

Multi-level blood biomarkers for early diagnosis of ischaemic stroke: a systematic review and meta-analysis

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Supplementary Table 1: Search strategies

PubMed: 1971 to 4 June 2022

#1	Blood[MeSH] OR blood[Title/Abstract] OR plasma[Title/Abstract] OR serum[Title/Abstract]
#2	“Biomarkers”[MeSH] OR biomarker*[Title/Abstract] OR “biological marker”[Title/Abstract] OR “biologic marker”[Title/Abstract] OR “serum marker”[Title/Abstract] OR “biochemical marker”[Title/Abstract] OR “laboratory marker”[Title/Abstract]
#3	Diagnosis[MeSH] OR diagnos*[Title/Abstract] OR differentiat*[Title/Abstract]
#4	Stroke[MeSH] OR “stroke”[Title/Abstract] OR “cerebrovascular accident”[Title/Abstract] OR “brain vascular accident”[Title/Abstract] OR “brain infarct”[Title/Abstract] OR “intracerebral hemorrhage”[Title/Abstract] OR “cerebral hemorrhage”[Title/Abstract]
#5	1 AND #2 AND #3 AND #4

Ovid Embase: 1974 to 4 June 2022

#1	'blood'/exp
#2	blood:ab,ti OR plasma:ab,ti OR serum:ab,ti
#3	#1 OR #2
#4	'biological marker'/exp
#5	biomarker:ab,ti OR biomarkers:ab,ti
#6	biologic:ab,ti AND marker:ab,ti
#7	biologic:ab,ti AND markers:ab,ti
#8	biochemical:ab,ti AND marker:ab,ti
#9	biochemical:ab,ti AND markers:ab,ti
#10	laboratory:ab,ti AND marker:ab,ti
#11	laboratory:ab,ti AND markers:ab,ti
#12	#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11

#13	'diagnosis'/exp
#14	diagnosis:ab,ti OR diagnoses:ab,ti OR diagnose:ab,ti OR diagnostic:ab,ti OR diagnostics:ab,ti OR diagnostically:ab,ti
#15	differentiation:ab,ti OR differentiate:ab,ti OR differentiating:ab,ti OR differentiability:ab,ti
#16	#13 OR #14 OR #15
#17	'cerebrovascular accident'/exp
#18	stroke:ab,ti OR strokes:ab,ti
#19	cerebrovascular:ab,ti AND accident:ab,ti
#20	cerebrovascular:ab,ti AND accidents:ab,ti
#21	brain:ab,ti AND vascular:ab,ti AND accident:ab,ti
#22	brain:ab,ti AND vascular:ab,ti AND accidents:ab,ti
#23	brain:ab,ti AND infarction:ab,ti
#24	brain:ab,ti AND infarct:ab,ti
#25	cerebral:ab,ti AND hemorrhage:ab,ti
#26	intracerebral:ab,ti AND hemorrhage:ab,ti
#27	#17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26
#28	#3 AND #12 AND #16 AND #27

Cochrane library: 1993 to 4 June 2022

#1	MeSH descriptor: [Blood] this term only
#2	MeSH descriptor: [Plasma] this term only
#3	MeSH descriptor: [Serum] this term only
#4	(blood):ti,ab,kw OR (plasma):ti,ab,kw OR (serum):ti,ab,kw in Trials (Word variations have been searched)
#5	#1 OR #2 OR #3 OR #4
#6	MeSH descriptor: [Biomarkers] this term only
#7	(biomarker):ti,ab,kw OR (biomarkers):ti,ab,kw in Trials (Word variations have been searched)
#8	(biological):ti,ab,kw OR (biologic):ti,ab,kw OR (biomedical):ti,ab,kw OR (laboratory):ti,ab,kw in Trials (Word variations have been searched)

#9	(marker):ti,ab,kw OR (markers):ti,ab,kw in Trials (Word variations have been searched)
#10	#8 AND #9
#11	#6 OR #7 OR #10
#12	MeSH descriptor: [Diagnosis] this term only
#13	(diagnoses):ti,ab,kw OR (diagnose):ti,ab,kw OR (diagnostic):ti,ab,kw OR (diagnostics):ti,ab,kw OR (diagnostically):ti,ab,kw in Trials (Word variations have been searched)
#14	(differentiate):ti,ab,kw OR (differentiation):ti,ab,kw OR (differentiating):ti,ab,kw OR (differentiability):ti,ab,kw in Trials (Word variations have been searched)
#15	#12 OR #13 OR #14
#16	MeSH descriptor: [Stroke] this term only
#17	(stroke):ti,ab,kw in Trials (Word variations have been searched)
#18	(cerebrovascular):ti,ab,kw AND (accident):ti,ab,kw in Trials (Word variations have been searched)
#19	(brain):ti,ab,kw AND (vascular):ti,ab,kw AND (accident):ti,ab,kw in Trials (Word variations have been searched)
#20	(brain):ti,ab,kw AND (infarction):ti,ab,kw in Trials (Word variations have been searched)
#21	(cerebral):ti,ab,kw AND (hemorrhage):ti,ab,kw in Trials (Word variations have been searched)
#22	(intracerebral):ti,ab,kw AND (hemorrhage):ti,ab,kw in Trials (Word variations have been searched)
#23	#16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 in Trials
#24	#5 AND #11 AND #15 AND #23 in Trials

Web of science: 1900 to 4 June 2022

#1	blood (Topic) or plasma (Topic) or serum (Topic)
#2	biomarkers (Topic) or biomarker (Topic)
#3	biological (Topic) and marker (Topic)
#4	biologic (Topic) and marker (Topic)

#5	biochemical (Topic) and marker (Topic)
#6	laboratory (Topic) and marker (Topic)
#7	#2 OR #3 OR #4 OR #5 OR #6
#8	diagnosis (Topic) or diagnoses (Topic) or diagnose (Topic) or diagnostic (Topic) or diagnostics (Topic) or diagnostically (Topic)
#9	differentiate (Topic) or differentiation (Topic) or differentiating (Topic) or differentiability (Topic)
#10	#8 OR #9
#11	Stroke (Topic)
#12	cerebrovascular (Topic) and accident (Topic)
#13	brain (Topic) and vascular (Topic) and accident (Topic)
#14	brain (Topic) and infarction (Topic)
#15	brain (Topic) and infarct (Topic)
#16	cerebral (Topic) and hemorrhage (Topic)
#17	intracerebral (Topic) and hemorrhage (Topic)
#18	#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17
#19	#1 AND #7 AND #10 AND #18

