COVID-19 and stroke:
What are the pressing challenges?

25 Nov 2020 16:00 Brazil
19:00 GMT

Chair: Dr Felipe Von Glehn
University of Brasília, Brazil

A PANORAMA OF THE PROBLEM

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WHO NeuroCOVID Working Group

HOW WE ARE FACING IT IN BRAZIL

Dr Lucia Brito
Ministério da Saúde, Brazil
WHO NeuroCOVID Working Group

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Brain Infections Global

COVID-19 and Stroke:
what are the pressing challenges

Alessandro Padovani
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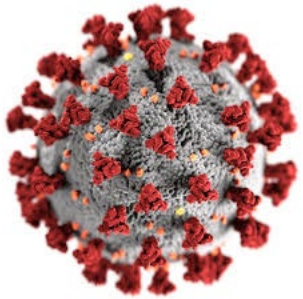
Chief complaint - timeline

- Male, 64 y.o.
- Indipendent at instrumental and daily living activities
- Past medical history: diabetes mellitus from 2015

March 12-22:
high temperatur
diarrhea

May 4: progressiv
psychomotor slowi

May 17:
Right arm and leg weakness

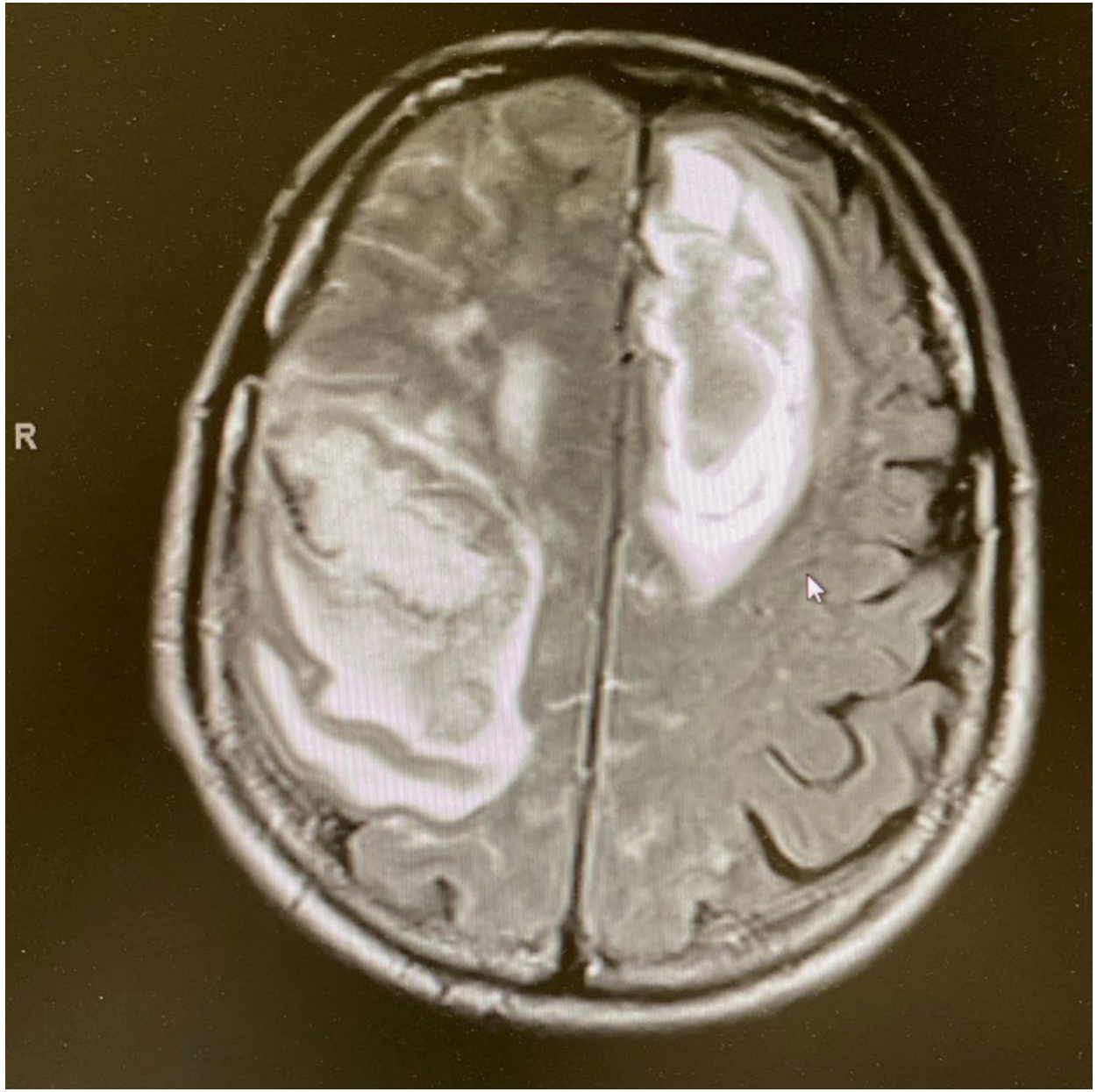


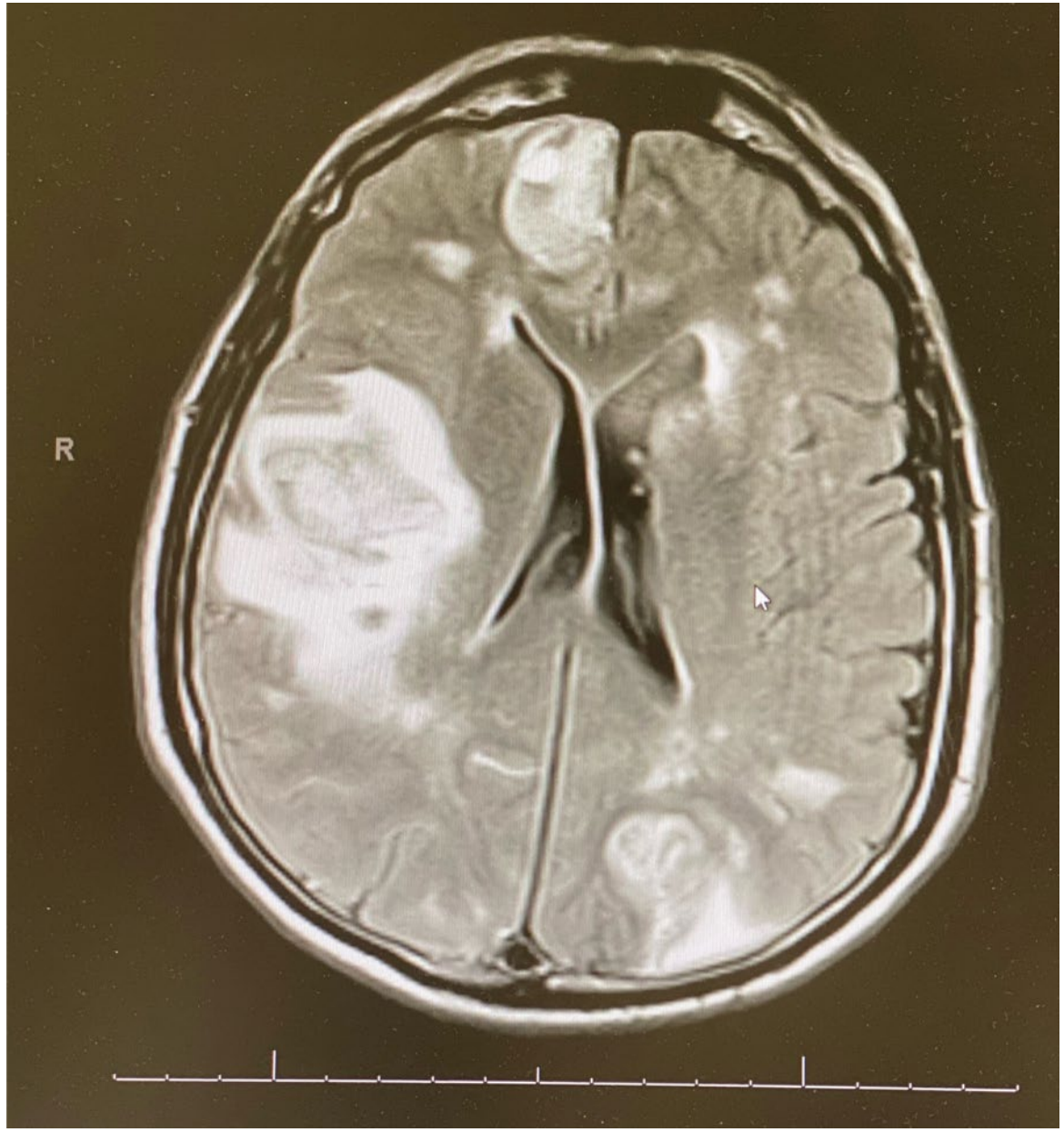
Neurological examination

Mental Status: alert, disoriented to place and time. Speech and thought process are slow.
*Cranial Nerves: v*isual fields normal in all quadrants. Pupils are round, reactive to light and accommodation. Extraocular movements are intact without ptosis. Facial sensation is intact to bilaterally to dull, sharp, and light touch stimuli. Impaired facial muscle strength on the left side.
Hearing is normal bilaterally. Palate and uvula elevate symmetrically, with intact gag reflex. Voice is normal. Shoulder shrug strong, and equal bilaterally. Tongue protrudes midline and moves symmetrically.
Motor: left arm and leg weakness.
Reflexes: Biceps, brachioradialis, triceps, patellar, and Achilles are 2/4 bilaterally. No clonus. Plantar reflex is downward bilaterally.
Sensation: Sensation is intact bilaterally to pain and light touch. Two-point discrimination is intact.
Cerebellar: Finger-to-nose and heel-to-shin test normal bilaterally.

Other information: headache.

FLAIR MRI sequences

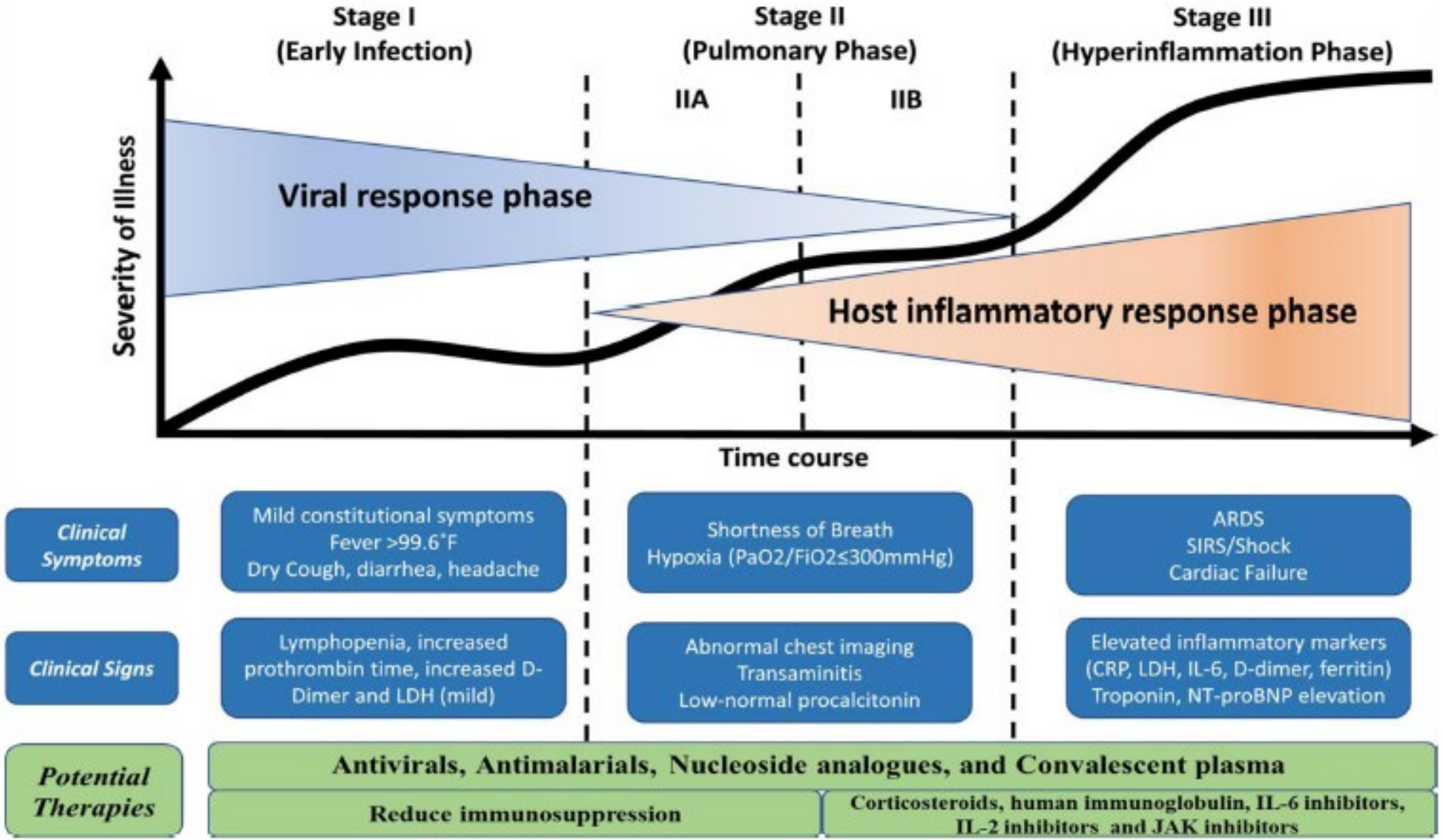




Possible mechanisms of ICH in COVID-19

- **Direct and indirect endothelial toxicity**: the former via direct endothelial cell invasion; the latter through a combination of systemic factors including prothrombotic factors, inflammatory cytokine production, activation of coagulation cascades, and complement-mediated microvascular thrombosis (Ronaldson and Davis, 2017, Keep, et al., 2008). Disruption of tight junction protein complexes would occur, leading to blood brain barrier compromise and ICH (Ronaldson and Davis, 2017, Keep, et al., 2008).

