SUPPLEMENTAL MATERIAL.

Characteristics and outcomes in patients with COVID-19 and acute ischemic stroke

- I. Supplementary methods
- II. Supplementary tables

I. Supplementary methods

Statistical analysis

In the descriptive part of our study, we expressed continuous variables as mean values ± standard deviation or median and inter-quartile range (25th to 75th percentile). Accordingly, nominal variables are presented as absolute numbers and percentages. We used histograms and plotted kernel density estimates to illustrate the distribution of stroke severity scale in the two registries (the Global COVID-19 Stroke Registry and the Acute STroke Registry and Analysis of Lausanne (ASTRAL) Registry).

Subsequently, we employed a non-parsimonious multivariable probit regression model and we calculated propensity scores for the conditional probability of classification (COVID-19 Stroke Registry versus ASTRAL Registry) in 174 patients with COVID-19 and 5,684 stroke patients who suffered an ischemic stroke from 2013 to 2019 (i.e. the ASTRAL registry). Baseline characteristics (age and gender), previous history of ischemic stroke, risk factors and co-morbidities (smoking, diabetes mellitus, hypertension, hyperlipidemia, atrial fibrillation, heart failure, coronary artery disease, obesity and active cancer) were included in the final model for calculating the propensity score for each subject. A 1:1 matching algorithm of the nearest neighbor with no replacement was used with a caliper of 0.01 (equal to 0.2*standard deviation of the propensity score). For assessment of differences in stroke outcomes between the two Registries, a second propensity matching was performed with similar specifications plus additional control for the different type of interventions administered. Covariate balance between matched patients of the two Registries was adjudicated for each variable by i) Student's T-Tests for equality of means in the two samples, ii) the reduction in the standardized percentage bias (difference of the sample means in the matched and non-matched sub-samples as a percentage of the square root of the average of the sample variances) and iii) excluding that the ratio of the variance of the residuals orthogonal to the linear index of the propensity score in the matched group over the non-matched group exceeds the 0.5 to 2 range. We also calculated measures of overall covariate balance as follows: i) median overall bias before and after matching ii) P-values of the likelihood-ratio test of the joint insignificance of all the covariates before and after matching and iii) Rubin's R as the ratio of matched to non-matched variances of the propensity score index and testing if R values exceed the range 0.5 to 2.

In the matched population, we used the non-parametric Wilcoxon signed-rank test to compare continuous outcomes between patients with COVID-19 and subjects from the ASTRAL registry. For assessing differences in dichotomous and ordinal outcomes, we implemented multi-level mixed effects logistic and ordinal logistic models which accounted for the correlation within each pair of matched patients. We derived 95% confidence intervals around the mean estimates by using robust standard errors (i.e. Huber/White/sandwich estimator). We confirmed the direction and the significance of our findings with fixed-effects conditional logistic models and ordinal regression models with robust standard errors for clustering of observations. Finally, we performed a sensitivity analysis for potential hidden bias in our matched database by calculating Rosenbaum bounds for average treatment effect on the treated in the presence of unobserved heterogeneity between matched patients.

This analysis indicated that our results showing increased mortality and worse Rankin score in COVID-19 were robust to unobserved covariates that would increase the odds of a patient's conditional classification by up to 130% and 45% respectively while being unrelated to the selected propensity model.

We used data from all patients with COVID-19 and acute stroke recruited consecutively from participating centres between January 2020 and May 2020; respectively, we utilized the full ASTRAL database in the context of propensity score matching. Therefore, no formal power calculations were performed. All tests were two-tailed. We deemed statistical significance at p=0.05. Statistical analysis was conducted with STATA 13, College Station, Texas 77845 USA.

