SUPPLEMENTAL MATERIAL

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SARS-CoV-2 is a Culprit for Some, but not All Acute Ischemic Strokes

A Report from the Multinational COVID-19 Stroke Study Group

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SUPPLEMENTAL DOCUMENT 1. SEARCH STRATEGY IN PUBMED

1. "Cerebrovascular Disorders"[MeSH Terms]
2. "Brain Ischemia"[MeSH Terms] OR "Hypoxia-Ischemia, Brain"[MeSH Terms] OR "Ischemic Attack, Transient"[MeSH Terms]
3. "Stroke"[MeSH Terms] OR "Stroke, Lacunar"[MeSH Terms] OR "Infarction, Posterior Cerebral Artery"[MeSH Terms] OR "Brain Stem Infarctions"[MeSH Terms] OR "Infarction, Middle Cerebral Artery"[MeSH Terms] OR "Infarction, Anterior Cerebral Artery"[MeSH Terms]
4. Stroke[Title/Abstract] OR cerebr vascul infarct[Title/Abstract] OR cerebrovasc infarct[Title/Abstract] OR cerebr vasc event[Title/Abstract] OR cerebrovasc event[Title/Abstract] OR CVA[Title/Abstract] OR transient ischemic attack[Title/Abstract]
5. “Intracranial Hemorrhages”[MeSH Terms] OR “Subarachnoid Hemorrhage”[MeSH Terms] OR “Putaminal Hemorrhage”[MeSH Terms] OR “Putaminal Hemorrhage”[MeSH Terms] OR “Basal Ganglia Hemorrhage”[MeSH Terms]
6. intra?cerebral hemorrhage[Title/Abstract] OR intra?parenchymal hemorrhage[Title/Abstract] OR “SAH” [Title/Abstract]
7. “venous sinus thrombosis, cranial”[MeSH Terms] OR “Cranial Sinuses”[MeSH Terms]
8. “cerebral venous thrombosis”[Title/Abstract] OR “cerebral sinus thrombosis” [Title/Abstract] OR “CVT” [Title/Abstract]
9. Neurologic[Title/Abstract]
10. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
11. COVID-19 [Supplementary Concept] OR “severe acute respiratory syndrome coronavirus 2 [Supplementary Concept]
12. SARS-CoV-2[Title/Abstract] OR COVID-19[Title/Abstract] OR coronavirus covid-19[Title/Abstract]
13. #10 OR #11

("Cerebrovascular Disorders"[MeSH Terms] OR "Brain Ischemia"[MeSH Terms] OR "Hypoxia-Ischemia, Brain"[MeSH Terms] OR "Ischemic Attack, Transient"[MeSH Terms] OR "Stroke"[MeSH Terms] OR "Stroke, Lacunar"[MeSH Terms] OR "Infarction, Posterior Cerebral Artery"[MeSH Terms] OR "Brain Stem Infarctions"[MeSH Terms] OR "Infarction, Middle Cerebral Artery"[MeSH Terms] OR "Infarction, Anterior Cerebral Artery"[MeSH Terms] OR Stroke[Title/Abstract] OR cerebr vascul infarct[Title/Abstract] OR cerebrovasc infarct[Title/Abstract] OR cerebr vasc event[Title/Abstract] OR cerebrovasc event[Title/Abstract] OR CVA[Title/Abstract] OR transient ischemic attack[Title/Abstract] OR “Intracranial Hemorrhages”[MeSH Terms] OR “Subarachnoid Hemorrhage”[MeSH Terms] OR “Putaminal Hemorrhage”[MeSH Terms] OR “Putaminal Hemorrhage”[MeSH Terms] OR “Basal Ganglia Hemorrhage”[MeSH Terms] OR intra?cerebral hemorrhage[Title/Abstract] OR intra?parenchymal hemorrhage[Title/Abstract] OR “SAH” [Title/Abstract] OR “venous sinus thrombosis, cranial”[MeSH Terms] OR “Cranial Sinuses”[MeSH Terms] OR “cerebral venous thrombosis”[Title/Abstract] OR “cerebral sinus thrombosis” [Title/Abstract] OR “CVT” [Title/Abstract] OR Neurologic[Title/Abstract]) AND (COVID-19 [Supplementary Concept] OR “severe acute respiratory syndrome coronavirus 2 [Supplementary Concept] OR SARS-CoV-2[Title/Abstract] OR COVID-19[Title/Abstract] OR coronavirus covid-19[Title/Abstract])

SUPPLEMENTAL DOCUMENT 2. DETAILED DESCRIPTION OF THE CLUSTERING

The patients were clustered based on the laboratory findings and comorbidities. We used clinicians' EXpert opinion (EX models), or unsupervised Machine Learning algorithms (ML models) for defining the clusters. The results of different models were compared through the contingency matrix (a.k.a contingency table).[3] The models for clustering the patients based on the comorbidities are as follows:

A. Clinical Risk Scoring Models Based on the EXpert opinion (EX models)

Patients were categorized based on the number of the existing comorbidities. We either considered All eleven comorbidities (EX-A models; including hypertension, diabetes mellitus, ischemic heart disease, atrial fibrillation, carotid stenosis, chronic kidney disease, cardiac ejection fraction less than 40%, active neoplasm, rheumatological diseases, history of transient ischemic attack or stroke, and current smoking), or Selected number of vascular comorbidities (EX-S models; including hypertension, diabetes mellitus, ischemic heart disease, atrial fibrillation, carotid stenosis, chronic kidney disease, previous transient ischemic attack or stroke, and current smoking). We further clustered the patients under each of these models to two (EX-A_2 and EX-S_2) or three (EX-A_3 and EX-S_3) subgroups.