- **A disruption of the renin-angiotensin system (RAS)**. The RAS has distinct regulatory pathways in both the periphery and the brain, which could be impacted by SARS-CoV-2 via down regulation of endothelial ACE2 receptors, leading to cerebral blood flow dysautoregulation (Divani et al., 2020, Zhang et al., 2020 Apr 1).


Stage I
(Early Infection)
Stage II
(Pulmonary Phase)
IIA
IIB
Stage III
(Hyperinflammation Phase)
Severity of Illness
Viral response phase
Host inflammatory response phase
Time course
Clinical Symptoms
Mild constitutional symptoms
Fever >99.6˚F
Dry Cough, diarrhea, headache
Shortness of Breath
Hypoxia (PaO2/FiO2≤300mmHg)
ARDS
SIRS/Shock
Cardiac Failure
Clinical Signs
Lymphopenia, increased prothrombin time, increased D-Dimer and LDH (mild)
Abnormal chest imaging
Transaminitis
Low-normal procalcitonin
Elevated inflammatory markers (CRP, LDH, IL-6, D-dimer, ferritin)
Troponin, NT-proBNP elevation
Potential Therapies
Antivirals, Antimalarials, Nucleoside analogues, and Convalescent plasma
Reduce immunosuppression
Corticosteroids, human immunoglobulin, IL-6 inhibitors, IL-2 inhibitors and JAK inhibitors

Pathophysiology of CNS Involvement with SARS-CoV-2

SARS-CoV-2 INVASION

- Direct infection injury
  - Haematogenous pathway
    - Myeloid cell trafficking
      Cytokine release
      Endothelial damage in BBB
  - Neural pathway
    - Demyelination
      Neuroinflammation
- Hypoxic injury
  - Anaerobic metabolism
- ACE2
- Immune injury
  - SIRS
- Hypercoagulability
  - Elevated D-dimer

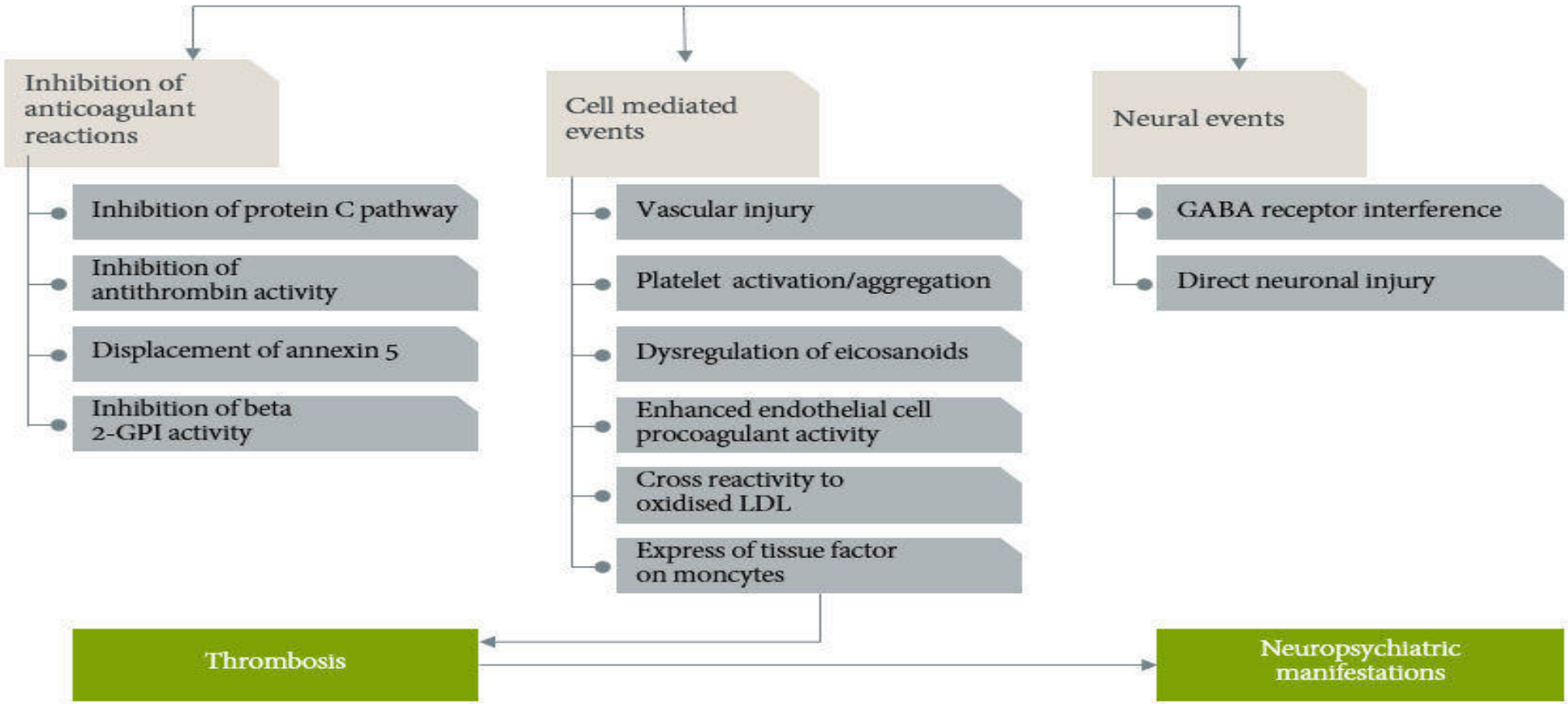
BBB = Blood brain barrier
ACE2 = Angiotensin-converting enzyme 2
SIRS = Systemic inflammatory response syndrome

- Infectious toxic encephalopathy
- Viral encephalitis
- Acute cerebrovascular disease

Adapted and modified from Wu, Y., Xu, X., Chen, Z., Duan, J., Hashimoto, K., Yang, L., ... & Yang, C. (2020). Nervous system involvement after infection with COVID-19 and other coronaviruses. *Brain, Behavior, and Immunity*.

Activation of APS pathogenesis

Binding of aPL antibodies (APA) to Beta 2-GPI



Rege, S., & Mackworth-Young, C. (2015). Antiphospholipid antibodies as biomarkers in psychiatry: review of psychiatric manifestations in antiphospholipid syndrome. Translational Developmental Psychiatry, 3(1), 25452.

Activation of APS pathogenesis

Binding of aPL antibodies (APA) to Beta 2-GPI

Binding of APA to endothelial cells and platelets

APA binding to β_2-glycoprotein, proteins C and S, and annexin V interferes with coagulation cascade

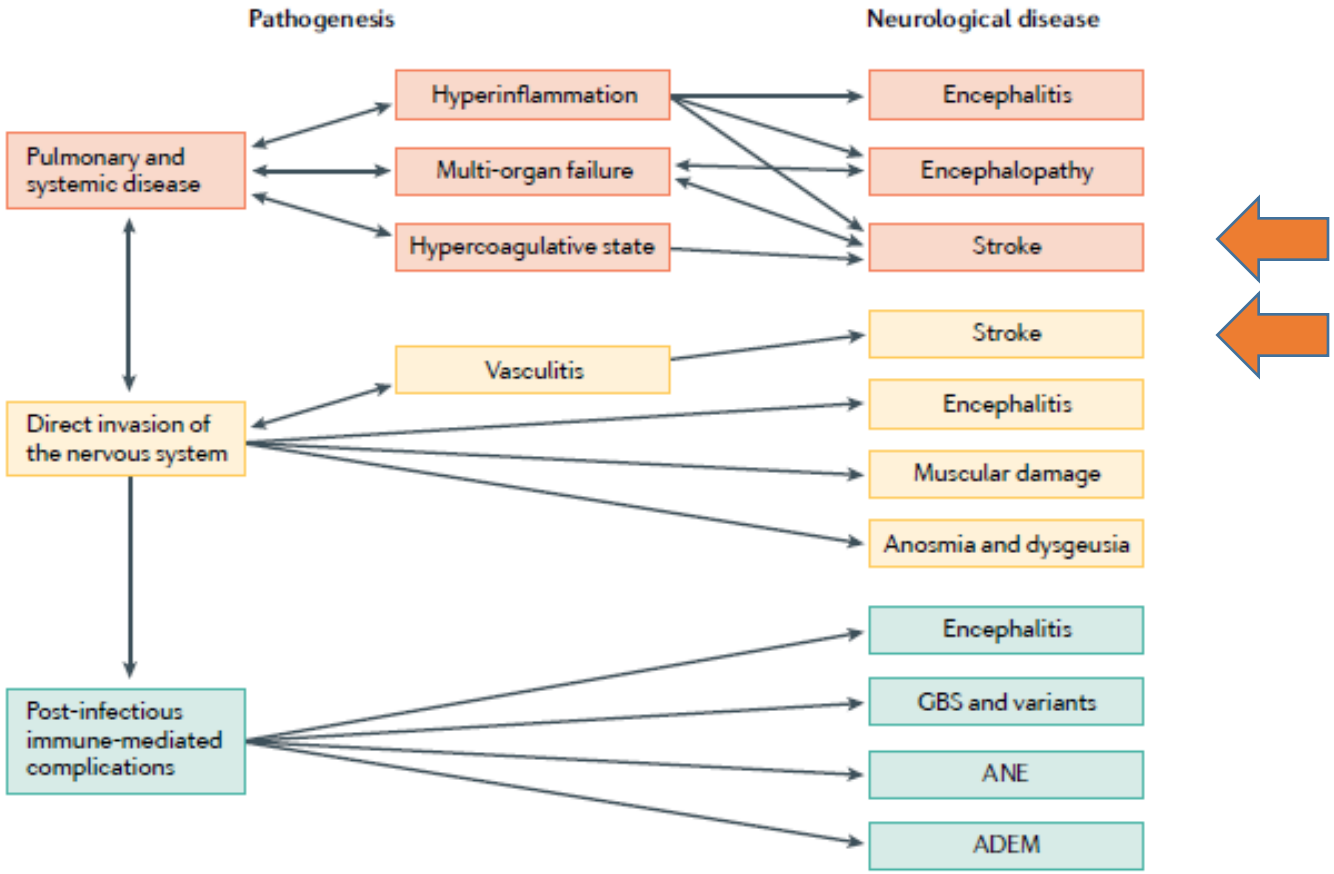
Rege, S., & Mackworth-Young, C. (2015). Antiphospholipid antibodies as biomarkers in psychiatry: review of psychiatric manifestations in antiphospholipid syndrome. Translational Developmental Psychiatry, 3(1), 25452.

Lifting the mask on neurological manifestations of COVID-19

Alessandro Pezzini and Alessandro Padovani

Nat Rev Neurol . 2020 Nov;16(11):636-644

Possible mechanisms underlying neurological manifestations in patients with SARS-CoV-2 infection

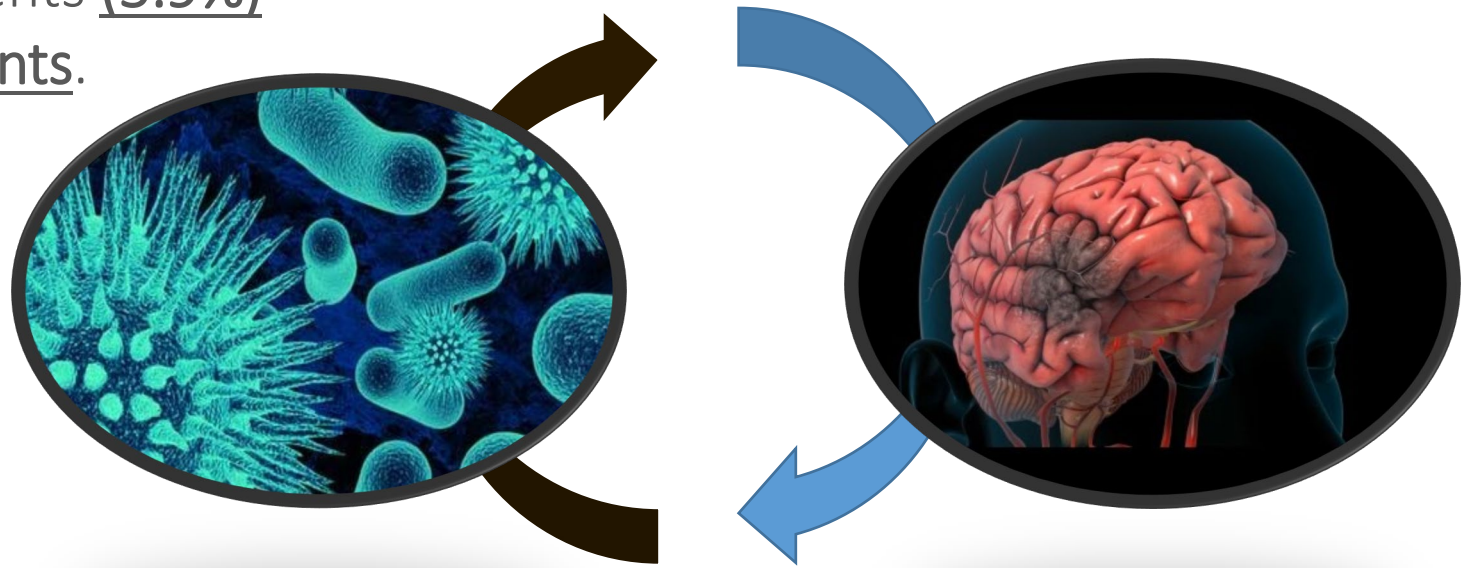


Stroke has been reported among the most frequent neurological features of coronavirus viremia, complicating 2.8% of COVID-19 patients, according to a recent report from three hospital in Wuhan, China.