Supplementary Table 2: Concise characteristics of 182 included studies

Study ID	Country	Design	Comparison	Setting	Reference	Specimen	Sampling time	Omics	Biomarkers
Zhou 2021 (1)	China	Case control study	IS vs. Controls	Not stated	CT; MRI	serum	24h	transcripts	miR-124
Zhang 2022 (2)	China	Case control study	IS vs. Controls	Not stated	Not stated	serum	9h	proteins	JKAP
Yang 2022 (3)	China	Case control study	IS vs. Controls	Not stated	Not stated	plasma; exosome	12h	Transcriptomics	circ_0112036, circ_0066867, circ_0093708, circ_0041685
Turek-Jakubowska 2022 (4)	Poland	Case control study	IS vs. Controls	Neurology ward	CT	plasma	24h	Proteomics	Alpha-1B-glycoprotein
Tian 2022 (5)	China	Case control study	IS vs. Controls	Neurovascular centre	Not stated	whole blood	6h	Transcriptomics	lncRNA NR_120420
Rahmati 2021 (6)	Iran	Case control study	IS vs. Controls	Not stated	MRI	serum	24h	transcripts; proteins	miR-210, HIF-1a
Li 2021 (7)	China	Case control study	IS vs. Controls	Not stated	CT; MRI	serum	24h	proteins; metabolites	uric acid, CRP, NT-proBNP
Induruwa 2022 (8)	UK	Prospective study	IS vs. Controls; HS vs. Controls; Total stroke vs. controls	ED	Not stated	whole blood; platelet	8h	proteins; platelet	IS vs. control: GPVI-dimer, HS vs. control: GPVI-dimer, total stroke vs. control: GPVI, GPVI-dimer, platelet P-selectin
Gawryś 2022 (9)	Poland	Case control study	IS vs. Controls	Neurology ward	CT	platelet	24h	Proteomics; platelet	Beta-amyloid protein A4, Amyloid-like protein 2, coactosin-like protein, thymidine phosphorylase 4 (TYMP-4), interferon regulatory factor 7 (IRF7), vitamin K-dependent protein S, histone proteins (H2A type 1 and 1-A, H2A types 2B and J, H2Av, -z, and -x), platelet basic protein
Cho 2022 (10)	not stated	Case control study	IS vs. Controls	ED	Not stated	PBMCs	24h	PBMC number	NK cells, CD14+ monocytes
Intiso 2004 (11)	Italy	Prospective study	IS vs. Controls	Neurology ward	CT; MRI	serum	24h	proteins	TNFa
Perini 2001 (12)	Italy	Prospective study	IS vs. Controls	Stroke Unit	CT	serum	12h	proteins	IL-6, IL-10
Pedersen 2004 (13)	Norway	Case control study	IS vs. Controls	Not stated	CT; MRI	plasma	24h	proteins	CRP
Nayak 2011 (14)	India	Case control study	IS vs. Controls	Not stated	CT	serum	24h	proteins	IMA
Senes 2007 (15)	Turkey	Prospective study	IS vs. Controls	Not stated	Not stated	serum	24h	metabolites	nitrite, nitrate, IMA, TBARS
Feng 2019 (16)	China	Case control study	IS vs. Controls	Not stated	CT; MRI	plasma	24h	transcripts	lncRNA ANRIL
Blann 1999 (17)	UK	Prospective study	IS vs. Controls	Not stated	Not stated	serum; plasma	12h	proteins	ICAM-1, E-selectin, VCAM-1, vWF
Shyu 1997 (18)	China (Taiwan)	Prospective study	IS vs. Controls	ED	CT	serum	24h	proteins	ICAM-1, E-selectin

Liu 2015 (19)	China	Prospective study	IS vs. Controls	Not stated	CT; MRI	serum	24h	proteins	CXCL12
Supanc 2011 (20)	Croatia	Prospective study	IS vs. Controls	Neurology ward	CT	serum	24h	proteins	ICAM-1, VCAM-1
Wunderlich 2005 (21)	Germany	Prospective study	IS vs. Controls	Neurology ward	CT	serum	24h; 18h; 12h; 6h; 3h; 2h; 1h	proteins	B-FABP, H-FABP
Hu 2016 (22)	China	Case control study	IS vs. HS	Not stated	Not stated	whole blood	12h	metabolites	Asn, C5:1, Arg/Om, Val/Phe, (C0 +C2 + C3 + C16 + C18:1)/Cit
Uno 2003 (23)	Japan	Prospective study	IS vs. Controls	department of neurological surgery	CT; MRI	plasma	24h	proteins	OxLDL
Sun 2019 (24)	Germany	Prospective study	IS vs. Controls	ED	CT; MRI	serum	24h	Metabolomics	tetradecanedioate, hexadecanedioate
Song 2006 (25)	Korea	Prospective study	IS vs. Controls	Not stated	CT; MRI	plasma	24h	proteins	IL-6,PAI-1,PAP
Zitnanova 2016 (26)	Slovakia	Case control study	IS vs. Controls	Neurology ward	CT	plasma	24h	proteins	lipid peroxides, superoxide dismutase activity, catalase activity, paraoxonase activity, glutathione peroxide activity
Can 2015 (27)	Turkey	Prospective study	IS vs. Controls	ED	MRI	serum	12h	proteins	MBP, IMA
Kimberly 2013 (28)	USA	Prospective study +animal experiment study	IS vs. Controls	ED	MRI	plasma	2h; 9h	Metabolomics; targeted	BCAA (leucine, isoleucine, valine), carnitine, threonine, histidine, glucose, methionine, glycine, proline, lysine, cysteamine, uridine, 5'-adenosylhomocysteine, creatinine, N-carbamoyl-beta-alanine, cis/trans hydroxyproline, asparagine
Abboud 2007 (29)	France	Prospective study	IS vs. HS; Total stroke vs. TIA	ED	CT; MRI	serum	3h	proteins	IMA
Tang 2006 (30)	USA	Case control study	IS vs. Controls	Not stated	CT	whole blood	24h; 5h; 3h	Genomics	Hox 1.11 gene, CKAP4 gene, S100A9 gene, MMP9 gene, S100P gene, F5 gene, FPR1 gene, S100A12 gene, RNASE2 gene, ARG1 gene, CA4 gene, LY96 gene, SLC16A6 gene, HIST2H2AA gene, ets-2 gene, BCL6 gene, PYGL gene, NPL gene
Rainer 2007 (31)	China	Prospective study	IS vs. HS	ED	CT; MRI	plasma	24h	proteins; cfDNA	cfDNA, S100
Tiedt 2018 (32)	Germany	Prospective study	IS vs. Controls	ED	MRI	serum	24h	proteins	NfL
Zhu 2019 (33)	China	Case control study	IS vs. Controls	Not stated	CT; MRI	PBMC	24h	transcripts	PBMC circ-DLGAP4
Zhu 2018 (34)	China	Case control study	IS vs. Controls	Not stated	MRI	leukocytes	24h	transcripts	lncRNA MIAT
Zhou 2016 (35)	China	Prospective study	IS vs. HS	ED	CT	plasma	6h	proteins	S100B
Zhou 2018 (36)	China	Case control study	IS vs. Controls	Not stated	MRI	serum; exosome	24h	transcripts	miR-134
Zhou 2022 (37)	China	Case control +animal study	IS vs. Controls	Neurology department	CT; MRI	Serum (small extracellular vesicles)	24h	Transcriptomics	miR-9-3p, miR-124-3p, miR-143-3p, miR-93-5p