1. EX-A_2: based on expert opinion and including all comorbidities, in two subgroups.
    a. Subgroup a: zero or one comorbidity,
    b. Subgroup b: more than one comorbidity.
2. EX-S_2: based on expert opinion and including selected comorbidities, in two subgroups.
    a. Subgroup a: zero or one comorbidity,
    b. Subgroup b: more than one comorbidity.
3. EX-A_3: based on expert opinion and including all comorbidities, in three subgroups.
    a. Subgroup a: zero comorbidity,
    b. Subgroup b: one or two comorbidities,
    c. Subgroup c: more than two comorbidities.
4. EX-S_3: based on expert opinion and including selected comorbidities, in three subgroups.
    a. Subgroup a: zero comorbidity,
    b. Subgroup b: one or two comorbidities,
    c. Subgroup c: more than two comorbidities.

B. Models Based on Machine Learning Algorithms (ML models)

We used unsupervised machine learning algorithms for clustering. Hierarchical (complete linkage method) and K-means (Hartigan-Wong algorithm) clustering (ML-K models) and Spectral clustering (ML-S models) were used. We grouped the patients into two (ML-K_2 and ML-S_2), three (ML-K_3 and ML-S_3), four (ML-K_4 and ML-S_4), and five (ML-K_5 and ML-S_5) clusters.

B1: Hierarchical and k-mean clustering

1. ML-K_2: Based on hierarchical and K-means clustering, dividing the patients into two subgroups.
2. ML-K_3: Based on hierarchical and K-means clustering, dividing the patients into three subgroups.
3. ML-K_4: Based on hierarchical and K-means clustering, dividing the patients into four subgroups.
4. ML-K_5: Based on hierarchical and K-means clustering, dividing the patients into five subgroups.

B2: Spectral clustering

1. ML-$S_{2:}$ Based on spectral clustering, dividing the patients into two subgroups.
2. ML-$S_{3:}$ Based on spectral clustering, dividing the patients into three subgroups.
3. ML-$S_{4:}$ Based on spectral clustering, dividing the patients into four subgroups.
4. ML-$S_{5:}$ Based on spectral clustering, dividing the patients into five subgroups.

SUPPLEMENTAL TABLE 1. DIVIDING THE SARS-COV-2 INFECTED ACUTE ISCHEMIC STROKE PATIENTS INTO 4 AND 5 SUBGROUPS BASED ON K-MEAN CLUSTERING

The table shows the structure of the models for grouping the patients into 4 and 5 subgroups using machine learning (ML) models (K-Mean) by considering the present comorbidities. ML-S_4 used spectral clustering to divide the patients into 4 groups while ML-S_5 separated the patients into 5 subgroups.

	Machine Learning Algorithm, K-Mean										
	ML-K_4 (K-Mean)					ML-K_5 (K-Mean)					
	a N= 74 (25.3%)	b N= 95 (32.5%)	c N= 62 (21.2%)	d N= 61 (20.9 %)	P-Value	a N= 85 (29.1%)	b N= 39 (18.8%)	c N= 55 (18.8%)	d N= 49 (16.8%)	e N=64 (21.9%)	P-Value
Hypertension (%)	100.0	0.0	87.1	83.6	<0.001	0.0	74.4	81.8	83.7	100.0	<0.001
Diabetes Mellitus (%)	0.0	0.0	58.1	100.0	<0.001	0.0	33.3	100.0	59.2	0.0	<0.001
Ischemic Heart Disease (%)	0.0	9.5	100.0	0.0	<0.001	5.9	43.6	0.0	100.0	0.0	<0.001
Atrial Fibrillation (%)	13.5	8.4	27.4	9.8	0.006	0.0	100.0	0.0	4.1	0.0	<0.001
Carotid Stenosis (%)	10.8	4.2	29.0	13.1	<0.001	4.7	5.1	12.7	34.7	12.5	<0.001
Chronic Kidney Disease (%)	20.3	12.6	6.5	16.4	0.12	12.9	7.7	16.4	8.2	21.9	0.178
Cardiac Ejection Fraction<40% (%)	12.2	1.1	14.5	8.2	0.01	1.2	20.5	7.3	12.2	7.8	0.006
Active Neoplasm (%)	5.4	1.1	21.0	4.9	<0.001	0.0	7.7	5.5	22.4	6.3	<0.001
Rheumatological Disease (%)	4.1	1.1	0.	1.6	0.29	0.0	5.1	0.0	0.0	4.7	0.05
Previous Stroke/TIA (%)	1.4	1.1	3.2	1.6	0.76	1.2	2.6	1.8	2.0	1.6	0.99
Current Smoker (%)	23.0	7.4	25.8	13.1	0.006	5.9	7.7	14.5	36.7	21.9	<0.001

