STROKE IN COVID-19: A SYSTEMATIC REVIEW AND META-ANALYSIS

Supplementary material

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eMethods.

Search terms: ((((COVID 19) OR COVID19 OR (COVID-19) OR (2019 nCoV) OR 2019nCoV OR (2019-nCoV) OR (2019 novel coronavirus) OR (new coronavirus) OR (novel coronavirus) OR (SARS CoV-2) OR (SARS-CoV-2) OR (SARS-CoV) OR (Wuhan AND coronavirus)))) AND (((Stroke OR (acute cerebrovascular disease) OR (brain infarction) OR (intracranial hemorrhage) OR (cerebral hemorrhage) OR ICH OR (cerebral thrombosis) OR (cerebral venous thrombosis)))

Variables definition: For each study included in the quantitative analysis, we extracted the following variables:

1. Study information: study design and country
2. Number of included patients: including stroke patients with COVID-19, and eventually COVID-19 control group (i.e. COVID-19 patients who did not have stroke) and stroke control group (i.e. contemporary or historical stroke patients without COVID-19).
3. Demographic variables: age, and proportion of female.
4. Vascular risk factors: History of hypertension, dyslipidemia, diabetes mellitus, atrial fibrillation, active smoking, coronary artery disease, of prior stroke or transient ischemic attack (TIA).
5. Stroke subtypes: acute ischemic stroke, TIA, intracerebral hemorrhage (ICH), cerebral venous thrombosis (CVT).
6. Stroke-related clinical variables: admission National Institutes of Health Stroke Scale (NIHSS) score for AIS patients (median value); vigilance impairment at stroke onset for AIS patients; delay since COVID-19 symptoms onset to stroke onset (days, median value); reason for hospital admission (stroke vs COVID-19).
7. COVID-19-related clinical variables: presence of COVID-19 symptoms at stroke onset; severity of COVID-19 (severe(1) vs not severe), intubation at stroke onset, radiological signs of pneumonia, radiological signs of pulmonary embolism.
8. Laboratory variables: plasmatic D-dimer level (μg/L, level closest to the time of the stroke median value), plasmatic fibrinogen level (mg/L, median value), lupus anticoagulant, anti-phospolipidies antibodies, therapeutic anticoagulation at the time of stroke onset.
9. Imaging variables for AIS patients: vascular territory involved (anterior vs posterior circulation), infarct pattern (multiple vs single vascular territories), presence of proximal large artery occlusion (defined as occlusion of the intracranial internal carotid artery, M1, and M2 segments of the middle cerebral artery, basilar artery, or P1 segment of the posterior cerebral artery).

10. Imaging variables for ICH patients: location of intraparenchymal hematoma (lobar vs not lobar), bilateral location, ICH leading to intracranial herniation.
11. Acute stroke in-hospital treatment: number of patients undergoing intravenous thrombolysis (IVT), endovascular treatment (EVT), and number of successful recanalization after EVT (defined as TICI score=2b-3)(2).
12. Stroke etiology: classified based on the Trial of ORG 10172 in Acute Stroke Treatment classification(3), including: large artery atherosclerosis, cardioembolism, small vessel disease, other determined mechanism (defined as an alternative mechanism such as dissection or known hypercoagulability, excluding de novo hypercoagulability in the setting of a COVID-19) and cryptogenic (defined as cases not meeting criteria for any of the above stroke subtypes, including those with incomplete workup or with multiple competing high-risk mechanisms).
13. Discharge outcomes: in-hospital mortality, discharge disposition (home, rehabilitation or not discharged at the time of publication).

eTable 1. Study information and number of participants of each study on acute cerebrovascular diseases and COVID-19 included in the systematic review (but not in the meta-analysis).