Zhao 2016 (38)	China	Prospective study	IS vs. Controls	Neurology ward	Not stated	serum	24h	proteins	Apolipoprotein A1-Unique Peptide (APOA1-UP)
Zhao 2017 (39)	China	Case control study	IS vs. Controls; HS vs. Controls	ED, neurology department	CT; MRI	plasma; neutrophils, lymphocytes	6h	transcripts	miR-99a-5p
Zhao 2016 (40)	China	Prospective study	IS vs. Controls	Neurology ward	MRI	plasma	24h	transcripts	miR-335
Zhang 2017 (41)	China	Case control study	IS vs. HS; IS vs. Controls; HS vs. Controls	Not stated	CT; MRI	dried blood spot	12h	Metabolomics	IS vs. control: C22, C5, C3DC, C4, C5DC/C5-OH, C3DC/C10, C14:2, C10:2, (0+2+3+16+18:1)/Cit, Arg, Pro HS vs. control: C16-OH/C16, C16:1-OH, C10, C5/C3, C12, C18, C18:1, C4DC, Val/Phe, C16, Arg, Thr IS vs. HS: C4-OH, C5DC, C14, C16-OH, Tyr/Cit, Val/Phe, C5DC/C5-OH, C5DC/C16, C18-OH, (0+2+3016+18:1)/Cit, C3/Met
Zhang 2020 (42)	China	Prospective study	IS vs. Controls	Not stated	CT; MRI	plasma; endothelial microvesicles	24h	transcripts; endothelial microvesicles	EMVs, EMVs-miR-155
Zaremba 2006 (43)	Poland	Case control study	IS vs. Controls	Not stated	CT	serum	24h	proteins	IL-12
Yuan 2020 (44)	China	Case control study + animal experiment study	IS vs. Controls	Neurology ward	CT; MRI	plasma	24h	proteins	GMFB
Yigit 2017 (45)	Turkey	Case control study	IS vs. Controls; HS vs. Controls	ED	Not stated	serum	24h	proteins	UCH-L1
Yang 2016 (46)	China	Case control study	IS vs. Controls	Not stated	CT; MRI	plasma	24h	transcripts	miR-107, miR-128b, miR-153
Xiong 2015 (47)	China	Prospective study	IS vs. HS	Not stated	CT; MRI	serum	6h	proteins	GFAP
Wu 2020 (48)	China	Case control study	IS vs. Controls	Neurology ward	CT; MRI	plasma	6h	transcripts	miR-99b
Williams 2007 (49)	USA	Prospective study	IS vs. SM	ED	MRI	plasma	24h	Endothelial microparticles (EMPs)	number of Endothelial microparticles
Wang 2017 (50)	China	Case control study	IS vs. Controls	ED	CT; MRI	serum	6h	transcripts	miR-221-3p, miR-382-5p
Wang 2014 (51)	China	Prospective study	IS vs. Controls	Not stated	MRI	plasma	24h	transcripts	miR-106b-5P, miR-4306, miR-320e, miR-320d
Wang 2018 (52)	China	Case control study	IS vs. Controls	Neurology ward	CT; MRI	plasma; exosome	6h	transcripts	miR-21-5p, miR-30a-5p
Wang 2017 (53)	China	Case control study + animal experiment study	IS vs. Controls	Not stated	MRI	plasma; lymphocytes	3h	transcripts	lncRNA H19
Walsh 2016 (54)	USA	Case control study	IS vs. HS; IS vs. Controls; HS vs. Controls	ED, neurology department	Not stated	plasma	12h	proteins	Apo A-I, Apo C-I, Apo C-III, MMP-3, MMP-9, paraoxonase-1

				ent, NICU					
Vukasovic 2006 (55)	Croatia	Case control study	IS vs. Controls	Not stated	CT	serum	24h	proteins	MMP-2, TIMP-2
von Recum 2015 (56)	Germany	Prospective study	IS vs. TIA	ED	Not stated	serum	4.5h	proteins	copeptin
Unden 2009 (57)	Sweden	Prospective study	IS vs. HS	Not stated	CT	not stated	24h	proteins	S100B, NSE, GFAP, APC-PCI
Tunç 2018 (58)	Turkey	Prospective study	IS vs. Controls	Not stated	CT; MRI	serum	24h	proteins	SPA
Tiedt 2017 (59)	Germany	Prospective study	IS vs. TIA; IS vs. Controls	ED	CT; MRI	plasma	24h	Transcriptomics	miR-125a-5p, miR-125b-5p, miR-143-3p
Tiedt 2020 (60)	Germany	Prospective study	IS vs. SM; IS vs. Controls	ED	CT; MRI	serum	24h	Metabolomics	asymmetrical dimethylarginine (ADMA), symmetrical dimethylarginine (SDMA), pregnenolone sulphate, adenosine
Tian 2015 (61)	China	Prospective study	IS vs. Controls	Not stated	CT; MRI	serum	24h	proteins	PCT, hsCRP, HCY
Tian 2016 (62)	China	Prospective study	IS vs. Controls	Cerebrovascular Disease Centre	Not stated	plasma	6h	Transcriptomics	miR-16
Taema 2014 (63)	Egypt	Prospective study	IS vs. HS	Not stated	CT	serum	24h	proteins	CRP
Stejskal 2011 (64)	Czech Republic	Case control study	IS vs. Controls	Not stated	CT; MRI	serum	3h	proteins	VILIP-1
Stanca 2015 (65)	Romania	Prospective study	IS vs. HS	ED	CT	serum	24h; 12h	proteins	GFAP, antibodies against NMDA receptor subunit NR2
Stamova 2010 (66)	USA	Case control study	IS vs. Controls	Not stated	Not stated	whole blood	24h; 5h; 3h	Genomics	GENES (ABCA1, PGM5, CCDC144C /// LOC100134159, LECT2, SHOX, TBX5, SPTLC3, SNIP, RBMS3, P704P, THSD4, FAT3, SNRPN, GLYATL1, GADL1, DKFZP434L187, CXADR, OVOL2, RNF141, CLEC4E, ELL2, SPIB, BXDC5, UNC5B, TIMP2, ASTN2, FLJ35934, ANKRD28, CCDC144A, TIMM8A, ALDOAP2, LDB3, PTPRD, LOC729222 ///PPFIBP1, CCRL1, HNRNPUL2, FCRL4, ELAVL2, PRTG, DLX6, FOXA2, SCD5, GABRB2, GYPA, OSBPL1A, PHTF1, CKLF, CKLF, RRAGD, CLEC4E, CKLF, FGD4, CPEB2, LOC100290882, UBXN2B, ENTPD1, BST1,LTB4R,F5,IFRD1,KIAA0319, CHMP1B, MCTP1, VNN3, AMN1, LAMP2, FCHO2, ZNF608, REM2, QKI, RBM25, FAR2, ST3GAL6, HNRNPH2, GAB1, UBR5,VAPA,THBD,LOC283027, LOC344595,RPL22, LOC100129488, RPL22, MCTP1, SH3GL3)
Stamova 2019 (67)	USA	Case control study	IS vs. HS; IS vs. Controls; HS vs. Controls	Not stated	CT; MRI	not stated	24h	Transcriptomics	HS vs. control: 489 transcripts; IS vs. control: 396 transcripts; IS vs. HS: 256 transcripts
Song 2019 (68)	USA	Case control study	IS vs. Controls	Not stated	CT; MRI	serum	24h	Proteomics	clusterin, cystatin C (CST3)
Simats 2020 (69)	Spain	Case control study + animal	IS vs. SM	ED	Not stated	plasma	6h	Transcriptomics; Proteomics	CTNND2

