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LONG TERM FOLLOW-UP OF A MULTICENTRE COHORT OF COVID-19 PATIENTS WITH PULMONARY EMBOLISM: ANTICOAGULATION MANAGEMENT AND OUTCOMES

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BACKGROUND

Incidence of COVID-19 related pulmonary embolism (PE) varies between 1 and 20% of all patients hospitalized for SARS-CoV-2 infection [1, 2, 3]. The pathogenesis of these PE is not yet completely clear. Cytokine storm promoted by the inflammatory response to the viral infection seems to cause the deregulation of endothelial activity and a pro-coagulant state, triggering the state of thrombo-inflammation immediately observed during autopsies carried out in the early stages of the pandemic [4, 5, 6, 7]. It can be hypothesized that, once the inflammation has been controlled, the thrombotic risk is likely also attenuated. However, the cessation of the procoagulant state at the end of the infection is not certain [7]. Currently, the duration of anticoagulant therapy in these patients is not defined. Whyte et al described a cohort of patients with COVID-19 related PE, treated with anticoagulants for a median period of 3 months, with a median follow-up of 5 months and found a high rate of death (21%) with a low rate of recurrent venous thromboembolism (VTE) (1.7%) [8]. Ritchie et al reported the radiological resolution of the thrombus in 47 patients discharged after COVID-19 related PE. The mortality rate in this study was 19% and the median duration of anticoagulation was 5 months [9]. Langella et al followed 50 patients discharged after COVID-19 related PE treated with edoxaban for up to 50 days and demonstrated the safety and efficiency of this therapy [10]. According to the latest update of the American College of Chest Physicians (ACCP) guidelines, a thromboembolic event caused by a removable trigger can be treated with anticoagulant therapy for 3 months while the presence of a non-removable trigger or an unprovoked thromboembolic event calls for continuation in the anticoagulant therapy beyond 3 months (extended therapy) [11]. On the one hand, the removal of the trigger factor, the SARS-CoV-2 infection, could justify an anticoagulant therapy of only 3 months. However, the absence of clear evidence that the prothrombotic state caused by the viral infection is transient and not permanent, could justify extended anticoagulant therapy beyond 3 months. Since few follow-up data are available, it remains unclear whether prolonged anticoagulation could improve the long-term outcomes of patients with COVID-19 related PE. The objective of this study is to verify whether there are differences in long-term outcomes in patients with COVID 19-related PE treated with 3 months of anticoagulant therapy (non-extended therapy) and those treated with anticoagulated therapy beyond 3 months (extended therapy).

METHODS

We conducted a multicenter retrospective study carried out at 4 Italian centers between 1 March 2020 and 31 May 2021: the Alto Vicentino Hospital in Santorso, the Santa Maria della Misericordia Hospital in Rovigo, the Cittadella Hospital and the Tappeiner Hospital in Merano. The study was conducted in agreement with the local health authorities and according to the current rules of the local ethical committees.

All patients hospitalized for COVID-19 during the study period in the study centers were considered and their records were extracted from the respective computer databases. Through manual review of records by at least two physicians from each center, only patients diagnosed with COVID-related PE were selected for the study. The diagnosis of PE was made according to CT pulmonary angiogram findings whereas the diagnosis of COVID-19 was made only in the presence of a molecular swab positive for SARS-CoV-2.

Patients who died during hospitalization or before follow-up at 3 months, as well as patients with other indications for lifelong anticoagulation were excluded. Furthermore, patients under the age of 18 and pregnant patients were also excluded.

Patients who survived for 3 months after the embolic event and with a subsequent follow-up were divided into two study groups: patients treated with anticoagulant therapy for a maximum of 3 months (non-extended therapy) and patients treated with anticoagulation therapy for more than three months (extended therapy).

Outcome

The primary study outcome was the assessment of the recurrence of VTE (PE or deep vein thrombosis) during follow-up. Secondary outcomes were the risk of clinically overt hemorrhage as defined by the guidelines of the International Society of Hemostasis and Thrombosis [9] and all-cause mortality. Outcomes were determined at outpatient visits following hospitalization or through telephone interviews with each patient. The disease-free period for individual outcomes was considered as the time interval in months between patient enrollment (three months after the PE event) and follow-up contact or occurrence of the outcome.

Statistic analysis

Categorical variables were expressed as a percentage and number of events out of the total while the continuous variables were described as mean and standard deviation or as median and interquartile range according to their normality. Univariate comparisons were conducted respectively with Fischer's exact test or Student's or Mann-Whitney's T-test, when appropriate. Incidence rates and incidence ratios with 95% CI were estimated by organizing the data into an events-time table and estimating on this table a Poisson regression model with 1000 person-months as an offset. A p less than 0.05 was considered significant. All statistical analyzes were conducted with STATA 13 software.