First author (ref)	Country	Study design	COVID-19 patients with acute CVD (n)	Patients with AIS (n)	Patients with ICH (n)
Agarwal A(4)	India	Cohort study	2	0	2
Al Saiegh F(5)	USA	Case series	2	1	0
Argirò R(6)	Italy	Case series	6	0	0
Avula A(7)	USA	Case series	4	4	0
Baldacini M(8)	France	Case report	1	1	0
Barrios-López JM(9)	Spain	Case series	2	2	0
Baudar C(10)	Belgium	Case report	1	0	0
Bigliardi G(11)	Italy	Case report	1	1	0
Bolaji P(12)	UK	Case report	1	0	0
Bonardel C(13)	France	Case report	1	1	0
Brüggemann B(14)	Netherlands	Case report	1	1	0
Burkert J(15)	UK	Case report	1	1	0
Carroll E(16)	USA	Case series	2	0	2
Castillo PR(17)	USA	Case series	2	0	2
Cavalcanti DD(18)	USA	Case series	3	0	0
Cavallieri F(19)	Italy	Case report	1	1	0
Chen W(20)	China	Case report	1	1	0
Chibane S(21)	Canada	Case report	1	1	0
Chougar L(22)	France	Case report	1	0	0
Co C(23)	Philippines	Case report	1	1	0
Deliwala S(24)	USA	Case report	1	1	0
Diaz-Segarra N(25)	USA	Case series	4	4	0
Duroi I(26)	Belgium	Case report	1	1	0
Fara MG(27)	USA	Case series	3	3	0
Frisullo G(28)	Italy	Case report	1	1	0
Garaci F(29)	Italy	Case report	1	0	0
Garg A(30)	USA	Case report	1	1	0
Gemcioglu E(31)	Turkey	Case report	1	1	0
Ghani MU(32)	USA	Case series	3	0	3
Gill I(33)	USA	Case report	1	1	0
Goldberg MF(34)	USA	Case report	1	1	0
González-Pinto T(35)	Spain	Case report	1	1	0
Griffin D(36)	USA	Case report	1	1	0
Guillan M(37)	Spain	Case report	1	1	0
Gulko E(38)	USA	Case series	2	2	0
Gunasekaran K(39)	USA	Case report	1	1	0
Helms J(40)	France	Cohort study	4	3	1
Helms J(41)	France	Cohort study	3	3	0

Heman-Ackah SM(42)	USA	Case series	2	0	2
Hemasian H(43)	Iran	Case report	1	0	0
Hoelscher C(44)	USA	Case report	1	0	0
Hossri S(45)	USA	Case report	1	1	0
Hughes C(46)	UK	Case report	1	0	0
Jensen MP(47)	UK	Case series	1	1	0
Kariyanna PT(48)	USA	Case report	1	1	0
Khan AW(49)	Pakistan	Case report	1	1	0
Klein DE(50)	USA	Case report	1	0	0
Li J(51)	China	Case report	1	0	1
Lima CFC(52)	Brasil	Case report	1	1	0
Llansó L(53)	Spain	Case report	1	0	0
Mahboob S(54)	USA	Case report	1	1	0
Maldonado S(55)	Belgium	Case report	1	1	0
Malentacchi M(56)	Italy	Case report	1	1	0
Moshayedi P(57)	USA	Case report	1	1	0
Motoie R(58)	Japan	Case report	1	0	1
Muhammad S(59)	Germany	Case report	1	0	1
Nicholson P(60)	Canada	Case series	4	0	4
Papi C(61)	Italy	Case report	1	1	0
Poillon G(62)	France	Case series	2	0	0
Radmard S(63)	USA	Case series	4	3	1
Rinkel LA(64)	Netherlands	Cohort study	7	7	0
Roy-Gash F(65)	France	Case report	1	0	0
Rudilosso S(66)	Spain	Case report	1	1	0
Saggese CE(67)	Italy	Case report	1	1	0
Salahuddin H(68)	USA	Case report	1	1	0
Sangalli D(69)	Italy	Case series	4	4	0
Scullen T(70)	USA	Cohort study	4	4	0
Seabra C(71)	Portugal	Case report	1	1	0
Sharifi-Razavi A(72)	Iran	Case report	1	0	1
Sharifi-Razavi A(73)	Iran	Case series	3	3	0
Sparr SA(74)	USA	Case series	4	4	0
Trifan G(75)	USA	Case report	1	0	1
Tunc A(76)	Turkey	Case series	4	4	0
Usman AA(77)	USA	Case series	3	0	3
Valderrama EV(78)	USA	Case report	1	1	0
Viguier A(79)	France	Case report	1	1	0
Vu D(80)	USA	Case report	1	1	0
Wee NK(81)	Singapore	Case report	1	0	1
Williams OH(82)	UK	Case report	1	1	0
Zahid MJ(83)	USA	Case report	1	0	1
Zayet S(84)	France	Case series	2	2	0
Zhai P(85)	China	Case report	1	1	0

Zhang Y(86)	China	Case series	3	3	0
Zhou B(87)	China	Case report	1	1	0

eTable 2. Study information, number of participants and main findings of each study on acute cerebrovascular diseases and COVID-19 entered in the meta-analysis. We also reported if each included study was suitable for the four main aims of our meta-analysis, with 1) indicating stroke incidence, 2) risk factors for stroke, 3) stroke features and 4) clinical outcome of COVID-19-associated stroke.