Previous studies have suggested that bacterial and/or viral infection, may be a trigger for acute ischemic stroke, probably related to the prothrombotic effect of the inflammatory response

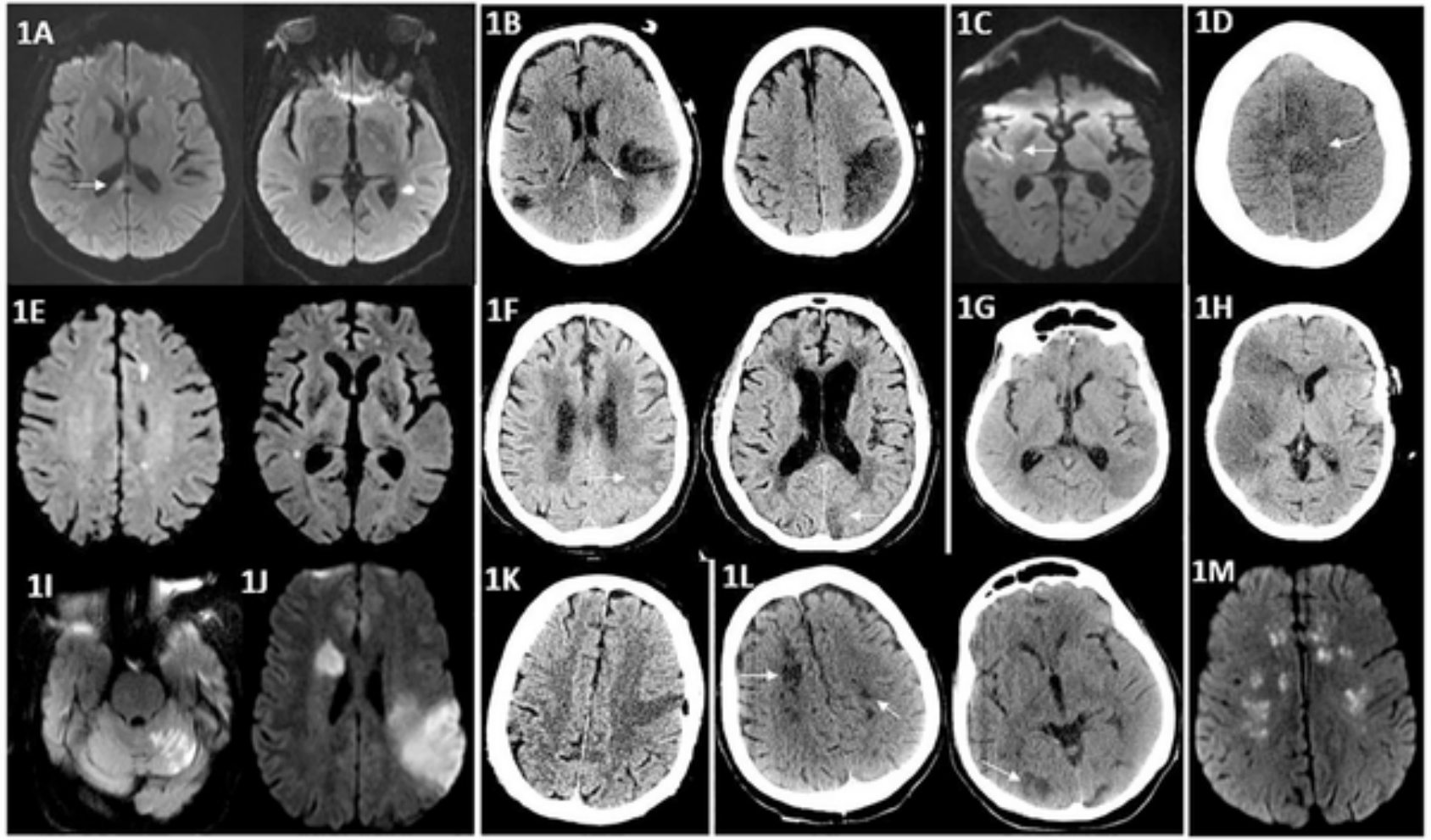
In a retrospective study of 214 hospitalized COVID-19 patients from Wuhan, **5.7% of the severe patients suffered a stroke** (*Mao L. et al. 2020*).

A further single centre retrospective study of 221 admitted COVID-19 patients in Wuhan, *Li et al. (Lancet, 2020)* found that 13 patients **(5.9%) developed acute cerebrovascular events**.



Clinical feature or diagnosis	Mao et al.[7]	Romero-Sánchez et al.[8]	Pinna et al.[9]	Karadaş et al.[10]	Xiong et al.[11]	Helms et al.[12]	Benussi et al.[13]	Paterson et al.[14]	Chen et al.[15]
COVID-19 (total number of patients)	214	841	650	239	917	58	56	43	274
COVID-19 with neurological manifestations (number (%) of patients)	78 (36.4)	483 (57.4)	50 (7.7)	83 (34.7)	39 (4.2)	49 (84.4)	56 (100)[b]	43 (100)[b]	78 (28.4)
CNS manifestations[a]									
Overall	53 (67.9)	NR	NR	NR	NR	NR	NR	35 (81.4)	NR
Dizziness	36 (46.1)	51 (10.5)	NR	16 (19.2)	NR	NR	NR	NR	21 (7.6)
Headache	28 (35.9)	119 (24.6)	12 (24)	64 (77.1)	2 (5.1)	NR	NR	NR	31 (11.3)
Impaired consciousness	16 (20.5)	165 (34.1)	30 (60)	23 (27.7)	25 (64.1)	NR	NR	7 (16.2)	26 (9.5)
Acute stroke	6 (7.7)	14 (2.9)	20 (40)	9 (10.8)	10 (25.6)	NR	43 (76.8)	8 (18.6)	NR
Ataxia	1 (1.3)	NR	1 (2)	NR	NR	NR	NR	NR	NR
Seizures	1 (1.3)	6 (1.2)	13 (26)	NR	0 (0.0)	NR	4 (7.1)	NR	NR
Agitation	NR	NR	NR	NR	NR	40 (6.9)	NR	NR	NR
Confusion	NR	69 (14.2)	NR	NR	NR	26 (65.0)	NR	10 (23.2)	NR
Corticospinal tract signs	NR	NR	NR	NR	NR	39 (67.2)	NR	5 (11.6)	NR
Dysexecutive syndrome	NR	NR	NR	NR	NR	14 (35.8)	NR	NR	NR
Other	NR	NR	NR	NR	NR	NR	9 (16.1)	3 (6.9)	NR
Neuropsychiatric symptoms	NR	167 (34.5)	NR	NR	NR	NR	NR	NR	NR
Movement disorders	NR	6 (1.2)	NR	NR	2 (5.1)	NR	NR	NR	NR
Encephalitis	NR	1 (0.2)	NR	NR	0 (0.0)	NR	NR	12 (27.9)	NR
PNS manifestations[a]									
Overall	19 (24.3)	NR	NR	53 (22.1)	NR	NR	NR	8 (18.6)	NR
Anosmia	11 (14.1)	41 (8.5)	3 (6)	18 (21.7)	NR	NR	NR	NR	NR
Dysgeusia	12 (15.4)	52 (10.7)	5 (10)	16 (19.2)	NR	NR	NR	NR	NR
Dysautonomia	NR	21 (4.3)	6 (12)	NR	NR	NR	NR	NR	NR
AIDP	NR	1 (0.2)	0 (0)	1 (1.2)	NR	NR	NR	7 (16.2)	NR

The Neuroradiological Findings in COVID-19 related Stroke



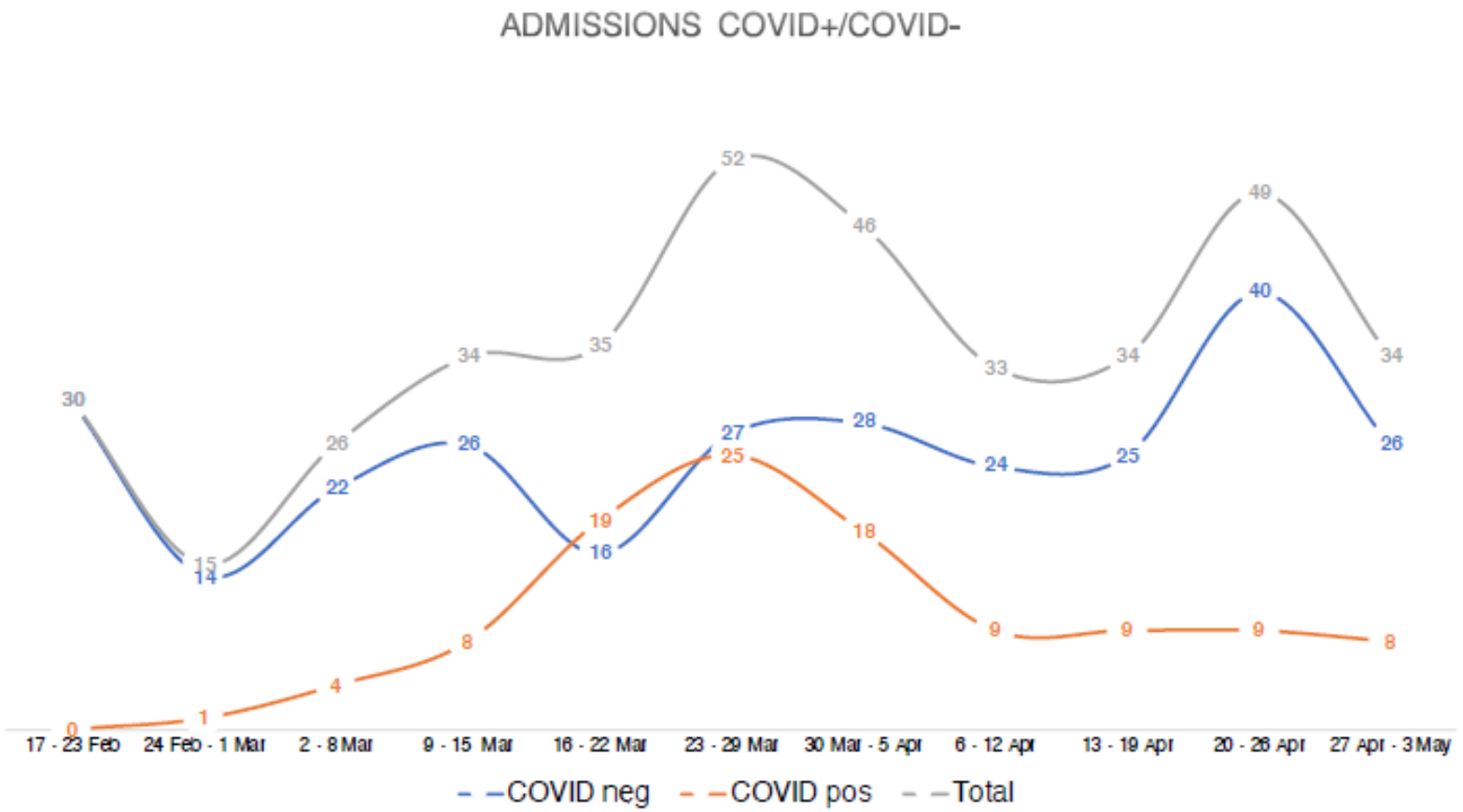
Jillella DV, Janocko NJ, Nahab F, Benameur K, Greene JG, et al. (2020) Ischemic stroke in COVID-19: An urgent need for early identification and management. PLOS ONE 15(9): e0239443. https://doi.org/10.1371/journal.pone.0239443

Is SARSCOV-2 related to Stroke?

COVID-19 impact on consecutive neurological patients admitted to the emergency department

