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Venous thromboembolism in critically ill patients affected by ARDS related to COVID-19 in Northern-West Italy

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Abstract. – OBJECTIVE: Coronavirus disease 2019 (COVID-19) is an emerging infectious disease that was first reported in Wuhan, China, and has subsequently spread worldwide. An association between increased venous thromboembolism in patients with pneumonia-related to COVID-19 has not yet been well described.

PATIENTS AND METHODS: We aimed to illustrate cases of pulmonary thromboembolism in patients with acute respiratory distress syndrome related to COVID-19 treated in our intensive care unit. The medical records of patients affected by COVID-19 with acute respiratory distress syndrome in our institute from 1/3/2020 to 31/3/2020 were retrospectively reviewed.

RESULTS: Our center registered a high prevalence of thromboembolic events among 62 patients affected by acute respiratory distress syndrome related to COVID-19 despite a regular antithrombotic prophylaxis. Out of these, 32 patients were transferred to other hospitals, and 30 were treated in our center. Venous thromboembolism was registered in 12 (19.3%) cases. In particular, 11 diagnoses of pulmonary embolism and 1 diagnosis of deep vein thrombosis were formulated. We described a case series of venous thromboembolism in nine patients treated in our Intensive Care Unit (ICU). Main pulmonary arteries were always involved in these patients. None of them died.

CONCLUSIONS: In conclusion, critically ill patients with ARDS related to COVID-19 may have an increased risk of VTE that could be a leading cause of mortality. These patients require a high index of clinical suspicion and an accurate diagnostic approach, in order to immediately start an appropriate anticoagulant treatment.

Key Words:
COVID-19, Acute Respiratory Distress Syndrome, Pulmonary embolism, Deep vein thrombosis.

Introduction

Coronavirus disease 2019 (COVID-19) was first described in Wuhan, China, and has subsequently spread worldwide[1]. Its outcome seems to be determined by the extent of the host immune system imbalance. The primary immune response usually leads to viral clearance. However, for unclear reasons, the secondary immune response may be exaggerated and, in some cases, may lead to multiple organ failure, acute respiratory distress syndrome (ARDS) and death[2]. This exaggerated response is known as cytokine release syndrome (CRS), and it has an important role in the activation of coagulation. Clinical observations have shown that patients with severe COVID-19 pneumonia have coagulation dysfunction[3,4].

In recent studies, thromboembolic events were registered in patients with COVID-19 pneumonia[5-7].

We retrospectively described cases of venous thromboembolism (VTE) in patients with ARDS related to COVID-19 that have been treated in our intensive care unit (ICU).

Patients and Methods

We retrospectively reviewed the medical records of patients affected by ARDS related to

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COVID-19 in our ICU from 1/3/2020 to 31/3/2020. COVID-19 diagnosis was made by clinical features and nose swab positivity. ARDS diagnosis followed the Berlin definition criteria[8]. All patients admitted to our ICU were intubated and mechanically ventilated. After the stabilization of clinical parameters, some patients were transferred to other hospitals due to the overwhelming inflow of COVID-19 patients. Information about the outcome of transferred patients was obtained by interview over the phone. All patients treated in our center were handled in accordance with guidelines on the management of critically ill adults with COVID-19[9]. All described patients received antithrombotic prophylaxis with Enoxaparin 100 U/kg/24h. Patients more than 80 kg received Enoxaparin 5000 U twice a day. Specific antiviral therapy includes Lopinavir/Ritonavir and hydroxychloroquine. In case of clinical signs of bacterial coinfection confirmed by procalcitonin elevation and/or cultural positivity, antibiotic therapy was introduced.

Results

Alessandria hospital ICU admitted 62 patients with diagnosis of ARDS related to COVID-19. In this population, 12 VTE were registered (19.3%), in particular, 11 diagnoses of pulmonary embolism (PE) and one of deep vein thrombosis (DVT) were made (Figure 1). Only 25% of patients complicated by thromboembolism were represented by females and patients' median age was 53 (50-59) years old.