First author (ref)	Country	Study design	COVID-19 patients (n)	COVID-19 patients with acute CVD (n)	Patients with AIS (n)	Patients with ICH (n)	Age, median	Sex, F (n)	COVID-19 symptoms at stroke onset	COVID-19 to stroke onset, median (d)	NIHSS, median	LVO	Control group(s)	Aims for meta-analysis
Al Kasab S(88)	Usa	Retrospective observational		13	13		58	5			19	13	445 stroke cases without COVID-19	3; 4
Altschul DJ (b)(89)	USA	Retrospective observational		13	13			8			16	13	23 stroke cases without COVID-19	3; 4
Altschul DJ(90)	USA	Retrospective observational	5227	35		35	67	14						1; 3
Annie F(91)	USA	Retrospective observational	9358	64	64			40					9294 COVID-19 patients without stroke	1; 2; 3
Ashrafi F(92)	Iran	Case series		6	6	0	43.5	3	6		10	6		3
Belani P(93)	USA	Case control		19	19									3
Benger M(94)	UK	Case series		5		5	52.2	2	5	32				3
Benussi A(95)	Italy	Retrospective observational		43	35	3	76.9	21			10		68 stroke cases	3; 4

													without COVID-19	
Berekashvili K(96)	USA	Case series		10	10		55	6	10	5.5	13	5		3
Beyrouti R(97)	UK	Case series		6	6		68.5	1	5	11.5		6		3
Cantador E(98)	Spain	Case series	2115	8	7	0	76.4	1	8	6.3	4	4		1; 3
Cappellari M(99)	Italy	Case series		47	47		77	15		5	12	34		3
Chougar L(100)	France	Retrospective observational	1176	18	17	0								1
D'Amore F(101)	Italy	Case series		6	5	1	75.5	3				2		3
D'Anna L(102)	UK	Case series		8	7	1	74	1	8	7	8.5	3		3
Dmytriw A(103)	USA	Case series		69	69			30	61			31		3
Dogra S(104)	USA	Retrospective observational	3824	33		33	62	7		17				1; 3
Escalard S(105)	France	Retrospective observational		10	10		59.5	2	8	6	22	10	27 stroke cases without COVID-19	3; 4
Fan S(106)	China	Retrospective observational	86	6	6	0	68.2	1	6				80 COVID-19 patients without stroke	1; 2; 3

Hernández-Fernández F(107)	Spain	Retrospective observational	1683	23	17	5		6	12	5	16	10		1; 3; 4
Immovilli P(108)	Italy	Case series		19	17	2	76	9	15					3
Jain R(109)	USA	Retrospective observational	3218	35	26	9	66					17		1; 3
Jillella DV(110)	USA	Case series		8	8		64	3		2				3
John S(111)	United Arab Emirates	Retrospective observational	673	20	15		46.5	1	9		21.5	15		1; 3
Karadas O(112)	Turkey	Retrospective observational	239	9	4	2								1
Katz JM(113)	USA	Retrospective observational	10596	86	72	14		38				49	499 stroke cases without COVID-19	1; 3; 4
Khan M(114)	Arab Emirates	Case series		22	22		46.3	2	16	12.5		16		3
Kihira S(115)	USA	Case-control		126	126			49				40	203 stroke cases without COVID-19	3
Klok FA(116)	Netherlands	Retrospective observational	184	5	5				5					1; 3
Kremer S(117)	France	Retrospective observational		17	17		75	6	5			8		3
Kvernland A(118)	UsA	Retrospective observational	4071	19		19	60	4					44 stroke cases without COVID-19	1; 3; 4

Lapergue B(119)	France	Case series		6	6		52	2	6	11.5	20	6		3
Li Y(120)	China	Retrospective observational	221	13	11	1	73.5	6	7	12			208 COVID-19 patients without stroke	1; 2; 3
Liang JW(121)	USA	Case series		7	7		57	1	7		18	7		3
Lin C(122)	Usa	Retrospective observational		9	9			6					51 stroke cases without COVID-19	3; 4
Lodigiani C(123)	Italy	Retrospective observational	388	9	9		71	3	3					1; 3
Majidi S(124)	USA	Case-control		24	24			5	14		13	24	21 stroke cases without COVID-19	3
Mao L(125)	China	Retrospective observational	214	6	5	1			4	9				1; 3
Mehrpour M(126)	Iran	Retrospective observational		10	9	1		5			20	7	120 stroke cases without COVID-19	3; 4
Meppiel E(127)	France	Case series		63	52	5	65	23		12		16		3
Merkler AE(128)	USA	Retrospective observational	2132	31	31		69	13			16		2101 COVID-19 cases without stroke	1; 2; 3

