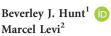then converts plasminogen to plasmin, which cleaves local fibrin.

COVID-19 infection has many clinical and histological similarities to Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV). Gralinski et al.[4] have shown in a mouse model of SARS-CoV a critical role for the urokinase pathway in regulating severe end-stage lung disease outcomes following SARS-CoV infection. They showed that the larger the dose of SARS the more severe was the clinical manifestation and greater the rise in lung urokinase expression. Lastly, another marker of COVID-19 pneumonia is the presence of many macrophages within the lung tissue. Macrophages are well known to generate plasmin and metalloproteinases (MMPs), but they have also been described to produce fibrinolysis by an alternative pathway — fibrin and fibrinogen bind to CD11b/CD16 (also known as Mac-1) and are internalised into lysosomes where cathepsin D can degrade fibrin and fibrinogen independently of plasmin.[5]

Based on the above evidence we suggest it is logical to consider that D-dimer levels, like those of other acute-phase proteins such as CRP, ferritin and fibrinogen, which are similarly very high in severe COVID-19 infections, represent the degree of lung inflammation present within the lungs in COVID-19 infection. Being related to the extent of lung inflammation would therefore explain why their plasma levels relate to clinical outcome .

Conflicts of interest

The authors declare to have no potential conflicts of interest regarding the present work.

Beverley J. Hunt[1] (ID)
Marcel Levi[2]

[1]Thrombosis & Haemophilia Centre, Guy's & St Thomas' NHS Foundation Trust, and [2]Department of Medicine and Cardiometabolic Programme-NIHR UCLH/UCL BRC, University College London Hospitals NHS Foundation Trust, London, UK.
E-mail: Beverley.hunt@gstt.nhs.uk

References

1. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054–62. https://doi.org/10.1016/S0140-6736(20)30566-3
2. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020;18(4):844–7. https://doi.org/10.1111/jth.14768
3. Taylor FB Jr, Toh CH, Hoots WK, Wada H, Levi M. Scientific Subcommittee on Disseminated Intravascular Coagulation (DIC) of the International Society on Thrombosis and Haemostasis (ISTH). Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. Haemost Thromb. 2001;86(5):1327–30.
4. Gralinski LE, Bankhead A 3rd, Jeng S, Menachery VD, Proll S, Belisle SE, et al. Mechanisms of severe acute respiratory syndrome coronavirus-induced acute lung injury. mBio. 2013;4(4). pii: e00271-13. https://doi.org/10.1128/mBio.00271-13
5. Loscalzo J. The macrophage and fibrinolysis. Semin Thromb Hemost. 1996;22(6):503–6.

Prevalence of venous thromboembolism in critically ill patients with COVID-19

COVID-19, the disease caused by the novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), was first reported in January 2020.[1,2] It has become apparent that coagulopathy is a hallmark of the disease.[3,4] Additionally, thrombotic complications, including venous thromboembolism (VTE), have been reported to occur in 27–69% of critically ill patients with SARS-CoV-2.[5–9] As a result of these reports and other anecdotal evidence, many critically ill patients are receiving empiric therapeutic anti-coagulation. Yet, experts generally recommend against the use of therapeutic anti-coagulation prior to the development of VTE or another clinical indication.[4,10,11]

In order to further our understanding of VTE in COVID-19, we evaluated its prevalence as diagnosed through usual care in patients admitted to our intensive care unit (ICU).

We also sought to determine the association between a diagnosis of VTE and clinical outcomes. We describe the clinical characteristics of our critically ill patients, frequency of VTE diagnosis, and potential clinical and laboratory predictors of a VTE diagnosis. Last, we performed a multivariate analysis to investigate the association between presence of a VTE diagnosis and mortality.

Patients and methods

We performed a retrospective cohort study of critically ill patients with laboratory-confirmed COVID-19 admitted to an academic medical centre in Colorado. We included adult patients (age ≥18 years old) who received ICU care. The Colorado Multiple Institutional Review Board approved the study.

Clinical data were abstracted from the electronic health record. Data were last collected on 6 May 2020 for all patients. Descriptive statistics were used to analyse continuous and categorical variables. Logistic regression was used to estimate the unadjusted and adjusted associations between presence of VTE and mortality. We included key confounders *a priori* based on clinical importance in the adjusted model including age, need for invasive mechanical ventilation, need for vasopressors, and presence of any co-existing conditions. All data analyses were performed using STATA software version 13.0 (STATACorp, College Station, TX, USA).

