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LETTER TO THE EDITOR

Transfusion requirements in patients with COVID-19

Since the emergence of COVID-19 in late 2019, our knowledge of the clinical implications of infection with SARS-CoV-2 has steadily grown. The clinical spectrum of COVID-19 is broad, ranging from asymptomatic infection to multi-organ failure. COVID-19 induces a proinflammatory state, activating systemic coagulation and resulting in markedly elevated D-dimers, fibrinogen and a prolongation of the prothrombin time (PT).[1] Initial studies reported the development of disseminated intravascular coagulation (DIC), associated with poorer outcomes.[1] DIC results from perturbations in the normal haemostatic balance and may produce a clinical phenotype of thrombosis, bleeding or a combination thereof. Subsequently, the International Society on Thrombosis and Haemostasis (ISTH) issued guidance on the management of DIC in this setting.[2] This guidance was controversial, recommending admission based on coagulation parameters and more liberal transfusion thresholds (maintaining platelets > 25 in non-bleeding patients). At this time, COVID-19 represented a particular challenge to transfusion services as concerns existed that transfusion requirements may be increased at a time of limited donor availability. Despite increasing data on thrombotic sequelae of COVID-19, there remains a paucity of information on transfusion requirements in this clinical setting. This is of importance, not only for physicians, but also for clinical transfusion services in order to plan stock management during the pandemic. To address this deficit, we retrospectively analysed the transfusion records and outcomes of a large cohort of patients with COVID-19.

Consecutive adult patients with COVID-19 requiring admission to Beaumont Hospital Dublin (8 March-21 April 2020) were included and followed until discharge or 21 May 2020. Ethical approval for this audit was provided by the hospital Research Ethics Committee. All laboratory testing was performed at disease onset. Coagulation assays [prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen, D-dimer] were performed on an ACL Top 550 analyser using standard HemosIL reagents. COVID-19 real-time reverse-transcription PCR was performed on combined throat/nasopharyngeal swabs using Altona Diagnostics RealStar SARS-CoV-2 RT-PCR. Data were analysed according to distribution using the mean (standard deviation, SD) or median (range) and using standard t-test or Mann-Whitney U test for comparisons (*P* value <.05 considered significant).

Overall, 333 patients (61.6% male) were admitted during the observation period, 70% were managed at ward level until discharge, 19.5% died at ward level, and 10.5% required escalation to critical care (4/35 of whom subsequently died). Ethnic variation was seen between subgroups with an increased number of non-Caucasians requiring critical care (28.6% vs 8.6% at ward level; Table 1). The critical care cohort was significantly younger with lower frailty scores and higher body mass index (BMI) but less cardiac comorbidities than other subgroups (Table 1). Blood group distribution was similar across all three subgroups (Table 1).

The previously reported increases in PT, fibrinogen and D-dimers were noted in our cohort (Table 1). In comparison with survivors at ward level, significantly higher D-dimers were seen in critical care patients (median 0.9 versus 3.21, $P < .0001$) and those who died at ward level (median 0.9 vs 2.04, $P = .002$). The PT did not significantly differ between these three groups, and the PT prolongations seen were often subtle (Table 1). Using the ISTH DIC score, no patient fulfilled the criteria for DIC. Overall, 13.2% of patients were receiving anticoagulation at admission for cardiac or thrombotic indications (Table 1). All other patients were risk assessed, and thromboprophylaxis was initiated, where appropriate, with low molecular weight heparin or unfractionated heparin according to renal function.

Laboratory coagulation alterations did not translate to increased rates of transfusion; cumulatively, only 23 patients (6.9%) required any blood products during their admission. Platelet transfusion was rare, with only 3 patients (1%) requiring platelets, two with pre-existing bone marrow failure and one on an extracorporeal carbon dioxide removal device. Fresh-frozen plasma (FFP) for correction of coagulopathy was used in only two patients (0.6%) with malignancy-associated gastrointestinal bleeds.

Of the ward-based patients, 14 of 298 (4.6%) patients received red cell concentrate (RCC) (median 2.5 units, range 1-11); three patients postorthopaedic surgery, one patient admitted with a bleed prior to their diagnosis and four patients who developed anaemia during the course of COVID-19 infection. Six patients had pre-existing bone marrow failure or malignancy, three of whom experienced major bleeding related to their malignancy (two gastrointestinal bleeds and one perinephric haematoma).