II. Supplementary Tables

Variable	Available observations	Summary estimate
L	Demographics	
Total N, n	174	
Centres/Countries, n	174	28/16
Age, mean±SD [years]	174	71.2 (12.3)
Gender, n (%) [males]	174	108 (62.07)
Previous stroke, n (%)	174	20 (11.49)
11000330000,11 (70)	Risk factors	20 (11.45)
Smoking, n (%)	174	49 (28.16)
Hypertension, n (%)	174	119 (68.39)
Diabetes mellitus, n (%)	174	54 (31.03)
Obesity, n (%)	174	65 (37.36)
Alcohol abuse, n (%)	174	14 (8.05)
Atrial fibrillation, n (%)	174	41 (23.56)
Coronary artery disease, n (%)	174	30 (17.24)
Heart Failure, n (%)	174	20 (11.49)
Peripheral artery disease, n (%)	174	17 (9.77)
rempheral areasy alsease, in (76)	Comorbidities	1, (3.,,,)
Severe liver disease, n (%)	174	3 (1.72)
Lung disease, n (%)	174	14 (8.05)
Renal disease, n (%)	174	2 (1.15)
Active cancer, n (%)	174	48 (27.59)
	Pre-stroke medication	
Antiplatelet, n (%)	174	40 (22.99)
Oral anticoagulants, n (%)	174	21 (12.07)
Antihypertensive medication, n (%)	174	105 (60.34)
Statin, n (%)	174	59 (33.91)
	Stroke characteristics	•
NIHSS, median (IQR)	125	10 (4-18)
Arterial Territory, n (%) [anterior/middle]	163	103 (63.19)
Weakness, n (%)	174	118 (67.82)
Sensory deficits, n (%)	174	73 (41.95)
Aphasia, n (%)	174	60 (34.48)
Dysarthria, n (%)	174	80 (45.98)
Dysphagia, n (%)	174	43 (24.71)
Imbalance, n (%)	174	44 (25.29)
paired level of Consciousness, n (%)	174	44 (25.29)
Underlying cardiac rhythm, n (%) [Atrial fibrillation]	171	39 (22.81)
Laterality, n (%) [left]	151	59(39.07)
Brain imaging, n (%) [CT or MRI]	174	152(87.35)

	Stroke related treatment							
Antiplatelets, n (%)	171	100 (58.48)						
Statins, n (%)	170	102 (60.00)						
Antihypertensives, n (%)	170	109 (64.12)						
Anticoagulants, n (%)	169	33 (19.53)						
Intervention	173							
Thrombolysis, n (%)		22 (12.72)						
Thrombolysis and		12 (6.04)						
thrombectomy, n (%)		12 (6.94)						
Endovascular thrombectomy, n (%)		9 (5.2)						
	Stroke diagnostic wo	ork-up						
Echocardiography performed, n (%)	172	54 (31.40)						
Holter monitoring, n (%)	167	16 (9.58)						
Vascular imaging, n (%)	174	125 (71.84)						
Lak	poratory parameters a	t admission						
WBC, median (IQR) [count/μl]	171	9,700 (7,300-13,110)						
Lymphocytes, median (IQR) [count/μl]	166	900 (540-1440)						
Lymphocytopenia, n (%)	166	91 (54.82)						
Platelets, median (IQR) [count/µl]	171	220,000 (159,000-303,000)						
Thrombocytopenia, n (%)	171	39 (22.81)						
Thrombocytosis, (n%)	171	7 (4.1%)						
Hemoglobin, median (IQR) [mg/dl]	171	12 (10.2-13.7)						
C-reactive protein, median (IQR)	142	11.3 (2.42-28.3)						
[mg/dl]								
Creatinine, median (IQR) [mg/dl]	171	0.97 (0.788-1.39)						
	COVID-19 related chara	icteristics						
Diagnosis with RT-PCR, n (%)	174	167 (95.98)						
COVID-19 symptoms to stroke onset,	156	7 (2-15)						
median (IQR) [days]	130	/ (2-15)						
Fever, n (%)	174	96 (55.17)						
Cough, n (%)	174	93 (53.45)						
Dyspnoea, n (%)	174	76 (43.68)						
Taste impairment, n (%)	174	15 (8.62)						
Gastrointestinal, n (%)	174	19 (10.92)						
Lung imaging, n (%) [Chest CT]	174	112 (64.37)						
Lung opacities, n (%)	174	131 (75.29)						
Chloroquine, n (%)	172	65 (37.79)						
Azithromycin, n (%)	172	40 (23.26)						
Lopinavir, n (%)	172	14 (8.14)						
Tocilizumab, n (%)	172	11 (6.40)						
Anakinra, n (%)	171	0 (0.00)						
Steroids, n (%)	171	44 (25.73)						
Plasma transfusion, n (%)	171	2 (1.17)						
Heparin, n (%)	170	115 (67.65)						
	Outcomes							
Oedema, n (%)	79	4 (5.06)						