RESULTS

During the study period there were 173 patients with COVID-19-related PE.

Of these, 16.2% (28/173) died during hospitalization, 7% (12/173) died after discharge but within the first 3 months, and 0.6% (1/173) were lost during follow-up and 20.2% (35/173) were excluded due to indication for lifelong anticoagulation.

The remaining 51.4% (97/173) of patients with COVID-related PE were enrolled in the study and the baseline characteristics of two study groups are listed in table 1.

Of these patients, 21.6% (21/97) did not continue anticoagulants beyond 3 months (non-extenced therapy), while the remaining 78.4% (76/97) continued treatment. For those treated with anticoagulation more than 3 months after discharge, the mean anticoagulation period was 9.6 months (SD 4.7). The majority of patients anticoagulated over 3 months were treated with direct oral anticoagulants (DOACS) instead of warfarin or low weight molecular heparin (88.2 vs 11.8%, p=0.003) and edoxaban and rivaroxaban were the most commonly used DOACs. Few differences in baseline characteristics appeared between the two groups: the diagnosis of chronic obstructive pulmonary disease (0% vs 21.1%, p=0.019) and the diagnosis of peripheral vascular disease (9.5% vs 35.5%, p=0.029).

Table 2 shows the study outcomes divided into the two study groups.

Recurrent VTE incidence in the study cohort during the follow-up period was 4.1% (4/97). Overall, the mean duration of anticoagulation for patients who had recurrent VTE was 10 months (SD 6.8) and 7.9 (SD 5.1) in patients without recurrence, p=0.446. No difference in the risk of recurrence of VTE after the episode of COVID-related PE was observed for the two treatment groups (4.7% vs 3.9%, p=0.604). In the only patient with PE in the 3 months group, the recurrence of PE occurred 20 months after the previous event and 17 months after the end of the 3 months anticoagulant therapy. None of the three VTE recurrences occurred during anticoagulant therapy in the

extended treatment group. Of these, one recurrence occurred at the immediate suspension of anticoagulant therapy and 13 months after the episode of COVID-related PE, while the other two occurred at 2 and 6 months, respectively, after the interruption of anticoagulant therapy and 8 and 24 months after the previous PE event.

The absence of differences between the two treatment groups was confirmed analyzing incidence rates and incidence ratios reported per 1000 patient-months. In the overall cohort, the incidence rate (IR) for recurrent VTE was 2.527 (95% CI 0.948-6.732). The IR in patients who did not continue anticoagulation beyond three months was 2.710 (95% CI 0.382-19.238) while in patients with anticoagulation beyond three months the IR was 2.471 (95% CI 0.797- 7,662). The incidence rate ratio (IRR) of with extended anticoagulant treatment was 0.912 (95% CI 0.073-47.871) not being protective against VTE recurrence, p=0.443. No differences between the two groups were reported also for secondary outcomes as shown in table 2. Clinical relevant hemorrhages were respectively a intracranial hemorrhage in the non-extended treatment group and two gastrointestinal bleeds and one intracranial hemorrhage in the extended treatment group.

DISCUSSION

The study attempted to analyze differences in the medium-long term outcomes of patients with COVID-related PE treated with short term or extended anticoagulant therapy. According to our current knowledge, the data presented here are the first available indications about extended anticoagulant treatment in patients with COVID-related PE. It would appear that there is no difference in terms of medium-long term thromboembolic recurrence between patients treated for three months or for extended periods beyond three months.

It is known that COVID-19 infection carries an important risk of associated thrombotic events [1, 2, 3]. Many mechanisms triggered by the infection and the consequent immune response are implicated in promoting a procoagulant state leading to thrombotic phenomena both in small and large blood vessels, especially the lungs [12, 13]. COVID infection is recognized as a risk factor for the development of a PE with an IRR of 12.01 (95% CI, 9.91 to 14.56) [14]. Orthopedic surgery for fractures and malignancies have respectively odds ratio (OR) of 8.34 (95% CI, 6.07-11.45) and 6.7 (95% CI, 5.2-8.6) for the development of PE [15, 16]. According to international guidelines, a PE secondary to similar risk factors if removable, should be treated for 3 months [11]. A recent literature review conducted by Kreidieh and colleagues suggested that oral anticoagulant therapy should be continued for at least 3 months after the acute event in patients with COVID-19-related PE, underlining however the absence of evidence and regarding the time interval over which the thrombotic risk is increased [17]. Whyte et al. reported a median duration of anticoagulation in patients discharged for COVID related PE of 3 months, lower than the one reported on our study. This finding could be explained by the high rate of death reported in Whyte's study (21%) while in our study mortality during early follow-up (first 3 months) was a criteria of exclusion. Whyte describes also a lower rate of recurrent VTE (1.7%) and this could be due to shorter follow-up after therapy suspension. No comparison between extended or not-extended therapy was performed [8].