Results

One-hundred and six patients were admitted to the University of Colorado Hospital in Aurora, CO, between 18 March and 14 April 2020. One patient developed nosocomial SARS-CoV-2 infection and had been in the hospital since November 2019. A total of 107 patients were evaluated for inclusion. Six patients were excluded as they received therapeutic anti-coagulation for chronic atrial fibrillation ($n = 4$), chronic VTE ($n = 2$), or a mechanical heart valve ($n = 1$). An additional 11 patients required extracorporeal membrane oxygenation

Table I. Patient characteristics and hospital admission laboratory values compared between patients with and those without a diagnosis of venous thromboembolism (VTE).

	VTE ($n = 24$)	No VTE ($n = 67$)	P-value
Patient characteristics			
Age, mean (*SD*)	55 (13)	57 (17)	0·29
Male sex, % (*n*)	58 (14)	58 (39)	0·99
Body Mass Index, kg/m^2 (*SD*)	32·1 (8·5)	32·5 (10·4)	0·85
Vasopressor use, % (*n*)	79 (19)	63 (42)	0·14
Invasive mechanical ventilation, % (*n*)	92 (22)	82 (55)	0·27
Hospital length of stay, mean (*SD*)	26 (7)	16 (10)	0·001
Any malignancy, % (*n*)	0 (0)	5 (3)	0·56
Any co-existing medical condition, % (*n*)	67 (16)	82 (54)	0·13
Chronic lung disease, % (*n*)	9 (2)	23 (15)	0·13
Diabetes mellitus, % (*n*)	32 (7)	33 (21)	0·89
Cardiovascular disease, % (*n*)	14 (3)	27 (17)	0·20
Renal disease, % (*n*)	9 (2)	14 (9)	0·53
Immunosuppressed, % (*n*)	9 (2)	6 (4)	0·67
Pregnancy, % (*n*)	6 (1)	2 (1)	0·43
Former smoker, % (*n*)	20 (4)	22 (12)	0·84
Alcohol use, % (*n*)	24 (4)	37 (20)	0·31
Laboratory values at time of hospital admission*, Mean (*SD*)			
WBC 10^9/l	7·7 (3·2)	8·7 (4·1)	0·27
Absolute lymphocytes 10^9/l	1050 (484)	1093 (626)	0·76
Haemoglobin g/l	144 (19)	143 (21)	0·81
Platelets 10^9/l	198 (109)	201 (84)	0·86
Sodium mmol/l	135 (7)	136 (5)	0·30
Potassium mmol/l	4 (1·2)	4 (0·7)	0·75
Chloride mmol/l	99 (8)	102 (6)	0·15
Bicarbonate mmol/l	22 (4)	22 (5)	0·91
BUN mg/dl	24 (14)	23 (18)	0·75
Creatinine mg/dl	2·46 (4·4)	1·27 (0·9)	0·04
Glucose mg/dl	166 (109)	174 (104)	0·74
AST U/l	46 (27)	48 (45)	0·82
ALT U/l	33 (29)	29 (20)	0·39
Total bilirubin mg/dl	0·71 (0·37)	0·66 (0·31)	0·53
Albumin g/dl	3·6 (0·6)	3·6 (0·4)	0·66
LDH U/l	398 (156)	445 (206)	0·36
CRP mg/l	170 (74)	131 (85)	0·06
D-dimer fibrinogen equivalent units	1071 (637)	3625 (11924)	0·53

SD, Standard Deviation; WBC, White Blood Cell Count; BUN, blood urea nitrogen; AST, Aspartate Aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; CRP, C-reactive protein

*Data were missing for absolute lymphocytes in six patients, sodium in one patient, potassium in one patient, chloride in one patient, bicarbonate in one patient, BUN in one patient, creatinine in one patient, glucose in one patient, AST in five patients, ALT in five patients, total bilirubin in five patients, albumin in five patients, LDH in 14 patients, CRP in seven patients, and D-dimer in 47 patients.

(ECMO) therapy and were analysed separately for VTE presence and excluded from additional analyses. Based upon these exclusions, a total of 91 patients were included in our analyses. VTE was defined by radiographic identification in the routine course of care either by doppler ultrasound of the extremities or computed tomography pulmonary angiography.