Mohamud AY(129)	USA	Case series		6	6		65.8	1	4	5.5	24.5	4		3
Morassi M(130)	Italy	Case series		6	4	2	69	1	4	19.5				3
Nalleballe K(131)	USA	Retrospective observational	40469	406	406	0								1
Nawabi J(132)	Germany	Case series		18		18	49.5	9	16	11				3
Ntaios G(133)	Greece	Retrospective observational		174	174		71.2	66		7	10		174 stroke cases without COVID-19	3; 4
Oxley TJ(134)		Case series		5	5		41	1	3		17	5		3
Paterson RW(135)	UK	Retrospective observational	43	8	8	0	62.5	2		8		4		3
Pinna P(136)	USA	Retrospective observational	650	19	10	8								1; 3
Pons-Escoda A(137)	Spain	Retrospective observational	2249	20	13	7	71	7	20			8		1; 3
Pop R(138)	France	Case series		13	13		78	8	4		13	13		3
Reddy ST(139)	USA	Case series		12	10	2	56.5	6	11	7	11			3
Rothstein A(140)	USA	Retrospective observational	844	28	20	8	60.5	12	28	23		3		1; 3

Shahjouei S(141)	USA	Retrospective observational		432	323	68	68	183		2.3	9	126		3
Siegler JE(142)	USA	Retrospective observational	14483	172	156	28		68			13	57		1; 3
Sweid A(143)	USA	Case series		22	17	3	59.5	12		8.8	14	15		3
Varatharaj A(144)	UK	Prospective observational	125	66	57	9	71	44						3
Wang A(145)	USA	Case series		5	5		52.8	1			27	5		3
Xiong W(146)	China	Retrospective observational	917	10	10	0			10					1; 3
Yaeger KA(147)	USA	Case series		5	5				3			5		3
Yaghi S(148)	USA	Retrospective , cohort study	3556	32	32		63	9	27	10	19	10	126 stroke cases without COVID-19	1; 3; 4

Table e3. Quality assessment of the cohort studies included in the meta-analysis based on the Newcastle-Ottawa scale.

Paper	**Selection**				**Comparability**	**Outcome**			**SCORE**
First author[ref]	**Representati-veness of the exposed cohort**	**Selection of the non exposed cohort**	**Ascertainment of exposure**	**Demonstration that outcome of interest was not present at start of study**	**Comparability of cohorts on the basis of the design or analysis**	**Assessment of outcome**	**Was Follow-Up Long Enough for Outcomes to Occur**	**Adequacy of Follow Up of Cohorts**	**(quality)**
Al Kasab S[88]	*	*	*	*	**	*	*	*	9 (high)
Altschul DJ (b)[89]	*	*	*	*	**	*	*	*	9 (high)
Altschul DJ(90)	*	*	*	*		*	*	*	7 (fair)
Annie F(91)	*	*	*	*	**	*	*	*	9 (high)
Benussi A(95)	*	*	*	*	**	*	*	*	9 (high)
Chougar L(22)	*	*	*	*		*	*		6 (moderate)
Dogra S(104)	*	*	*	*		*	*	*	7 (fair)
Escalard S(105)	*	*	*	*	**	*	*	*	9 (high)
Fan S(106)	*	*	*	*	**	*	*	*	9 (high)
Hernández-Fernández F(107)	*	*	*	*	**	*	*	*	9 (high)
Jain R(109)	*	*	*	*		*	*	*	7 (fair)
John S[111]	*		*	*		*	*	*	7 (fair)
Karadas O(112)	*	*	*	*		*	*		6 (moderate)