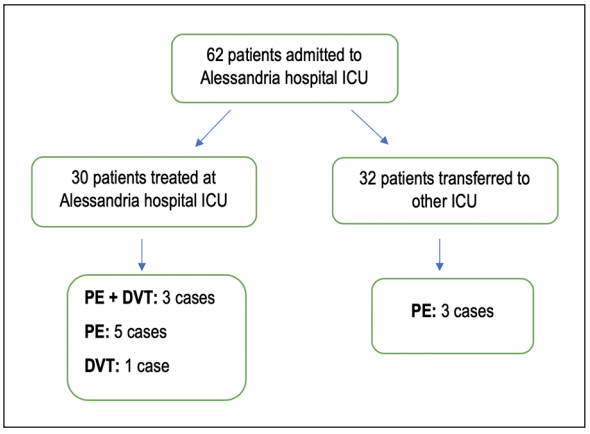

Figure 1. Algorithm of thromboembolic complication distribution in intubated patients with moderate or severe ARDS related to Covid-19. All pulmonary embolism diagnoses were confirmed by CT angiography except one, that was confirmed by transesophageal ultrasound due to patients' very high hemodynamic instability. Legend: PE, pulmonary embolism; DVT, deep vein thrombosis.

Among 62 patients, 32 patients were transferred to other hospitals and 30 were treated in our center. Nine of reported diagnosis of VTE were made in our ICU; thus, the prevalence of VTE registered in our center is 30%. Thrombotic events took place on average after 6[4-9] days after ICU admission and 14[11-15] days after symptoms onset. Demographic data and disease severity are shown in Table I. Principal clinical parameters registered the day when VTE was diagnosed are summarized in Table II and patients' laboratory test results are described in Table III.

Only two patients (Patient 1 and Patient 3) with PE registered important hemodynamic instability which led to the diagnosis. In other cases, the clinical suspicion stemmed from alteration of gaseous exchanges and/or hemodynamic values not fully explained by the clinical picture. In the vast majority of patients, D-Dimer values were increased the day of diagnosis. However, only in five cases these values were markedly altered (Table III). In all patients with PE main pulmonary arteries were involved (Table II). In Figure 2, computed tomography scan imaging of ARDS and pulmonary emboli related to patient 1 are shown. DVT was associated to PE in three cases and in one case it is the only VTE finding. All of these patients were treated with the load and subsequent continuous infusion of Heparin. In addition, in patient 3, thromboendoarterectomy was performed directly in ICU and in patient 1 i.v. thrombolytic therapy was administered. None of the described patients died.

Discussion

A correlation between increased VTE events and ARDS related to COVID-19 was observed. Out of these 62 patients 19.3% had a thromboembolic complication. Several factors contribute to the increase of VTE risk in ICU patients. Recognized risk factors for DVT are related to one or more elements of Virchow's triad: flow stasis, vessel injury and hypercoagulability. Flow stasis, due to prolonged immobility, mechanical ventilation, use of sedatives and neuromuscular block plays a major role in ICU patients[10-12]. Moreover, in this population, vessel injury may be due to catheter insertion in central veins and hypercoagulability may be induced by sepsis or

Table I. Demographic and clinical history of patients at ICU admission who subsequently developed thromboembolic events.

	Gender	Age (years)	BMI	Comorbidities	PaO_2/FiO_2	PEEP (cm H_2O)	Driving pressure (cm H_2O)	SAPS score
Patient 1	Female	53	32	Obesity Hypertension	150	15	9	32
Patient 2	Male	63	33	Obesity	150	15	8	33
Patient 3	Male	59	29	Absent	180	14	10	29
Patient 4	Male	58	25	Rheumatoid arthritis Hypertension Rectal cancer (currently in chemotherapy)	80	15	12	25
Patient 5	Male	51	26	Absent	105	15	12	26
Patient 6	Male	49	26	Epilepsy	90	14	11	26
Patient 7	Female	50	24	Endometriosis	130	14	11	36
Patient 8	Male	50	27	Absent	70	14	11	28
Patient 9	Male	68	26	Hypertension				

