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LETTER TO THE EDITORS

Comment on "Stroke in patients with SARS-CoV-2 infection: case series" from a London hospital experience

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Dear Sirs,

We read with interest Morassi et al. case series, [2] where they and others [1, 3] reported stroke as a complication of severe COVID-19 infection. The effect of COVID-19 on acute stroke patients (ischaemic and haemorrhagic) who may catch the disease concomitantly with stroke or after stroke but not as a cause of severe COVID-19 disease is not known. Therefore, we detail the demographic, clinical, radiological, laboratory results, treatment and outcomes of 22 consecutive COVID-19-positive (confirmed by reverse-transcriptase polymerase chain reaction (RT-PCR)) stroke patients diagnosed during the lockdown period 23rd March to 1st May 2020 inclusive at a tertiary London neuroscience centre. The mean age is 70.3 ± 2.2 years (range 49–83 years old, 14 (64%) males and 8 (36%) females). We classified these patients into (i) hospital acquired COVID-19; those who developed COVID-19 in the hospital while being treated for stroke, (ii) community acquired COVID-19; patients who had COVID-19 symptoms in the community shortly before attending the hospital with stroke and (iii) stroke as a direct complication of COVID-19; patients who were treated in intensive care with obvious prothrombotic state.

Table 1 cases 1–5 are hospital acquired COVID-19, this category of patients has not been described before. These were the patients being treated for stroke in mid-March 2020, when wearing personal protective equipment (PPE) was not recommended for staff looking after non-COVID-19 patients. In addition, relative visiting rules were not restricted. Cases 2–5 had high poor functional status before hospital admission and high frailty score on admission. They presented with mild fever at the time of testing and normal chest X-ray. They received oxygen therapy by nasal canulae for their COVID-19 and did not require or proceed for intensive care input. Cases two and three were discharged home at similar level of function as before and the others deceased. It is interesting to note the two discharged patients had minimum elevation of high-sensitivity C-reactive protein (CRP). None of these patients had worsening of stroke symptoms.

Twelve community acquired COVID-19 patients (Cases 6–17) developed stroke within 72 h of showing COVID-19 symptoms. Ten patients presented with fever, six had also cough, three patients had severe hypoxia on admission (87% on 15 L O_2 in case 7, 70% on 15 L O_2 in case 16 and 89% on 15 L O_2 in case 17). These three patients are care home residents, have high pre-admission mRS and frailty score. Cases 6–8, 10–12, 14–15 and 17 had confirmed large vessels stroke. Two cases (13 and 16) were clinically unstable on admission and diagnosed without brain imaging. Cases 6, 9–14 and 17 of ischaemic stroke patients with known symptom onset presented late (> 4.5 hr). Case nine had intraventricular haemorrhage due to a suspected arterio-venous malformation (AVM). We noted that the majority of the patients who died had high CRP. Patients who had hypoxia and abnormal chest X-ray at presentation except case 14, did not survive. Difficult to ascertain whether patients of community acquired COVID-19 developed stroke as a different disease process or as a result of COVID-19. The patients' pre-morbid status and clinical findings in this group suggest that perhaps these patients developed stroke as an additional disease to their COVID-19 infection.

We report five cases (18–22) where patients had severe COVID-19 disease and developed (apart from case 22 which is a stroke mimic) multiorgan failure and large vessel stroke. These patients are middle age males with pre-admission mRS of zero and very low frailty score. Presenting

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Table 1 Demographic, clinical, radiological, laboratory findings, management and outcome of stroke patient who acquired COVID-19 at the hospital

