 25 (42%) and 21 (35%) cases, respectively. Revascularization was attempted in 27 patients (45%), by open surgery in 16 cases, using endovascular techniques in 8 cases and with a hybrid approach in three cases. Six patients (22%) required reinterventions. The duration of hospitalization was 12 ± 9 days. Early mortality (in-hospital or at 30 days) was 30% ($n = 18$). Nine (15%) patients presented severe nonlethal ischemic complications.

Conclusions: Arterial involvement is rare during COVID-19 infection. The aorta and the arteries of the limbs are the privileged sites. The morbi-mortality of these patients is high. Future studies will have to determine if the systematization of anticoagulation therapy decreases the incidence and the severity of the condition.

INTRODUCTION

The Sars-Cov2/COVID-19 infection quickly spread worldwide, in particular in France. The first cases identified in our country were diagnosed at the end of February 2020. Nearly seven million infections were counted at the end of 2021, including 120,000 deaths. The major complication of this infection is acute respiratory distress syndrome. It occurs because of in situ thrombotic phenomena in the pulmonary vessels.¹ Venous thromboembolic events are now well described among patients with Sars-Cov2/COVID-19 with an incidence up to 49% in patients hospitalized in the intensive care unit.² Deep venous thromboses of the limbs, pulmonary embolisms but also in situ pulmonary thromboses were reported, associated with an increased mortality and nonlethal complications. Various recommendations for their prevention, their diagnosis, and their management with anticoagulation have been proposed.^{3–6}

More rarely, arterial thromboses (COV-ATs) occur in medium-sized and large arteries.^{2,7,8} Their causes are still poorly understood, but links have been suggested with an endothelial dysfunction, a coagulopathy, and cardiac rhythm disorders.^{9–13} The incidence, the topography, and the prognosis of COV-ATs remain poorly known. The objective of this study was to report the overall experience of the Greater Paris University Hospitals (Assistance Publique - Hôpitaux de Paris, AP-HP) during the first wave of COVID-19 infection.

MATERIAL AND METHODS

This study named COVIVASC was initiated by the Vascular Surgery College of the Greater Paris

University Hospitals (Collegiale de Chirurgie Vasculaire de l'AP-HP) that include all vascular surgeons of our institution, in order to collect all the COV-AT cases observed in the Greater Paris University Hospitals between March and May 2020 during the first epidemic wave and the first lockdown.

Data Sourcing

We used the AP-HP Clinical Data Warehouse (CDW). The CDW includes the healthcare information of more than 11 million patients seen in the outpatient clinics or hospitalized in one of the 39 AP-HP hospitals. The CDW collects information from the Orbis (Agfa Healthcare) electronic medical record,¹⁴ which includes the demographic data, the therapeutic management, the medico-administrative data issued from the Computerized Medical Information Systems Program (PMSI), the medical file, and the results of biology and imagery. The secure platform storing these data was validated by the French Data Protection Authority (CNIL, Paris, France). The data are kept up-to-date regularly and can be used to conduct clinical studies on existing data after an authorization from the scientific and ethics committee of the CDW. This authorization was obtained for two years on April 4, 2020 (ref. CSE 20-34_COVID). The study met the criteria of conformity of the Declaration of Helsinki, 1992.

Selection of the Patients

To identify all the patients presenting a COV-AT during the first wave of the disease (March–May 2020), the data were collected on June 4, 2020. This provided a follow-up of at least 30 days for all the patients. The selected patients had to present at least one episode

of arterial thrombosis in the 14 days preceding or following the diagnosis of Sars-Cov2/COVID-19 infection. We relied on the kind of PMSI encoding to include all the codes compatible with the International Classification of Diseases (ICD-10). The COVID-19 diagnosis was based on the presence of one of the following criteria: (1) a positive polymerase chain reaction (PCR) test, (2) a positive serology, (3) a thoracic computed tomography (CT) scan compatible with the diagnosis in accordance with well-admitted criteria,^{15,16} or (4) a PMSI ICD-10 U07 code (code for the Sars-Cov2/COVID-19 infection).