In the 35 patients who required critical care, clinical and transfusion records were reviewed to determine the rates of clinically relevant non-major bleeding (CRNMB), major bleeding (MB), thrombosis and clotting of lines/circuits. CRNMB (largely blood-stained tracheal secretions) was reported in 6 (17.1%) patients with MB complications in three patients (8.6%). Of these individuals, two were postabdominal surgery; one complicated by intra-abdominal sepsis (13 units of RCC total over 21 days, on prophylactic heparin-developed intra-abdominal bleed, ooze from lines, drains). The second postoperative

TABLE 1 Baseline demographics and laboratory tests of COVID-19 cohort

	Total (n = 333)	Ward-level survivors (n = 233)	ward level non-survivors (n = 65)	Critical care (n = 35)
Age median (range)	71.0 (20.8-96.0)	68.7 (20.9-96)	78.6 (33.8-95.8)	56.0 (28-75.8)
Sex (M/F)	205/ 128	135/ 98	45/ 20	25/ 10
Ethnicity (n, %)				
Caucasian	303 (90.9%)	213 (91.4%)	65 (100%)	25 (71.4%)
Other	30 (9.1%)	20 (8.6%)		10 (28.6%)
Comorbidities (%)				
Respiratory	29.9%	27.5%	46.1%	25.7%
Cardiac	36.6%	36.9%	54.4%	11.4%
Diabetes	18.9%	17.2%	26.2%	22.8%
CKD	11.9%	8.6%	23.1%	14.3%
HTN	53.5%	51.9%	70.8%	48.6%
Active malignancy	13.1%	11.6%	24.6%	5.7%
Immunosuppressed	14.5%	13.3%	26.2%	8.6%
On anticoagulation on admission	43 (12.9%)	25 (10.7%)	18 (27.6%)	1 (3.1%)
BMI median (range)	26.0 (12-56.5)	26.4 (12-48.1)	24.0 (14-44)	32.0 (20.9-56.5)
ABO blood group (where known)				**General Irish population**
Group O	104 (50.2%)	66 (47.5%)	29 (56%)	9 (56%)	55%
Group A	61 (29.4%)	41 (29.5%)	15 (28.8%)	5 (31.3%)	31%
Group B	32 (15.5%)	23 (16.5%)	8 (15.4%)	1 (6.3%)	11%
Group AB	10 (4.8%)	9 (6.5%)	0	1 (6.3%)	3%
Laboratory parameters Mean (SD) unless stated				**Normal reference range**
PT (s)	13.48 (2.8)	13.3 (3.0)	14.1 (2.8)	13.6 (1.48)	10-13.2
APTT (s)	30.5 (5.9)	29.2 (3.7)	32.5 (8.1)	34.0 (8.5)	24 - 36
Fibrinogen (g/L)	5.03 (1.7)	4.33 (1.2)	4.6 (2.0)	5.82 (1.68)	1.9-3.5
D-dimer (ug/mL) median (range)	1.3 (0.2-100.3)	0.9 (0.2-66.1)	6.7 (0.3-100.3)	14.48 (0.5-88.6)	0 - 0.5
Platelets (10^9/L)	362 (171)	356 (171)	321 (137)	486 (184)	140-400
Haemoglobin (g/dL)	13.1 (2.0)	13.21 (1.9)	12.82 (2.3)	13.8 (1.8)	13 - 17.5
C-reactive protein (mg/L)	156 (133)	114 (109)	222 (128)	299 (136)	0.0-5.0

patient had a central line–associated thrombosis and upper limb deep vein thrombosis (DVT), treated with unfractionated heparin (UFH) (three units of RCC over five days for bleeding from operative site, haematuria, bloody tracheal secretions). The third patient required therapeutic UFH to facilitate extracorporeal carbon dioxide removal and developed oozing from venous access sites and haematuria (8 units of RCC, 4 pools of platelets over 6 days). Five other critical care patients received transfusion (median 4 units of RCC, range 3-6) in the absence of MB, four for prolonged hospitalisation (median 47.4 days, range 38-57) and one for a pre-existing haemolytic anaemia.