		experiment study							
Simats 2018 (70)	Spain	Case control study+ animal experiment study	IS vs. Controls	Not stated	Not stated	plasma	6h	Proteomics; proteins	CKB, CMPK
Simats 2018 (71)	Spain	Prospective study + animal experiment study	IS vs. Controls	ED	Not stated	serum	6h; 4.5h	proteins	CCL23, CCL9
Sharma 2014 (72)	USA	Prospective study	IS vs. HS; IS vs. SM; Total stroke vs. SM	ED	CT; MRI	plasma	24h	proteins	eotaxin, epidermal growth factor receptor, S100A12, metalloproteinase inhibitor-4 (TIMP-4), prolactin
Sharma 2015 (73)	India	Case control study	IS vs. Controls	Not stated	CT; MRI	serum	24h	Proteomics	vWF, ADAMTS13, S100A7
Shaker 2020 (74)	Iraq	Case control study	IS vs. Controls	Not stated	CT	plasma	24h	proteins	GPBB
Sepramaniam 2014 (75)	Singapore	Prospective study+ animal experiment study	IS vs. Controls	Not stated	CT; MRI	whole blood	24h	Transcriptomics	miR-125b-2*, miR-27a*, miR-422a, miR-488, miR-627
Sayan 2016 (76)	Turkey	Prospective study	IS vs. Controls	Neurology ward	CT	plasma	24h	proteins	BNP
Rozanski 2017 (77)	Germany	Prospective study	IS vs. HS	Stroke Emergency Mobile	CT	plasma	3h; 1h	proteins	GFAP
Roudbary 2011 (78)	Iran	Cross sectional study	IS vs. HS	Neurology ward	CT	serum	24h	proteins	hsCRP
Rico Santana 2014 (79)	Spain	Case control study	IS vs. Controls	ED, neurology department	CT; MRI	serum	6h	Proteomics	2155-Da peptide
Richard 2016 (80)	France	Case control study	IS vs. Controls	Not stated	CT; MRI	plasma	24h; 6h; 3h	proteins	PRDX1
Reynolds 2003 (81)	USA	Case control study	IS vs. HS; IS vs. TIA; IS vs. Controls; HS vs. TIA; HS vs. Controls; Total stroke vs. controls	ED	CT; MRI	serum	24h; 12h; 6h; 3h	proteins	S100B, BNGF, vWF, MMP9, MCP-1
Ren 2016 (82)	China	Case control study	IS vs. HS; IS vs. Controls; HS vs. Controls	ED	CT; MRI	serum	24h; 4.5h	proteins	UCH-L1, GFAP
Ranga 2016 (83)	India	Cross sectional study	IS vs. Controls	Not stated	CT; MRI	serum	24h	proteins	CEA
Rahmati 2020 (84)	Iran	Case control study	IS vs. Controls	Neurology ward	CT; MRI	serum	12h	transcripts; proteins	S100B, miR-602

Qi 2021 (85)	China	Case control study	IS vs. Controls	Not stated	CT; MRI	serum; extracellular vesicle (EV)-derived	6h	transcripts	miR-124-3p
Paycheva 2021 (86)	Bulgaria	Cross-sectional study	IS vs. Controls	Neurology ward	CT	serum	24h	proteins	fibrinogen
Perovic 2017 (87)	Croatia	Case control study	IS vs. Controls	Neurology ward	CT	serum	24h	proteins	resistin, copeptin
Penn 2018 (88)	Canada	Prospective study	IS vs. Controls	ED	CT; MRI	plasma	24h	Proteomics	E-selectin, Apolipoprotein C-I, Calponin, Coagulation factor XII, Clusterin, CRP, IGF-1, Complement component 4b (C4b and C4a), Serum paraoxonase/aryl esterase 1 (Paraoxonase- PON1), Prothrombin/thrombin, Plasminogen/plasmin/angiostatin, Vitamin K-dependent protein S (Protein S), Serum paraoxonase/lactonase 3 (Paraoxonase- PON3), Vitamin K-dependent protein C (Protein C), Antithrombin III, Vitamin K-dependent protein Z (Protein Z), Coagulation factor V, Apolipoprotein D, Coagulation factor XI, Insulin-like growth factor-binding protein 3 (IBP 3), L-selectin, Plasma protease C1 inhibitor (C1 inhibitor), Plasma serine protease inhibitor (Protein C inhibitor), IL-6, S100A12, Fatty acid binding protein 3 (FABP3), Guanylate cyclase A(NPR1) (ANPR1), Epidermal growth factor receptor (EGFR), Platelet endothelial cell adhesion molecule (PECAM 1), Prolactin
Park 2013 (89)	Korea	Prospective study	IS vs. SM	Not stated	CT; MRI	plasma	24h	proteins	H-FABP, S100B
Park 2018 (90)	USA	Prospective study	IS vs. Controls	Not stated	CT; MRI	plasma	12h	proteins	GPBB
Pan 2020 (91)	China	Case control study	IS vs. Controls	Not stated	Not stated	platelet	7.5h	Genomics	EGR2 gene
Palm 2018 (92)	Germany	Case control study	IS vs. Controls	Not stated	CT; MRI	serum	24h	proteins	MMP-8, MPO, TIMP-1
Oraby 2019 (93)	Egypt	Case control study	IS vs. Controls	Neurology ward	CT; MRI	serum	24h	proteins	thioredoxin
O'Connell 2019 (94)	USA	Case control study	IS vs. SM	ED	CT; MRI	whole blood	24h	genes; leukocyte count	PLXDC2 gene, STK3 gene, ANTXR2 gene, KIF1B gene, CD163 gene, PDK4 gene, CTSZ gene, GRAP gene, MAL gene, ID3 gene
O'Connell 2019 (95)	USA	Case control study	IS vs. HS; Total stroke vs. SM ; Other: HS vs. IS+SM	ED	CT; MRI	whole blood	12h	Proteomics	NVAVAQDENLAG, NNYWANVASGLG, QSLKPKGVALSG, GASVHDGVALSG, GEYFRWNWDSVA,APFGQKDVALGL, GDRRPLGVALSG,KGQRGYHLKHDA, AEQREFNKHLSA,PEFRELSKHDVA, PKPHGFPGQEYV,KPEKLNGLVALSG, NSLKENGVALSG,VLGPRHEPDSGA, EKLYYHDSQEKH,AWQKSGVALSG, QRPDPKDGQAKD
O'Connell 2016 (96)	USA	Case control study	IS vs. SM; IS vs. Controls	ED	MRI	whole blood	4.5h; 5.3h	Genomics	ANTXR2 gene, STK3 gene, PDK4 gene, CD163 gene, MAL gene, GRAP gene, ID3 gene, CTSZ gene, KIF1B gene, PLXDC2 gene
O'Connell 2017 (97)	USA	Case control study	IS vs. SM	ED	CT; MRI	plasma	4.5h	cell free DNA	cfDNA