Among the patients with Sars-Cov2/COVID-19 as per these criteria, we selected the associated codes which could suggest a concomitant episode of COV-AT. Thirty six ICD-10 codes were explored: G45, G46, G81, H34, I26, I27, I28, I51, I63-I69, I70-I79, I89, I97-I99, K55, R02, R09, T80-T82, T87, T88, and Z8 (Table I). Overall, 466 anonymized files were analyzed by two blind operators (R.C. and J.C.). Among these files, 451 presented sufficient data for analysis. The patients who presented a coronary or intracranial thrombosis, the decompensation of a chronic ischemia (ischemic status for more than two weeks),¹⁷ a small vessel vasculitis, or iatrogenic thrombosis or stenosis (ischemia due to femoral circulatory assistance, thrombosis of a radial or femoral catheter) were excluded (Fig. 1). Only the patients presenting a spontaneous COV-AT of medium-sized or large vessels were then included. As the hospitals in which the patients were treated were identifiable, all the departments of vascular surgery from the AP-HP were contacted to double-check and confirm that the number of patients found agreed with the number of patients treated in each center.

Collected Data

The demographic characteristics of the patients, the comorbidities, the preoperative treatments (antiplatelet agents and anticoagulants), the delay between diagnosis of COV-AT and the diagnosis of Sars-Cov2/COVID-19 infection, the biological results contributing to the diagnosis, the medical treatments, the preoperative and postoperative events, and the perioperative data were collected. Primary outcome was 30-day mortality. Major postoperative events were defined as complications due to COV-AT that were potentially life-threatening or could compromise the functional prognosis and were also analyzed.

Data Analysis

The results for qualitative variables were expressed as absolute values and percentages.

The quantitative variables were expressed as mean and standard deviation when they followed a normal distribution.

RESULTS

Incidence and Demographic Data

Among the 25,345 patients with a Sars-Cov2/COVID-19 infection enrolled in the CDW over the study period, 60 presented a COV-AT during the same period, corresponding to a 0.2% incidence of COV-AT. There were 42 (70%) men and the mean age of the population was 71 ± 14 years. At the time of diagnosis, 37% ($n = 22$) of the patients were hospitalized in intensive care unit and 10% ($n = 6$) of them presented a respiratory distress. The cardiovascular risk factors were tobacco use in 40% of the patients, previous ($n = 16$) or active ($n = 8$), arterial hypertension in 65% ($n = 39$) of the patients, ischemic heart disease in 17% of the cases ($n = 10$), and diabetes in 37% ($n = 22$). Fifteen percent ($n = 9$) of the patients had chronic renal failure including one patient on chronic hemodialysis. Twenty three percent ($n = 14$) of the patients had a history of vascular surgery: eight previous angioplasties with stenting of the lower extremities, three previous femoropopliteal bypasses, two previous aortic surgeries (one aorto-bifemoral bypass and one angioplasty of the infrarenal aorta), and one stenting of the superior mesenteric artery. Thirty percent of the patients ($n = 18$) already received anticoagulation and 42% ($n = 25$) received antiplatelet agents. The main demographic data are summarized in Table II.

Clinical Presentation

Overall, 77% ($n = 46$) of the patients had a positive PCR for Sars-Cov2/COVID-19 and 88% ($n = 53$) presented pulmonary signs on the thoracic angio-CT. At the time of diagnosis, the main symptoms presented by the patients were fever (37%, $n = 22$), cough (30%, $n = 18$), and dyspnea (45%, $n = 27$). In 30% ($n = 18$) of the cases, COV-AT was the inaugural symptom of the Sars-Cov2/COVID-19 infection. COV-AT appeared three to seven days after the beginning of the Sars-Cov2/COVID-19 infection. The principal territories concerned by the disease were the lower limbs (58%, $n = 35$), the abdominal aorta (17%, $n = 10$), the thoracic aorta (12%, $n = 7$), the carotid arteries (12%, $n = 7$), the upper limbs arteries (12%, $n = 7$), and the superior mesenteric artery (10%, $n = 6$). Multifocal