Katz JM(113)	*	*	*	*	**	*	*	*	9 (high)
Klok FA(116)	*	*	*	*		*	*		6 (moderate)
Kremer S(117)	*		*	*		*	*		5 (moderate)
Kvernland A(118)	*	*	*	*	**	*	*	*	9 (high)
Li Y(120)	*	*	*	*	**	*	*	*	9 (high)
Lin C(122)	*	*	*	*	**	*	*	*	9 (high)
Lodigiani C(123)	*	*	*	*		*	*	*	7 (fair)
Mao L(125)	*	*	*	*		*	*		6 (moderate)
Mehrpour M(126)	*	*	*	*	**	*	*	*	9 (high)
Merkler AE(128)	*	*	*	*	**	*	*	*	9 (high)
Nalleballe K(131)	*	*	*	*		*	*		6 (moderate)
Paterson RW(135)	*	*	*	*		*	*	*	7 (fair)
Pinna P(136)	*	*	*	*		*	*		6 (moderate)
Pons-Escoda A(137)	*	*	*	*		*	*		6 (moderate)
Rothstein A(140)	*	*	*	*		*	*	*	7 (fair)
Shahjouei S(141)	*		*	*		*	*	*	6 (moderate)
Siegler JE(142)	*		*	*		*	*	*	7 (fair)
Varatharaj A(144)	*		*	*		*	*		5 (moderate)
Xiong W(146)	*	*	*	*		*	*	*	7 (fair)

Yaghi S(148)	*	*	*	*	**	*	*	*	9 (high)

Newcastle-Ottawa scale for cohort studies:

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability. Blank: information not available, therefore not granted a star

Selection

1) Representativeness of the exposed cohort

a) truly representative of the average __of COVID-19 patients__ (describe) in the community ✸ (eg, consecutively admitted COVID-19 patients at one hospital)

b) somewhat representative of the average _____ in the community ✸

c) selected group of users eg nurses, volunteers

d) no description of the derivation of the cohort

2) Selection of the non exposed cohort

a) drawn from the same community as the exposed cohort ✸ (information of COVID-19 patients without stroke or non-infected stroke patients during the same study period)

b) drawn from a different source

c) no description of the derivation of the non exposed cohort

3) Ascertainment of exposure

a) secure record (eg surgical records) ✸ (confirmation of SARS-CoV-2 infection)

b) structured interview ✸

c) written self report

d) no description

4) Demonstration that outcome of interest was not present at start of study

a) yes ✸ (new acute CVD on hospital admission or during the hospitalization in COVID-19 patients, excluding personal history of previous stroke)

b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis

a) study controls for _____age_____ (select the most important factor) ✸ (comparison between stroke and non-stroke patients with COVID-19; or comparison between stroke patients with and without COVID-19)

b) study controls for any additional factor ✸ (This criteria could be modified to indicate specific control for a second important factor. Any VRF)

Outcome

1) Assessment of outcome (i.e.occurrence of acute CVD in COVID-19 patients)

a) independent blind assessment ✸

b) record linkage ✸

c) self report

d) no description

2) Was follow-up long enough for outcomes to occur

a) yes (select an adequate follow up period for outcome of interest) ✸

b) no

3) Adequacy of follow up of cohorts

a) complete follow up - all subjects accounted for at least discharge modalities ✸

b) subjects lost to follow up unlikely to introduce bias - small number lost - > _10% (select an adequate %) follow up, or description provided of those lost) ✸

c) follow up rate < ____% (select an adequate %) and no description of those lost