SUPPLEMENTAL TABLE 2. DIVIDING THE SARS-COV-2 INFECTED ACUTE ISCHEMIC STROKE PATIENTS INTO 4 AND 5 SUBGROUPS BY SPECTRAL CLUSTERING

The table shows the structure of the models for grouping the patients into 4 and 5 subgroups using machine learning (ML) models (spectral clustering) by considering the present comorbidities. ML-S_4 used spectral clustering to divide the patients into 4 groups while ML-S_5 separated the patients into 5 subgroups.

Models	Machine Learning Algorithm, Spectral										
	ML-S_4 (Spectral)					ML-S_5 (Spectral)					
Comorbidities	a N = 57 (19.3%)	b N = 112 (37.8%)	c N = 38 (12.8%)	d N = 89 (30.1%)	P-value	a N = 20 (6.8%)	b N = 89 (30.1%)	c N = 112 (37.8%)	d N = 19 (6.4%)	e N = 56 (18.9%)	P-value
Hypertension (%)	100.0	0.0	89.5	100.0	<0.001	95.0	100.0	0.0	84.2	100.0	<0.001
Diabetes Mellitus (%)	100.0	11.6	73.7	0.0	<0.001	85.0	0.0	13.4	52.6	100.0	<0.001
Ischemic Heart Disease (%)	10.5	11.6	100.0	16.9	<0.001	95.0	16.9	11.6	100.0	10.7	<0.001
Atrial Fibrillation (%)	10.5	8.0	44.7	11.2	<0.001	10.0	11.2	6.3	89.5	10.7	<0.001
Carotid Stenosis (%)	14.0	3.6	44.7	10.1	<0.001	85.0	10.1	3.6	5.3	12.5	<0.001
Chronic Kidney Disease (%)	14.0	12.5	7.9	18.0	0.46	15.0	18.0	12.5	0.0	14.3	0.34
Cardiac Ejection Fraction<40% (%)	7.0	1.8	21.1	11.2	0.001	15.0	11.2	1.8	26.3	7.1	0.002
Active Neoplasm (%)	1.8	3.6	26.3	6.7	<0.001	30.0	6.7	4.5	15.8	1.8	<0.001
Rheumatological Disease (%)	1.8	0.9	0.0	3.4	0.46	0.0	3.4	0.9	0.0	1.8	0.62
Previous Stroke/TIA (%)	1.8	0.9	5.3	1.1	0.32	5.0	1.1	0.9	5.3	1.8	0.50
Current Smoker (%)	14.0	6.3	31.6	23.6	<0.001	65.0	23.6	6.3	0.0	12.5	<0.001

SUPPLEMENTAL TABLE 3. THE CHARACTERISTICS OF SARS-COV-2 INFECTED STROKE PATIENTS IN ORIGINAL DATASET AND LITERATURE REVIEW.

Parameter	AIS-Original Data N = 323	AIS-Literature Review N= 145	P Value
Age; Mean (SD); Years	67.2 ± 15.2	63.0 ± 14.0	0.005
Sex; Men; N (%)	193 (59.8)	62 (57.4)	0.62
National Institutes of Health Stroke Scale (NIHSS); Median [IQR]	9 [4-17]	15 [9-21]	0.11
Large Vessel Occlusion; N (%)	126 (44.5)	45 (83.3)	<0.0001
Imaging Pattern of Ischemia			
Embolic/Large Vessel Athero-thromboembolism; N (%)	206 (80.8)	25 (83.4)	0.73
Lacunar; N (%)	26 (10.2)	4 (13.3)	0.60
Borderzone; N (%)	23 (9.0)	1 (3.3)	0.26
TOAST Criteria			
Large Artery Atherosclerosis; N (%)	56 (32.9)	12 (10.0)	<0.0001
Cardioembolism; N (%)	46 (27.1)	17 (14.2)	0.009
Small Artery Occlusion; N (%)	17 (10.0)	8 (6.7)	0.32
Other Determined Etiologies; N (%)	13 (7.6)	37 (30.8)	0.0001
Undetermined Etiology; N (%)	38 (22.4)	46 (38.3)	0.003
Disposition			
Discharged Home; N (%)	127 (42.8)	23 (20.2)	<0.0001
In-Hospital Mortality; N (%)	82 (27.6)	39 (34.2)	0.19
Still in Hospital, or Dispositioned to Subacute Care; N (%)	88 (29.6)	52 (45.6)	0.002
Comorbidities			
Hypertension; N (%)	202 (63.1)	64 (54.7)	0.09
Diabetes Mellitus; N (%)	111 (34.6)	43 (36.8)	0.65
Ischemic Heart Disease; N (%)	72 (24.3)	8 (6.8)	<0.001
Atrial Fibrillation; N (%)	45 (14.1)	14 (12.0)	0.53
Carotid Stenosis; N (%)	38 (12.8)	3 (2.6)	0.0006
Chronic Kidney Disease; N (%)	42 (13.1)	4 (3.4)	0.001
Cardiac Ejection Fraction <40%; N (%)	24 (8.1)	2 (1.7)	0.007
Active Neoplasm; N (%)	21 (7.1)	0 (0.0)	0.001
Rheumatological Disease; N (%)	5 (1.7)	0 (0.0)	0.11
Prior Stroke or Transient Ischemic Attack; N (%)	5 (1.7)	9 (7.6)	0.85
Smoking; N (%)	53 (16.6)	10 (8.5)	0.02
Laboratory findings			
White Blood Cell Count; Mean (SD); x109/L	9.8 ± 4.8	13.9 ± 8.7	<0.0001
Neutrophil Count; Mean (SD); x109/L	7.7 ± 4.5	10.7 ± 5.3	<0.0001
Lymphocyte Count; Mean (SD); x109/L	1.5 ± 1.5	1.2 ± 1.0	0.03
Platelet Count; Mean (SD); x109/L	314.5 ± 440.7	232 ± 110	0.03
Alanine Transaminase (ALT); Mean (SD); U/L	63.3 ± 86.3	51.0 ± 69.0	0.13
Aspartate Transaminase (AST); Mean (SD); U/L	32.1 ± 26.8	53.0 ± 43.0	<0.0001
Creatinine; Mean (SD); mg/dl	1.5 ± 1.7	1.4 ± 1.0	0.51
C-Reactive Protein (CRP); Mean (SD); mg/L	61 ± 131	99.4 ± 96.7	0.002
Lactate Dehydrogenase (LDH); Mean (SD); U/L	604.8 ± 1536.7	517.3 ± 360.3	0.50