Legend: BMI, body mass index; DM, diabetes mellitus; PEEP, positive end-expiratory pressure; Driving Pressure = Plateau pressure – PEEP; SAPS, simplified acute physiology score.

dehydration[10,11]. Under such pathophysiological conditions, the occurrence of additional DVT risk factors related to COVID-19 can precipitate thrombosis. The impact of COVID-19 on blood clotting has not yet been completely investigated. However, we know that CRS is thought to play an important role in disease severity[13]. CRS is associated with increased levels of inflammatory cytokines and activation of T lymphocytes, macrophages, and endothelial cells. In particular, interleukin 6 and tumor necrosis factor seems to hold a key role leading to vascular leakage and to activation of complement, tissue factor and coagulation cascade[14,15]. Thus, the high prevalence of the thrombotic events in patients with ARDS by COVID-19 may be induced by cross-talking between immune and coagulation systems.

PE is stratified into massive, sub-massive, and low-risk based upon the presence or absence of hypotension and right ventricular dysfunction or dilation. This stratification is associated with mortality risk[16]. However, many patients, including those with large PE, have mild symptoms or are asymptomatic[17]. This nonspecific presentation may be magnified in patients mechanically ventilated with ARDS COVID-19 related. This is due to an overlap between PE manifestations and COVID-19 ARDS clinical signs. In fact, alteration of arterial blood gases, D-dimer levels, and echocardiography are neither sensitive nor specific as diagnostic of suspected PE in this situation. All our patient at ICU admission had severe or moderate ARDS and increased of D-dimer values. Only in five cases, D-Dimer was markedly increased on the day of diagnosis. All patient on the day of diagnosis were deeply sedated and treated with high PEEP and aminic support before PE suspect. Only patient 1 and patient 3 registered severe hemodynamic instability and deterioration of respiratory function due to PE (Table II). Instead, Patient 2 registered moderate hemodynamic instability with difficult control of blood pressure without impact on gas exchange. Those three cases of PE stemmed a clinical suspicion of VTE in other COVID-19 patients. Thus, even if other patients registered only minor alteration of gaseous exchanges and/or hemodynamic alterations, PE diagnosis was made. Moreover, considering other VTE risk factors of our patients, Table I shows that only two subjects were obese and only one patient had a history of cancer.

Our experience emphasizes that identifying a PE in patients with COVID-19 ARDS is really challenging. On the other hand, a delay in diagnosis of PE is associated with a poor outcome[18]. As a consequence, these patients require a high

Table II. Clinical parameters of patients the day of diagnosis of thromboembolic event, diagnostic confirmation, treatment and outcome 48h after the diagnosis.