	Case 1	Case 2	Case 3	Case 4	Case 5
Age/sex	75/M	67/F	83/F	74/M	81/F
Ethnicity	White	Black	White	White	White
Past medical history	None	Previous stroke, HTN, HL, T2DM	AF on warfarin, HTN, IHD, CCF	T2DM, IHD, CCF, AF, Non-Hodgkin's lymphoma	Asthma, HTN, previous, stroke, AF
Medications	Bisoprolol, Ramipril, Levetiracetam, Lansoprazole,	Aspirin, atorvastatin, insulin, lansoprazole, levothyroxine, mirtazapine pregabalin, sitagliptin, quinine	Bisoprolol, Ramipril, bumetanide, simvastatin, warfarin	Amiodarone, Amlodipine, atorvastatin, bisoprolol, tamsulosin, sitagliptin, bumetanide, candesartan, Edoxaban	Amlodipine, Apixaban, Bisoprolol, Quetiapine, sertraline, salbutamol
Pre-stroke mRS	1	4	4	5	4
Frailty score	2	6	6	8	6
COVID symptoms and duration	Patient was about to be discharged home from 8 weeks inpatient stroke rehab developed fever at the beginning of lockdown	After 4 weeks inpatient stroke rehab developed fever at the beginning of lockdown	After 10 days inpatient stroke rehab developed mild dry cough at the beginning of lockdown	After 8 weeks inpatient rehab for stroke and infected prosthetic knee developed fever at the beginning of lockdown	After 8 weeks inpatient stroke rehab developed fever at the beginning of lockdown
$SatO_2/PaO_2$ (ABG) at the time of diagnosis	98% RA	96% RA	96% RA	96% RA	96% RA
Chest X-ray/CT at presentation	Lung clear	Lung clear	Lung clear	Left lung mass and supradiaphragmatic lymph nodes	Lung clear
COVID treatment	NC O_2, antibiotics, complicated with chest abscess, required chest drain	NC O_2	NC O_2	NC O_2, antibiotics	NC O_2
Signs and symptoms of stroke	2-day history of expressive dysphasia and disorientation	Dysarthria, left sided weakness	Dysarthria with word finding difficulty	Vertigo	Left sided weakness and neglect
Vascular territory	–	Posterior circulation	Bilateral MCA	Left PCA	Right MCA
Imaging for diagnosis	CT	MRI	MRI	MRI	CT
Imaging findings	Left frontal haematoma with diffuse blood in convexity sulci bilaterally, cerebral Amyloid angiopathy	Left paramedian pontine infract	Bilateral embolic infarct in the right insula, right posterior temporal lobe, left frontal operculum and left occipital lobe	Left PCA embolic infarct	Right parietal infarct
Change in stroke after COVID-19	No more bleed after COVID-19	None	None	None	None
Evidence of PE	Large saddle PE	No CT-PA	No CT-PA	No PE on CT-PA	No CT-PA
White-cell count-$\times 10^9$/L	25.9↑	10.7	4.2	2.0↓	10.4
Lymphocytes count-$\times 10^9$/L	0.8↓	1.4	0.6↓	0.7↓	0.4↓
Platelet count-$\times 10^9$/L	214	179	156	180	235
High-sensitivity C reactive protein-mg/L	215↑↑	27↑	28↑	354↑↑	215↑↑

Table 1 (continued)

	Case 1	Case 2	Case 3	Case 4	Case 5
Prothrombin time/INR	1.4↑	1.2↑	1.2↑	2.5↑	1.4↑
Activated partial thromboplastin time ratio	1.01	1.00	0.96	1.01	0.87
Fibrinogen-mg/dl	5.3↑	4.4	2.5	10.9↑	4.0
D-Dimer-ng/ml	–	–	–	–	639↑
Ferritin-µg/ml	–	–	–	899↑	406↑
Albumin-g/L	27↓	28↓	31↓	20↓	24↓
Clinical outcome	Palliated after confirmed PE, deceased at 28 days after confirmed COVID-19 (mRS 6)	Improved continue inpatient rehabilitation, then discharged home. (mRS 4)	Improved, continued inpatient rehabilitation, then discharged home. (mRS 4)	Deteriorated with ongoing suspected primary lung cancer, deceased 28 days after confirmed COVID-19 (mRS 6)	3 weeks after Covid-19 positive, patient suffered a STEMI required PCI and coronary stenting. Cardiac arrest and deceased 7 days later (mRS 6)

	Case 6	Case 7	Case 8	Case 9	Case 10	Case 11	Case 12	Case 13	Case 14	Case 15	Case 16	Case 17
Age/sex	75/M	68/F	68/F	75/M	77/M	83/F	50/M	76/F	49/M	74/M	83/M	78/F
Ethnicity	White	Asian	White	White	White	Black	Asian	Black	Black	White	White	Asian
Past medical history	Terminal gastric cancer, IHD, AF, HTN, T2DM, CKD	Traumatic brain injury PEG feed, Tracheostomy, T2DM, previous TIA	HTN, CKD	None	HTN, T2DM	Dementia, T2 DM	None	T2DM, CKD4, HTN, IHD	Previous stroke, HTN, T2DM, HL	AF on warfarin, schizophrenia, T2DM, HTN, IHD, CCF, hypothyroidism	Dementia	Dementia, Pulmonary TB in 2012
Medications	Apixaban, Amiodarone, Bisoprolol, Furosemide, Mirtazapine, Omeprazole,	Amoxicillin, Citalopram, insulin, Levetiracetam, Metformin lansoprazole, Ramipril	LMWH, levothyroxine, Mirtazapine, Ramipril, Metoclopramide	None	Amlodipine, Ramipril, Metformin, Gliclazide, Empagliflozin, Atorvastatin	Donepezil	None	Furosemide, Tolterodine, Linagliptin, indapamide, pregabalin, Amlodipine, Aspirin, Simvastatin	Atorvastatin, Amlodipine, clopidogrel, lansoprazole, metformin, gliclazide, perindopril, doxazosin	Warfarin, citalopram, furosemide, levothyroxine, metformin, simvastatin, bisoprolol	Donepezil	Clopidogrel, atorvastatin, Doxazosin, Irbesartan, Etoricoxib, Metoprolol, Lansoprazole
Admitted from	Home	Care home	Care home	Home	Home	Home	Home	Home	Home	Home	Care home	Care home
Pre-stroke mRS	3	5	4	1	2	4	0	3	1	4	4	5
Frailty score	9	8	6	2	3	7	1	5	3	6	7	7