d) no statement

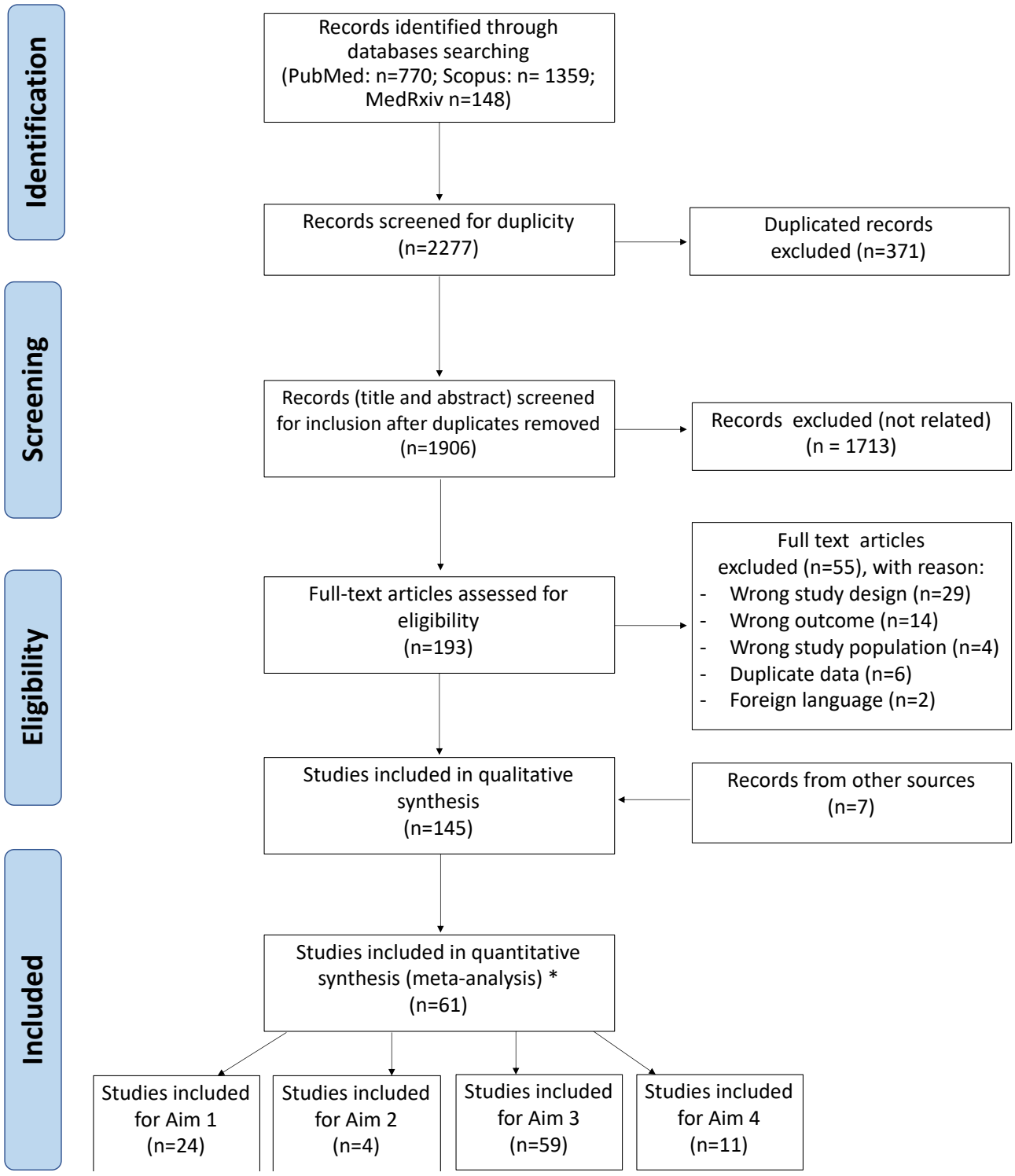
Table e4. Clinical characteristics of cerebrovascular disease (CVD) patients with or without COVID-19.

Variable	N of valid studies	CVD patients with COVID-19	CVD patients without COVID-19	OR (95% CI) or pooled median
Demographics				
Age, median	11	590	1194	-6.0 (-12.3;-1.4)*
Sex, female	11	150/395	773/1670	0.71 (0.51;0.99)*
Vascular risk factors				
Hypertension	10	257/385	835/1128	0.65 (0.45;0.96)*
Hypercholesterolemia	10	140/385	471/1128	0.84 (0.65;1.08)
Diabetes mellitus	10	152/385	248/1128	1.66 (0.97;2.85)
Atrial fibrillation	9	73/342	108/1060	1.13 (0.32;4.06)
Smoking	8	56/342	146/1063	0.77 (0.41;1.45)
Coronary artery disease	5	39/234	72/496	1.05 (0.50;2.20)
Previous stroke	4	11/146	159/720	0.34 (0.18;0.63)*
Stroke characteristics				
AIS from LVO	8	127/251	613/1031	2.73 (1.63;4.57)*
NIHSS for AIS patients	10	477	1204	5 (3;9)*
AIS in anterior circulation	4	55/60	463/516	1.12 (0.36;3.51)
Acute stroke treatment				
IVT	10	80/428	379/1569	1.06 (0.64;1.76)
EVT	10	78/428	579/1569	1.13 (0.71;1.80)
Successful recanalization after EVT	3	24/26	399/481	1.48 (0.30;7.29)
Discharge outcomes				
In-hospital death	11	144/432	191/1643	5.21 (3.43;7.90)*

*denotes significant result

Legend: AIS= acute ischemic stroke; LVO= large vessel occlusion; IVT= intravenous thrombolysis; EVT=endovascular treatment.

Figure e1. PRISMA flow diagram based on literature search at 14.09.2020**.**



Legend: * After excluding articles reporting less than 5 cases stroke in COVID-19.
Aim 1) indicates stroke incidence, 2) risk factors for stroke, 3) stroke features and 4) clinical outcome of COVID-19-associated stroke.