Haemorrhagic transformation, n (%)	162	22 (13.58)
Craniectomy, n (%)	164	3 (1.83)
Transfer to ICU, n (%)	174	40 (22.99)
Intubation, n (%)	174	27 (15.5)
Rankin Score, median (IQR)	125	4 (2-6)
Survivor with severe functional deficit, n (%)	96	49 (51.0)
In hospital death, n (%)	174	48 (27.59)
COVID-19 related death, n (%)	174	22 (12.64)
In hospital death and/or severe functional deficit, n (%)	174	97 (55.75)
Discharge from hospital, n (%)	174	110 (63.22)

Abbreviations: COVID-19, Coronavirus disease 2019; CT, computed tomography; ICU, Intensive Care Unit; IQR: inter-quartile range; MRI, magnetic resonance imaging; NIHSS, The National Institutes of Health Stroke Scale; RT-PCR, real time polymerase chain reaction; SD, standard deviation

Supplementary Table II. Covariate balance after propensity matching in 179 patients with COVID-19 and 5,684 patients from the ASTRAL registry resulting in a total population of 328 subjects

Variable	Status	COVID-19 Stroke Registry	ASTRAL Registry	%bias	%reduction in bias	P-value
Age	Unmatched	71.59	71.4	1.2		0.887
	Matched		72.6	-8	-58.4	0.45
Gender	Unmatched	0.619	0.551	13.7		0.08
	Matched	0.6	0.618	-3.7	73	0.736
Smoking	Unmatched	0.283	0.231	12		0.11
	Matched	0.279	0.255	5.5	53.6	0.62
Previous Stroke	Unmatched	0.116	0.193	-21.4		0.011
	Matched	0.121	0.121	0	100	0.999
Hypertension	Unmatched	0.682	0.719	-7.9		0.296
	Matched	0.673	0.649	5.3	33.4	0.643
Dyslipidemia	Unmatched	0.341	0.28	13.1		0.082
	Matched	0.333	0.321	2.6	80	0.815
DM	Unmatched	0.312	0.191	28.1		<0.001
	Matched	0.279	0.224	12.7	54.9	0.255
AF	Unmatched	0.231	0.3	-15.7		0.051
	Matched	0.242	0 .285	-9.6	38.6	0.383
CAD	Unmatched	0.173	0.183	-2.4		0.76
	Matched	 0.176	0.188	-3.2	-32.6	0.776
HF	Unmatched	0.116	0.166	-14.5		0.079
	Matched	0.121	0 .146	-7	51.8	0.519
Obesity	Unmatched	0.375	0.481	-21.3		0.007
	Matched	0.382	0.352	6.1	71.1	0.569
Active cancer	Unmatched	0.278	0.058	61.5		< 0.001
	Matched	0.242	0.249	-1.7	97.2	0.899
Intervention	Unmatched	0.422	0.561	-16.4		0.036
	Matched	0.412	0.497	-10	39	0.359
Motor deficit	Unmatched	0.682	0.776	-21.3		0.004
	Matched	0.691	0.667	5.5	74.3	0.638
Dysarthria	Unmatched	0.457	0.534	-15.5		0.045
	Matched	0.455	0.43	4.9	68.8	0.659
Sensory deficit	Unmatched	0.422	0.484	-12.4		0.109
	Matched	0.43	0.388	8.5	31.5	0.435

Overall covariate imbalance								
	Joint LR chi2	P-value	Mean Bias	Median Bias	*Rubin's R	**%Variance		
Unmatched	129.24	<0.001	17.4	15	2.4	50		
Matched	7.13	0.971	5.9	5.5	0.65	0		

^{*} Rubin's R exceeding the range 0.5 to 2 denotes overall covariate imbalance

^{**} Indicates the percentage of all covariates orthogonal to the propensity score with variance ratios exceeding the range of 0.5 to 2
Abbreviations: ASTRAL, the Acute STroke Registry and Analysis of Lausanne; AF, atrial fibrillation; COVID-19, Coronavirus disease 2019; DM, diabetes mellitus; CAD, coronary artery disease; HF, heart failure; LR, likelihood ratio

Supplementary Table III. Comparisons in ischemic stroke severity and outcomes between COVID-19 and ASTRAL registry patients