Table 1 (continued)

	Case 6	Case 7	Case 8	Case 9	Case 10	Case 11	Case 12	Case 13	Case 14	Case 15	Case 16	Case 17
COVID symptoms and duration before stroke	24 h fever cough	2-day history of fever	Low grade fever on 1 day after admission	Low grade fever dry cough 2 days after admission	2-day history of fever, dizziness	2-day history of fever	3-day history of low-grade fever, cough	1-day history of shortness of breath	3-day history of feeling unwell	2-week history of fever cough, confirmed COVID-19 positive 10 days before	2-day history of fever and cough	24 h prior to admission fever, cough, hypoxia on admission
$SatO_2/PaO_2$ (ABG) on admission	98% on RA	87% on 15L	98% on RA	98% on RA	92% on RA	92% on RA	99% on RA	93% on 15 L O_2	96% on RA	92% on RA	70% on 15 L O_2	89% on RA
Chest X-ray/CT at presentation	Ground-glass air space shadowing in the periphery	Mild peripheral infiltration	Ill-defined consolidation in the right mid zone	Normal	Bilateral multiple scattered air space opacities	Normal	Nonspecific patchy bi-basal consolidation	Bilateral mid/lower zone patchy opacification	Patchy air space shadowing bilateral upper and mid zone	Bilateral lower zone patchy opacification	Diffuse bilateral fine opacification	Right cardiophrenic angle opacity long standing
COVID treatment	NC O_2, antibiotics	NC O_2	NC O_2	NC O_2	Intubation, Remdesivir, LMWH	NC O_2	NC O_2	NC O_2,	None	NC O_2	NC O_2	ICU non-invasive ventilator
Signs and symptoms of stroke	Aphasia, right side and left leg weakness NIHSS 15	Reduced GCS, worsening right side weakness	Acute right arm weakness, NIHSS 8	Dizziness and unsteady gait, NIHSS 4	TIAx2 last 7 days, acute left facial droop, right sided weakness	Mild expressive aphasia, NIHSS 7	Vertigo, unsteadiness, left facial numbness	Aphasia, right side weakness	Slurred speech, right side weakness, NIHSS 7	Slurred speech, left sided weakness, NIHSS 17	Left sided weakness, with right eye deviation	Unresponsive, left sided weakness, NIHSS 32
Stroke onset to presentation (hr)	15 h	Unknown	2 h, not thrombolysed due to recent hip surgery	20 h	12 h	7 h	6 h	9 h	8 h	3 h not thrombolysed, on warfarin INR 3.6	1 h not thrombolysed as too unwell	6 h
Vascular territory	Left MCA, right ACA	Left MCA	Bilateral MCA	–	Posterior circulation	Left MCA	Posterior circulation	Left MCA	Left MCA	Right MCA	Right MCA	Right MCA, right M1 clot
Imaging for diagnosis	CT	MRI	MRI	CT	CT	CT	CT	Not stable for CT	CT/MRI	CT	Not stable for CT	CT

Table 1 (continued)

