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The clinical spectrum of pulmonary thromboembolism in patients with coronavirus disease-2019 (COVID-19) pneumonia: A European case series

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ABSTRACT

Purpose: To describe the clinical characteristics and outcomes of coronavirus disease-2019 (COVID-19)-associated pulmonary thromboembolism (PTE).

Materials and methods: A case series of five patients, representing the clinical spectrum of COVID-19 associated PTE. Patients were admitted to four hospitals in Germany, Italy, and France. Infection with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was confirmed using a real-time reverse transcription polymerase chain reaction test.

Results: The onset of PTE varied from 2 to 4 weeks after the occurrence of the initial symptoms of SARS-CoV-2 infection and led to deterioration of the clinical picture in all cases. PTE was the primary reason for hospital admission after a 2-week period of self-isolation at home (1 patient) and hospital readmission after initial uncomplicated hospital discharge (2 patients). Three of the patients had no past history of clinically relevant risk factors for venous thromboembolism (VTE). Severe disease progression was associated with concomitant increases in IL-6, ferritin, and D-Dimer levels. The outcome from PTE was related to the extent of vascular involvement, and associated complications.

Conclusion: PTE is a potential life-threatening complication, which occurs frequently in patients with COVID-19. Intermediate therapeutic dose of anticoagulants and extend thromboprophylaxis are necessary after meticulous risk-benefit assessment.

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List of abbreviations

aPTT	Activated partial thromboplastin time
BE	Base excess
ECMO	Extra corporeal membrane oxygenator
GGO	Ground glass opacities
CTA	Computer Tomographic Angiography
COVID-19	Corona virus disease-2019
DVT	Deep vein thrombosis
ICU	Intensive care unit
IL	Interleukin

IMC	Intermediate Care Unit
INR	International normalized ratio
I.U.	International unit
IQ	interquartile range
LMWH	Low molecular weight heparin
MAP	Mean arterial pressure
PT	Prothrombin time
PAP	Pulmonary artery pressure
PTE	Pulmonary thromboembolism
RT-PCR	Real-time reverse transcription polymerase chain reaction
r-tPA	Recombinant tissue-type plasminogen activator
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
TT	Thrombin time
VTE	Venous thromboembolism

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1. Introduction

Pulmonary thromboembolism (PTE) is a potentially fatal complication that has been frequently reported in patients with coronavirus disease-2019 (COVID-19) [1–4]. Infection with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is associated with coagulation abnormalities [4–7], which predispose to considerable procoagulant effects [4,5,8].

In this report, we describe the clinical characteristics and outcomes of five patients admitted to four hospitals in Germany, Italy, and France with COVID-19-associated PTE and discuss the diagnostic and therapeutic implications of PTE in COVID-19.

2. Main text

2.1. Case series

2.1.1. Case #1

A 66-year-old male patient was admitted to the interdisciplinary intensive care unit (ICU) of Jena University Hospital with rapidly progressive dyspnea and swelling of the right thigh. Two weeks prior to ICU admission, the patient had complained of cough, malaise, and fever up to 38 °C. He self-isolated at home after being tested positive for SARS-CoV-2 using a real-time reverse transcription polymerase chain reaction (RT-PCR) test. The patient was known to have systemic hypertension, treated with an angiotensin converting enzyme inhibitor.

Initial clinical examination on admission to the ICU revealed marked dyspnea and arterial oxygen saturation (SO₂) of 92% (with a 10 L/min oxygen mask). Transthoracic echocardiography showed a markedly dilated right ventricle and paradoxical septal motion. Bilateral peripheral ground glass opacities (GGO) were observed on the computed tomography angiography (CTA) scan, together with bilateral central PTE with subtotal occlusion of the left lower lobe and right upper lobe arteries, and multiple segmental occlusions of the right upper and lower lung lobes (Fig. 1). A right femoral vein thrombosis was identified on compression ultrasonography of the lower limb. Angiographic ultrasound-enhanced lysis was performed with infusion of recombinant tissue-plasminogen activator (r-tPA) and heparin (800–1200 IU/h).