	Stroke sever	ity/outcome scales	Odds ratio (95% CI)	P-value
Endpoint	COVID-19 Stroke Registry	ASTRAL Registry	COVID-19 versus ASTRAL	
NIHSS, median (IQR)	10 (4-18)	6 (3-14)		0.03
Higher NIHSS score			1.69 (1.082-2.65)	0.021
In hospital death			4.3 (2.22-8.30)	<0.001
Non-Covid-19 related death			2.02 (1.01-4.04)	0.048
Transfer to ICU			3.86 (1.85-8.04)	<0.001
Adverse functional outcome			1.79 (1.01-3.14)	0.045
Rankin score, median (IQR)	4 (2-6)	2 (1-4)		<0.001
Higher Rankin Score			3.13 (2.02-4.85)	<0.001
In hospital death and/or adverse functional outcome			1.63 (1.04-2.55)	0.033
Haemorrhagic transformation			1.05 (0.449-2.45)	0.911
Brain oedema			2.11 (0.375-11.89)	0.396

P-values are derived from Wilcoxon signed rank tests for the NIHSS and the Rankin scale and multi-level mixed effects logistic or ordinal logistic models for dichotomous and ordinal outcomes. The ASTRAL registry is the reference category for provided odds ratios.

Abbreviations: ASTRAL, the Acute STroke Registry and Analysis of Lausanne; COVID-19, Coronavirus disease 2019; ICU, intensive care unit; IQR, inter-quartile range; NIHSS, The National Institutes of Health Stroke Scale

Supplementary Table without COVID-19	IV. Outcomes	per intervention	in the matche	d cohort of str	oke patients wi	th and
		COVID-19 patient	:s		ASTRAL Registry	/
	Overall, n	In hospital death, n	Survivors with severe functional deficit, n	Overall, n	In hospital death, n	Survivor with severe functional deficit, n
N with available information on intervention	167	167	81	167	167	143
No intervention	126	34	31	103	14	31
Thrombolysis	21	5	7	46	3	18
Thrombolysis and thrombectomy	12	3	8	12	0	3
Endovascular thrombectomy	8	5	3	6	1	2

Supplementary Table V. Recruiting centres and patients per centre of the Global COVID-19 Stroke Registry							
Patient's Ascending number	Centre	Patients per centre	City	Country	Is the hospital a COVID-19 reference hospital?		
1	1	Patient 1	Lausanne	Switzerland	Yes		
2	1	Patient 2	Lausanne	Switzerland	Yes		
3	1	Patient 3	Lausanne	Switzerland	Yes		
4	1	Patient 4	Lausanne	Switzerland	Yes		
5	1	Patient 5	Lausanne	Switzerland	Yes		
6	1	Patient 6	Lausanne	Switzerland	Yes		
7	1	Patient 7	Lausanne	Switzerland	Yes		
8	2	Patient 1*	London	England			
9	2	Patient 2*	London	England			
10	2	Patient 3*	London	England			
11	2	Patient 4*	London	England			
12	2	Patient 5*	London	England			
13	2	Patient 6*	London	England			
14	3	Patient 1	Moedling	Austria	Yes		
15	3	Patient 2	Moedling	Austria	Yes		
16	3	Patient 3	Moedling	Austria	Yes		
17	3	Patient 4	Moedling	Austria	Yes		
18	4	Patient 1	Mexico City	Mexico	Yes		
19	4	Patient 2	Mexico City	Mexico	yes		
20	4	Patient 3	Mexico City	Mexico	Yes		
21	5	Patient 1	Armenia	Colombia	Yes		
22	6	Patient 1	Paris	France	No		
23	6	Patient 2	Paris	France	No		
24	6	Patient 3	Paris	France	No		
25	6	Patient 4	Paris	France	No		
26	6	Patient 5	Paris	France	No		
27	6	Patient 6	Paris	France	No		
28	6	Patient 7	Paris	France	No		
29	6	Patient 8	Paris	France	No		
30	6	Patient 9	Paris	France	No		
31	6	Patient 10	Paris	France	No		
32	6	Patient 11	Paris	France	No		
33	7	Patient 1	Savona	Italy	Yes		
34	7	Patient 2	Savona	Italy	Yes		
35	7	Patient 3	Savona	Italy	Yes		
36	7	Patient 4	Savona	Italy	Yes		