Due to missingness, we provided the valid percentages in this table.

SUPPLEMENTAL 4. THE CHARACTERISTICS OF THE PATIENTS FROM THE LITERATURE REVIEW DATASET DIVIDED BASED ON CLINICAL RISK SCORING MODELS.

Parameters	Clinical Risk Scoring													
	EX-A_2 (All comorbidities)			EX-S_2 (Selected Comorbidities)			EX-A_3 (All comorbidities)				EX-S_3 (Selected Comorbidities)			
	a N = 71 (60.7%)	b N = 46 (39.3%)	P-value	a N = 71 (60.7%)	b N = 46 (39.3%)	P-value	a N = 33 (28.2%)	b N = 38 (32.5%)	c N =46 (39.3%)	P-value	a N = 33 (28.2%)	b N = 38 (32.5%)	c N =46 (39.3%)	P-value
Age; Mean (SD); Years	63±16	62±16	0.72	63±16	62±16	0.72	62±16	65±15	62±13	0.65	62±16	65±15	62±13	0.65
Sex; Male; N (%)	30 (53.6)	24 (68.6)	0.16	30 (53.6)	24 (68.6)	0.16	16 (59.3)	14 (48.3)	24 (68.6)	0.26	16 (59.3)	14 (48.3)	24 (68.6)	0.26
Large Vessel Occlusion; N (%)	22 (91.7)	18 (75.0)	0.12	22 (91.7)	18 (75.0)	0.12	8 (80.0)	14 (100.0)	18 (75.0)	0.13	8 (80.0)	14 (100.0	18 (75.0)	0.13
Intravenous Thrombolysis; N (%)	5 (45.5)	3 (30.0)	0.47	5 (45.5)	3 (30.0)	0.47	1 (33.3)	4 (50.0)	3 (30.0)	0.68	1 (33.3)	4 (50.0)	3 (30.0)	0.68
Mechanical Thrombectomy; N (%)	11 (39.3)	6 (31.6)	0.59	11 (39.3)	6 (31.6)	0.59	7 (53.8)	4 (26.7)	6 (31.6)	0.28	7 (53.8)	4 (26.7)	6 (31.6)	0.28
National Institutes of Health Stroke Scale (NIHSS); Median [IQR]	15 [10-19]	13 [7-23]	0.78	15 [10-19]	13 [7-23]	0.78	6 [10-19]	7 [10-16]	9 [13-20]	0.59	6 [10-19]	7 [10-16]	9 [13-20]	0.59
TOAST Criteria														
Large-Artery Atherosclerosis; N (%)	6 (10.5)	3 (7.9)		6 (10.5)	3 (7.9)		2 (6.70)	4 (14.8)	3 (7.9)		2 (6.7)	4 (14.8)	3 (7.9)	
Cardio-embolism; N (%)	10 (17.5)	4 (10.5)		10 (17.5)	4 (10.5)		6 (20.0)	4 (14.8)	4 (10.5)		6 (20.0)	4 (14.8)	4 (10.5)	
Small-Vessel Occlusion; N (%)	4 (7.00)	2 (5.30)	0.71	4 (7.00)	2 (5.30)	0.71	3 (10.0)	1 (3.7)	2 (5.3)	0.77	3 (10.0)	1 (3.7)	2 (5.3)	0.77
Stroke of Other Determined Etiology; N (%)	19 (33.3)	12 (31.6)		19 (33.3)	12 (31.6)		11 (36.7)	8 (29.6)	12 (31.6)		11 (36.7)	8 (29.6)	12 (31.6)	
Stroke of Undetermined Etiology; N (%)	18 (31.6)	17 (44.7)		18 (31.6)	17 (44.7)		8 (26.7)	10 (37.0)	17 (44.7)		8 (26.7)	10 (37.0	17 (44.7)	
Imaging Patterns														
Embolic-Appearing; N (%)	7 (77.8)	12 (85.7)		7 (77.8)	12 (85.7)		2 (66.7)	5 (83.3)	12 (85.7)		2 (66.7)	5 (83.3)	12 (85.7)	
Lacune; N (%)	1 (11.1)	2 (14.3)	0.44	1 (11.1)	2 (14.3)	0.44	0 (0.00)	1 (16.7)	2 (14.3)	0.12	0 (0.00)	1 (16.7)	2 (14.3)	0.12