Twenty-four patients (26·1%) were found to have VTE during their hospitalization. Of these, 21% ($n = 5$) were found to have a lower-extremity deep vein thrombosis (DVT), 25% ($n = 6$) an upper-extremity DVT, 33% ($n = 8$) an internal jugular thrombus, and 21% ($n = 5$) pulmonary emboli. In patients who required ECMO support, 73% developed VTE. Twenty patients (21·7%) without a documented thrombus received therapeutic anti-coagulation for suspicion of VTE or clinician's concern for hypercoagulability. Six patients received anti-coagulation for acute onset atrial fibrillation ($n = 4$) or an elevated troponin level ($n = 2$). Most patients (54·3%) received therapeutic anti-coagulation during their hospitalization.

Characteristics of patients found to have a VTE compared to those without VTE are shown in Table I. Patients without a diagnosis of VTE were more likely to have a co-existing medical condition (81% vs. 58%, $P = 0·03$). Only three patients had a known underlying malignancy with no known malignancy in the VTE group. Patients with VTE required mechanical ventilation (92% vs. 82%) and vasopressors (79% vs. 63%) more frequently than non-VTE patients, although these differences were not significant. Average creatinine level was higher in those with VTE than those without VTE (2·46 vs. 1·27, $P < 0·05$). Average hospital length of stay was significantly longer for patients with VTE than those without VTE (26 vs. 16 days, $P = 0·001$). Other factors known to be associated with

VTE including obesity,[12] diabetes mellitus,[13] and smoking[14] were not significantly different between groups.

Patient outcomes and results of univariate and multivariate models examining the association between VTE and mortality are shown in Table II. Both groups had comparable rates of extubation, discharge from the ICU, and discharge from the hospital. Patients with VTE were on the ventilator an average of 15 days compared to 11 days for patients without VTE ($P = 0·02$). Presence of VTE was not significantly associated with mortality in unadjusted or adjusted analyses. Increasing age and the need for vasopressors were independently associated with increased mortality.

Discussion

Our findings indicate a high prevalence of VTE in critically ill patients with COVID-19, which is consistent with previous clinical[5–9] and *post-mortem* reports.[15] As all patients were not routinely screened for VTE, it is likely that our findings underestimate the true prevalence of VTE in this patient population. To our knowledge our report is the second-largest investigating this important question. Uniquely, we found that elevated creatinine at time of hospital admission and hospital length of stay were associated with a VTE diagnosis. Patient outcomes were similar for VTE and non-VTE patients in our cohort in contrast to previous reports suggesting worse outcomes amongst patients found to have VTE.[6] This discrepancy may have been related to missed diagnoses of VTE in our cohort and/or inclusion of arterial thrombi (i.e. stroke, myocardial infarction, and other systemic arterial thrombi) in the previous report. Further, the small numbers of overall events in our cohort may have limited our inferences. In conclusion, our

Table II. Clinical outcomes, univariate, and multivariate models of mortality.

	VTE ($n = 24$)	No VTE ($n = 67$)	P-value
Patient outcomes			
Mortality, % (n)	9 (2)	30 (20)	0·05
Discharged alive from ICU, % (n)	79 (19)	63 (42)	0·19
Discharged alive from hospital, % (n)	54 (13)	46 (31)	0·64
Extubated, % (n)	63 (15)	43 (29)	0·31
Tracheostomy, % (n)	17 (4)	6 (4)	0·22
Ventilator days, mean (SD)	15 (8)	11 (7)	0·03
	OR	95% CI	P-value
Models of mortality			
Unadjusted model			
VTE	0·21	0·05–1·00	0·051
Adjusted model			
VTE	0·23	0·05–1·10	0·07
Age	1·07	1·02–1·12	0·01
Invasive mechanical ventilation	0·23	0·03–1·56	0·13
Vasopressor use	5·83	1·05–32·48	0·04
Presence of any co-existing medical condition	1·56	0·40–6·07	0·52

VTE, venous thromboembolism; ICU, intensive care unit; SD, standard deviation; OR, Odds Ratio.

findings provide further evidence for a high prevalence of VTE in critically ill patients with SARS-CoV-2 infection. These findings are important for identifying a high risk group for adverse outcomes and to raise clinicians' awareness of VTE risk amongst critically ill COVID-19 patients.