37	9	Patient 1	Copenhagen	Denmark	Yes
38	9	Patient 2	Copenhagen	Denmark	Yes
39	9	Patient 3	Copenhagen	Denmark	Yes
40	9	Patient 4	Copenhagen	Denmark	Yes
41	9	Patient 5	Copenhagen	Denmark	Yes
42	9	Patient 6	Copenhagen	Denmark	Yes
43	9	Patient 7	Copenhagen	Denmark	Yes
44	9	Patient 8	Copenhagen	Denmark	Yes
45	10	Patient 1	Madrid	Spain	Yes
46	10	Patient 2	Madrid	Spain	Yes
47	10	Patient 3	Madrid	Spain	Yes
48	10	Patient 4	Madrid	Spain	Yes
49	11	Patient 1	Copenhagen	Denmark	No
50	11	Patient 2	Copenhagen	Denmark	No
51	11	Patient 3	Copenhagen	Denmark	No
52	12	Patient 1	Wuhan	China	Yes
53	12	Patient 2	Wuhan	China	Yes
54	12	Patient 3	Wuhan	China	Yes
55	12	Patient 4	Wuhan	China	Yes
56	12	Patient 5	Wuhan	China	Yes
57	12	Patient 6	Wuhan	China	Yes
58	12	Patient 7	Wuhan	China	Yes
59	12	Patient 8	Wuhan	China	Yes
60	12	Patient 9	Wuhan	China	Yes
61	12	Patient 10	Wuhan	China	Yes
62	12	Patient 11	Wuhan	China	Yes
63	12	Patient 12	Wuhan	China	Yes
64	12	Patient 13	Wuhan	China	Yes
65	12	Patient 14	Wuhan	China	Yes
66	12	Patient 15	Wuhan	China	Yes
67	12	Patient 16	Wuhan	China	Yes
68	12	Patient 17	Wuhan	China	Yes
69	12	Patient 18	Wuhan	China	Yes
70	12	Patient 19	Wuhan	China	Yes
71	12	Patient 20	Wuhan	China	Yes
72	12	Patient 21	Wuhan	China	Yes
73	12	Patient 22	Wuhan	China	Yes
74	12	Patient 23	Wuhan	China	Yes
75	12	Patient 24	Wuhan	China	Yes
76	12	Patient 25	Wuhan	China	Yes
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104 18 Patient 2 Vienna Austria no	
105 19 Patient 1 Helsinki Finland yes	
106 20 Patient 1 Philadelphia USA Yes	
107 20 Patient 2 Philadelphia USA Yes	
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111 20 Patient 6 Philadelphia USA Yes	
112 21 Patient 1 Bucharest Romania Yes	
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115 21 Patient 4 Bucharest Romania Yes	
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117						
119	117	21	Patient 6	Giurgiu	Romania	Yes
120	118	21	Patient 7	Bucharest	Romania	Yes
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	153	24	Patient 3	Madrid	Spain	Yes
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156 24 Patient 6 Madrid Spain Yes	156	24	Patient 6	Madrid	Spain	Yes

24	Patient 7	Madrid	Spain	Yes
24	Patient 8	Madrid	Spain	Yes
24	Patient 9	Madrid	Spain	Yes
24	Patient 10	Madrid	Spain	Yes
24	Patient 11	Madrid	Spain	Yes
24	Patient 12	Madrid	Spain	Yes
24	Patient 13	Madrid	Spain	Yes
24	Patient 14	Madrid	Spain	Yes
24	Patient 15	Madrid	Spain	Yes
24	Patient 16	Madrid	Spain	Yes
24	Patient 17	Madrid	Spain	Yes
25	Patient 1	Athens	Greece	Yes
26	Patient 1	Lugano	Switzerland	No
26	Patient 2	Lugano	Switzerland	No
27	Patient 1	Mexico City	Mexico	No
27	Patient 2	Mexico City	Mexico	No
28	Patient 1	Linz	Austria	Yes
28	Patient 2	Linz	Austria	Yes
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^{*} Details about these patients were previously published (Beyrouti R., et al. Characteristics of ischaemic stroke associated with COVID-19. J Neurol Neurosurg Psychiatry. 2020 Apr 30. pii: jnnp-2020-323586. doi: 10.1136/jnnp-2020-323586)

Abbreviations: COVID-19, Coronavirus disease 2019