Borderzone; N (%)	1 (11.1)	0 (0.00)		1 (11.1)	0 (0.00)		1 (33.3)	0 (0.0)	0 (0.0)		1 (33.3)	0 (0.0)	0 (0.0)	
Interval Between Infection Onset to Stroke; Median [IQR]; Days	6 [2-16]	7 [2-14]	0.40	6 [2-16]	7 [2-14]	0.40	6 [1-6]	9 [5-20]	6 [2-14]	0.03	6 [1-6]	9 [5-20]	6 [2-14]	0.03
Mechanical Ventilation; N (%)	10 (25.0)	4 (20.0)	0.42	10 (25.0)	4 (20.0)	0.42	7 (33.3)	3 (15.8)	4 (20.0)	0.32	7 (33.3)	3 (15.8)	4 (20.0)	0.32
Disposition														
Discharged Home; N (%)	14 (24.6)	5 (13.5)		14 (24.6)	5 (13.5)		6 (22.2)	8 (26.7)	5 (13.5)		6 (22.2)	8 (26.7)	5 (13.5)	
In Hospital Mortality; N (%)	17 (29.8)	14 (37.8)	0.40	17 (29.8)	14 (37.8)	0.40	8 (29.6)	9 (30.0)	14 (37.8)	0.73	8 (29.6)	9 (30.0)	14 (37.8)	0.73
Still in Hospital/Subacute Care; N (%)	26 (45.6)	18 (48.6)		26 (45.6)	18 (48.6)		13 (48.1)	13 (43.3)	18 (48.6)		13 (48.1)	13 (43.3	18 (48.6)	
Comorbidities														
Hypertension; N (%)	20 (28.2)	44 (95.7)	<0.001	20 (28.2)	44 (95.7)	<0.001	0 (0.0)	20 (52.6)	44 (95.7)	<0.001	0 (0.0)	20 (52.6)	44 (95.7)	<0.001
Diabetes Mellitus; N (%)	10 (14.1)	33 (71.7)	<0.001	10 (14.1)	33 (71.7)	<0.001	0 (0.0)	10 (26.3)	33 (71.7)	<0.001	0 (0.0)	10 (26.3)	33 (71.7)	<0.001
Ischemic Heart Disease; N (%)	1 (1.40)	7 (15.2)	0.004	1 (1.40)	7 (15.2)	0.004	0 (0.0)	1 (2.6)	7 (15.2)	0.01	0 (0.0)	1 (2.6)	7 (15.2)	0.01
Atrial Fibrillation; N (%)	2 (2.80)	12 (26.1)	<0.001	2 (2.80)	12 (26.1)	<0.001	0 (0.0)	2 (5.3)	12 (26.1)	0.001	0 (0.0)	2 (5.3)	12 (26.1)	0.001
Carotid Stenosis; N (%)	0 (0.00)	3 (6.50)	0.03	0 (0.00)	3 (6.5)	0.03	0 (0.0)	0 (0.0)	3 (6.50)	0.09	0 (0.0)	0 (0.0)	3 (6.5)	0.09
Chronic Kidney Disease; N (%)	0 (0.00)	4 (8.70)	0.01	0 (0.00)	4 (8.7)	0.01	0 (0.0)	0 (0.0)	4 (8.70)	0.04	0 (0.0)	0 (0.0)	4 (8.7)	0.04
Cardiac Ejection Fraction <40%; N (%)	0 (0.00)	1 (2.20)	0.21	0 (0.00)	1 (2.2)	0.21	0 (0.0)	0 (0.0)	1 (2.20)	0.46	0 (0.0)	0 (0.0)	1 (2.2)	0.46
Active Neoplasm; N (%)	0 (0.00)	0 (0.00)	-	0 (0.00)	0 (0.00)	-	0 (0.0)	0 (0.0)	0 (0.00)	1.00	0 (0.0)	0 (0.0)	0 (0.0)	1.00
Rheumatological Disease; N (%)	0 (0.00)	0 (0.00)	-	0 (0.00)	0 (0.00)	-	0 (0.0)	0 (0.0)	0 (0.00)	1.00	0 (0.0)	0 (0.0)	0 (0.0)	1.00
Prior Stroke or Transient Ischemic Attack; N (%)	0 (0.00)	9 (19.6)	<0.001	0 (0.00)	9 (19.6)	<0.001	0 (0.0)	0 (0.0)	9 (19.6)	0.001	0 (0.0)	0 (0.0)	9 (19.6)	0.001
Smoking; N (%)	5 (7.00)	5 (10.9)	0.47	5 (7.00)	5 (10.9)	0.47	0 (0.0)	5 (13.2)	5 (10.9)	0.11	0 (0.0)	5 (13.2)	5 (10.9)	0.11