Twenty-four hours following ICU admission, the patient's dyspnea and preexisting hypoxemia worsened despite oxygen therapy. Non-invasive ventilation was started but when there was no marked improvement in the respiratory condition after 2 h, tracheal intubation and controlled invasive mechanical ventilation were necessary and prone positioning was started. The hemodynamic situation deteriorated rapidly after intubation and a CTA scan revealed progression of the PTE into the segmental arteries of the right upper lobe and both lower lung lobes, in addition to progression of the GGO bilaterally. Systemic lysis

was performed using intravenous r-tPA. Over subsequent days, the patient developed progressive multi-organ failure (Table 1). Despite maximal supportive therapy, the patient died on the 6th day in the ICU due to therapeutic refractory shock and multi-organ failure.

2.1.2. Case #2

A 65-year-old male patient presented to the emergency room of Ospedale Guglielmo da Saliceto (Piacenza, Italy) with thoracic pain and dyspnea. He had no history of comorbid conditions. Two weeks prior to his emergency room presentation, he had been discharged home from the same hospital, where he had been admitted for 7 days because of a 10-day history of cough and fever. A CT scan of the lungs at that time had shown bilateral peripheral GGO (Fig. 1 of the electronic supplement material) and a nasopharyngeal swab confirmed SARS-CoV-2 infection using RT-PCR. During this presentation to the emergency room, his SO₂ was 82% while breathing ambient air. The initial blood gas analysis showed mild hypoxemia (arterial partial pressure of oxygen (PaO₂) 73 mmHg) on 4 L/min oxygen via nasal prongs. Transthoracic echocardiography showed mild dilatation of the right ventricle, with preserved left ventricular function (Fig. 2 of the electronic supplement material). Compression ultrasound of the lower extremities excluded deep vein thrombosis. A CTA scan showed evidence of subtotal occlusion of the right pulmonary artery at the level of the middle lung lobe and subsegmental obstruction at the level of the inferior lobes (Fig. 2). The patient was admitted to the intermediate care unit (IMC) and treated with 8000 IU b.i.d. of low molecular weight heparin (LMWH, enoxaparin sodium) and standard oxygen therapy. The clinical picture improved over the subsequent 5 days and the patient was discharged home after resolution of the respiratory dysfunction to continue therapeutic anticoagulation using LMWH.

2.1.3. Case #3

A 56-year-old male patient was admitted to the emergency room of Ospedale Guglielmo da Saliceto (Piacenza, Italy) because of sudden-onset, progressive dyspnea. He had no past history of comorbid conditions. Two days before presentation, he had been discharged from the same hospital, where he had been admitted for 13 days because of confirmed SARS-CoV-2 infection with dyspnea. A CT scan of the lungs had shown extended bilateral GGO and inferior lobar pneumonia in the right lung (Fig. 3 of the electronic supplement material).

At his subsequent presentation to the emergency room, his oxygen saturation was 88% while breathing ambient air. Arterial blood gas analysis showed moderate hypoxemia (pH 7.45, arterial partial pressure of carbon dioxide (PaCO₂) 37 mmHg, PaO₂ 86 mmHg on 12 L/min). Lung CTA confirmed thromboembolic obstruction of lobar and segmental vessels of the pulmonary artery of both superior and inferior lobes and of the middle lobe (Fig. 4 of the electronic supplement material). The

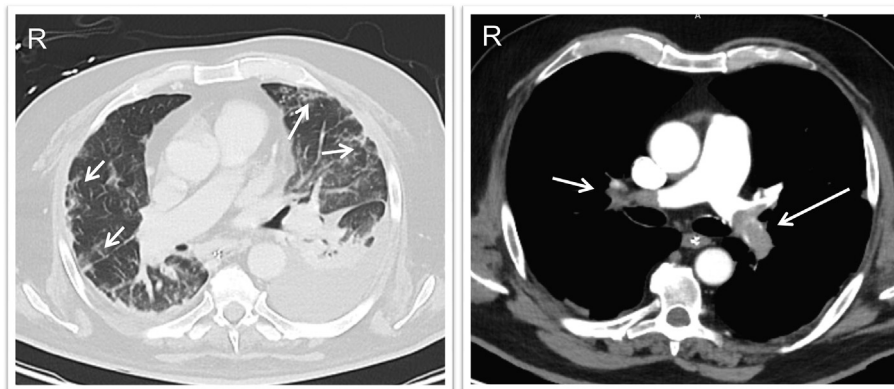


Fig. 1. Computed tomography scan images (case #1), showing bilateral ground glass opacities (arrows, left panel) and central thrombi occluding the main pulmonary arteries bilaterally (arrows, right panel).