Figure e2. Clinical characteristics of COVID-19 patients with (CVD group) and without new onset of acute CVD (No CVD group). Figure 2a reports distribution of female sex (Sex_F); Figure 2b proportions of hypertension (HTN); Figure 2c proportions of diabetes mellitus (DM); Figure 2d proportions of coronary artery disease (CAD); Figure 2e proportions of smoking; and Figure 2f proportions of severe COVID-19 (COVID severe).

Figure 2a.

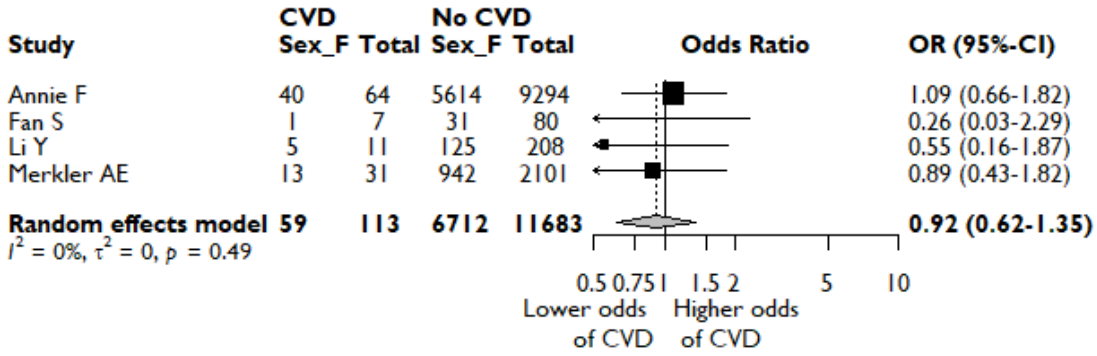


Figure 2b.

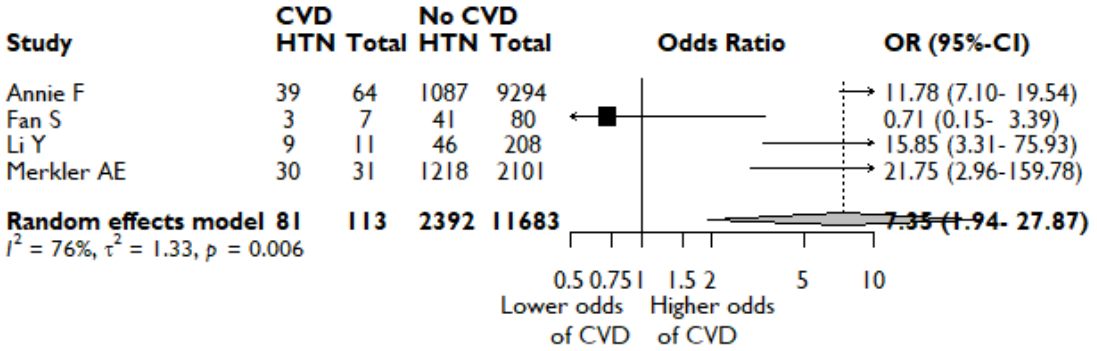


Figure 2c.

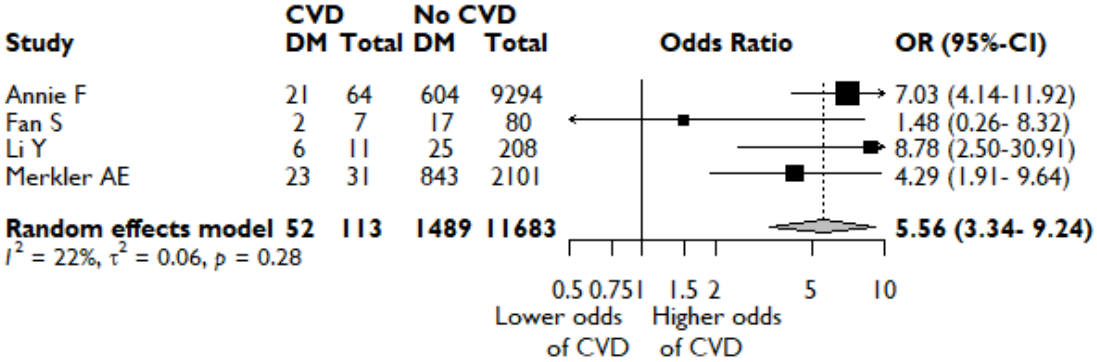


Figure 2d.