O'Connell 2017 (98)	USA	Case control study	IS vs. Controls	public platform	Not stated	whole blood	24h; 5h; 3h	genes	ANTXR2 gene, STK3 gene, PDK4 gene, CD163 gene, MAL gene, GRAP gene, ID3 gene, CTSZ gene, KIF1B gene, PLXDC2 gene
O'Connell 2020 (99)	USA	Case control study	IS vs. Controls	ED	CT; MRI	plasma	24h	proteins	NfL, Tau
Nielsen 2020 (100)	Denmark	Prospective study	IS vs. TIA; IS vs. Controls	Neurology ward	CT; MRI	plasma	8h	proteins	NfL, VEGF-A, VCAM-1, ICAM-1, IL-6, S100B, E-selectin
Nguyen 2020 (101)	Netherland	Prospective study	IS vs. HS; IS vs. SM; IS vs. Controls; HS vs. SM	ED	CT	plasma	6h	Transcriptomics	tRNA-TyrGTA, tRNA-ThrCGT, tRNA-ValCAC
Nahan 2017 (102)	USA	Case control study	IS vs. HS; IS vs. Controls; HS vs. Controls	ED	Not stated	plasma	12h	Proteomics	IS vs. control (As, Co, Fe, Li, Sr, U, Se, Cd), HS vs. control (Ag, Al, As, Co, Ni, U, Zn, Fe, Sr, Cd, Pb, Se); HS vs. IS (Ag, Co, Fe, Al, As, Li, Ni, U, W), IS special markers (calpain-15, titin Isoform 3, tropomyosin alpha-4 chain); HS special markers (bestrophin-3, GIRK-1, TTBK1, CAB3)
Montaner 2012 (103)	Spain	Prospective study	IS vs. HS	ED	CT	plasma	6h	proteins	S100B, sRAGE
Menon 2018 (104)	India	Prospective study	IS vs. Controls	Not stated	Not stated	serum	24h; 1h	proteins	IMA
Mattila 2021 (105)	Finland	Prospective study	IS vs. HS	ED	Not stated	plasma	3h; 1h	proteins	GFAP
Matsuo 2013 (106)	Japan	Prospective study	IS vs. Controls	Not stated	CT; MRI	plasma	24h	proteins	VEGF
Matsumori 2002 (107)	Japan	Case control study	IS vs. Controls	Not stated	CT	serum	24h	proteins	HGF
Maly 2021 (108)	Czech Republic	Cross-sectional study	IS vs. Controls	Not stated	Not stated	plasma	4.5h	Metabolomics; lipidomics	FA (20:2), FA (20:3), FA (20:4), FA (20:5), FA (22:4), FA (22:5), FA (22:6), FA (16:1), FA (17:1), AHFA (14:0/16:2), FAHFA (16:1/18:3), FAHFA (18:1/20:3), FAHFA (18:2/20:4), FAHFA (20:4/18:3), LPC (20:5), LPC (22:5), LPC (22:6), LPE (18:2), LPE (20:4), LPE (22:6), LPI (18:1), LPI (18:2), TG (14:0_16:1_20:3), TG (16:0_16:1_18:0), TG (16:0_18:2_18:3), TG (16:0_18:2_22:6), TG (17:1_17:2_19:0)
Mahovic 2013 (109)	Croatia	Prospective study	IS vs. Controls	Not stated	CT	serum	24h	proteins	soluble Fas/APO 1 (sFas/APO 1)
Ma 2019 (110)	China	Case control study	IS vs. Controls	ED + Neurology department	CT; MRI	plasma	6h	transcripts	miR-93
Luger 2017 (111)	Germany	Retrospective study	IS vs. HS; Other: HS vs. IS+SM	ED + Neurology department	CT; MRI	serum	6h	proteins	GFAP
Lu 2020 (112)	China	Case control study +	IS vs. Controls	Not stated	MRI	whole blood	24h; 3h	Transcriptomics	circ-PHKA2, circ-BBS2

		animal experiment study							
Long 2013 (113)	China	Cross-sectional study	IS vs. Controls	Not stated	Not stated	plasma	24h	transcripts	miR-30a, miR-126, let-7b
Llombart 2016 (114)	Spain	Retrospective study	IS vs. HS	ED	CT	plasma	6h	proteins	RBP4, GFAP
Liu 2015 (115)	China	Prospective study	IS vs. Controls	Neurology ward	MRI	serum	24h	transcripts; proteins	miR-124, miR-9, miR-219, MMP9
Liu 2017 (116)	China	Case control study	IS vs. Controls	Not stated	CT; MRI	serum	9h	Metabolomics	serine, isoleucine, betaine, PC (5:0/5:0), LysoPE (18:2)
Liu 2020 (117)	China	Case control study	IS vs. HS; IS vs. Controls	Neurology ward	CT; MRI	serum	24h	proteins	Sphingosine 1-phosphate (S1P)
Liswati 2009 (118)	Indonesian	Case control study	IS vs. HS	Not stated	CT	plasma	24h	proteins	S100B, MBP
Li 2021 (119)	China	Case control study	IS vs. Controls	Neurology ward	MRI	serum	24h	proteins	Lp-PLA2
Li 2015 (120)	China	Case control study	IS vs. Controls	Not stated	CT; MRI	serum	24h	Transcriptomics	miR-32-3p, miR-106-5p, miR-532-5p, miR-1246
Li 2018 (121)	China	Prospective study	IS vs. Controls	ED	CT; MRI	plasma; lymphocytes, neutrophils	6h	transcripts; proteins	miR-424, TNFa, IGF1
Leung 2014 (122)	China	Prospective study	IS vs. HS; IS vs. Controls; HS vs. Controls	ED	CT; MRI	plasma	24h; 6h	transcripts	miR-124-3p, miR-16
Laterza 2006 (123)	USA	Case control study + animal experiment study	IS vs. Controls	Not stated	Not stated	plasma	24h	Genomics; proteins	VLP-1 gene, VLP-1
Laskowitz 2009 (124)	USA	Prospective study	IS vs. HS; Total stroke vs. SM; Total stroke vs. TIA	Not stated	CT; MRI	serum	24h; 12h; 6h; 3h	proteins	MMP9, BNP, D-dimer, S100B
Kokocinska 2007 (125)	Poland	Case control study	IS vs. Controls	Neurology ward	CT	plasma	24h	proteins	S100B, Tissue Polypeptide Antigen (TPA)
Kokocinska 2005 (126)	Poland	Case control study	IS vs. Controls	Neurology ward	CT	serum	12h	proteins	S100B
Kodali 2013 (127)	USA	Case control study	IS vs. HS; IS vs. SM; HS vs. SM	ED	Not stated	plasma	12h	Proteomics	Fibrinogen gamma chain, Protein kinase C eta type, Fibrinogen beta chain, Fibrinogen alpha chain, Complement C3, Methylenetetrahydrofolate reductase, Antithrombin-III, Collagen alpha-1(IV) chain
Kodali 2012 (128)	USA	Case control study	IS vs. HS; IS vs. SM; HS vs. SM	ED	Not stated	plasma	12h	Proteomics	metalloproteins: Mg, Mn, Cu, Se, Pb, Mo
Kochanowski 2012 (129)	Poland	Case control study	IS vs. Controls	Neurology ward	CT	plasma	24h	proteins	resistin, TNFa
Kavalci 2011 (130)	Turkey	Prospective study	IS vs. HS	ED	Not stated	serum	24h	proteins	BNP, D-dimer, MMP-9, S100B
Katsanos 2017 (131)	Greece	Prospective study	IS vs. HS; HS vs. SM; HS vs. Controls	ED	Not stated	plasma	6h	proteins	GFAP