Table 1

Case #1: Laboratory parameters during the ICU stay.

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
C-reactive protein, mg/dL	85	82	101	137	135	89
Procalcitonin, ng/ml	0.18	0.21	4.34	16	17	7.2
Interleukin-6, pg/ml	47	76	776	168	401	2464
Leukocyte count, $\times 10^3/\mu\text{L}$	7.1	7.2	18.1	10.1	14.2	13.6
Lymphocyte count, $\times 10^3/\mu\text{L}$	0.87		.	0.68		
Creatinine, $\mu\text{mol/l}$	83	68	194	303	364	293
Urea, mmol/l	5.6	5.8	6.8	7.2	8.5	6.3
Bilirubin, $\mu\text{mol/l}$	15	15	38	43	74	116
Thrombocytes, $\times 10^3/\mu\text{L}$	176	154	155	193	120	54
aPTT, sec	25–39	24–71	48–150	74–61	70–80	65
Arterial blood gases						
pH, range	7.47	7.18–7.49	7.18–7.29	7.17–7.29	7.18–7.38	7.24–7.33
PCO ₂ , kPa, range	4.23–5.41	4.76–11.1	6.66–10.7	5.65–7.67	5.57–7.67	4.88–6.56
PO ₂ , kPa, range	11.4–14.6	6.56–15.5	10.8–17.8	8.1–21.1	10–19.9	9.6–9.8
SO ₂ %, range	97	85–98	94–98	91–99	94–99	91–92
Serum lactate, mmol/L, range	2.5	1.5–6.2	6.2–11.6	5.7–13.3	6.9–20	20–21
Ferritin, $\mu\text{g/l}$	1267	1029	30,116	170,694	43,615	24,688
Troponin I, pg/ml	96.5	91.6	959	483	4227	4113
BNP, pg/ml	289	–	16,389	1212	695	–
LDH, $\mu\text{mol/l}$	6.4	8.11	41.2	132	58	41
ASAT, $\mu\text{mol/l}$	0.69	0.9	23.2	170	94.9	85.3
ALAT, $\mu\text{mol/l}$	0.52	0.54	11.5	46.4	32	55.6
Gamma GT, $\mu\text{mol/l}$	1.38	1.26	3.46	2.78	2.39	1.46
GLDH, $\mu\text{mol/l}$	54	69	1049	34,800	30,398	13,932
AT III, %	70	54	37	33	10–60	32
D-Dimer, $\mu\text{g/l}$	857	31,608	65,448	48,588	17,605	8682
Fibrinogen, g/l	3.6	3	2.2	2.3	0.8	1
Blood sugar, mmol/l, range	16.7–9.4	8.9–15.6	6.2–10.2	5.3–7.3	3.9–6.4	5.1–5.4

aPTT: activated partial thromboplastin time, ALT: Alanin-Aminotransferase, AST: Aspartat-Aminotransferase, AT: antithrombin, BNP: B-Typ Natriuretisches Peptid, LDH: lactate dehydrogenase.

patient was admitted to the IMC and anticoagulation initiated with a bolus of 6000 IU of LMWH (enoxaparin sodium) followed by 8000 IU daily. A three-point compression ultrasound of the lower extremities was negative for deep vein thrombosis. During the IMC stay, the patient remained hemodynamically stable and afebrile. Dyspnea resolved within 3 days. He was discharged home after resolution of the respiratory dysfunction to continue therapeutic LMWH anticoagulation.