Table I. The ICD-10 codes selected for the study

G45	Transient cerebral ischemic attacks and related syndromes
G46	Vascular cerebral syndromes in cerebrovascular diseases
G81	Hemiplegia and hemiparesis
H34	Retinal vascular occlusions
I26	Pulmonary embolism
I27	Other pulmonary heart diseases
I28	Other diseases of pulmonary vessels
I51	Complications and ill-defined descriptions of heart disease
I63	Cerebral infarction
I64	Stroke, not specified as hemorrhage or infarction
I65	Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction
I66	Occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction
I67	Other cerebrovascular diseases
I68	Cerebrovascular disorders in diseases classified elsewhere
I69	Sequelae of cerebrovascular disease
I70	Atherosclerosis
I71	Aortic aneurysm and dissection
I72	Other aneurysm and dissection
I73	Other peripheral vascular diseases
I74	Arterial embolism and thrombosis
I77	Other disorders of arteries and arterioles
I78	Diseases of capillaries
I79	Disorders of arteries, arterioles, and capillaries in diseases classified elsewhere
I89	Other noninfective disorders of lymphatic vessels and lymph nodes
I97	Intraoperative and postprocedural complications and disorders of circulatory system, not elsewhere classified
I98	Other disorders of circulatory system in diseases classified elsewhere
I99	Other and unspecified disorders of circulatory system
K55	Vascular disorders of intestine
R02	Gangrene, not elsewhere classified
R09	Other symptoms and signs involving the circulatory and respiratory system
T80	Complications following infusion, transfusion, and therapeutic injection
T81	Complications of procedures, not elsewhere classified
T82	Complications of cardiac and vascular prosthetic devices, implants, and grafts
T87	Complications peculiar to reattachment and amputation
T88	Other complications of surgical and medical care, not elsewhere classified
Z89	Acquired absence of limb

COV-ATs were observed in 22% ($n = 13$) of the cases (Table II). Among the 14 patients with a history of previous vascular surgery, 50% ($n = 7$) presented a thrombosis in the previously revascularized territory. However, the causal relation between the Sars-Cov2/COVID-19 infection and the thromboses was impossible to clarify.

Treatment

In 55% ($n = 33$) of the cases, including five patients receiving palliative care, effective anticoagulation only with unfractionated intravenous heparin or low-molecular weight subcutaneous heparin was instituted. The remaining 45% ($n = 27$) of the patients had a revascularization procedure associated with effective heparin anticoagulation. Techniques

of revascularization were endovascular in eight patients, with two thromboaspirations of the supra-aortic arteries, two thromboaspirations of the iliac axis associated with one external iliac artery stent, one bilateral iliac stenting, two thromboaspirations of the leg arteries, and one thromboaspiration of the superior mesenteric artery. Open surgery was used in 16 patients, with one aorto-bifemoral bypass, two femoropopliteal saphenous vein bypasses, nine thrombectomies of the ilio-femoro-popliteal axis, two thrombectomies of the leg arteries, two upper limb thrombectomies, and one Fogarty thrombectomy of the superior mesenteric artery. Hybrid procedures were carried out in three patients. In 22% ($n = 6$) of the revascularized patients, reinterventions for iterative revascularization were necessary.