Kashyap 2009 (132)	India	Case control study	IS vs. Controls	Neurology ward	CT	serum	24h	proteins	ITIH4
Kara 2014 (133)	Turkey	Prospective study	IS vs. Controls	ED	MRI	serum	24h	proteins	hsCRP, Lp-PLA2
Kalra 2021 (134)	Germany	Prospective study	IS vs. HS; HS vs. IS+SM	Neurology ward	CT; MRI	serum	12h	proteins	GFAP
Kalani 2020 (135)	USA	Prospective study	IS vs. HS	ED	CT; MRI	plasma	24h	Transcriptomics; extracellular vesicles	miR-150-3p, miR-4286, miR-132-3p, miR-30e-3p, miR-21-3p, miR-27b-3p, miR-342-3p, miR-186-5p, miR-338-3p, miR-5010-5p, miR-134-5p, miR-7c-5p, miR-485-5p
Jin 2017 (136)	China	Case control study	IS vs. Controls	Neurology ward	CT; MRI	plasma	24h	transcripts	miR-126, miR-130a, miR-222, miR-218, miR-185
Jiang 2011 (137)	China	Case control study	IS vs. Controls	Not stated	CT; MRI	serum	6h	Metabolomics	folic acid, cysteine, S-adenosyl-homocysteine, oxidized glutathione, Tetrahydrofolate, Hydroxy eicosatetraenoic acid, Adenosine, Aldosterone, Hydroxy octadecadienoic acid, Deoxocathasterone, Sucrose 6-phosphate, Betanin
Jia 2015 (138)	China	Prospective study	IS vs. Controls	Neurology ward	MRI	serum	24h	transcripts; proteins	miR-145, miR-23a, miR-221, hsCRP, IL-6
Ji 2016 (139)	China	Case control study	IS vs. Controls	Neurology ward	CT; MRI	serum; exosome	24h	transcripts	miR-9, miR-124
Inoue 2019 (140)	Japan	Prospective study	IS vs. HS	Not stated	CT; MRI	serum	24h	proteins	LOX-1
Itumur 2006 (141)	Turkey	Case control study	IS vs. Controls	NICU	CT; MRI	plasma	24h	proteins	NT-proBNP, troponin I, CK-MB
Herisson 2010 (142)	France	Prospective study	IS vs. HS; Total stroke vs. controls	stroke department	CT; MRI	serum	4.5h	proteins	IMA, HFABP
Han 2012 (143)	China	Case control study	IS vs. Controls; HS vs. Controls	Not stated	CT; MRI	serum	3h	proteins	IMA
Gunduz 2008 (144)	Turkey	Case control study	IS vs. HS; IS vs. Controls; HS vs. Controls	ED	CT; MRI	serum	24h	proteins	IMA
Gunaydin 2014 (145)	Turkey	Prospective study	IS vs. Controls	ED	CT; MRI	plasma	12h; 6h	proteins	SCUBE1
Glickman 2011 (146)	USA	Prospective study	IS vs. SM	ED	CT	plasma	5h	proteins	BNP, MMP-9, D-dimer, S100B, CRP
Giannopoulos 2008 (147)	Greece	Case control study	IS vs. Controls	Not stated	CT	plasma	24h	proteins	Endothelin-1, CRP, fibrinogen
Garlichs 2003 (148)	Germany	Case control study	IS vs. TIA; IS vs. Controls; TIA vs. Controls	Neurology ward	CT	serum; plasma	24h	proteins	platelet CD154, platelet P-selectin, soluble CD154, monocyte CD40, MCP-1
Foerch 2012 (149)	Germany	Prospective study	IS vs. HS; IS vs. SM; HS vs. SM	Stroke centre	CT; MRI	plasma	4.5h	proteins	GFAP
Foerch 2006 (150)	Germany	Prospective study	IS vs. HS	Stroke unit or NICU	CT; MRI	serum	6h	proteins	GFAP
Fiszer 1998 (151)	Poland	Case control study	IS vs. Controls	Not stated	CT	whole blood	12h	proteins	CD54, CD11a, CD11b, CD18
Fassbender 1997 (152)	Germany	Case control study	IS vs. Controls	Not stated	CT	serum	24h; 10h, 8h, 4h	proteins	S100B, NSE

Fang 2018 (153)	China	Prospective study	IS vs. HS; IS vs. SM; IS vs. Controls; HS vs. SM; HS vs. Controls; Total stroke vs. controls	ED	Not stated	plasma	24h	proteins	S100B, CRP, IL-6, PAI-1, MMP-9, P-selectin, ICAM-1, TNF α , LDL, IL-10, NO, GFAP
Ewida 2021 (154)	Egypt	Prospective study	IS vs. HS; IS vs. Controls; HS vs. Controls; Total stroke vs. controls	Neurology ward	CT; MRI	serum	24h	transcripts; proteins	IS vs. HS(lncRNAs HIF1A-AS2, lncRNAs LINK-A, mRNA HIF1- α , MDA, VEGF), IS vs. control (PI3K, p?Akt, VEGFR2, TIE2), HS vs. control (PI3K, p?Akt, VEGFR2, TIE2), total stroke vs. control(lncRNAs HIF1A-AS2, lncRNAs LINK-A, mRNA HIF1-?, TAC, VEGF, ANG1, BDNF, PI3K, p?Akt, VEGFR2, TIE2)
Ekingen 2017 (155)	Turkey	Prospective study	IS vs. Controls	ED	CT	serum	24h	proteins	Galectin-3, GFAP
Dvorak 2009 (156)	Germany	Prospective study	IS vs. HS	Not stated	CT; MRI	serum	6h; 4h; 3h; 2h	proteins	GFAP
Duan 2015 (157)	China	Prospective study	IS vs. Controls	ED	CT; MRI	serum	24h	proteins	CXCL12
De Marchis 2018 (158)	Switzerland	Prospective study	IS vs. TIA; IS+TIA vs. control	ED	MRI	serum	24h	proteins	NfL
Dassan 2012 (159)	UK	Prospective study	IS vs. SM	ED	MRI	serum	24h	proteins	VEGF
Dambinova 2003 (160)	Russia	Prospective study	IS vs. HS; IS vs. TIA; IS vs. Controls; TIA vs. Controls	Neurology and Neurosurgery Department	CT; MRI	serum	3h	proteins	NR2A/2B aAb
Dambinova 2012 (161)	USA	Prospective study	IS vs. Controls	ED	CT; MRI	plasma	12h	proteins	NR2 peptide
Cheng 2018 (162)	China	Prospective study	IS vs. Controls	ED	CT; MRI	serum	24h	transcripts	miR-148b-3p, miR-151b, miR-27b-3p
Chen 2018 (163)	China	Prospective study	IS vs. Controls	Not stated	MRI	serum; plasma	24h	transcripts; proteins	miR-146b, hsCRP, IL-6
Cavrak 2021 (164)	USA	Case control study	IS vs. TIA; IS vs. SM; TIA vs. SM	ED	MRI	whole blood	24h	cell count and percentage	neutrophil percentage > 60
Cano 2003 (165)	Venezuela	Prospective study	IS vs. Controls	ED	CT	serum	24h	metabolites	malondialdehyde, nitric oxide
Cakmak 2014 (166)	Turkey	Prospective study	IS vs. Controls	ED	CT; MRI	serum	24h	proteins	IMA, S100B, NSE
Büttner 1997 (167)	Germany	Prospective study	IS vs. Controls	Not stated	CT	serum	24h; 12h	proteins	S100B
Bustamante 2021 (168)	Spain	Prospective study	IS vs. HS	ED	CT; MRI	plasma	4.5h	proteins	GFAP, RBP-4, NT-proBNP, endostatin
Bustamante 2017 (169)	Spain	Prospective study	IS vs. HS; Total stroke vs. SM	ED	CT; MRI	plasma	6h	proteins	NT-proBNP, IGFBP-3, TNF-R1, GroA, FasL, IL-6, D-dimer, vWF, VAP-1, Endostatin, S100B, Hsc70, Apo CIII, NCAM, MMP-9, bNGF, Caspase-3, NSE, cFn, IL-2RG, IL-17A