2.1.4. Case #4

A 41-year-old male was admitted to the emergency room of Hôpital Nord Marseille (Marseille, France) because of progressive dyspnea. The patient had diabetes mellitus type II and hypothyroidism in his past medical history. Flu-like symptoms had started 7 days prior to admission and the patient was treated on an ambulatory basis. Initial clinical examination revealed marked dyspnea and a

SaO₂ 94% (under 10 L/min oxygen). A chest CT scan revealed multifocal GGO and nasopharyngeal RT-PCR swab was positive for SARS-CoV-2. The patient was transferred to the ICU, where tracheal intubation and invasive mechanical ventilation were necessary because of severe dyspnea, metabolic acidosis, and hypoxemia despite oxygen therapy (15 L/min via oxygen mask). Prophylactic anticoagulation was given with LMWH (enoxaparin at 0.4 IU/d).

At day 3, the patient developed ventilator-associated pneumonia due to *Enterobacter cloacae* and was treated with cefepime for 7 days. His clinical condition improved over the subsequent days, and he was successfully weaned from mechanical ventilation; his trachea was extubated on day 7 in the ICU. However, the patient suddenly developed severe hypoxemia (PaO₂:FiO₂ ratio at 90 mmHg) on day 8, so that invasive mechanical ventilation and prone positioning were again necessary. Hemodynamics deteriorated rapidly after intubation and

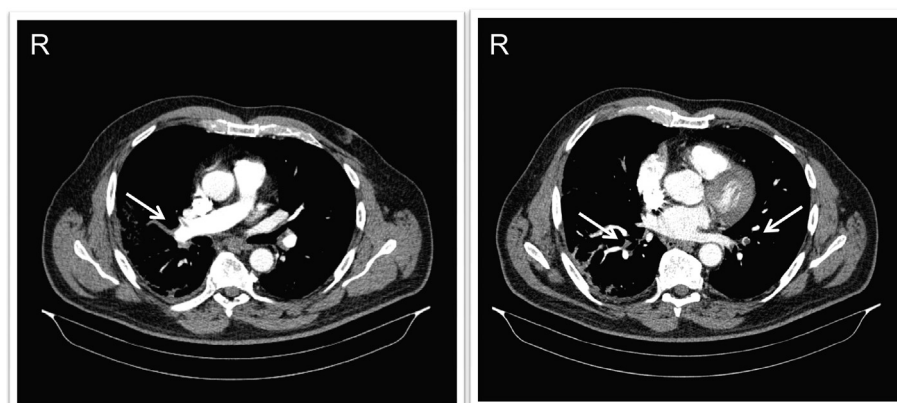


Fig. 2. Computed tomographic angiography images showing subtotal occlusion of the right pulmonary artery at the level of the middle lung lobe (arrows, left panel) and subsegmental obstruction at the level of the inferior lobes (arrows, right panel).

high dose norepinephrine was needed. Transesophageal echocardiography showed acute right heart failure with paradoxical septal motion (Fig. 5 of the electronic supplement material). Compression ultrasonography of the lower extremities showed extended thrombosis of the left femoral vein (Fig. 6 of the electronic supplement material). Transesophageal echocardiography revealed a large thrombus in the right pulmonary artery (Fig. 5 of the electronic supplement material). Thrombolysis with r-tPA was unsuccessful so that veno-arterial extracorporeal membrane oxygenation (ECMO) was initiated because of marked hemodynamic instability and ultrasound-enhanced thrombolysis was performed with subsequent successful dissolution of the clot.

Although evolution was favorable and ECMO was weaned on day 27, thrombi were identified in the internal right jugular vein and the left femoral vein. Because of persistent thrombosis the patients was treated with tinzaparine (18,000 IU/d). After gradual weaning from mechanical ventilation, the patient's trachea was successfully extubated on day 35. He was discharged to a medical ward in the same institution on day 40 on therapeutic LMWH.

2.1.5. Case #5

A 49-year-old male patient was admitted to the emergency department of S.Orsola-Malpighi Hospital (Bologna, Italy) because of acute respiratory failure. Fever and cough had started 15 days prior to admission and SARS-CoV-2 infection had been confirmed 10 days earlier with a RT-PCR positive swab. The patient had been self-isolating at home. Known comorbidities were obesity and diabetes mellitus type II.