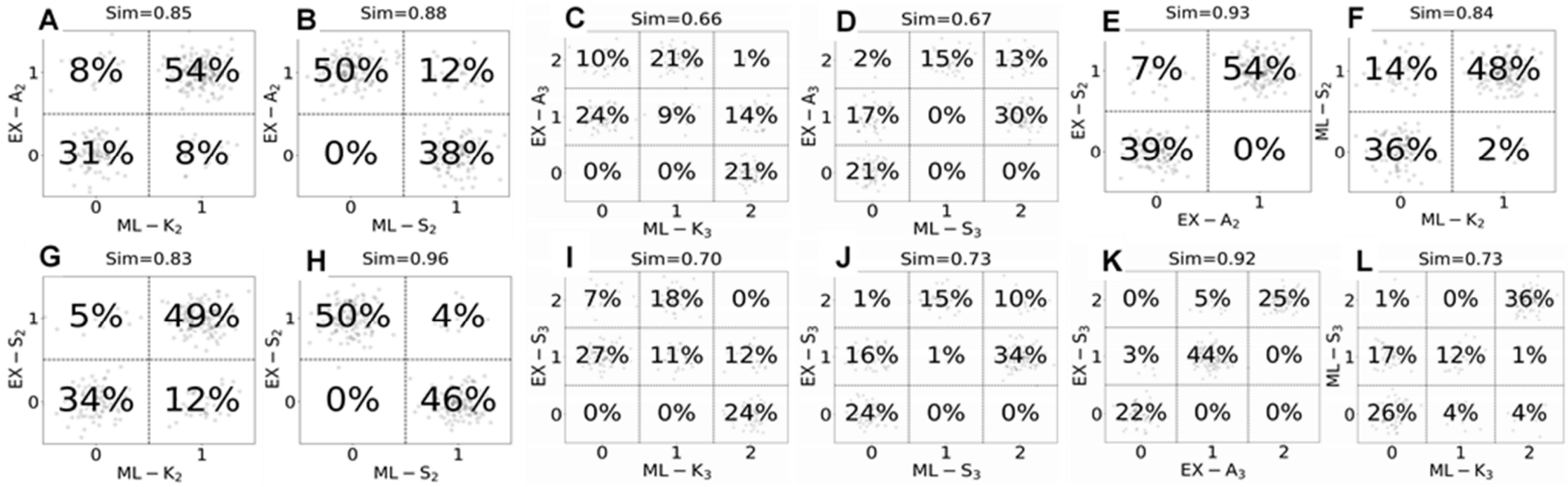
EX-A_2: clinical risk-scoring (expert opinion) model including all comorbidities; a, 0-1 comorbidity; b, >1 comorbidity; EX-S_2: clinical risk-scoring model including selected comorbidities; a, 0-1 comorbidity; b, >1 comorbidity; EX-A_3: clinical risk scoring model including all comorbidities; a, 0 comorbidity; b, 1-2 comorbidities, c, >2 comorbidities; EX-S_3: clinical risk scoring model including selected comorbidities; a, 0 comorbidity; b, 1-2 comorbidities, c, >2 comorbidities. Due to missingness, we provided the valid percentages in this table.

SUPPLEMENTAL 5. THE CHARACTERISTICS OF THE PATIENTS FROM THE LITERATURE REVIEW DATASET DIVIDED BASED ON UNSUPERVISED MACHINE LEARNING MODELS.