Resolution of the infectious event and the supposed cessation of the COVID-related inflammatory state, could classify COVID infection as a removable risk factor. Elevated D-dimer values observed at emergency department admission in patients with sars-CoV-2, both in the presence and absence of pathological thromboembolic states, seem to progressively attenuate in patients with benign course of COVID [18]. The processes that lead to an increase in COVID-related thrombotic risk seem strongly linked to the present inflammatory state and it seems reasonable to think of a reduction in thrombotic risk with containment of the infection itself.

The study has some limitations: firstly, the nature of the study is subject to the typical biases for this class of retrospective analysis; secondly, the not extended follow-up period, obviously due to the novelty of the disease, did not allow for higher outcome rates to be achieved; thirdly, the cohort of patients, despite being the first available and coming from different centers, remains numerically limited; fourthly, continuation of oral anticoagulant therapy beyond three months has not been standardized and therefore there are differences in the extended therapy group; fifthly, we didn't registered time to therapeutic range in patients treated with warfarin; sixthly, indicator of PE risk at presentation was not recorded and lastly, the decision to continue anticoagulation was left to physician discretion.

CONCLUSION

The prolongation of oral anticoagulant therapy beyond 3 months for treatment of a COVID-related PE does not appear to be associated with differences in the risk of recurrence of PE or with the risk of clinically evident bleeding compared with treatment of 3 months or less. Continuing anticoagulant therapy beyond 3 months would not seem to provide better medium-long term outcomes in COVID-19 patients. Given the lack of clinical evidence and the importance of providing standardized and safe therapy, further prospective studies are needed to confirm these preliminary data.

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Table 1

Variable	Total	Not extended anticoagulation	Extended anticoagulation	P
Patients, n (%)	97 (100)	21 (21.6)	76 (78.4)	
Gender, n (%)				0.065
Female	21 (21.6)	3 (14.3)	28 (36.8)	
Male	76 (78.4)	18 (85.7)	48 (63.2)	
Age, years	66.4 (12.7)	60.9 (13.1)	66.7 (12.4)	0.067
Clinical characteristics, n (%)				
Obesity	20 (20.6)	4 (19)	16 (21.1)	1.000
Previous VTE	13 (13.4)	2 (9.5)	11 (14.5)	0.728
COPD	16 (16.5)	0 (0.0)	16 (21.1)	0.019
Ischemic cardiomiopathy	7 (7.2)	0 (0.0)	7 (9.2)	0.341
Vascular disease	29 (29.9)	2 (9.5)	27 (35.5)	0.029
Chronic kidney disease	12 (12.4)	2 (9.5)	10 (13.2)	1.000
Arterial Hypertension	66 (68)	11 (52.4)	55 (72.4)	0.112
Diabetes	23 (23.7)	2 (9.5)	21 (27.6)	0.145
Concomitant DVT, n (%)	27 (27.8)	5 (23.8)	22 (28.9)	0.786
Anticoagulant at discharge, n (%)				0.003
Warfarin/LWMH	18 (18.6)	9 (42.9)	9 (11.8)	
DOAC	79 (81.4)	12 (57.1)	67 (88.2)	
Apixaban	18 (23)			
Dabigatran	6 (8)			
Edoxaban	29 (37)			
Rivaroxaban	26 (33)			

Table 2.

Outcomes	Not extended anticoagulation	Extended anticoagulation	p
VTE recurrences, n (%)			1.000
No	20 (95.2)	73 (96.1)	
Yes	1 (4.8)	3 (3.9)	
Clinical relevant hemorrages, n (%)			1.000
No	20 (95.2)	73 (96.1)	
Yes	1 (4.8)	3 (3.9)	
Death during FU, n (%)			1.000
No	20 (95.2)	73 (96.1)	
Yes	1 (4.8)	3 (3.9)	

Declaration of interest statement
I do not have any conflict of interest to declare.

Declaration of interests

x The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

HIGHLIGHTS

PE during hospitalization for COVID-19 seems to be provoked by sars-cov2 infection.

3 months of anticoagulation in these patients seems to be safe and efficacious.

Extended anticoagulation in these patients does not improve outcomes.