On presentation, the patient was febrile (39 °C) and his respiratory rate was >30 breaths/min. Blood gas analysis showed hypoxemia despite oxygen therapy (non-rebreather facemask 15 L/min) and respiratory acidosis, so that tracheal intubation and invasive mechanical ventilation were necessary and the patient was referred to the ICU. CT scan showed diffuse GGOs with multiple zones of consolidation (Fig. 7 of the electronic supplement material). Prophylactic LMWH was started (enoxaparin at 4000 IU/d). As the patient showed no signs of clinical improvement, a CTA of the lung was performed on day 9, and revealed a thrombus in the right interlobar artery extending into segmental arteries of the right lower lobe. Worsening of the right lower lobe consolidation was also observed (Fig. 8 of the electronic supplement material). Upper and lower limb Doppler ultrasonography excluded deep vein thrombosis. LMWH dosage was increased to 8000 IU B.I.D. On day 14, chest CTA was repeated and showed necrotizing pneumonia of the right lower lobe with persistence of diffuse GGOs without further extension of the pulmonary thrombosis. Despite full clinical and therapeutic support, the patient died of refractory septic shock on day 16.

3. Discussion

The clinical cases we describe represent the broad spectrum of PTE in patients with COVID-19. The onset of PTE varied from 2 to 4 weeks after the occurrence of the initial symptoms of SARS-CoV-2 infection and led to deterioration of the clinical picture in all cases. In 100 hospitalized patients with COVID-19, Grillet et al. [2] found radiologic evidence of PTE in 23% of cases in CTA, performed in the average of 12 days after the onset of symptoms. This underscores the importance of adequate follow-up of these patients and the relatively high degree of clinical suspicion to early detect and treat PTE. Indeed, 3 patients in our series developed acute severe respiratory failure after a rather stable early clinical course of the disease, necessitating mechanical ventilation and/or ECMO therapy.

Interestingly, 3 of the patients had no past history of clinically relevant risk factors for venous thromboembolism (VTE) and one patient (Case #4) developed PE despite prophylactic anticoagulation using LMWH. The occurrence of PTE despite of standard prophylactic thromboprophylaxis underscores the potential procoagulant effect of COVID-19 and the likely inadequacy of standard prophylactic anticoagulation in these patients. Although embolic events are possible

in patients with COVID-19, pulmonary microthrombosis (PMT) may be another relevant phenotype in these patients [9]. The pronounced inflammation of the lung tissue due to viral infection triggers activates hemostasis and may induce the formation of thrombi in the microvasculature as a physiological effort to limit the viral load. This may be explained by the interaction between platelets and endothelium, inducing endothelial dysfunction, which may play a major role in COVID-19 associated microthrombosis [10,11]. Subsequent platelet aggregation and leukocytes' recruitment may extend PMT to sufficiently occlude large pulmonary vessels [10]. These aggregates continue to grow until they become sufficiently large to induce extended PMT.

Few studies [12–18], mostly retrospective [13–18], have reported the epidemiology and clinical characteristics of patients with COVID-19 requiring ICU admission. The incidence of PTE was 13.6–35.3% in this population despite of prophylactic anticoagulation. The hypercoagulable state observed in these patients is probably multifactorial and can be explained by several mechanisms, including cytokine release [19], complement activation [20], endothelial dysfunction [21,22], and interactions between hemostatic and immune systems [21]. Taken together, intermediate dose of LMWH (e.g., enoxaparin 1 mg/kg/day in patients with normal renal function) is a reasonable option in patients with risk factors for VTE [23], especially those who require ICU admission [1,2,12–18,24–27].

We may also speculate that COVID-19 may predispose to a resistance to heparin therapy as evident from the relatively high dose of heparin needed to achieve the therapeutic target in Case #1. Similarly, Beun et al. [16] reported that high dose unfractionated heparin (UFH) of more than 35,000 IU/day was required in 4 patients with PTE to achieve therapeutic targets. Monitoring and dose-adjustment of anticoagulation therapy in these patients is, therefore, of utmost importance to avoid life-threatening thromboembolic events. In particular, obese patients may require higher weight-based doses [28,29].