	Case 6	Case 7	Case 8	Case 9	Case 10	Case 11	Case 12	Case 13	Case 14	Case 15	Case 16	Case 17
Imaging findings	Left MCA, right ACA infarct	Left MCA embolic infarct	Bilateral border zone between MCA PCA, left more than right	IVH possibly secondary to AVM	SVD, no large infarct	SVD, no large infarct	No acute change on CT, right VA dissection on CTA	n/a	Left uncus and internal capsule, and right corona radiata small infarct	Initial CT right MCA early ischemia, 24 h CT confirmed complete right MCA infarct	Clinical right MCA stroke	Complete right MCA infarct
Evidence of PE	No CTPA	No CTPA	No CTPA	No CTPA	No PE on CTPA	No CTPA	No CTPA	No CTPA	No CTPA	No CTPA	No CTPA	No CTPA
White-cell count-$\times 10^9$/L	8.2	2.4↓	10.5↑	17.1↑	15.2↑	7.8	6.7	6.2	8.0	6.7	21.3↑	8.3
Lymphocytes count-$\times 10^9$/L	0.7↓	0.6↓	0.6↓	1.0↓	0.3↓	0.8↓	0.8↓	1.2	1.5	0.4↓	1.4	1.1
Platelet count-$\times 10^9$/L	185	224	302	281	264	223	149	259	698↑	155	446	342
High-sensitivity C reactive protein-mg/L	151↑	134↑	84↑	61↑	318↑↑	59↑	12↑	136↑	3	83↑	418↑↑	12↑
Prothrombin time/INR	1.2↑	1.1	1.0	1.0	1.3↑	1.1	1.0	1.2	1.0	3.6↑	–	1.0
activated partial thromboplastin time ratio	0.96	1.27↑	0.94	0.89	1.23↑	0.83	0.89	1.01	1.26↑	1.34↑	–	1.00
Fibrinogen-mg/dl	5.9↑	6.3↑	4.9↑	2.7	7.8↑	5.2↑	2.4	7.4↑	8.4↑	5.1↑	–	4.9↑
D-Dimer-ng/ml	–	–	909↑	–	3210↑	–	94	–	–	–	–	–
Ferritin-μg/ml	–	–	603↑	–	3957↑	–	595↑	–	–	–	–	628↑
Albumin-g/L	33↓	24↓	19↓	35	17↓	32↓	36	30↓	30↓	24↓	29↓	25↓
Clinical outcome	Deceased on day 3, after 40 min rapid deterioration in hypoxia and fast AF (mRS 6)	Increased oxygen needs, Palliated deceased on day 4. (mRS 6)	Improved continue inpatient rehabilitation (mRS 4)	Improved, discharged home (mRS 1)	Multiorgan failure, deceased on day 21 (mRS 6)	Improved discharged home on day 3. (mRS 4)	Improved, transfer to local hospital for stroke rehabilitation, then discharged home. (mRS 1)	Palliated, deceased on day 2. (mRS 6)	Improved, transferred to local hospital to rehabilitation then discharged home. (mRS 2)	Palliated, deceased on day 5. (mRS 6)	Palliated, deceased 12 h after admission. (mRS 6)	Palliated, deceased on day 12. (mRS 6)

Table 1 (continued)

	Case 18	Case 19	Case 20	Case 21	Case 22
Age/sex	61/M	67/M	66/M	64/M	52/M
Ethnicity	Asian	White	Black	White	Asian
Past medical history	HTN, HL	HTN, T2DM	None	Glucose intolerance	Asthma
Medications	Atorvastatin, amlodipine, clopidogrel	Amlodipine, Ramipril, Sitagliptin, Metformin	None	None	None
Pre-stroke mRS	0	0	0	0	0
Frailty score	1	1	1	2	2
COVID symptoms and duration	Developed cough while inpatient rehab after heart valve intervention	3-day history of fever, cough, loss of taste	5-day history of fever, mild diarrhoea, nausea, dry cough	10-day history of cough and chest pain	3-day history of dry cough, fever; 24 h shortness of breath
$SatO_2/PaO_2$ (ABG) on admission	89% on 3L O_2	78% on RA/PaO_2 7.31 kPa on ABG	92% on 15L O_2	89% on 15L O_2/PaO_2 7.89 on ABG	60% on RA
Chest X-ray/CT at presentation	Widespread bilateral air space infiltrates with pulmonary oedema	Bilateral lower zone air space opacities. Obscuration of the left hemidiaphragm is indicative of left lower lobe consolidation	Extensive parenchymal lung disease essentially involving the entirety of both lungs, with a ground-glass and consolidative pattern	Scattered bilateral air space opacity	Bilateral lower lobe and peripheral predominant multiple opacities
COVID treatment	Intubation, LMWH	Intubation, antibiotics, prophylactic LWMH	Intubation, steroid, antibiotics, LMWH	Intubation, steroid, LMWH	Intubation, steroid, LMWH
Signs and symptoms of stroke	Patient did not wake up after sedation wean	Left arm no movement	Reduced GCS, no limb movement	New fixed dilated pupils	Slow wake up after sedation wean
Stroke onset to presentation	Unknown	Unknown	Unknown	Unknown	Unknown
Vascular territory	Bilateral MCA	Bilateral MCA	Right MCA and post circulation	Right MCA	–
Imaging for diagnosis	CT	MRI	CT	CT	MRI
Imaging findings	Bilateral MCA and thalami hypodensity, mostly acute ischemia	MRI: Multiple acute border zone infarcts bilaterally in the anterior circulation and some in the posterior circulation occurring in the context of multifocal proximal intracranial arterial stenoses	Right MCA and brainstem ischemia	Multifocal intraparenchymal cerebral haemorrhages and subarachnoid haemorrhage (haemorrhagic infarction), diffuse brain oedema	Diffuse haziness throughout the deep cerebral and cerebellar white matter, may be caused by the metabolic/physiological disturbance caused by critical illness
Evidence of PE	No PE on CT-PA	No CT-PA	No PE on CTPA	Small PE on CT-PA	Distal small PE on CT-PA
White-cell count-$\times 10^9$/L	19.8↑	14.9↑	38.4↑	18.8↑	11.4↑
Lymphocytes count-$\times 10^9$/L	0.4↓	0.2↓	0.3↓	0.5↓	0.4↓
Platelet count-$\times 10^9$/L	129	635↑	473↑	577↑	272
High-sensitivity C reactive protein-mg/L	364↑↑	335↑	345↑	388↑	338↑
Prothrombin time/INR	1.2↑	1.3↑	1.3↑	1.0	1.3↑