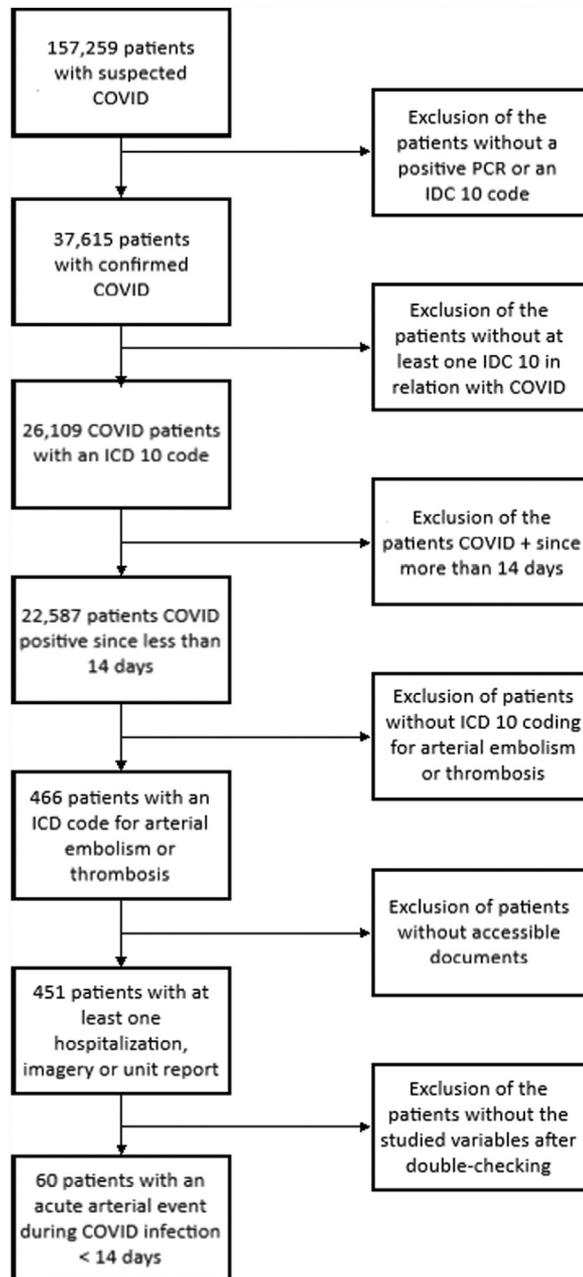


Fig. 1. Diagram of flow.

Evolution Following the Treatment

The duration of hospitalization was 12 ± 9 days, with an early 30-day death rate of 30% ($n = 18$). The causes of mortality were related to the Sars-Cov2/COVID-19 infection in 11 patients (hypoxemic pneumopathy, acute respiratory distress syndrome, and massive pulmonary embolism in spite of an effective anticoagulation) and related to the vascular pathology in seven patients (mesenteric infarction, shock due to the thrombosis of an

aorto-bifemoral bypass, organ failure on the second postoperative day, and cardiogenic shock). Moreover, 15% ($n = 9$) of the patients presented a serious unfavorable ischemic event (forefoot necrosis, hand necrosis, hemiplegia, and recurrent thrombosis) and 14% ($n = 8$) underwent a major amputation.

DISCUSSION

We present in this study the experience of the AP-HP on the incidence, the diagnosis, and the management of the cases of thromboses of medium-sized and large arteries related to the Sars-Cov2/COVID-19 infection during the first epidemic wave (March 2020 to May 2020) in the Ile de France region. We observed a relatively low incidence of COV-ATs (0.2%). The thoraco-abdominal aorta and the lower limbs were more frequently involved. The prognosis of these arterial lesions is severe with a 30% mortality rate, due to the severity of the Sars-Cov2/COVID-19 infection itself whose death rate was estimated at 19% during the first wave based on a study conducted by the Directorate for Research, Studies, Evaluation, and Statistics.¹⁸

The 0.2% incidence found in this study is reliable because data were exhaustive. AP-HP represents the greatest hospital complex of France and Europe with 39 hospitals organized into six University Hospital groups with more than 20,000 beds of hospitalization. During the first epidemic wave, the AP-HP was particularly involved in the management of the pandemic with 127,761 PCR tests carried out and 40,577 hospitalizations, including 8,554 in intensive care units.