Patient ID (diagnosis of VTE)	Days from ICU admission to VTE	Days from symptoms onset to PE/DVT	Clinical parameters at diagnosis of VTE					Diagnostic confirmation	Treatment	Clinical parameters 48 h after diagnosis of VTE				
			P/F	PEEP	DP	MAP	Aminic support (mcg/kg/min)			P/F	PEEP	DP	MAP	Aminic support (mcg/kg/min)
Patient 1 PE+DVT	4th	6th	50	15	10	72	NA 0.3	CT pulmonary angiography: filling defects of left branches of pulmonary artery and lobar, segmental and subsegmental branches of pulmonary artery of both lungs. Doppler US lower extremities: DVT of gastrocnemius medial veins bilaterally	Alteplase 100 mg Heparin 80 U/kg and continuous infusion of 15 U/kg/h	234	16	9	106	Absent
Patient 2 PE	6th	15th	177	14	8	86	NA 0.1 Dobut1.1	CT pulmonary angiography: Massive pulmonary embolism involving left and right pulmonary arteries associated to embolisms of lobar segmental and subsegmental branches of both pulmonary arteries.	Heparin 80 U/kg and continuous infusion of 15 U/kg/h	281	14	8	89	NA 0.1 Dobut 1.0
Patient 3 PE+DVT	3rd	15th	106	14	10	91	NA 0.25 Dobut 2.3	Transesophageal cardiac us: Massive pulmonary embolism with presence of thrombotic material in right atrium and right pulmonary artery Doppler US lower extremities: bilateral, floating deep vein thrombosis of popliteal arteries	Thromboembolectomy conducted during resuscitations maneuvers in CPB and in median longitudinal sternotomy performed in ICU	327	10	11	82	Absent
Patient 4 PE	3rd	11th	163	16	12	74	Dobut 2	CT pulmonary angiography: filling defects of lobar, segmental and subsegmental branches of pulmonary right, lower lobe	Heparin 80 U/kg and continuous infusion of 15 U/kg/h	122	18	11	88	NA 0.15, Dobut 5
Patient 5 PE	4th	10th	217	14	9	82	NA 0.04	CT pulmonary angiography: filling defects of right pulmonary artery, and bifurcation of left principal pulmonary artery. Peripherally, bifurcation of right pulmonary artery is involved.	Heparin 80 U/kg and continuous infusion of 15 U/kg/h	205	12	9	86	NA 0.06
Patient 6 PE	9th	18th	190	12	10	69	NA 0.3	CT pulmonary angiography: filling defects in right, lower lobe arterial branches.	Heparin 80 U/kg and continuous infusion of 15 U/kg/h	288	12	11	67	NA 0.3
Patient 7 PE+DVT	9th	14th	79	15	9	88	NA 0.5	CT pulmonary angiography: filling defects of lower branch of right pulmonary artery and is extended to arterial branches of right lower and medium lobes Doppler US lower extremities: DVT of left medial gastrocnemius vein	Heparin 80 U/kg and continuous infusion of 15 U/kg/h	182	14	9	79	NA 0.3
Patient 8 PE	6th	14th	106	14	9	80	NA 0.04	CT pulmonary angiography: submassive pulmonary embolism involving right pulmonary artery and segmental and subsegmental branches of medium and lower lobes of right lung	Heparin 80 U/kg and continuous infusion of 15 U/kg/h	210	14	10	63	Absent
Patient 9 DVT	9th	18th	194	14	12	81	NA 0.2	Doppler US: Bilateral thrombosis of gastrocnemius veins, partial involvement of popliteal veins. Femoral veins distended bilaterally.	Heparin 80 U/kg and continuous infusion of 15 U/kg/h	217	12	11	88	NA 0.1

Legend: VTE, venous thromboembolism; PE, pulmonary embolism; DVT, deep vein thrombosis; ICU, intensive care unit; P/F, PaO_2/FiO_2; DP, driving pressure; MAP, mean arterial pressure; NA, Noradrenaline; Dobut, Dobutamine; CT, computed tomography.

index of clinical suspicion. So, an appropriate treatment with anticoagulation can be initiated in a timely fashion.

One of the hypotheses to explain a large discrepancy between low hemodynamic alterations of PE and the radiological picture found in many of our patients may be a significant vasodilation of pulmonary circulation. Indeed, Zhao et al[19] showed that most patients with COVID-19 pneumonia have a vascular enlargement of the pulmonary lesion that might have been caused by an acute inflammatory response. This would allow to not dramatically increase the resistance of the pulmonary circulation with consequent lower hemodynamic impact.

As shown in Table II, VTE diagnosis has been confirmed by CT scan with typical alterations for all patients except case 3 suffering sudden cardiac arrest. In this case diagnostic confirmation was obtained performing transesophageal cardiac ultrasound during cardiopulmonary resuscitation. In the majority of patients, PaO_2/FIO_2 markedly improved 48 hours after diagnosis and treatment of PE.

Our data confirms previous studies that describe thromboembolic events in patients with COVID-19 pneumonia[5-7]. Similar data can be found in other viral pulmonary infections like ARDS related to H1N1[20,21]. In particular, Obi et al[20] demonstrate a high incidence of VTE (44%)

Table III. Lab test results related to the ICU patients' admission, the day of diagnosis of thromboembolic event and 48 hours after the diagnosis.