Another important observation in patient #1 was that the severe disease progression was associated with concomitant increases in IL-6, ferritin, and D-Dimer levels, which highlights the potential role of these markers for identifying severe cases of COVID-19 who may warrant a more meticulous diagnostic assessment to exclude the presence of PTE. These abnormalities were shown to be associated with poor prognosis these patients [5] and have been reported to predict VTE in COVID-19 patients and monitor the effectiveness of anticoagulant therapy [30]. They should be interpreted, however, within the clinical context and should not be used, per se, to establish the diagnosis of VTE or indicate the need for diagnostic procedures [30,31]. Clinical deterioration of the respiratory function or the lack of improvement despite of supportive therapy, together with laboratory evidence of severe inflammation and hypercoagulable state should prompt rapid diagnostic procedures to identify patients with PTE. Indeed, the International Society of Thrombosis and Haemostasis (ISTH) did not recommend the routine screening for DVT in COVID-19 patients. Nonetheless, high index of clinical suspicion of PTE should be adopted in these patients, especially those at increased risk of VTE [31].

In case #1, PTE was the primary reason for hospital and ICU admission after a 2-week period of self-isolation at home, raising concerns about the possible influence of self-isolation on potentiating the procoagulant effects of COVID-19 because of relative restrictions in physical activity. The magnitude of this problem is probably underestimated because of the lack of reliable data on the epidemiology of thromboembolic events in this population. It may reasonable, therefore, to consider prophylactic anticoagulation for 1–2 weeks in the pre-hospital phase during home self isolation, especially in patients with VTE risk factors, such as reduced mobility, obesity, and previous VTE [23].

Two patients (Cases #2 and #3) were readmitted after being discharged from the same hospital, suggesting that the assumed procoagulant effect of COVID-19 may extend some weeks after hospital discharge of apparently stable, asymptomatic patients. It would be

prudent, therefore, to have a high degree of clinical suspicion of PE in COVID-19 patients readmitted to the hospital after surviving an initial hospitalization. Extended post-discharge prophylactic anticoagulation for 1–2 weeks may also be useful in some patients after meticulous assessment of the risk-benefit ratio of this treatment [7,8,23]. Further studies are needed to assess these aspects.

The outcome from PTE seems to be related to the extent of the thromboembolism, associated complications (e.g., superinfections) and associated organ dysfunction/failure, especially cardiovascular failure. Highly invasive treatment options, such as ECMO, may be useful in selected cases but require long durations of therapy and adequate supportive treatment (Case #4). Indeed, therapeutic anticoagulation is the cornerstone in the management of these patients and should be adapted according to the preexisting comorbidities, such as renal dysfunction [7]. LMWH has been suggested as the first-line treatment, unless closer dose adjustment is required due to expected invasive procedures or in patients with severe renal impairment [32]. In the later cases intravenous UFH followed by the subcutaneous route is recommended to allow regular monitoring and dose adjustment. Urgent thrombolytic therapy should be considered in case of hemodynamic instability, evidence of new onset increased right-ventricular load, or pulmonary arterial hypertension [7,32].

4. Conclusion

PTE is a potential life-threatening complication, which occurs frequently in patients with COVID-19. Intermediate therapeutic dose of anticoagulants can be considered in patients with COVID-19 with risk factors for VTE, especially those requiring ICU admission. Extending thromboprophylaxis after hospital discharge or during home self-isolation may be reasonable after meticulous risk-benefit assessment, especially in patients with high risk of VTE.

Ethics approval and consent to participate

The report was approved by the institutional review board of Jena university hospital (Bachstrasse 8, 07743 Jena, Germany; Reference # 2020-585,174-Daten) and the corresponding institutional review board of the respective centers. Informed consents were waived due to the retrospective and anonymous nature of data collection.

Consent for publication

Informed consents were waived by the corresponding institutional review boards due to the retrospective and anonymous nature of data collection.

Availability of data and material

The datasets used and analysed during the current report are available from the corresponding author on reasonable request.

Authors' contributions

YS, IA, VMR, AK, MB, and ML, designed the scientific work. YS, SB, EA, and MG reviewed the literature. YS, EA, MG, ML, GP, TT, GD, and LZ wrote the first draft of the manuscript. All the authors reviewed, revised, and approved the submitted manuscript. YS, EA, ML, VMR, AK had complete access to the clinical and radiologic data of the reported cases and hold responsibility for integrity and correctness of data.

Declarations of Competing Interest

The authors declare that they do not have conflict of interests or financial relationship in relation to this manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jcrr.2020.09.021>.

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