The methodology applied to our study relies on the AP-HP CDW.¹⁴ The CDW is a recent big data tool allowing an exhaustive anonymous research with preset keywords in all the documents resulting from the hospitalization, operative, and radiological reports, also using the ICD-10 codes associated with the reports. Since March 1, 2020, a specific cohort of all the proven or suspected Sars-Cov2/COVID-19 infection patients was individualized to allow more specific research. The collection of data was double-checked by contacting all the departments of surgery directly vascular to confirm that the number of patients was consistent. Consequently, the incidence of COV-ATs reported in this study was reliable and concerns a large population of Sars-Cov2/COVID-19 patients. In this study, we considered all the patients with a confirmed diagnosis of Sars-Cov2/COVID-19, which implies a great variability in terms of severity (patients in reanimation, conventional hospitalization, or into ambulatory).

Table II. Demographic characteristics of the patients

Variables	Total, <i>n</i> = 60
Male gender (<i>n</i> , [%])	42 (70)
Age (mean, [SD])	71 (14)
Cardiac failure (<i>n</i> , [%])	11 (18.3)
Coronary disease (<i>n</i> , [%])	10 (16.7)
Arterial hypertension (<i>n</i> , [%])	39 (65)
Dyslipidemia (<i>n</i> , [%])	16 (26.7)
History of vascular surgery (<i>n</i> , [%])	13 (21.7)
Tobacco	
No (<i>n</i> , [%])	32 (53.3)
Stopped (<i>n</i> , [%])	16 (26.7)
Active (<i>n</i> , [%])	8 (13.3)
Home medications	
Antiplatelet agents (<i>n</i> , [%])	25 (42)
Anticoagulants (<i>n</i> , [%])	18 (30)
Renal function	
GFR >60 (<i>n</i> , [%])	50 (83.3)
GFR 30–60 (<i>n</i> , [%])	7 (11.7)
GFR <30 (<i>n</i> , [%])	1 (1.7)
Thoracic CT-scan	
Moderate lesions (<i>n</i> , [%])	25 (42)
Severe lesions (<i>n</i> , [%])	21 (31)
Associated symptoms	
Fever (<i>n</i> , [%])	18 (30)
Cough (<i>n</i> , [%])	18 (30)
Dyspnea (<i>n</i> , [%])	27 (45)
Locations	
Lower limbs (<i>n</i> , [%])	35 (58)
Abdominal aorta (<i>n</i> , [%])	10 (17)
Thoracic aorta (<i>n</i> , [%])	7 (12)
Upper limbs (<i>n</i> , [%])	7 (12)
Carotids (<i>n</i> , [%])	7 (12)
Superior mesenteric artery (<i>n</i> , [%])	6 (10)
Renal artery (<i>n</i> , [%])	2 (3)
Ophthalmic artery (<i>n</i> , [%])	1 (2)
Multiple location (<i>n</i> , [%])	13 (22)

This was a specific point of our study which distinguishes it from most previously published studies, which were focused mainly on the most serious patients, hospitalized and/or in intensive care

The reasons why COV-ATs occur remain uncertain but endothelial dysfunction, disorders of coagulation, cardiac arrhythmia, and local predisposing factors (such as catheters and the supine position of patients ventilated in intensive care) are involved.⁶ The receptor of the angiotensin 2–converting enzyme is probably the principal pathway used by the Sars-Cov2/COVID-19 infection. The angiotensin 2–converting enzyme is expressed in the lung, the heart, the kidneys, and the intestine but also by the endothelial cells.¹⁹ An endothelialitis due to a direct viral infection of the endothelial cells was demonstrated in the Sars-Cov2/COVID-19 infection²⁰ which may cause endothelial dysfunction and

apoptosis in several organs leading to procoagulant conditions.²¹ Various disorders of coagulation were also described in patients infected by Sars-Cov2/COVID-19. It should be noted that hypercoagulation may occur in patients presenting a serious infection because of an excessive generation of thrombin and a dysfunction of fibrinolysis.²² We observed 17 patients with an aortic COV-AT, and in the patients presenting multiple COV-ATs (22% in this series), an aortic starting point was found in eight patients. As per our study, the aorta may be the origin of distal embolism related to the formation of mural thrombus.