J Neurol Neurosurg Psychiatry 2020;**0**:1–3.
doi:10.1136/jnnp-2020-323929

Hospitalisation of COVID-19 related Neurological Syndromes



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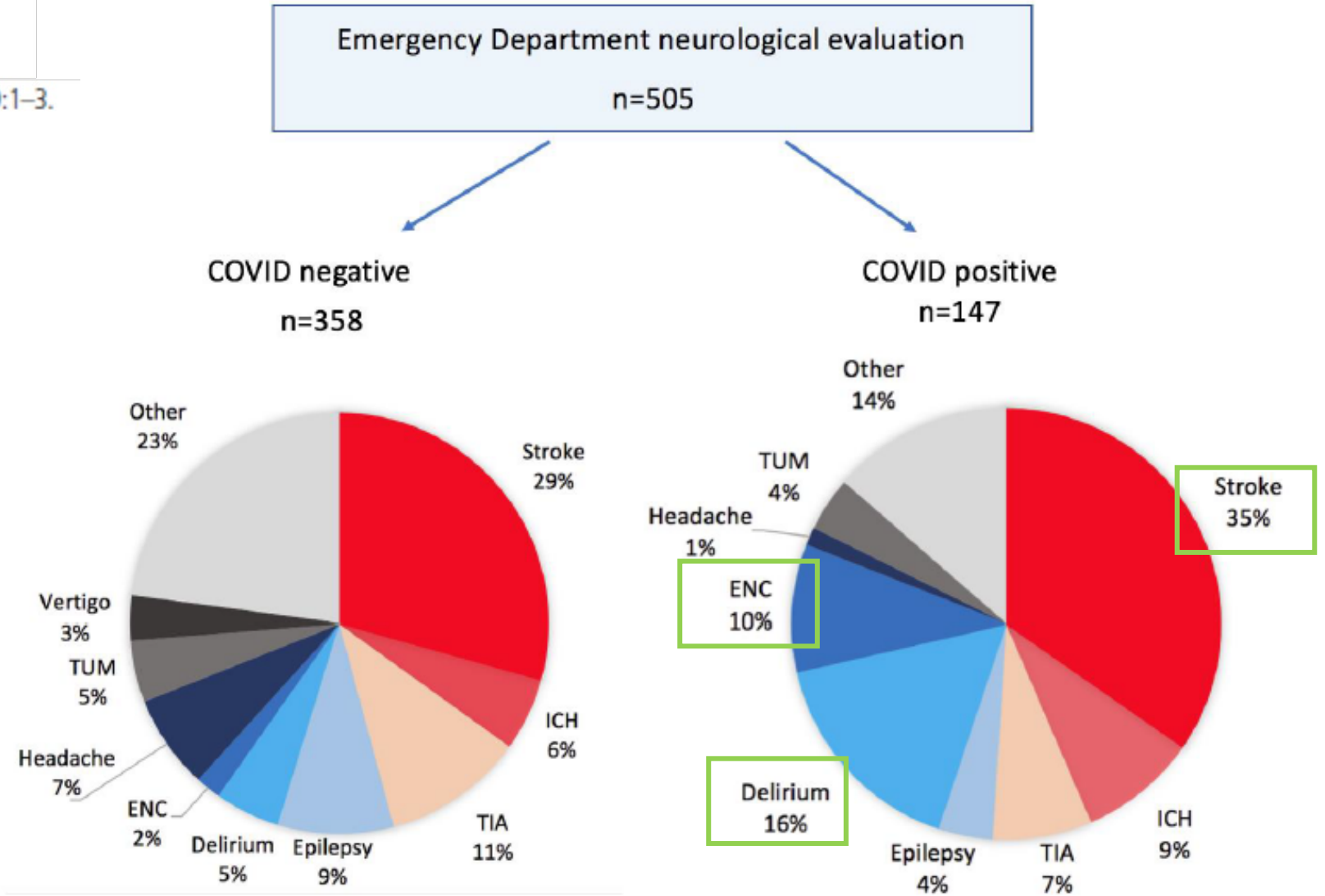
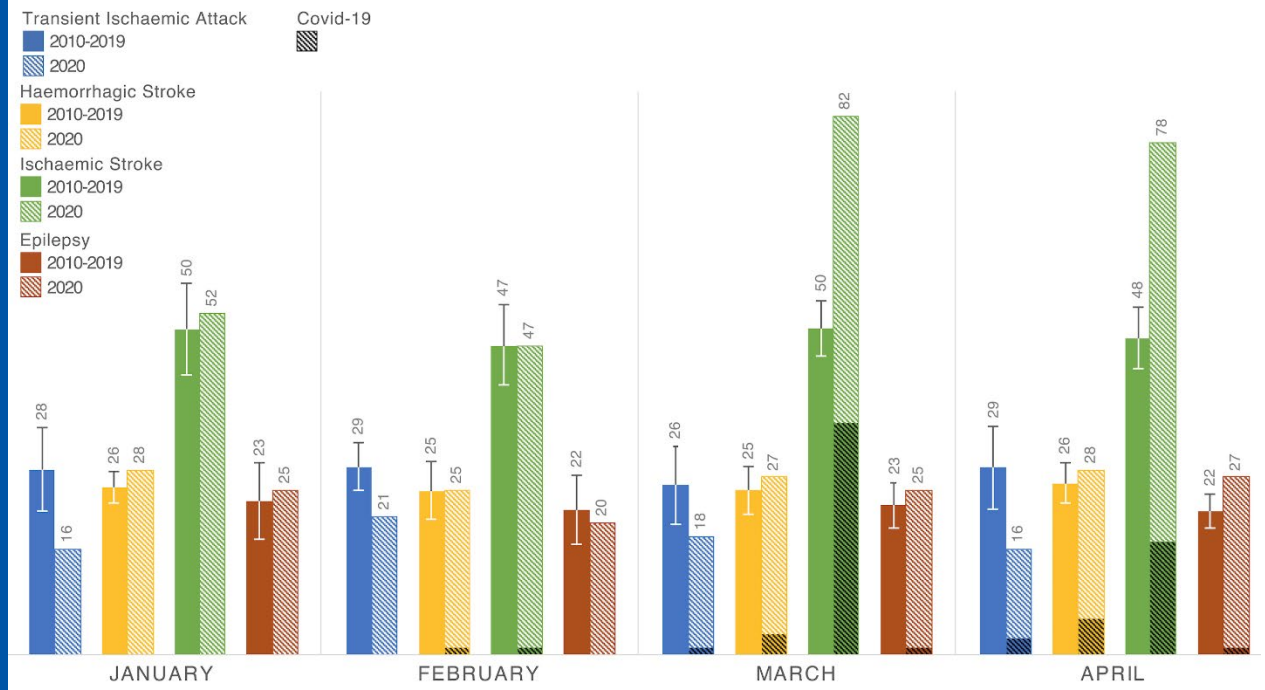
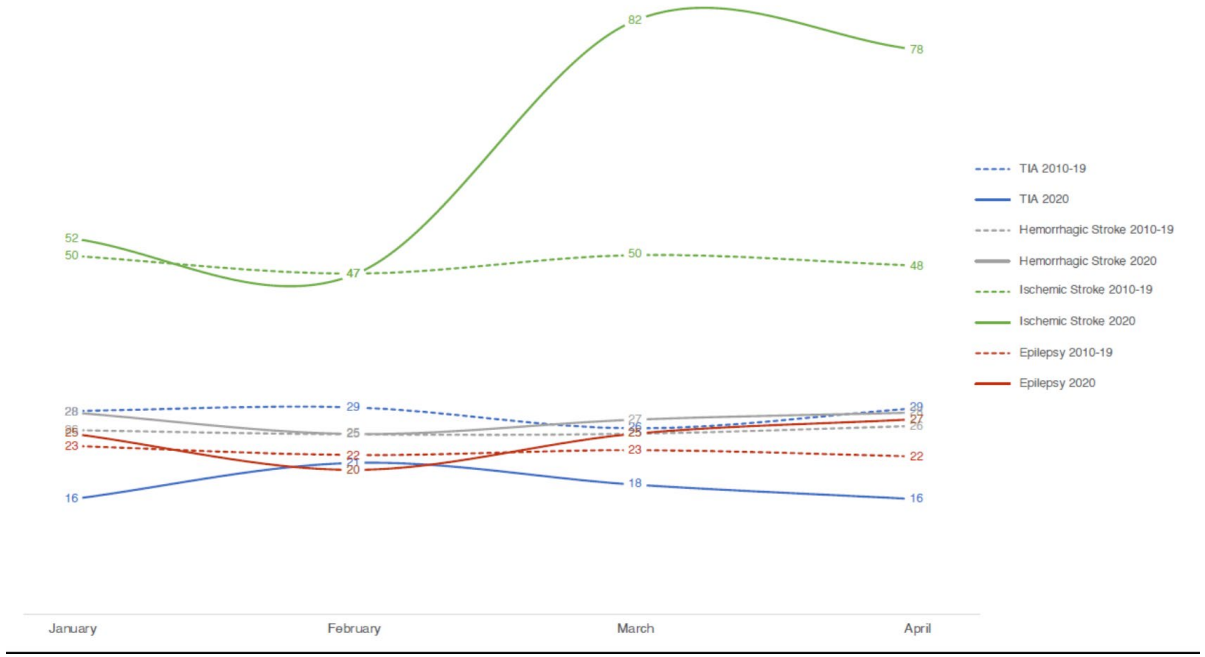


Dati riferiti al 30 aprile 2020

Increased incidence of stroke?

Still a very debated issue





Effects of COVID-19 outbreak on stroke admissions in Brescia, Lombardy, Italy

A. Benussi[a,b], E. Premi[c], A. Pilotto[a,b], I. Libri[a], A. Pezzini[a,b], C. Paolillo[d], B. Borroni[a,b], M. Magoni[c] and A. Padovani[a,b]

Risk of Ischemic Stroke in Patients With Coronavirus Disease 2019 (COVID-19) vs Patients With Influenza.

Merkler et al., JAMA Neurol. 2020;77(11):1366–1372.

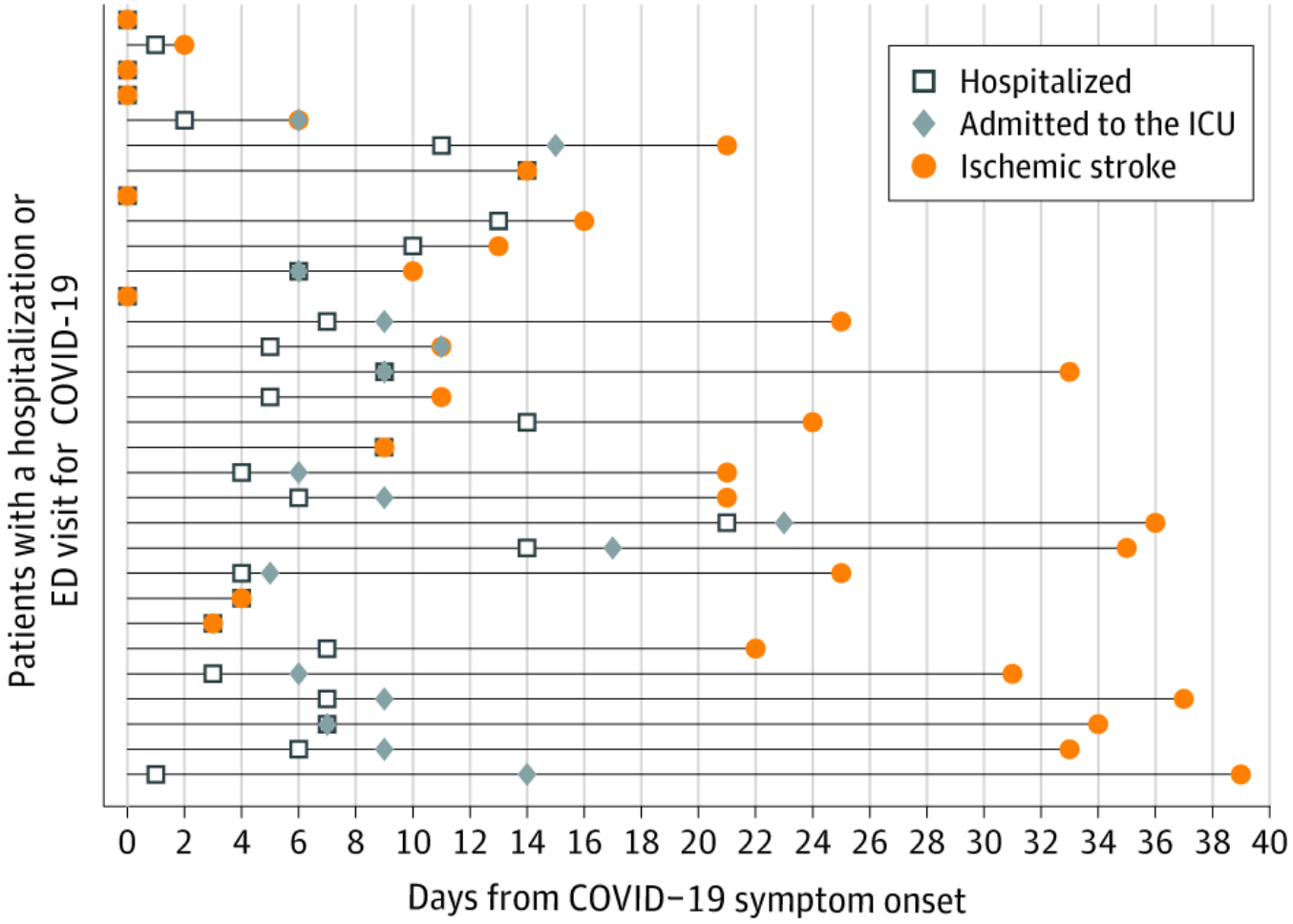


Table 1. Characteristics of Patients With COVID-19 Infection, Stratified by the Diagnosis of Acute Ischemic Stroke

Characteristic[a]	No. (%) Acute ischemic stroke (n = 31)	No. (%) No acute ischemic stroke (n = 1885)
Demographic		
Age, median (IQR), y	69 (66-78)	64 (50-76)
Men	18 (58)	1083 (57)
Race[b]		
White	9 (29)	537 (28)
Black	3 (10)	243 (13)
Asian	8 (26)	248 (13)
Other/unknown	11 (36)	857 (46)
Hispanic ethnicity	1 (3)	368 (20)
Vascular risk factors		
Body mass index[c]	28 (23-34)	28 (24-32)
Hypertension	30 (97)	1158 (61)
Diabetes	23 (74)	806 (43)
Hyperlipidemia	17 (55)	576 (31)
Atrial fibrillation	17 (55)	293 (16)
Chronic kidney disease	8 (26)	300 (16)
Coronary artery disease	16 (52)	479 (25)
COPD	4 (13)	181 (10)
Clinical characteristics		
ICU admission	19 (61)	455 (24)
Mechanical ventilation	11 (35)	319 (17)
Prone positioning	9 (29)	237 (13)
Laboratory data, median (IQR)		
Initial D-dimer, µg/mL	1.930 (0.559-5.285)	0.682 (0.340-1.986)
Initial ESR, mm/h	89 (60-106)	71 (45-99)
Initial WBC count, /µL	10 300 (6900-12 900)	6900 (5000-9700)
Initial platelet count, $\times 10^3$/µL	210 (178-269)	208 (160-275)
Initial troponin I, ng/mL	0.03 (0.03-0.09)	0.03 (0.03-0.06)

Risk of Ischemic Stroke in Patients With Coronavirus Disease 2019 (COVID-19) vs Patients With Influenza.

Merkler et al., JAMA Neurol. 2020;77(11):1366–1372.