Patient ID (diagnosis of VTE)		WBCs ($x10^3$/mcl)	Lymph ($x10^3$/mcl)	RCP (mg/dl)	PCT (ng/ml)	PLTS ($x10^3$/mcl)	PTT ratio	INR	Fibrinogen (mg/dl)	ATIII (%)	D-dimer (mcg/ml)
Patient 1	ICU admission	9790	558	5.69	0.52	477	0.84	1.03	598	87	2
(PE+DVT)	Day of PTE diagnosis	8750	708	4.67	0.12	336	1.35	1.1	214	88	>40
	48 h after PTE	15160	879	19.85	0.56	377	1.55	1.25	761	87	2.5
Patient 2	ICU admission	3600	590	6.1	0.12	181	1.07	1.05	704	87	1.78
(PE)	Day of PTE diagnosis	6970	1038	15.41	0.26	262	1.04	1.05	719	85	9.36
	48 h after PTE	10490	153	23.69	0.49	311	1.69	1.03	806	82	4.65
Patient 3	ICU admission	11850	1398	17.11	0.53	508	1.24	1.28	874	65	1.29
(PE+DVT)	Day of PTE diagnosis	21360	1794	7.32	0.38	263	2.43	1.3	255	34	>40
	48 h after PTE	15370	891	20.03	58.76	165	1.86	1.5	451	65	3.77
Patient 4	ICU admission	16300	521	22.10	/	290	1	1.48	742	78	8.76
(PE)	Day of PTE diagnosis	10820	508	25.16	/	210	1.11	1.44	472	66	12
	48 h after PTE	18360	734	44.96	2.01	239	2.21	1.45	695	70	6.65
Patient 5	ICU admission	5.890	630	17.75	0.37	318	1.07	1.17	743	65	3.32
(PE)	Day of PTE diagnosis	4700	870	16.56	/	316	1.08	1.08	796	62	2.74
	48 h after PTE	9470	947	19.64	0.52	331	1.59	1.07	779	69	2.04
Patient 6	ICU admission	6230	492	17.48	/	351	1.05	1.18	747	95	2.33
(PE)	Day of PTE diagnosis	9700	446	23.56	0.81	196	1.3	1.11	484	57	3.42
	48 h after PTE	8850	1115	15.51	0.42	275	2.43	1.05	487	70	5.15
Patient 7	ICU admission	6310	473	9.37	0.87	225	1.00	1.09	596	87	1.00
(PE+DVT)	Day of PTE diagnosis	9810	1030	31.24	/	313	1.65	1.07	501	54	10.18
	48 h after PTE	10290	1533	26.54	0.68	315	2.14	1.06	583	57	3.88
Patient 8	ICU admission	12560	741	13.11	0.37	226	0.89	1.06	724	70	0.84
(PE)	Day of PTE diagnosis	13020	690	31.47	1.09	266	0.97	1.05	824	72	12.45
	48 h after PTE	15390	661	14.74	0.51	278	1.45	0.97	666	80	5.96
Patient 9	ICU admission	6660	273	89.3	4.1	152	1.12	1.09	774	91	1.43
(DVT)	Day of PTE diagnosis	16710	401	94.2	2.4	255	1.31	1.37	1115	70	3.93
	48 h after PTE	16850	775	90	4.6	261	1.85	1.24	839	76	0.27

Legend: VTE, venous thromboembolism; PE, pulmonary embolism; DVT, deep vein thrombosis; ICU, intensive care unit; WBCs, white blood cells; Lymph, Lymphocytes; RCP, reactive C protein; PCT, procalcitonin; PLTS, platelets; PTT ratio, partial thromboplastin time; INR, international normalized ratio; ATIII, antithrombin III.

in observational cohort study of 36 critically ill patients with H1N1 ARDS. In this study PE was described in 10 patients and DVT in other 10 patients. Impressively this high rate of VTE was encountered despite antithrombotic prophylaxis. Cui et al[7] recently showed that 25% of patients with severe COVID-19 pneumonia admitted to ICU developed lower extremity venous thrombosis. The DVT group had older age, lower lymphocytes count, longer APTT and higher D-dimer.