Bolayir 2019 (170)	Turkey	Prospective study	IS vs. Controls	Neurology ward	CT; MRI	serum	24h	proteins	SCUBE1, hsCRP
Bibl 2012 (171)	Germany	Case control study	IS vs. Controls	Not stated	CT; MRI	plasma	12h	proteins	Abeta1-37, Abeta1-38
Barr 2010 (172)	UK	Case control study	IS vs. Controls	Not stated	MRI	whole blood	24h	Genomics	ARG1 gene, CA4 gene, CCR7 gene, CSPG2 gene, IQGAP1 gene, LY96 gene, MMP9 gene, ORM1 gene, S100A12 gene
Azarpazhooh 2010 (173)	Iran	Case control study	IS vs. HS; Total stroke vs. controls	Not stated	CT; MRI	serum	24h	proteins	anti-HSP27, hsCRP
Atik 2016 (174)	Turkey	Prospective study	IS vs. Controls; HS vs. Controls	ED	CT; MRI	serum	12h; 3h	proteins	albumin, ischemic modified albumin (IMA), IMA/albumin ratio (IMAR), total antioxidant status, total oxidant status (TOS), oxidative stress index (OSI)
Alvarez-Perez 2011 (175)	Portugal	Prospective study	IS vs. Controls	ED	Not stated	plasma	24h	proteins	fibrinogen, CRP
Allard 2004 (176)	Switzerland	Prospective study	IS vs. HS; IS vs. Controls; HS vs. Controls; Total stroke vs. controls	ED	CT; MRI	plasma	6h	Proteomics	ApoC-I, ApoC-III
Allard 2005 (177)	Switzerland	Retrospective study	IS vs. Controls; HS vs. Controls; TIA vs. Controls; Total stroke vs. controls	ED	CT; MRI	plasma	24h	proteins	PARK7, NDKA
Algin 2019 (178)	Turkey	Prospective study	IS vs. Controls	ED	MRI	serum	4h	proteins	BDNF, VILIP-1
Algawwam 2021 (179)	Iraq	Prospective study	IS vs. Controls	Not stated	Not stated	serum	24h	proteins	GPBB
Ahn 2011 (180)	Korea	Prospective study	IS vs. SM	ED	CT; MRI	serum	6h	proteins	IMA index, IMA
Sadik 2021 (181)	Egypt	Prospective study	IS vs. Controls	Not stated	CT	serum	12h	transcripts	miR-155, JAK2 mRNA, STAT3 mRNA
Abe 2020 (182)	Japan	Prospective study	IS vs. Controls	Not stated	Not stated	whole blood	12h	Transcriptomics	miR-505-5p, miR-1255b-5p, miR-550b-2-5p, miR-4523, miR-6795-3p

IS: ischemic stroke; HS: haemorrhagic stroke; SM: stroke mimics; TIA: transient ischemic attack

Supplementary Table 3: Brain-specific or enriched biomarkers for diagnosis of ischaemic stroke in early stage

Brain-specific/enriched biomarkers	Study ID	Study design	Sample size	Specimen	Time point	Comparison	Sensitivity	Specificity	AUC
BDNF	Algin 2019 (178)	Prospective	IS 75, control (healthy) 28	serum	4h	IS vs. control	100%	92%	0.983(0.966-1)
VILIP-1					NA		NA	NA	
B-FABP	Wunderlich 2005(21)	Prospective	IS 42, control (healthy) 80	serum	3,4,5,6, 12,18,24h		NA	NA	NA
MBP	Can 2015 (27)	Prospective	IS 50, control (healthy) 34	serum	12h		NA	NA	NA
miR-107	Yang 2016 (46)	Case control	IS 114, control (healthy) 58	plasma	24h		93.8%	92.2%	0.97
miR-128b							72.8%	92%	0.903
miR-153							91.2%	74%	0.893
miR-124	Zhou 2021 (1)	Case control	IS 108, control (healthy) 108	serum	24h		91.67 %	93.52%	0.9527
	Liu 2015 (115)	Prospective	IS 31, control (healthy) 11	serum	24h				0.76(0.61-0.92)
GMFB	Yuan 2020 (44)	Case control	IS 40, control (healthy) 40	plasma	24h		NA	NA	NA
miR-134	Zhou 2018 (36)	Case control	IS 50, control (healthy) 50	serum; exosome	24h		75.3%	72.8%	0.834(0.88-0.97)
miR-16	Tian 2016 (62)	Prospective	test cohort: IS 7, control(healthy) 4; validation cohort: IS 33, control (healthy) 23	plasma	6h		69.7%	87%	0.775
miR-9	Ji 2016 (139)	Case control	IS 65, control (non-stroke) 66	serum; exosome	24h		NA	NA	0.8026(0.7235-0.8816)
miR-124							NA	NA	0.6976(0.6506-0.7895)
NfL	Tiedt 2018 (32)	Prospective	IS 196, control (healthy) 30; cohort2: 95 IS	serum	24h		NA	NA	NA
NfL	O'Connell 2020 (99)	Case control	IS 14, control (risk factor non-neurological symptom) 33	plasma	24h		92.9%	84.9%	0.88(0.75-0.96)
Tau							85.7%	54.6%	0.69(0.54-0.82)
NfL+ Tau							71.4%	87.9%	0.81(0.67-0.91)
NfL	Nielsen 2020 (100)	Prospective	IS 31, TIA 9, control (healthy) 29	plasma	8h		NA	NA	NA
S100B							NA	NA	NA