Table 2. Characteristics of Acute Ischemic Stroke Among Patients With COVID-19 Infection

Characteristic[a]	Acute ischemic stroke (n = 31)
Stroke symptoms were presenting complaint	8 (26)
NIH Stroke Scale score, median (IQR)	16 (6-23)
Stroke mechanism[b,c]	
Cardioembolic	13 (42)
Large-artery atherosclerosis	2 (7)
Small vessel disease	0 (0)
Other determined	0 (0)
Cryptogenic	16 (52)
ESUS	5(16)
Multiple causes	3 (10)
Incomplete evaluation	8 (26)
Multiple cerebrovascular territories involved	17 (55)
Antiplatelet use prior to stroke	7 (23)
Anticoagulant use prior to stroke	4 (13)
Intravenous thrombolysis administered	3 (10)
Mechanical thrombectomy performed	2 (7)
Symptomatic hemorrhagic transformation	2 (7)

Table 3. Characteristics of Patients With COVID-19 Infection vs Patients With Influenza Infection

Characteristic[a]	No. (%)	
	COVID-19 (n = 1916)	Influenza (n = 1486)
Demographic		
Age, median (IQR), y	64 (51-76)	62 (42-78)
Men	1101 (57)	663 (45)
Race[b]		
White	546 (29)	631 (42)
Black	246 (13)	214 (14)
Asian	256 (13)	139 (9)
Other/unknown	868 (46)	502 (34)
Hispanic ethnicity	369 (19)	270 (23)
Vascular risk factors		
Body mass index, median (IQR)[c]	28 (24-32)	26 (23-30)
Hypertension	1188 (62)	487 (33)
Diabetes	829 (43)	396 (27)
Hyperlipidemia	593 (31)	539 (36)
Atrial fibrillation	310 (16)	125 (8)
Chronic kidney disease	308 (16)	168 (11)
Coronary artery disease	495 (26)	125 (8)
COPD	185 (10)	168 (11)
Clinical characteristics		
ICU admission	474 (25)	96 (6)
Mechanical ventilation	330 (17)	48 (3)
Prone positioning	246 (13)	2 (0)
Laboratory data, median (IQR)		
Initial D-dimer, μg/mL	0.687 (0.342-2.031)	0.402 (0.270-0.778)
Initial ESR, mm/h	71 (45-99)	41 (21-65)
Initial WBC count, μL	7000 (5000-9800)	6700 (4900-9000)
Initial platelet count, $\times 10^3/\mu L$	208 (161-274)	179 (141-222)
Initial troponin I, ng/mL	0.03 (0.03-0.06)	0.03 (0.02-0.05)

Risk of Ischemic Stroke in Patients With Coronavirus Disease 2019 (COVID-19) vs Patients With Influenza.

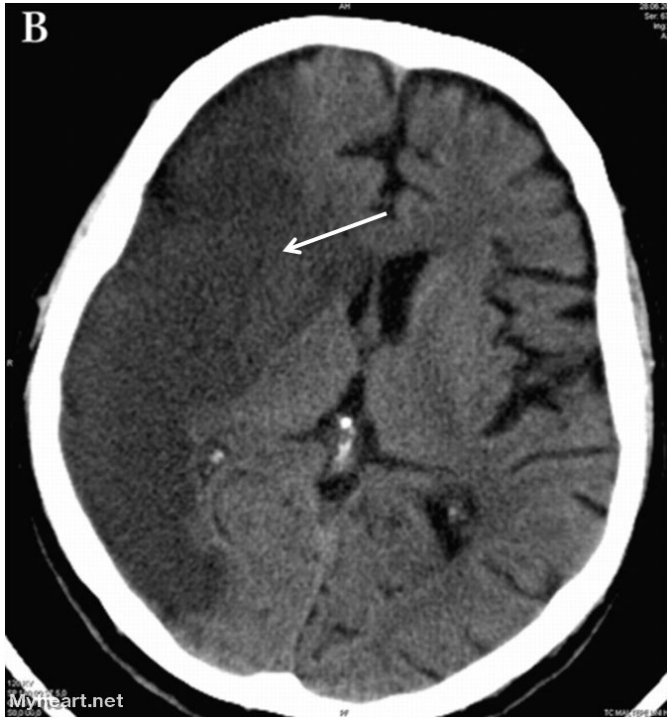
Merkler et al., JAMA Neurol. 2020;77(11):1366–1372.

Analysis	Odds ratio (95% CI)
Primary analyses[a]	
Unadjusted	8.1 (2.5-26.6)
Adjusted for age, sex, and race	7.6 (2.3-25.2)
Sensitivity analyses	
Primary model also adjusting for vascular risk factors[b]	6.2 (1.9-20.5)
Primary model also adjusting for vascular risk factors and ICU admission[c]	4.6 (1.4-15.7)
Patients with viral syndrome symptoms[d]	7.0 (2.1-23.4)
Patients with COVID-19 infection presenting from April 4, 2020, to May 2, 2020[e]	8.3 (2.4-28.5)
Patients admitted to the hospital[f]	5.6 (1.7-18.7)
Patients admitted to the hospital with viral syndrome symptoms[g]	4.0 (1.2-13.7)
Patients treated at the quaternary care center[h]	9.3 (2.8-30.8)

- In an unadjusted analysis, **patients with COVID-19 were more likely to have an acute ischemic stroke than patients with influenza**, also after adjustment for age, sex, and race (OR, 7.6; 95% CI, 2.3-25.2).
- **The association between COVID-19 and acute ischemic stroke persisted across multiple sensitivity analyses**, with the magnitude of relative associations ranging from 4.0 to 9.3, **even when adjusted for the number of vascular risk factors and ICU admissions** (OR, 4.6; 95% CI, 1.4-15.7).

Is stroke in COVID-19 different?

Worse neurological admission and prognosis
High mortality rate 10-30% according to different series



Pezzini et al- submitted

Multi-centre study 174 stroke 65 positive

Higher prevalence of atrial fibrillation

High frequency of large-vessel disease?

Association with LAC?

Large consortia are neede

A. Benussi[a,b], E. Premi[c], A. Pilotto[a,b], I. Libri[a], A. Pezzini[a,b], C. Paolillo[d], B. Borroni[a,b], M. Magoni[c] and A. Padovani[a,b]

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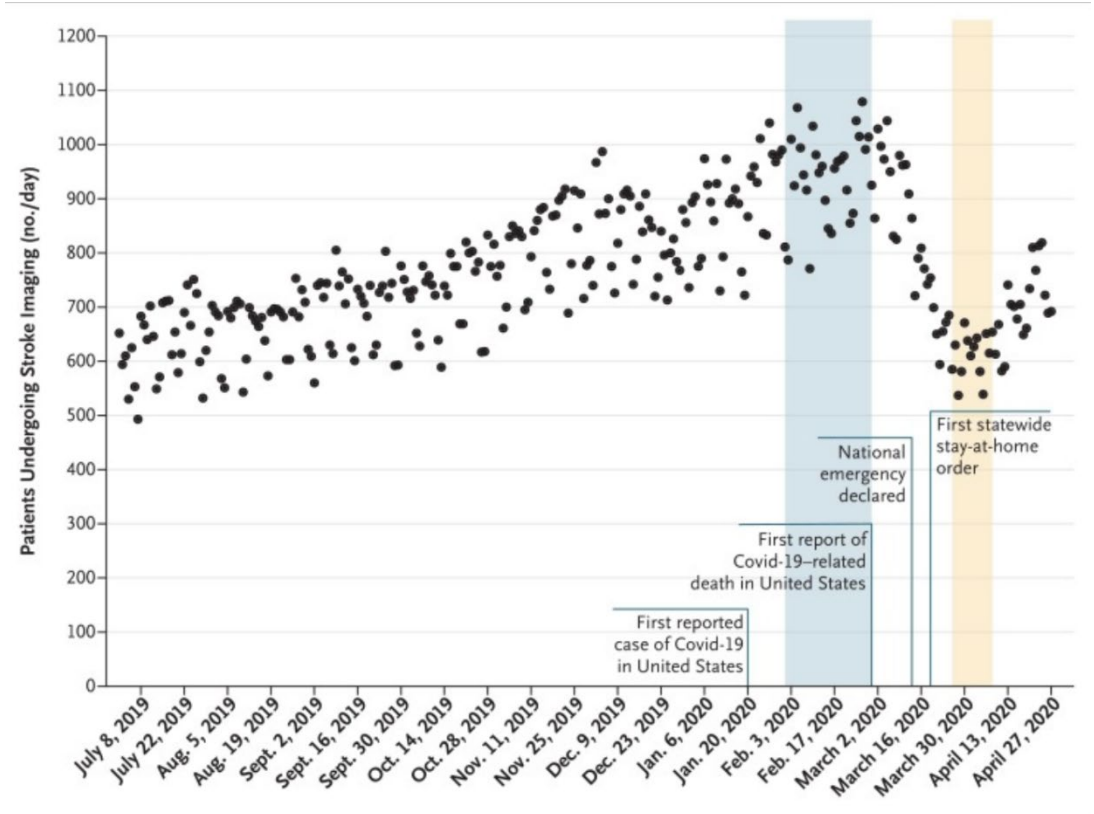
	TIA (n = 3561)	Ischaemic stroke (n = 6324)	Haemorrhagic stroke (n = 3100)	Epilepsy (n = 2678)
1 January 2010–20 February 2020				
Patients	3527	6164	3045	2626
Average monthly discharges	28.9 ± 8.2	50.5 ± 8.2	25.0 ± 4.9	21.5 ± 5.3
Age, years	72.9 ± 14.2	70.6 ± 14.1	66.0 ± 15.6	57.5 ± 9.7
Sex				
Female	1 836 (52.1%)	2 748 (44.6%)	1 490 (48.9%)	1 202 (45.8%)
Male	1 689 (47.9%)	3 414 (55.4%)	1 555 (51.1%)	1 423 (54.2%)
Hospital length of stay, days	8.9 ± 7.0	9.9 ± 7.5	13.5 ± 12.8	9.7 ± 9.4
In hospital mortality	1.9%	6.6%	22.3%	2.7%
21 February 2020–30 April 2020				
Patients	34	160	55	52
Average monthly discharges	17.0 ± 1.4	80.0 ± 2.8	27.5 ± 0.7	26.0 ± 1.4
Age, years	72.2 ± 13.7	72.3 ± 12.3	69.4 ± 15.8	59.3 ± 17.4
Sex				
Female	13 (38.2%)	67 (41.9%)	23 (41.8%)	23 (44.2%)
Male	21 (61.8%)	93 (58.1%)	32 (58.2%)	29 (55.8%)
SARS-CoV-2 positivity	3 (8.8%)	53 (33.1%)	8 (14.5%)	2 (3.8%)
Hospital length of stay, days	7.2 ± 5.7	7.0 ± 4.4	8.8 ± 8.0	7.5 ± 6.2
In hospital mortality	11.8%	12.5%	47.3%	7.7%

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TIA, transient ischaemic attack. Data are reported as mean ± SD or n (%).

Are COVID-19 Stroke patients adequately treated?

How manage stroke in COVID-19?

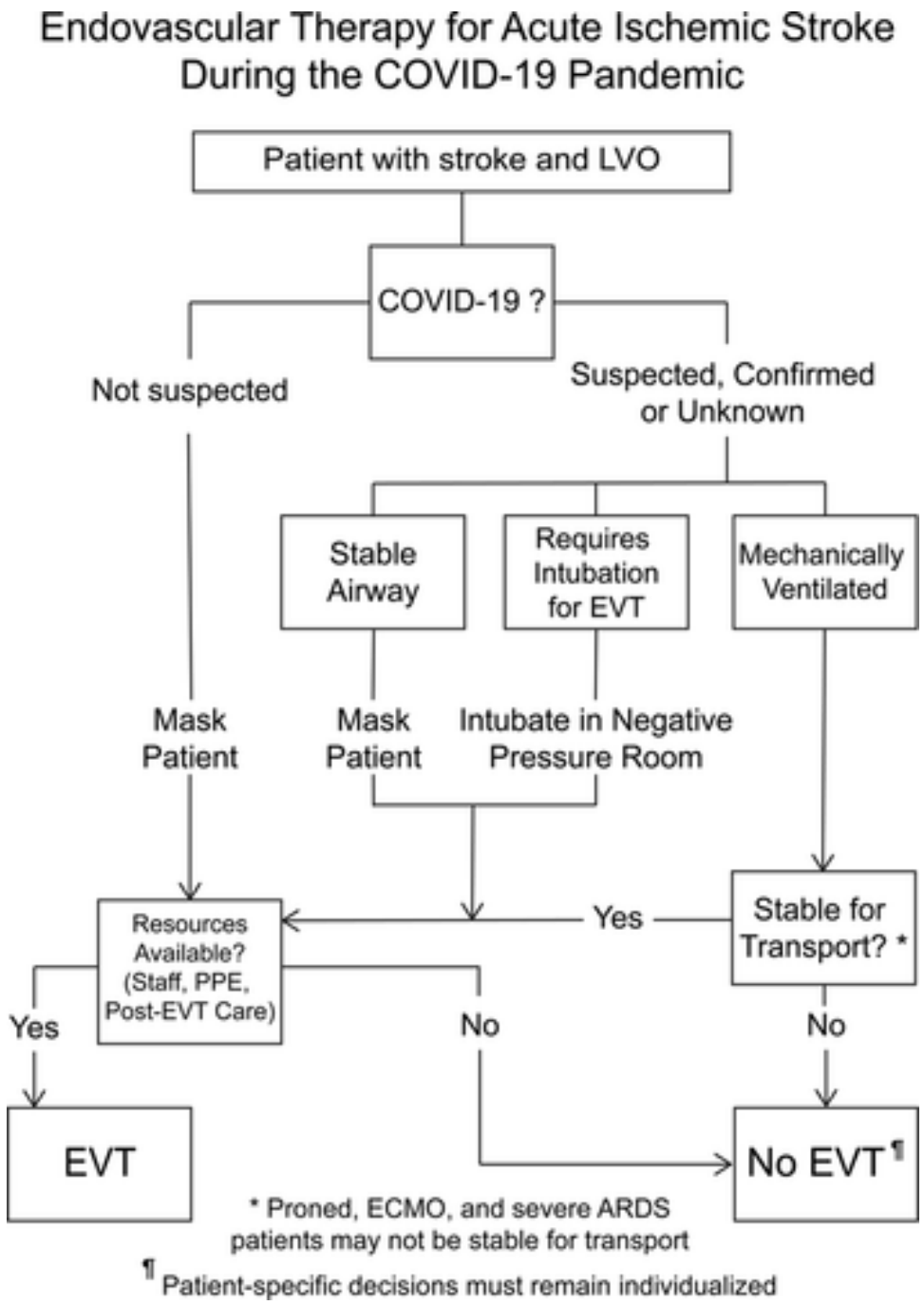


Kansagra et al 2020

Early management and Care

Endovascular treatments and Thrombolysis are NOT controindicate

Matthew S. Smith. Stroke. Endovascular Therapy for Patients With Acute Ischemic Stroke During the COVID-19 Pandemic: A Proposed Algorithm, Volume: 51, Issue: 6, Pages: 1902-1909, DOI: (10.1161/STROKEAHA.120.029863)