Table 1 (continued)

	Case 18	Case 19	Case 20	Case 21	Case 22
activated partial thromboplastin time ratio	2.8↑	1.11	2.5↑	2.52↑	1.64↑
Fibrinogen-mg/dl	6.3↑	13.7↑	8.3↑	8.7↑	7.9↑
D-Dimer-ng/ml	> 6000↑↑	4097↑	> 6000↑↑	> 6000↑↑	1124↑
Ferritin-µg/ml	927↑	1651↑	1049↑	4459↑	1233↑
Albumin-g/L	15↓	15↓	14↓	14↓	15↓
Clinical outcome	Deceased on day 28 (mRS 6)	Renal failure, deceased on day 11. (mRS 6)	Renal failure, deceased on day 4. (mRS 6)	Renal failure, deceased on day 17 (mRS 6)	Improved, continue ward rehabilitation (mRS 4)

ABG arterial blood gas, *AF* atrial fibrillation, *CT* computed tomography, *CTPA* CT pulmonary angiogram, *F* female, *HL* hyperlipidaemia, *HTN* hypertension, *ICU* intensive care unit, *INR* international normalized ratio, *LMWH* low molecular weight heparin, *M* male, *MCA* middle cerebral artery, *MRI* magnetic resonance imaging, *mRS* modified Rankin scale, *NC* nasal cannula, *NIHSS* national institute of health stroke scale, PaO_2 partial pressure of oxygen, *PCA* posterior cerebral artery, *PE* pulmonary embolus, *RA* room air, $SatO_2$ oxygen saturation, *T2DM* type II diabetes mellitus

The reference ranges are as follows: activated partial thromboplastin time ratio, albumin, 35–50 g/L; 0.85–1.15; D-dimer, 21–300 ng/ml; ferritin, 30–400 µg/ml; fibrinogen, 1.6–4.8 mg/dl; high-sensitivity C-reactive protein, 0–5 mg/L; lymphocyte count, 1.1–4.0 × 10^9/L, platelet count, 150–450 × 10^9/L, prothrombin time/INR ratio, 0.8–1.1; white-cell count, 4–11 × 10^9/L.

symptoms were typically of COVID-19. All shared chest radiographs abnormalities. They also had abnormally low oxygen saturation on admission and all needed intubation, ventilation and intensive care management. Apart from the stroke mimic case, all had high D-Dimer, ferritin and CRP. These cases share pro-thrombotic characteristics with most of the cases of Morassi et al. [2]. They all received full anticoagulation with low molecular weight heparin. Four out of these patients had CT pulmonary angiogram with no major pulmonary emboli (PE), suggesting PE may not be the major cause of their death. Further studies into this subpopulation are needed.

We included all COVID-19 stroke patients diagnosed within the period 23rd March and 1st May 2020. However, not all COVID-19 patients had brain scans and, therefore, the number of cases who were diagnosed with stroke due to severe COVID-19 disease may be underestimated. We present the management and outcome of a full spectrum of COVID-19-stroke patients in a tertiary centre. A pro-thrombotic state was found in severe COVID-19 patients, who did not do well, and stroke may be a late complication in these patients. Classifying COVID-19-stroke patients the way we did may help understand the disease and guide management.

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Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

Ethical approval Consents have been obtained from patients, next of kin or legal representative. No identifiable data is presented.

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