Parameter	Machine Learning Algorithms														
	ML-K_2 (K-Mean)			ML-S_2 (Spectral)			ML-K_3 (K-Mean)				ML-S_3 (Spectral)			
	a N = 50 (42.8%)	b N = 67 (57.2%)	P-value	a N = 10 (8.5%)	b N =107 (91.5%)	P-value	a N = 50 (42.7%)	b N = 48 (41.0%)	c N = 19 (16.2%)	P-value	a N = 10 (8.5%)	b N = 77 (65.8%)	c N = 30 (25.6%)	P-value
Age; Mean (SD); Years	62±15	63±15	0.86	53±6	63±15	0.34	57±16	64±15	62±15	0.42	53±6	64±14	61±18	0.45
Sex; Male; N (%)	21 (46.7)	24 (53.3)	0.37	10 (100.0)	46 (56.8)	<0.001	24 (63.2)	20 (51.3)	4 (66.7)	0.52	2 (100.0)	26 (51.0)	20 (66.7)	0.18
Large Vessel Occlusion; N (%)	15 (88.2)	25 (82.1)	0.58	0 (0.0)	40 (84.4)	<0.001	15 (88.2)	19 (82.6)	4 (21.1)	0.85	0 (0.0)	27 (84.4)	11 (84.6)	0.98
Intravenous Thrombolysis; N (%)	2 (40.0)	6 (40.0)	0.99	0 (0.0)	8 (40.0)	<0.001	2 (40.0)	4 (36.4)	2 (10.5)	0.89	0 (0.0)	7 (53.8)	1 (14.3)	0.09
Mechanical Thrombectomy; N (%)	8 (42.1)	9 (34.6)	0.61	0 (0.0)	17 (37.8)	<0.001	8 (42.1)	9 (40.9)	0 (0.00)	0.26	0 (0.0)	10 (31.3)	7 (53.8)	0.16
National Institutes of Health Stroke Scale (NIHSS); Median [IQR]	14 [10-16]	18 [7-21]	0.51	-	16 [8-21]		9 [10-16]	9 [7-21]	11 [6-21]	0.22	-	10 [6-24]	-	-
TOAST Criteria														
Large-Artery Atherosclerosis; N (%)	3 (6.8)	6 (11.8)		0 (0.0)	9 (9.7)		3 (6.80)	4 (10.3)	1 (9.1)		1 (25.0)	5 (7.90)	3 (10.7)	
Cardio-embolism; N (%)	7 (15.9)	7 (13.7)		0 (0.0)	14 (15.1)		7 (15.9)	5 (12.8)	2 (18.2)		0 (0.0)	10 (15.9)	4 (14.3)	
Small-Vessel Occlusion; N (%)	4 (9.1)	2 (3.9)	0.81	0 (0.0)	6 (6.4)	0.37	4 (9.10)	2 (5.1)	0 (0.0)	0.94	0 (0.0)	4 (6.3)	2 (7.1)	0.43
Stroke of Other Determined Etiology; N (%)	15 (34.1)	16 (31.4)		2 (100.0)	29 (31.2)		15 (34.1)	13 (33.3)	3 (27.3)		3 (75.0)	23 (36.5)	5 (17.9)	
Stroke of Undetermined Etiology; N (%)	15 (34.1)	20 (39.2)		0 (0.0)	35 (37.6)		15 (34.1)	15 (38.5)	5 (45.5)		0 (0.0)	21 (33.3)	14 (50.0)	
Imaging Patterns														
Embolic-Appearing; N (%)	3 (60.0)	16 (88.9)		-	19 (82.6)		3 (60.0)	11 (84.6)	5 (100.0)		3 (100.0)	3 (60.0)	13 (86.7)	
Lacune; N (%)	1 (20.0)	2 (11.1)	0.18	-	3 (13.0)	<0.001	1 (20.0)	2 (15.4)	0 (0.0)	0.44	0 (0.0)	1 (20.0)	2 (13.3)	0.18
Borderzone; N (%)	1 (20.0)	0 (0.0)		-	1 (4.4)		1 (20.0)	0 (0.00)	0 (0.0)		0 (0.0)	1 (20.0)	0 (0.00)	
Interval Between Infection Onset to Stroke; Median [IQR]; Days	5 [1-7]	9 [2-15]	0.01	-	6 [2-15]		7 [1-7]	7 [5-15]	8 [1-10]	0.003	-	8 [2-15]	6 [2-14]	0.033
Mechanical Ventilation; N (%)	10 (20.0)	4 (14.3)	0.08	1 (100.0)	13 (22.8)	0.21	10 (33.3)	3 (12.0)	1 (33.3)	0.21	1 (100.0)	7 (16.7)	6 (40.0)	0.16
Disposition														
Discharged Home; N (%)	9 (21.9)	10 (14.9)		0 (0.0)	19(20.4)		9 (22.0)	6 (15.0)	4 (28.6)		3 (42.8)	11 (17.7)	5 (20.0)	
In Hospital Mortality; N (%)	11 (26.8)	20 (37.7)	0.54	0 (0.0)	31 (33.3)	0.60	11 (26.8)	14 (35.0)	7 (50.0)	0.84	3 (42.8)	19 (30.6)	9 (36.0)	0.84
Still in Hospital/Subacute Care; N (%)	21 (42.0)	23 (34.3)		1 (100.0)	43 (46.3)		21 (51.2)	20 (50.0)	3 (21.4)		1 (14.2)	32 (51.6)	11 (44.0)	
Comorbidities														
Hypertension; N (%)	0 (0.0)	64 (95.5)	<0.001	0 (0.0)	64 (59.8)	<0.001	0 (0.0)	47 (97.9)	17 (89.5)	<0.001	0 (0.0)	45 (58.4)	19 (63.3)	0.16
Diabetes Mellitus; N (%)	10 (20.0)	33 (49.2)	0.002	0 (0.0)	43 (36.4)	<0.001	10 (20.0)	21 (43.8)	12 (63.2)	<0.001	0 (0.0)	32 (42.6)	11 (36.7)	0.57
Ischemic Heart Disease; N (%)	2 (4.0)	6 (9.0)	0.34	0 (0.0)	8 (7.5)	0.71	2 (4.0)	3 (6.30)	3 (15.8)	0.22	0 (0.0)	5 (6.5)	3 (10.0)	0.62
Atrial Fibrillation; N (%)	3 (6.0)	11 (18.6)	0.05	0 (0.0)	14 (13.1)	<0.001	3 (6.0)	0 (0.0)	11 (57.9)	<0.001	0 (0.0)	11 (14.3)	3 (10.0)	0.72
Carotid Stenosis; N (%)	0 (0.0)	4 (6.0)	0.11	0 (0.0)	3 (2.8)	0.81	0 (0.0)	3 (6.3)	0 (0.0)	0.14	0 (0.0)	2 (2.6)	1 (3.30)	0.95
Chronic Kidney Disease; N (%)	0 (0.0)	4 (6.0)	0.11	0 (0.0)	4 (3.7)	0.89	0 (0.0)	1 (2.1)	3 (15.8)	0.53	0 (0.0)	3 (3.9)	1 (3.30)	0.27
Cardiac Ejection Fraction <40%; N (%)	0 (0.0)	1 (1.5)	0.35	0 (0.0)	1 (0.9)	0.89	0 (0.0)	0 (0.0)	1 (5.3)	0.01	0 (0.0)	0 (0.0)	1 (3.30)	0.27
Active Neoplasm; N (%)	0 (0.0)	0 (0.0)	-	0 (0.0)	0 (0.0)	-	0 (0.0)	0 (0.0)	0 (0.0)	1.00	0 (0.0)	0 (0.0)	0 (0.00)	1.00
Rheumatological Disease; N (%)	0 (0.0)	0 (0.0)	-	0 (0.0)	0 (0.0)	-	0 (0.0)	0 (0.0)	0 (0.0)	1.00	0 (0.0)	0 (0.0)	0 (0.00)	1.00
Prior Stroke or Transient Ischemic Attack; N (%)	0 (0.0)	9 (13.4)	0.01	0 (0.0)	9 (8.4)	<0.001	0 (0.0)	6 (12.5)	3 (15.8)	0.04	0 (0.0)	5 (6.5)	4 (13.3)	0.19
Smoking; N (%)	4 (8.0)	6 (8.9)	0.54	0 (0.0)	10 (9.3)	<0.001	4 (8.0)	3 (6.3)	3 (15.8)	0.62	0 (0.0)	6 (7.8)	4 (13.3)	0.19