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With the outbreak of COVID-19, many extreme measures have been taken to contain the spread of the disease, which **include converting general medical wards to quarantine wards for patients who contracted the disease**, **locking down the communities, suspending routine outpatient clinics**, **stopping all elective procedures**, and providing treatment only for very highly selective cases

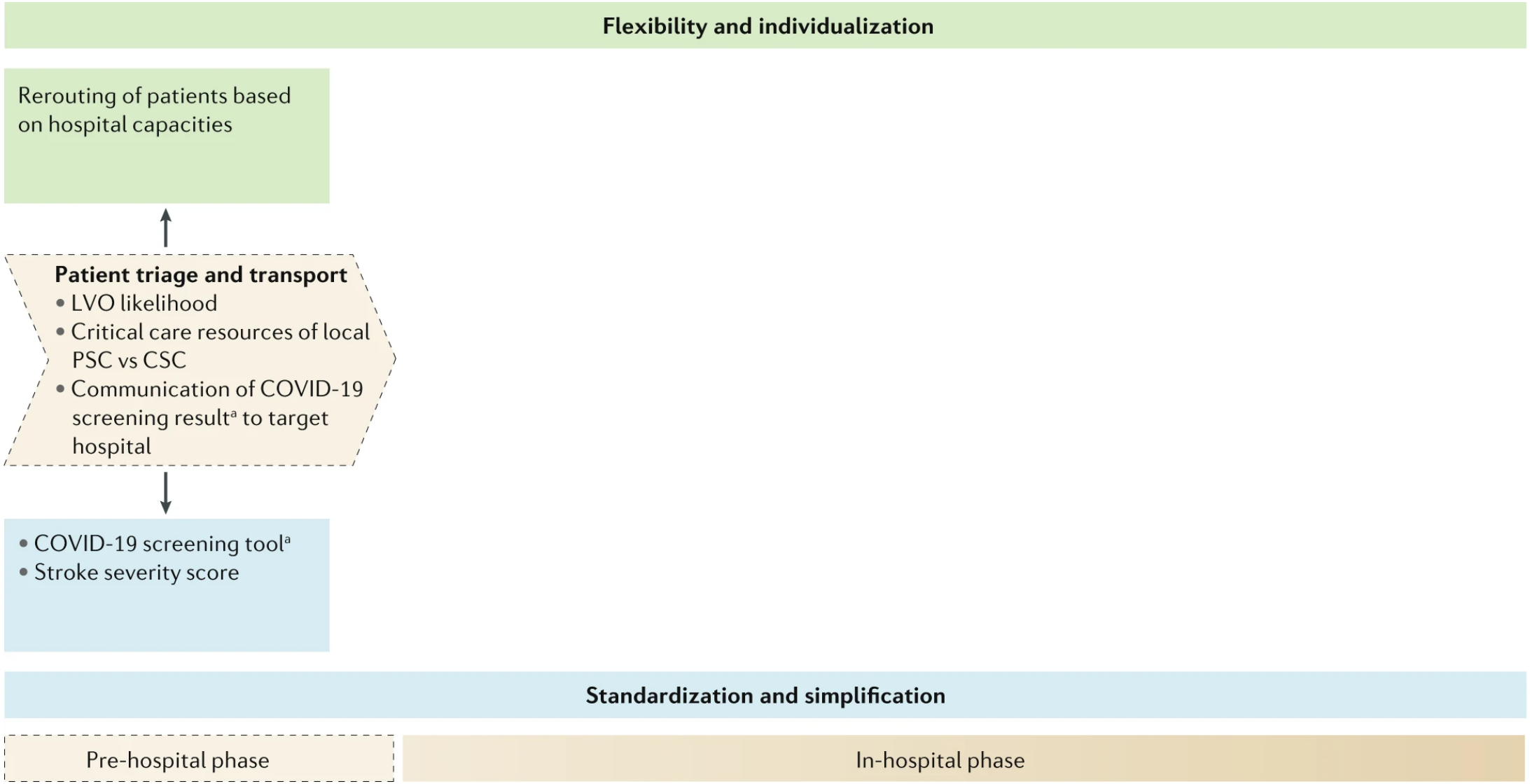
Normal medical care across the world has been seriously impaired with stroke being at the forefront given that it is the top cause of death and disability.

Many stroke centers across most countries have greatly reduced functioning because of fear of in-hospital cross infection and lack of experienced stroke care experts.

Some data showed that the number of thrombectomies decreased by 50% in the first month after the outbreak

The COVID-19 pandemic presents substantial challenges for acute stroke treatment. Not only do patients with COVID-19 seem to be more vulnerable to cerebral ischaemia, but the need to screen patients with acute stroke for COVID-19 symptoms and impose additional protective measures to promote infectious control in the ambulance and neuroangiography suite and on hospital wards carries the risk of substantial treatment delays.

COVID-19-related challenges in EVT workflows



Ospel, J.M., Goyal, M. Endovascular stroke treatment during the COVID-19 pandemic. Nat Rev Neurol 16, 351–352 (2020)

Strategies to be implemented to ensure that stroke patients do not suffer as a consequence of emergency response to epidemics taking priority

- The establishment of stroke networks and care systems able to deliver high-quality emergency stroke care at all times but particularly at times of crisis.

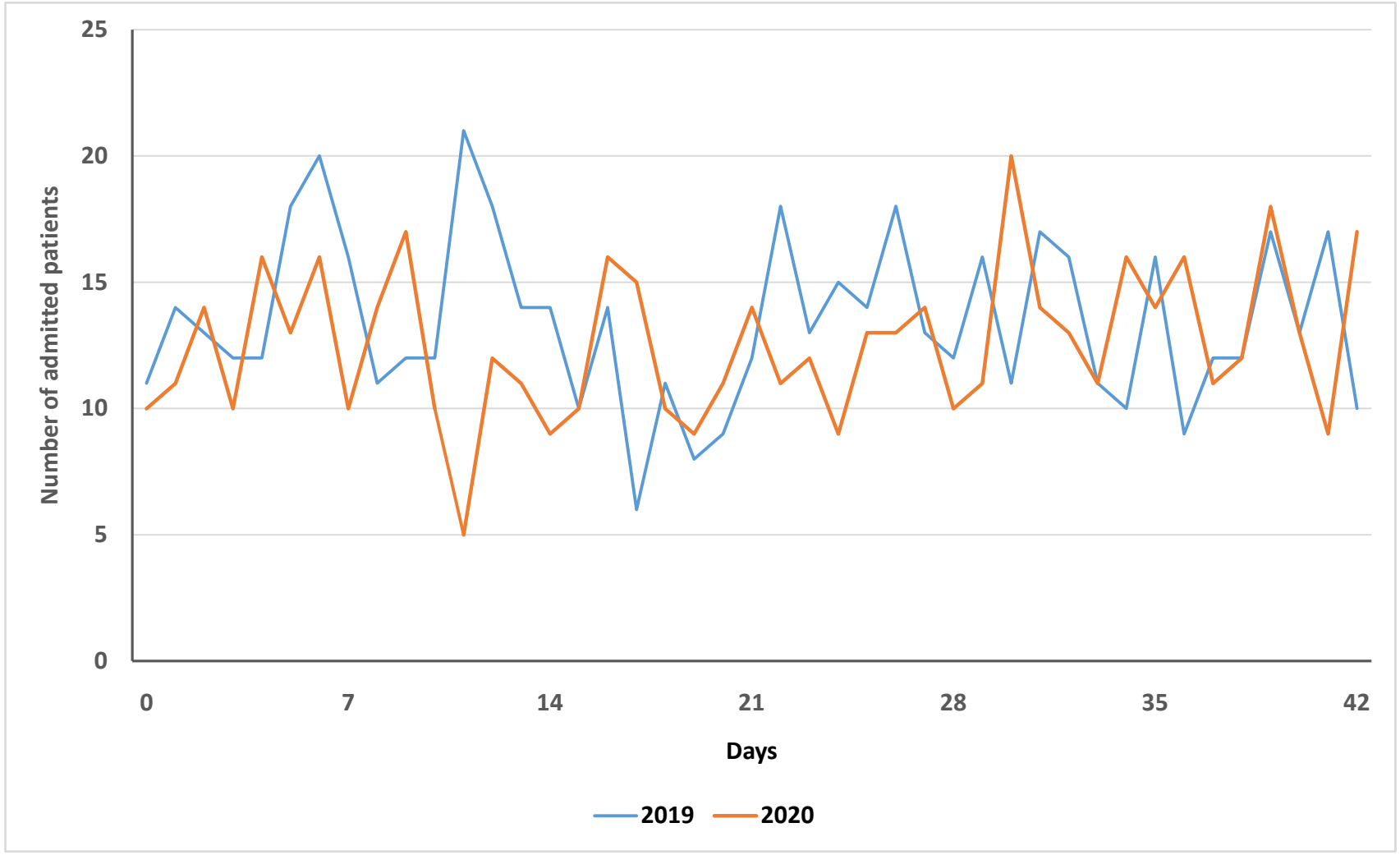
- The establishment of **centralized stroke treatment centers** where sufficient stroke care resource can be secured. Although there is a strong case for such centers to be the system of care at all times, it is particularly important at times of medical crisis to have services that can continue to function.

- Inform the emergency medical system and the public that these centers will be protected and will remain fully operational even during crises.

- **Improve education of health professionals and the public**, especially those who are at high risk of stroke, to recognize stroke and call emergency medical services immediately to be taken to one of the designated stroke centers so as to avoid significant delay in transferring patient from one hospital to the other.

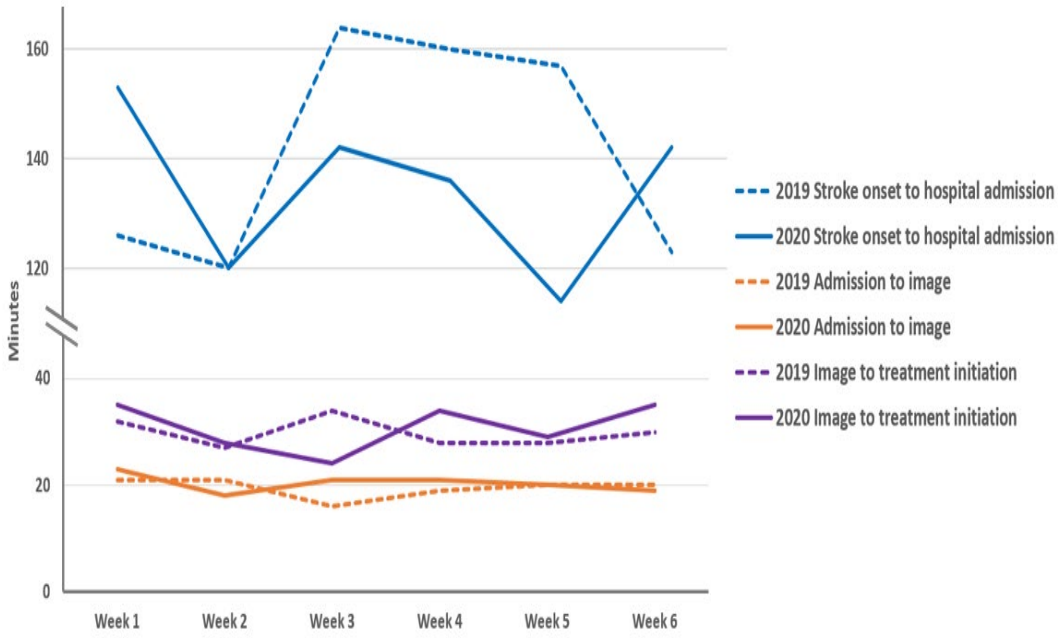
What’s the reality?