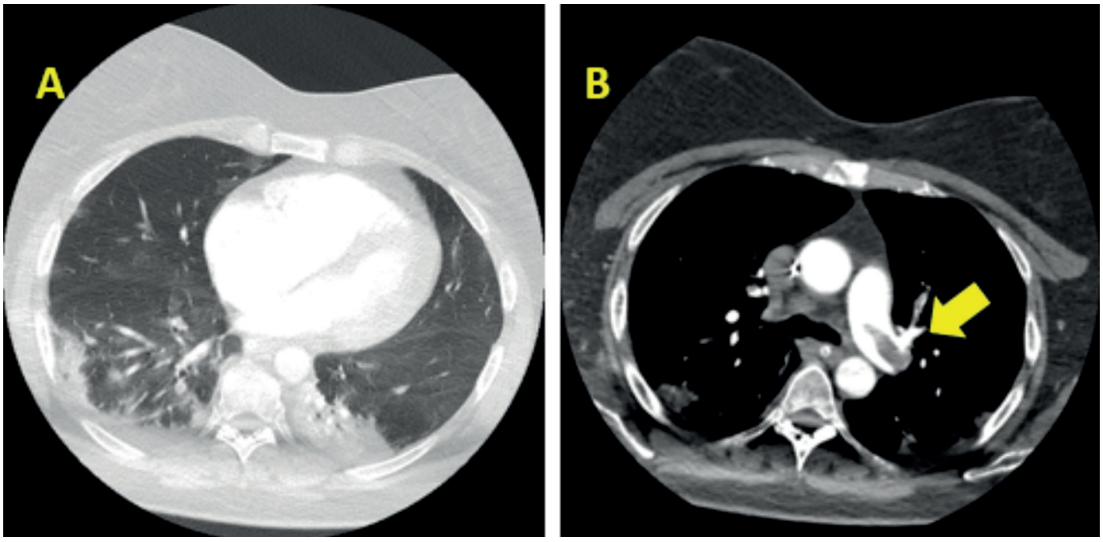

Figure 2. Computed tomography scan imaging of ARDS associated to COVID-19 and pulmonary emboli related to patient 1. **A,** Widespread bilateral consolidation and scattered patchy ground-glass opacities are concerning for ARDS. **B,** Pulmonary embolus across the bifurcation of pulmonary trunk is noted, as indicated by the *arrow.*

Moreover, two recent case reports describe three patients with COVID-19 pneumonia complicated by acute pulmonary embolism confirmed by CT pulmonary angiography showing bilateral filling defects involving lobar, segmental, and subsegmental branches of the pulmonary artery[5,6]. Lower-limb compression ultrasonography was negative in one patient[5] and was not reported in two other patients[6].

The concept of pulmonary thrombosis has been recently proposed as clinical pathological entity distinct from pulmonary embolism[22,23]. According to this hypothesis coagulative response induced by COVID-19 may promote a local disseminated intravascular coagulation and a pulmonary intravascular thrombosis. This pathophysiological mechanism may explain the presence of thrombotic material in pulmonary circulation in four of our patients, who did not show concomitant evidence of DVT. Thus, in our view, patients affected by ARDS related to COVID-19 may develop both pulmonary embolism and pulmonary thrombosis[22], even though this hypothesis needs further investigation.

Conclusions

Critically ill patients with ARDS related to COVID-19 may have increased risk of VTE, disseminated intravascular coagulation, pulmonary intravascular thrombosis and PE, which may represent a leading cause of mortality. Thus, these patients require a high index of clinical suspicion and an accurate diagnostic approach, in order to immediately start an appropriate anticoagulant treatment. Further studies are now needed to better understand the relationship between increased thrombotic events and ARDS related to COVID-19.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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