Early publications on COVID-19 highlighted concerns regarding the risk of development of coagulopathy; however, overt DIC did not occur and haemorrhage requiring transfusion was infrequent in our cohort. In particular, correction of thrombocytopenia was rare and related to the pre-existing conditions or the use of extracorporeal support. These data are in keeping with reports from other European cohorts in which DIC rarely occurred in patients with COVID-19 on thromboprophylaxis.[3] The high rates of clinical thrombosis [4,5] and postmortem thrombosis [6] suggest that "pulmonary intravascular coagulation" may be a more accurate descriptor for the coagulopathy encountered in COVID-19.[7] Our data demonstrate

that despite significant systemic disease, most patients do not experience bleeding complications or require transfusion, important for both clinicians and future transfusion service planning.

KEYWORDS

blood group, coagulopathy, COVID-19, haemorrhage, transfusion

CONFLICT OF INTEREST

The authors have no conflicts of interest relevant to this publication to declare.

AUTHOR CONTRIBUTIONS

AW, CK, A.O'N., M.O'D. and ML collected the data. AW, C.K, SG and PM analysed the data. All authors were involved in writing and reviewing the paper.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Amy P Worrall[1]
Claire Kelly[2]
Aine O'Neill[1]
Niamh Reidy[1]
Murray O'Doherty[1]
Lisa Griffin[2]
John Quinn[2,3]
Patrick Thornton[2,3]
Fidelma Fitzpatrick[4,5]
Ger F Curley[6]
Ross Morgan[7]
Siobhan Glavey[2,8]
Cora McNally[1,9]
Samuel McConkey[1,9]
Philip Murphy[2]
Eoghan de Barra[1,9]
Michelle Lavin[2,10]

[1]*Department of Infectious Diseases, Beaumont Hospital, Dublin, Ireland*
[2]*Department of Haematology, Beaumont Hospital, Dublin, Ireland*
[3]*School of Medicine, RCSI, Dublin, Ireland*
[4]*Department of Microbiology, Beaumont Hospital, Dublin, Ireland*
[5]*Department of Clinical Microbiology, RCSI, Dublin, Ireland*
[6]*Department of Anaesthesia and Critical Care, RCSI, Dublin, Ireland*
[7]*Department of Respiratory Medicine, Beaumont Hospital/RCSI, Dublin, Ireland*
[8]*Department of Molecular Medicine, RCSI, Dublin, Ireland*
[9]*Department of International Health and Tropical Medicine, RCSI, Dublin, Ireland*
[10]*Irish Centre for Vascular Research, School of Pharmacy & Biomedical Sciences, RCSI, Dublin, Ireland*

Correspondence
Michelle Lavin, Irish Centre for Vascular Biology, RCSI, 111 St. Stephen's Green, Dublin 2, Ireland.
Email: michellelavin@rcsi.ie

Amy P Worrall and Claire Kelly contributed equally to this work.

ORCID

Philip Murphy https://orcid.org/0000-0001-8340-1456
Michelle Lavin https://orcid.org/0000-0003-2999-4216

REFERENCES

1. 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;18:844-847.
2. Thachil J, Tang N, Gando S, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. *J Thromb Haemost*. 2020;18(5):1023-1026.
3. Fogarty H, Townsend L, Ni Cheallaigh C, et al. COVID19 coagulopathy in Caucasian patients. *Br J Haematol*. 2020;189(6):1044-1049.
4. Helms J, Tacquard C, Severac F, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. *Intensive Care Med*. 2020;46(6):1089-1098.
5. Middeldorp S, Coppens M, van Haaps TF, et al. Incidence of venous thromboembolism in hospitalized patients with COVID-19. *J Thromb Haemost*. 2020;18(8):1995-2002.
6. Fox SE, Akmatbekov A, Harbert JL, Li G, Quincy Brown J, Vander Heide RS. Pulmonary and cardiac pathology in African American patients with COVID-19: an autopsy series from New Orleans. *Lancet Respir Med*. 2020;8(7):681-686.
7. McGonagle D, O'Donnell JS, Sharif K, Emery P, Bridgewood C. Immune mechanisms of pulmonary intravascular coagulopathy in COVID-19 pneumonia. *Lancet Rheumatol*. 2020;2019:1-9.