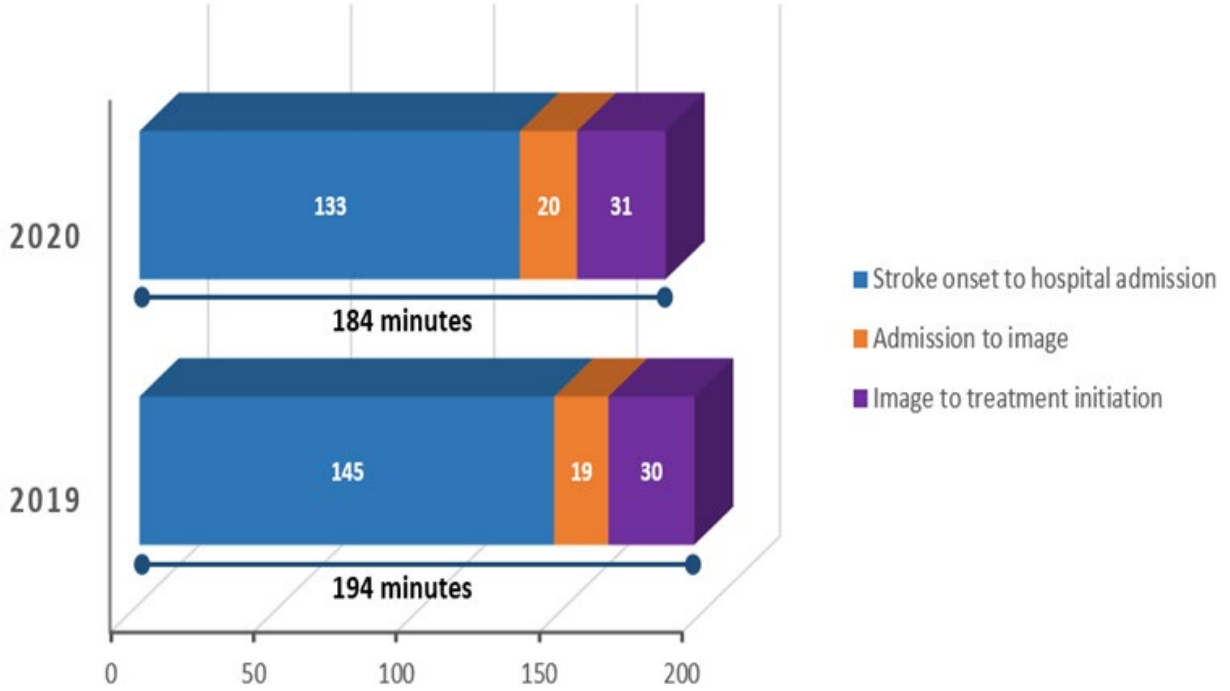
A European Survey on STROKE Management during the COVID-19 first Outbreak



Number of admitted IVT/EVT-treated patients each day after lockdown (2020) and during the reference period (2019)

Median time intervals per week after announcement of lockdown for different performance measures





	Total (n = 174)	COVID19+ (n = 65)	COVID19- (n = 109)	p-value
Age, years, median (IQR)	76 (65 - 83)	75 (66 - 83)	76 (63 - 83)	0.581
Sex, Male	107 (61.5)	43 (66.2)	64 (58.7)	0.329
Body Mass Index (kg/m^2)	25.8 (23.8 - 28.5)	25.9 (24.4 - 28.0)	25.7 (23.7 - 28.7)	0.555
Hypertension	134 (77.0)	45 (69.2)	89 (81.7)	0.060
Diabetes	40 (23.0)	14 (21.5)	26 (23.9)	0.853
Hypercholesterolemia	66 (37.9)	21 (32.3)	45 (41.3)	0.238
Smoking habit				0.034
Never smoker	119 (68.4)	52 (80)	67 (61.5)	
Former smoker	34 (19.5)	9 (13.8)	25 (22.9)	
Current smoker	21 (12.1)	4 (6.2)	17 (15.6)	
Coronary heart disease	42 (24.1)	19 (29.2)	23 (21.1)	0.272
Atrial fibrillation	43 (24.7)	23 (35.4)	20 (18.3)	0.018
Malignancies	15 (8.6)	4 (6.2)	11 (10.1)	0.419
Chronic kidney disease	11 (6.3)	3 (4.6)	8 (7.3)	0.541
Chronic obstructive lung disease	9 (5.2)	4 (6.2)	5 (4.6)	0.729
Personal history of ischemic stroke	32 (18.4)	7 (10.8)	25 (22.9)	0.067
Pre stroke modified Rankin Scale (mRS), median (IQR)	1 (0 - 2)	1 (0 - 2)	1 (0 - 1)	0.316

	COVID19+ (n = 65)	COVID19- (n = 109)	p-value
White blood cell count, x 10^9 per L	8.68 (6.30 - 12.23)	8.44 (6.95 - 11.07)	0.754
Lymphocyte count, x 10^9 per L	1.03 (0.74 - 1.35)	1.68 (1.25 - 2.09)	≤0.001
Neutrophil count, x 10^9 per L	7.31 (4.88 - 10.04)	5.76 (3.92 - 8.00)	0.027
Glucose, mg/dl	132 (110 - 177)	115 (96 - 166)	0.132
Haemoglobin, g/L	13.7 (11.8 - 16.7)	13.5 (11.9 - 15.2)	0.907
Platelet count, x 10^9 per L	250 (174.5 - 311.5)	254 (194.0 - 300.5)	0.531
International Normalized Ratio (INR)	1.07 (0.97 - 1.07)	1.00 (0.97 - 1.08)	0.265
ALT, U/L	28 (19 - 48)	18 (14 - 27)	0.004
Lactate dehydrogenase, U/L	342 (234.7 - 513.5)	222 (170.5 - 293)	≤0.001
Creatinine, mg/dl	1.00 (0.8 - 1.25)	1.00 (0.79 - 1.20)	0.880
Albumin, g/L	32 (29.2 - 36)	38 (35.42 - 41)	≤0.001
Creatine kinase, U/L	86.5 (51.7 - 233.2)	98.50 (63.7 - 173.5)	0.860
Prothrombin time, s	12.1 (1.15 - 14.9)	12 (10.65 - 12.65)	0.665
C reactive protein, mg/dl	19.7 (5.4 - 66.1)	2.9 (0.8 - 8.1)	≤0.001
Fibrinogen, mg/dl	503 (408 - 596)	333 (260 - 423)	≤0.001
High-sensitivity cardiac troponin I, pg/ml	15 (1.7 - 34.5)	2.6 (0.0 - 20.9)	0.028

	Total (n = 174)	COVID19+ (n = 65)	COVID19- (n = 109)	p-value
Systolic blood pressure on admission, mm Hg, median (IQR)	140 (125 - 160)	140 (120 - 150)	150 (127.5 - 160)	0.025
Dyastolic blood pressure on admission, mm Hg, median (IQR)	80 (70 - 90)	80 (70 - 90)	81.5 (70 - 90)	0.711
Stroke severity, NIHSS score, median (IQR)	6 (3 - 15.2)	10 (3 - 16.5)	5 (3 - 14)	0.015
Cause of stroke				0.039
Large-vessel disease	33 (19.0)	9 (13.8)	24 (22.0)	
Cardiac embolism	61 (35.1)	32 (49.2)	29 (26.6)	
Small-vessel disease	14 (8.0)	3 (4.6)	11 (10.1)	
Other determined etiology	5 (2.9)	1 (1.5)	4 (3.7)	
Undetermined etiology	61 (35.1)	20 (30.8)	41 (37.6)	
Revascularization therapy		9 (13.8)	26 (23.9)	0.340
IV thrombolysis	11 (6.3)	4 (6.2)	7 (6.4)	0.660
Endovascular thrombectomy	20 (11.5)	5 (7.7)	15 (13.8)	
IV thrombolysis and endovascular thrombectomy	6 (3.4)	2 (3.1)	4 (3.7)	
Process measures				
Time from stroke onset to hospital admission, minutes, median (IQR)	230 (120.5 - 511)	240 (144.5 - 556)	208 (111 - 479.5)	0.699
Time from stroke onset to brain imaging, minutes, median (IQR)	304 (168 - 673.5)	482 (188.5 - 932.2)	267 (155.7 - 508.5)	0.037

Although time from stroke symptoms onset to baseline brain imaging did not differ in the 2 groups, the median time from stroke symptoms onset to femoral puncture was longer in the COVID-19+ group than in the COVID-19- group (270 [IQR, 270 – 540] minutes vs 222.5 [IQR, 150 – 290] minutes; p = 0.030) and so was the median time from femoral puncture to recanalization (42 [IQR, 39 – 51] minutes vs 38 [IQR, 22 – 40] minutes; p = 0.026).

Stroke in COVID19: predictors of outcome

The complex interplay between aging, frailty, delirium and brain

Clinical characteristics and outcomes of inpatients with neurologic disease and COVID-19 in Brescia, Lombardy, Italy. Neurology. 2020 Aug 18;95(7):

	Total (n = 111)	Non–COVID-19 (n = 68)	COVID-19 (n = 43)	*p* Value
Cerebrovascular event, n (%)				0.560
TIA	13 (11.7)	8 (11.8)	5 (11.6)	
Ischemic stroke	85 (76.6)	50 (73.5)	35 (81.4)	
Hemorrhagic stroke	13 (11.7)	10 (14.7)	3 (7.0)	
Outcomes				
In hospital mortality, n (%)	19 (17.1)	4 (5.9)	15 (34.9)	<0.001
Incident delirium, n (%)	13 (11.7)	4 (5.9)	9 (20.9)	0.047
Fever during hospitalization, n (%)	29 (26.1)	8 (11.8)	21 (48.8)	<0.001
Hospital length of stay, d	5.0 (4.0–8.0)	5.0 (4.0–8.0)	6.0 (4.0–9.0)	0.425
mRS score premorbid	1.0 (0.0–2.0)	1.0 (0.0–2.0)	1.0 (0.0–1.0)	0.727
mRS score discharge	2.0 (1.0–5.0)	2.0 (1.0–3.0)	5.0 (2.0–6.0)	<0.001
Good outcome	59 (53.2)	48 (70.6)	11 (25.6)	<0.001
NIHSS admission	5.0 (2.0–15.0)	4.0 (2.0–14.8)	10.0 (3.0–15.0)	0.147
NIHSS discharge	3.0 (0.0–10.0)	2.0 (0.0–6.8)	9.0 (1.0–19.0)	0.005

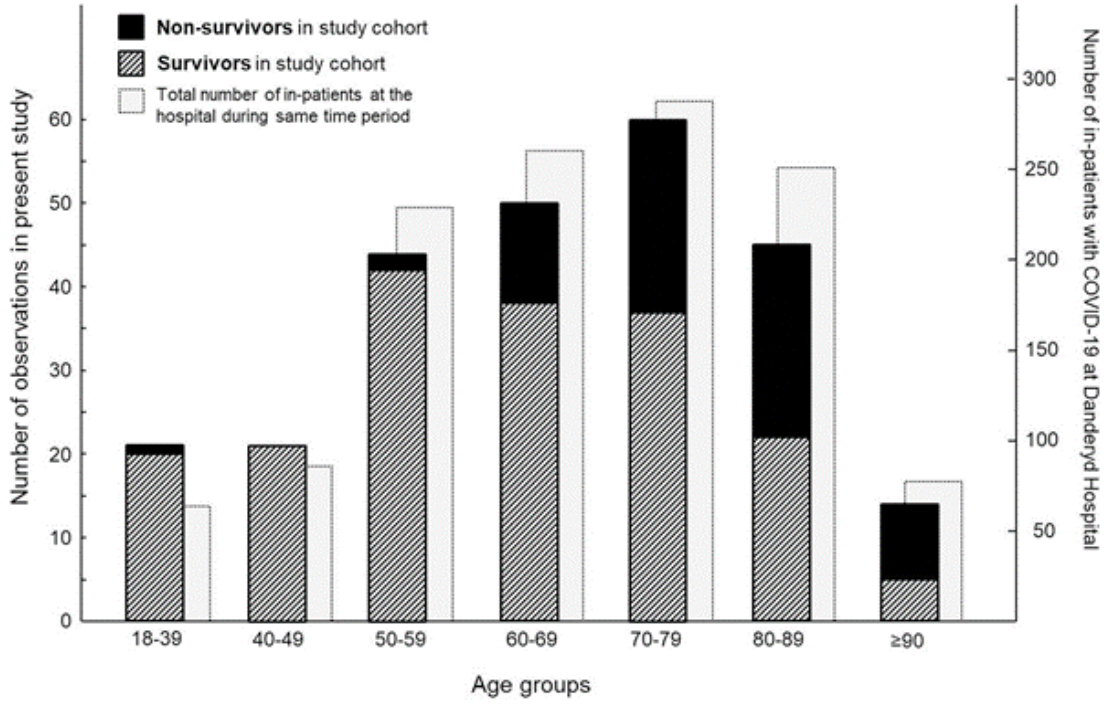
	Non-survivor (n = 27)	Survivor (n = 38)	p-value
Age, years, median (IQR)	81 (73 - 85)	70.5 (62.75 - 70.5)	0.068
Sex, Male	21 (77.8)	22 (57.9)	0.116
Stroke severity, NIHSS score, median (IQR)	15 (8 - 22)	6 (2.75 - 12.0)	0.013
qSOFA score	1 (1 - 2)	0 (0 - 1)	0.087
SARS-CoV-2-related clinical features			
Fever, (temperature ≥ 37.5° C)	13 (48.1)	9 (23.7)	0.062
Respiratory rate, > 24 breaths per minute	8 (47.1)	3 (10.0)	0.009
Dyspnoea	21 (77.8)	17 (44.7)	0.011
Cough	13 (48.1)	17 (44.7)	0.786
Sputum	4 (14.8)	4 (10.5)	0.709
Myalgia	6 (22.9)	4 (10.5)	0.297
Fatigue	16 (59.3)	14 (36.8)	0.074
Diarrhoea	1 (3.7)	1 (2.6)	1.000
Nausea or vomiting	0 (0.0)	4 (10.5)	0.135