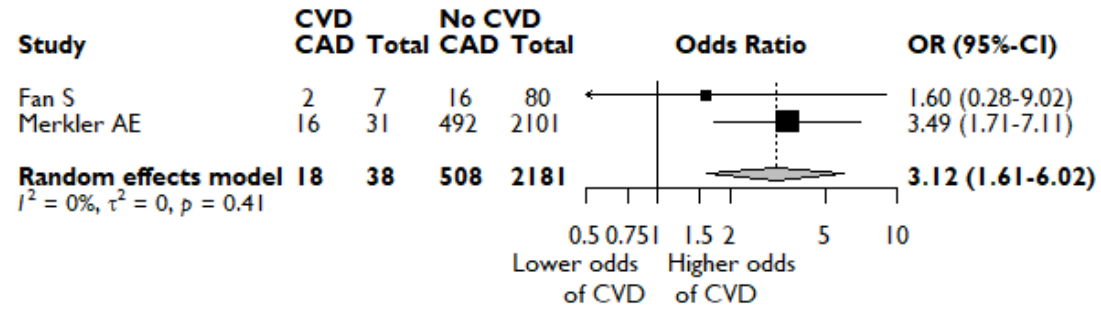


Figure 2e.

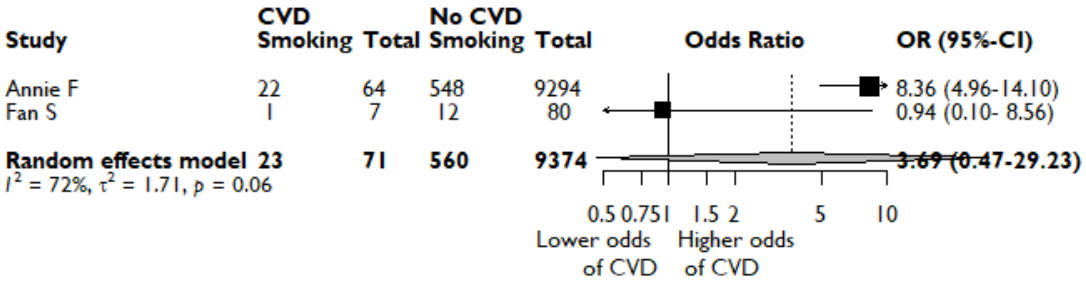
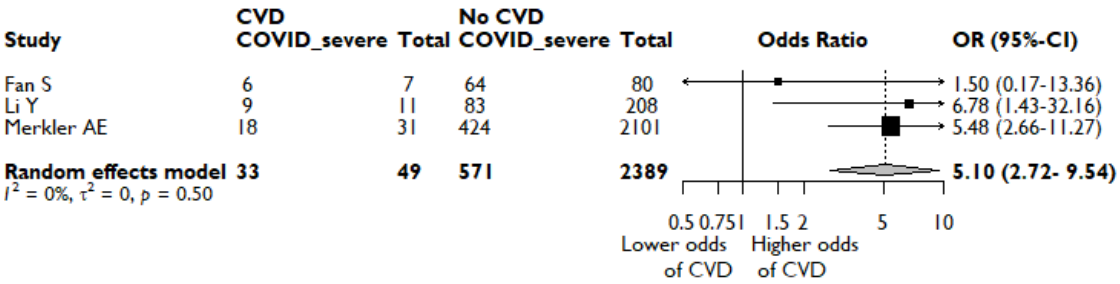
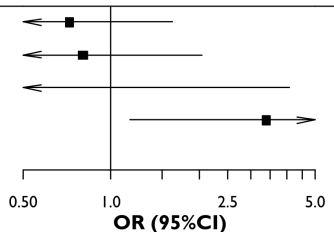


Figure 2f.



eFigure 3. Stroke etiologies among COVID-19 patients with stroke (Covid-19 group) and stroke patients without COVID-19 (No Covid-19 group), showing a significantly higher proportion of cryptogenic stroke in the Covid-19 group.

		Covid-19		No Covid-19			
Stroke etiology	**No. studies**	***Outcome***	***Total***	***Outcome***	***Total***	**OR (95%CI)**	**I^2**
Cardioembolic	2	9	41	49	177	0.72 (0.32-1.62)	0
Atherosclerosis	2	6	41	35	177	0.80 (0.31-2.04)	0
Small vessel disease	2	1	41	20	177	0.42 (0.04-4.07)	37
Cryptogenic	2	26	41	56	177	3.40 (1.16-10.00)	46



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