An update of the Guidelines of the European Society for Vascular Surgery was made regarding the management of acute ischemia related to Sars-Cov2/COVID-19 and recommends the realization of a computed tomography angiography including

the aorta in its totality and the iliac arteries.²³ Avila et al. reviewed 95 studies of the literature and reported that the lower limb arteries and the abdominal or thoracic aorta were the most frequent localizations of acute thrombotic events of arterial origin.²⁴ This is in line with our results which found that the lower limbs and the aorta, thoracic or abdominal, were the most frequent localizations of formation of arterial thrombus.

More than half of our patients received anticoagulation only, without revascularization. Several factors influenced this decision. First of all, the efficacy of anticoagulation to obtain the almost integral regression of the COV-ATs.²⁵ It was also shown that anticoagulation was a protective factor against thrombotic events.²⁶ The other factors which justified medical care only were a clinical condition considered too serious to perform an operation, a clinically moderate ischemia which was not the focus or a decision of palliative care only. These elements are to be weighted with the poor general prognosis of the patients; 18 patients died within the 30 postoperative days. Among the revascularized patients, we also noted a high morbidity rate and a 22% rate of reintervention, higher than in an Italian study which found a 13% reintervention rate in a cohort of 20 patients.²⁷ The reintervention rate found in our study was definitely higher than those reported in recent studies carried out in the SarsCov2/COVID-19 infection context. Skripochnik et al. reported an overall of 7% rate of 30-day postoperative reintervention, while Davis et al. reported 30-day rates of reintervention of 2.8%, 3.29%, and 1.66% after endovascular, open, and hybrid treatment, respectively.^{28,29} These facts underline the highly thrombogenic and inflammatory character of the Sars-Cov2/COVID-19 infection. A strategy of privileging medical care in patients without a risk of immediate limb loss could be licit. We also observed the complete repermeabilization of an acute aorto-bi-iliac occlusion with intravenous heparin. Such a result is seldom obtained in cases of acute limb ischemia outside the context of Sars-Cov2/COVID-19 infection.³⁰

This study has several limitations. First, it is retrospective and based on data collected from electronic medical files, which were incomplete or missing for certain variables such as the paraclinical examinations made at the time of diagnosis or the arterial territories presenting an asymptomatic thrombosis. Second, the use of the ICD-10 codes to recruit the patients presenting an arterial thrombosis depends on the exhaustiveness of the entry of the codes and we cannot exclude that some patients were not included because of a missing code of arterial

thrombosis. However, the data were double-checked in all the departments of vascular surgery which usually treat these patients and we did not find any inadequacy. Third, the fact that some patients could have a diagnosis of Sars-Cov2/COVID-19 infection before or after being referred to one of the AP-HP hospitals could affect the capture of arterial events. Finally, we do not have long-term data and we cannot exclude that some patients present important functional sequelae. This should be studied in future work. In spite of these limitations, this study had a good exhaustiveness by not selecting the patients on the severity of their infection, as most previous studies did. It will also be necessary to revisit this study to compare our results with those observed during the other pandemic waves of Sars-Cov2/COVID-19 and know the impact of the different variants and the current strategies of anticoagulation on the incidence, the presentation, and the prognosis of COV-ATs.

CONCLUSION

Arterial complications of the Sars-Cov2/COVID-19 infection are rare. The aorta and the limb arteries are the privileged sites. The morbi-mortality of these patients is high. Future data will have to determine if routine anticoagulation decreases the incidence and the gravity of COV-ATs.

The data were extracted from the Clinical Data Warehouse of Greater Paris University Hospitals (Assistance Publique–Hôpitaux de Paris).

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