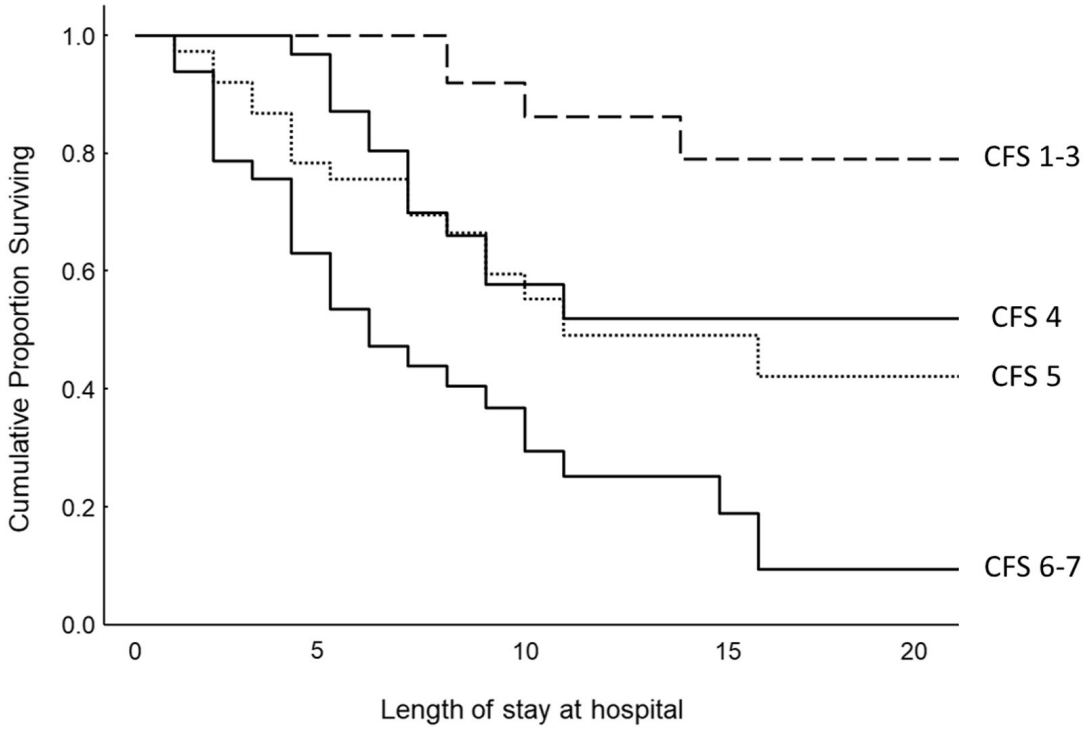
	Non-survivor (n = 27)	Survivor (n = 38)	p-value
White blood cell count, x 10^9 per L	10.1 (6.35 - 15.8)	8.29 (6.23 - 10.48)	0.266
Lymphocyte count, x 10^9 per L	0.96 (0.67 - 1.54)	1.05 (0.77 - 1.33)	0.782
Neutrophil count, x 10^9 per L	8.53 (4.78 - 11.87)	7.03 (4.98 - 8.59)	0.418
Glucose, mg/dl	147.5 (110.7 - 170.2)	132 (109 - 179)	0.678
Haemoglobin, g/dl	13.9 (10.9 - 16.3)	13.5 (12 - 17)	0.917
Platelet count, x 10^9 per L	202 (160 - 292)	261 (194.5 - 334.2)	0.160
International Normalized Ratio (INR)	1.12 (1.00 - 1.41)	1.02 (0.9 - 1.2)	0.072
ALT, U/L	36 (19 - 49)	27 (18.5 - 49)	0.266
Lactate dehydrogenase, U/L	481 (340 - 704)	278 (217 - 377.5)	0.007
Creatinine, mg/dl	1.01 (0.83 - 1.3)	0.9 (0.7 - 1.2)	0.420
Albumin, g/L	30.2 (26.3 - 37.7)	32.4 (29.9 - 36.2)	0.569
Creatine kinase, U/L	131 (69 - 384)	73 (39.5 - 155)	0.238
Prothrombin time, s	12.2 (1.11 - 15.4)	11.95 (1.23 - 13.5)	0.770
C reactive protein, mg/dl	25.1 (8.45 - 78.0)	17.7 (5.0 - 64.3)	0.718
Fibrinogen, mg/dl	484 (317 - 623.7)	515 (425 - 562)	0.815
High-sensitivity cardiac throponin I, pg/ml	29 (0 - 43)	14 (6 - 21.7)	0.874
d-Dimer, microg/ml	2589 (1882.7 - 28601.2)	1257 (668 - 3957)	0.605
Ferritin, microg/L	587 (280 - 2430)	612 (390 - 1238.5)	1.000
Procalcitonin, ng/ml	2.65 (0.27 - 8.32)	0.24 (0.1 - 0.53)	0.524
Interleukin 6, pg/ml	124.7 (32.4 - 291.2)	22.3 (15.0 - 46.8)	0.524

- Non-survivors were older, had a higher quick Sequential Organ Failure Assessment (qSOFA) score and increased serum concentration of LDH on admission.
- Conversely, apart for a more severe stroke presentation of COVID-19+ patients (NIHSS score, 15 [8-22] vs 6 [2.75-12.0]; p=0.013), the two groups did not differ in stroke characteristics.
- On multinomial logistic regression analysis including the NIHSS score, age, qSOFA and serum LDH levels**, increasing age (OR, 1.09; 95% CI, 1.00 – 1.19 per year increase) and higher qSOFA score (OR, 5.71; 95% CI, 1.56 – 20.84) were independently associated with in-hospital death,** while there was a trend towards association for serum LDH levels (OR, 1.00; 95% CI, 1.00 – 1.008).
- Conversely, baseline NIHSS score had no influence on in hospital outcome (OR, 1.06; 95% CI, 0.96 – 1.18).

The role of Frailty and Multi-Morbidity

Risk factors for death in adult COVID-19 patients: Frailty predicts fatal outcome in older patients
Sara Tehrani, Intern. J. Inf. Dis., 2020 oct, 29

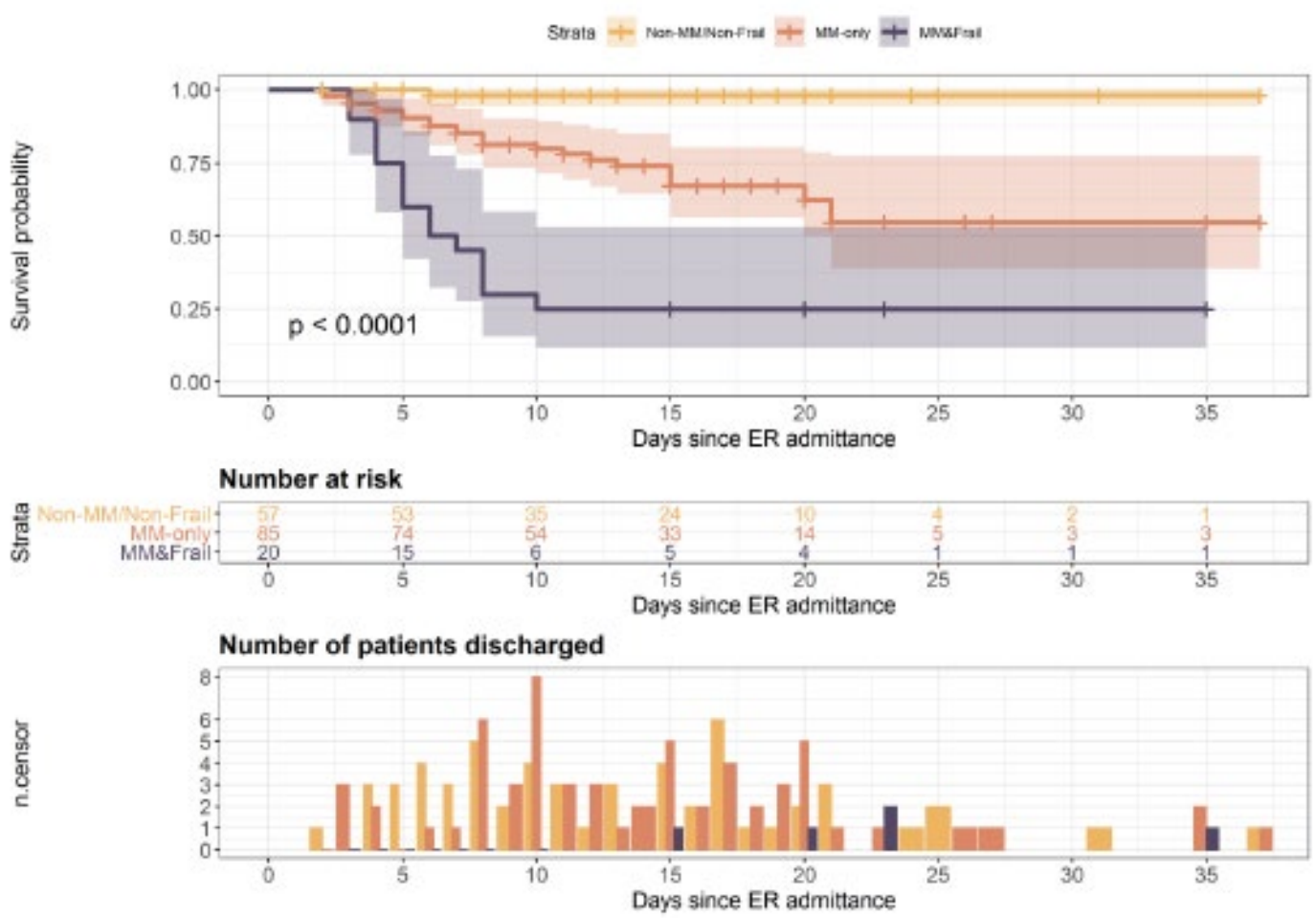


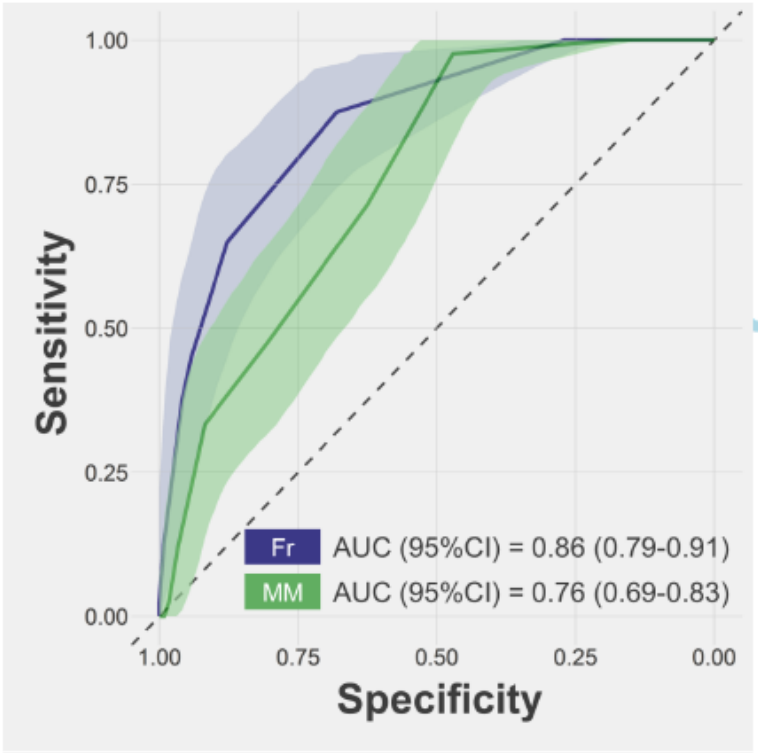


We found that 90% of fatal cases occurred among patients aged 65 years or older, where the death rate was as high as 44% (63 of 143 patients). In our multivariate analyses among older patients, age was not associated with death when data were adjusted for relevant comorbidities and frailty

International Journal of Infectious Diseases DOI: (10.1016/j.ijid.2020.10.071)

Frailty is the strogest predictor for survival in hospitalised COVID-19 patients





	Sens.	Spec.	PPV	NPV	LLR+	LLR-
CFS ≥ 6	0.38	0.96	0.75	0.82	9.15	0.65
2+ Chronic cond.	0.98	0.47	0.39	0.98	1.85	0.05

Marengoni A et al., In press

Clinical frailty independently predicts early mortality after ischaemic stroke

Nicholas R. Evans[1,2], Jasmine Wall[3], Benjaman To[1], Stephen J. Wallis[3], Roman Romero-Ortuno[3], Elizabeth A. Warburton[1]

	Non-frail (CFS 1–4)	Frail (CFS 5–8)	Significance
Number	199	234	
Median baseline NIHSS (IQR)	3 (1–7)	4.5 (1–12)	$P = 0.14$
Median age (IQR)	83 (77–86)	87 (83–92)	$P < 0.01$
Male sex	103 (51.8%)	87 (37.2%)	$P < 0.01$
Hypertension	129 (64.8%)	152 (65.0%)	$P = 0.98$
Diabetes mellitus	40 (20.1%)	48 (20.5%)	$P = 0.92$
Ischaemic heart disease	44 (22.1%)	50 (21.4%)	$P = 0.54$
Atrial fibrillation	92 (46.2%)	119 (50.9%)	$P = 0.34$
Thrombolysed	36 (18.1%)	27 (11.5%)	$P = 0.05$
28-day mortality	10 (5.0%)	39 (16.7%)	$P < 0.01$

	Odds ratio (95% CI)	Significance
CFS	1.03 (1.01–1.05)	$P < 0.01$
Baseline NIHSS	1.01 (1.001–1.02)	$P = 0.03$
Thrombolysis	0.82 (0.70–0.95)	$P = 0.01$
Age	1.00 (0.99–1.01)	$P = 0.26$
Male sex	0.72 (0.28–1.87)	$P = 0.50$
Hypertension	0.94 (0.88–1.01)	$P = 0.11$
Diabetes mellitus	1.04 (0.95–1.13)	$P = 0.43$
Atrial fibrillation	1.07 (0.97–1.17)	$P = 0.18$

Interval NIHSS change	Coefficient	Significance
CFS	1.07	$P = 0.03$
Diabetes mellitus	4.65	$P = 0.04$
Age	0.03	$P = 0.82$
Male sex	0.23	$P = 0.88$
Hypertension	0.26	$P = 0.87$
Atrial fibrillation	−0.24	$P = 0.88$
Baseline NIHSS	−0.06	$P = 0.63$

CONCLUSION

- Both ischemic and hemorrhagic stroke are a rather frequent complication of COVID-19
- Stroke might occur before the onset of COVID-19 and represent the first manifestation of the infection
- Stroke might also follow for weeks a previous SARS-COV2 infection
- Stroke is per se a risk factor for COVID-19 severity
- COVID-19 related stroke patients are at higher risk for poor prognosis and higher lethality, even controlling for multi-morbidity and frailty
- COVID-19 stroke should be guaranteed the same treatments and cares of non COVID-19 stroke