Acknowledgements

Author contributions

Joseph A. Hippensteel (iD)
Ellen L. Burnham (iD)
Sarah E. Jolley

Division of Pulmonary Sciences and Critical Care Medicine, University of Colorado Anschutz Medical Campus, Aurora, CO, USA.
E-mail: joseph.hippensteel@cuanschutz.edu

References

1. Lu H, Stratton CW, Tang YW. Outbreak of pneumonia of unknown etiology in Wuhan China: the mystery and the miracle. *J Med Virol.* 2020;**92**(4):401–2.

2. Zhu Na, Zhang D, Wang W, Li X, Yang Bo, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med.* 2020;**382**(8):727–33.

3. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York city area. *JAMA.* 2020;**323**(20):2052–9.

4. Barrett CD, Moore HB, Yaffe MB, Moore EE. ISTH interim guidance on recognition and management of coagulopathy in COVID-19: a comment. *J Thromb Haemost.* 2020. Online ahead of print. https://doi.org/10.1111/jth.14860

5. Klok, FA, Kruip MJHA, van der Meer NJM, Arbous MS, Gommers DAMPJ, Kant KM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thrombosis Research.* 2020;**191**:145–147. http://dx.doi.org/10.1016/j.thromres.2020.04.013

6. Klok FA, Kruip M, van der Meer N, Arbous MS, Gommers D, Kant KM, et al. Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: an updated analysis. *Thromb Res.* 2020;**3848**(20):148–50.

7. Middeldorp, S, Coppens, M, van Haaps, TF, Foppen, M, Vlaar, AP, Müller, MCA, et al. Incidence of venous thromboembolism in hospitalized patients with COVID-19. *J Thromb Haemost.* 2020.

8. Lodigiani C, Iapichino G, Carenzo L, et al. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. *Thromb Res.* 2020;**191**:9–14. Online ahead of print. https://doi.org/10.1111/jth.14888

9. Llitjos J-F, Leclerc M, Chochois C, Monsallier J-M, Ramakers M, Auvray M, Merouani K. High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. *J Thromb Haemost.* 2020. Online ahead of print. https://doi.org/10.1111/jth.14869

10. Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. *Blood.* 2020; blood.2020006000.**135** 23:2033–2040.

11. Bikdeli B, Madhavan MV, Jimenez D, et al. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up. *J Am Coll Cardiol.* 2020; S0735-1097(20)35008-7.**75** 23:2950–2973.

12. Stein PD, Beemath A, Olson RE. Obesity as a risk factor in venous thromboembolism. *Am J Med.* 2005;**118**:978–80.

13. Stein PD, Goldman J, Matta F, Yaekoub AY. Diabetes mellitus and risk of venous thromboembolism. *Am J Med Sci.* 2009;**337**:259–64.

14. Cheng Y-J, Liu Z-H, Yao F-J, Zeng W-T, Zheng D-D, Dong Y-G, et al. Current and former smoking and risk for venous thromboembolism: a systematic review and meta-analysis. *PLoS Medicine.* 2013;**10** (9):e1001515.

15. Wichmann D, Sperhake J-P, Lütgehetmann M, et al. Autopsy findings and venous thromboembolism in patients with COVID-19: a prospective cohort study. *Ann Intern Med.* 2020; M20-2003. Online ahead of print. https://doi.org/10.7326/M20-2003

Prevalence and mortality in β-thalassaemias due to outbreak of novel coronavirus disease (COVID-19): the nationwide Iranian experience

In late December 2019, an ongoing outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection that was termed Coronavirus Disease 2019 (COVID-19), was reported in Wuhan, China.[1]

A total of 3 018 681 patients have been reported globally and 92 584 confirmed cases have been documented in Iran, until April 29th, 2020. The death toll from the COVID-19 outbreak at that time was 207 973 worldwide, and 5877 in Iran.

Transfusion-dependent and non-transfusion-dependent thalassaemia (TDT and NTDT) patients may have coexistent comorbidities due to iron overload[2,3] that can expose them to a potentially higher risk of complications attributable to COVID-19, compared to the normal population.[4]

Limited data about frequency and outcomes of infected COVID-19 patients with thalassaemia are currently available in the literature. In this study, the primary aim was to