ML-K_2: machine learning model using K-mean, dividing the patients into 2 subgroups; ML-S_2: machine learning model using spectral, dividing the patients into 2 subgroups; ML-K_3: machine learning model using K-mean, dividing the patients into 3 subgroups; ML-S_3: machine learning model using spectral, dividing the patients into 3 subgroups. Please note a, b, and c in this table are not based on the number of comorbidities and just indicated a distinct subgroup detected by unsupervised algorithms. Due to missingness, we provided the valid percentages in this table.

SUPPLEMENTAL FIGURE 1. CONTINGENCY MATRICES



Supplemental Figure 1. The similarity of methods under different clustering models when grouping the patients with acute ischemic stroke into 2 and 3 subgroups. In models based on expert opinion (EX), EX-A included all 11 collected comorbidities and EX-S included 8 selected comorbidities. Patients were then clustered into two subgroups (EX-A_2 and EX-S_2), with "0" referring to patients with zero or one comorbidities and "1" referring to patients with >1 comorbidity, or three subgroups (EX-A_3 and EX-S_3), with "0" referring to patients without any known comorbidity, "1" referring to patients with one or two comorbidities, and "2" referring to patients with >2 comorbidities. In machine learning algorithms (ML) ML-K used hierarchal clustering and K-means, while ML-S used spectral clustering. Within each clustering, method patients were grouped into two (ML-K_2 and ML-S_2) and three (ML-K_3 and ML-S_3) clusters. Panel **A** shows the similarity between the 2 subgroups in EX-A_2 and ML-K_2. Panel **B** shows the similarity between the 2 subgroups in EX-A_2 and ML-S_2. Panel **C** shows the similarity between the 3 subgroups in EX-A_3 and ML-K_3. Panel **D** shows the similarity between the 3 subgroups in EX-A_3 and ML-S_3. Panel **E** shows the similarity between the 2 subgroups in EX-S_2 and EX-A_2. Panel **F** shows the similarity between the 2 subgroups in ML-S_2 and ML-K_2. Panel **G** shows the similarity between the 2 subgroups in EX-S_2 and ML-K_2. Panel **H** shows the similarity between the 2 subgroups in EX-S_2 and ML-S_2. Panel **I** shows the similarity between the 3 subgroups in EX-S_3 and ML-K_3. Panel **J** shows the similarity between the 3 subgroups in EX-S_3 and ML-S_3. Panel **K** shows the similarity between the 3 subgroups in EX-S_3 and EX-A_3. Panel **L** shows the similarity between the 3 subgroups in ML-S_3 and ML-K_3.

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