S100B	Kokocinska 2005 (126)	Case control	IS 47, control (healthy) 10	serum	12h		NA	NA	NA
	Büttner 1997 (167)	Prospective	IS 26, control (healthy) 26	serum	12h, 24h		NA	NA	NA
	Fang 2018 (153)	Prospective	IS 262, control (healthy) 200	plasma	24h		NA	NA	0.98
S100B	Fassbender 1997 (152)	Case control	IS 24, control (healthy) 24	serum	8h,10h, 24h		NA	NA	NA
NSE					NA		NA	NA	
S100B	Cakmak 2014 (166)	Prospective	IS 38, control (ED patients without acute focal neurological deficit) 30	serum	24h		87%	72%	0.89(0.81-0.96)
NSE							61%	53%	0.67(0.55-0.80)
S100B+NSE							92%	47%	NA
GFAP	Ekingen 2017 (155)	Prospective	IS normal CT 17, control (healthy) 50	serum	24h		70.59 %	70%	NA
VILIP-1(VLP-1)	Stejskal 2011 (64)	Case control	IS 16, control (healthy) 17	serum	3h		100%	100%	1.0 (0.93-1)
	Laterza 2006 (123)	Case control	IS 18, control not stated	plasma	24h		NA	NA	NA
GFAP	Bustamante 2021 (168)	Prospective	IS 154, HS 35, SM 62	plasma	4.5h	IS vs. HS	37.1%	99.4%	NA
GFAP	Stanca 2015 (65)	Prospective	IS 49, HS(ICH) 23, control (healthy) 52	serum	12h		94%	69%	NA
aAbs-NR2+GFAP							94%	91%	NA
GFAP	Xiong 2015(47)	Prospective	IS 65, HS(ICH) 43	serum	6h		86%	76.9%	0.901(0.808-0.95)
	Rozanski 2017 (77)	Prospective	IS 49, HS(ICH) 25	plasma	1h		24%	100%	NA
					3h		36%	100%	NA
	Mattila 2021 (105)	Prospective	IS 203(IS 195, TIA 8), HS 60 (ICH 50, SAH 2, both 8), SM 9	plasma	3h		96.6%	68%	0.781(0.712-0.85)
	Llombart 2016(114)	Retrospective	cohort1: IS 36, HS(ICH)10, cohort2: IS16, HS(ICH)16, cohort3: IS 38, HS(ICH)28	plasma	6h		68.4% (GFAP +RBP4)	84% (GFAP+ RBP4)	NA
	Katsanos 2017 (131)	Prospective	IS 121, HS 36(ICH 31, SAH 5), SM 31, control (healthy)79	plasma	6h		91%	97%	0.97(0.92-1.00)
	Foerch 2012 (149)	Prospective	IS 163, HS 39, SM 3	plasma	4.5h		84.2%	96.3%	0.915(0.847-0.982)
	Foerch 2006 (150)	Prospective	HS 42, IS 93	serum	6h		79%	98%	NA
		Prospective	IS 45, HS 18		2h		45%	100%	NA

	Dvorak 2009 (156)			serum	3h	HS vs. IS	65%	100%	NA
					4h		70%	100%	NA
					6h		71%	95%	NA
miR-124-3p					24h		68.4%	71.2%	0.70(0.59-0.79)
miR-16	Leung 2014 (122)	Prospective	IS 74, HS 19, control (healthy) 23	plasma			94.7%	35.1%	0.66(0.55-0.76)
	Rainer 2007 (31)	Prospective	IS 118, HS 35, image-negative clinical stroke 44	plasma	24h		NA	NA	NA
S100	Zhou 2016 (35)	Prospective	IS 71, HS(ICH) 46	plasma	6h		95.7%	70.4%	0.903
S100B+sRA GE	Montaner 2012 (103)	Prospective	IS 279, HS(ICH) 58	plasma	6h		22.7%	80.2%	NA
S100B	Kavalci 2011 (130)	Prospective	IS 71, HS 29, control 20	serum	24h		NA	NA	NA
S100B					24h		77.8%	69.2%	0.778(0.582-0.973)
MBP	Liswati 2009 (118)	Case control	IS 25, HS 19	plasma		88.9%	69.2%	0.855(0.699-1.000)	
					4.5h	NA	NA	0.64(0.47-0.81)	
UCH-L1					24h	NA	NA	0.62(0.51-0.72)	
					4.5h	61%	96%	0.86(0.73-0.99)	
GFAP	Ren 2016 (82)	Case control	ICH 45, IS 79, SAH 5, TIA 3, control (healthy) 57	serum	24h	67%	91%	0.87(0.80-0.94)	
CTNND2	Simats 2020 (69)	Case control	IS 71, SM 36	plasma	6h	IS vs. SM	NA	NA	0.76 (0.66-0.86)
	Glickman 2011 (146)	Prospective	IS 34, SM 29	plasma	5(3.5-8) h		NA	NA	NA
S100B	Park 2013 (89)	Prospective	IS 111, SM 127	plasma	24h		54%	83.5%	0.7
NfL	De Marchis 2018 (158)	Prospective	IS 504, TIA 111, control (healthy) 165	serum	24h	IS vs. TIA	NA	NA	NA

GFAP: Glial Fibrillary Acidic Protein; B-FABP: Brain-type Fatty Acid-Binding Proteins; MBP: Myelin Basic Protein; S100B: S100 calcium-binding protein B; NSE: Neuron-Specific Enolase; NfL, Neurofilament Light chain; CTNND2: Catenin delta-2; UCH-L1: Ubiquitin Carboxyl-terminal Hydrolase isozyme L1; VILIP-1(VLP-1): Visinin-like protein 1; GMFB: Glial Maturation Factor Beta; IS: ischaemic stroke; HS: haemorrhagic stroke; SM: stroke mimics; TIA: transient ischaemic attack; ICH: intracerebral hemorrhage; SAH: subarachnoid hemorrhage; ED: emergency department.

Supplementary Table 4: Characteristics of included high-throughput omics studies

Study ID	Design	Omics	Assay	Algorithm/method of data dimension-reduce	Cohort 1	Cohort 2	Cohort 3	Total sample size	Sampling time	Specimen	Biomarker NO.	As a Panel
Tang 2006 (30)	Case control study	Genomics	Oligonucleotide microarrays	The Prediction Analysis of Microarrays (PAM)	IS 15, control 3	NO	NO	18	24h; 5h; 3h	whole blood (Paxgene RNA tubes)	18	No
Stamova 2010 (66)	Case control study	Genomics	Whole genome microarray	The Prediction Analysis of Microarrays (PAM)	IS 70, control: healthy 38, vascular risk 52, myocardial infarction 17	NO	NO	177	24h; 5h; 3h	whole blood	97	Yes
Pan 2020 (91)	Case control study	Genomics	RNA sequencing, qRT-PCR	GO and KEGG enrichment to choose inflammation related genes	IS male 8, control (healthy male) 4	NO	NO	12	7.5h	Platelet	1	No
O'Connell 2016 (96)	Case control study	Genomics	RNA microarray	Machine-learning (GA/ KNN)	IS 39, control (neurologically asymptomatic) 24	IS 39, control 30, SM 20	NO	152	4.5h; 5.3h	whole blood (Paxgene RNA tubes)	10	Yes
Barr 2010 (172)	Case control study	Genomics	RNA gene expression profiling	BeadStudio; GeneSpring	IS 39, control (non-stroke) 25	NO	NO	63	24h	whole blood (Paxgene RNA tubes)	9	No
Laterza 2006 (123)	Case control study + animal experimental study	Genomics	Gene array, ELISA	No advanced algorithm	Mouse	NO	IS 18, control not stated	18	24h	Plasma	1	No
Zhang 2017 (41)	Case control study	Metabolomics	MS	Artificial neural network (ANN)	IS 103, HS(ICH)103, control(healthy) 65	IS 26, HS(ICH) 25	NO	322	12h	dried blood spot	36	Yes
Tiedt 2020 (60)	Prospective study	Metabolomics	UPLC-MS/MS	Random forest	IS 40, SM 33, control (neurological normal) 72	IS 105, SM 105, control 40	IS 289, SM 211	969	24h	Serum	4	Yes

Liu 2017 (116)	Case control study	Metabolomics	MS	Logistic regression, Naïve Bayes, Neural network, Random Forest, Support vector machine	IS 40, control 40	IS 26, control 23	NO	129	9h	Serum	5	Yes
Jiang 2011 (137)	Case control study	Metabolomics	UPLC-TOF-MS	K-Nearest Neighbour (KNN)	IS 67, control (routine physical check-up people) 62	NO	NO	129	6h	Serum	12	No
Maly 2021(108)	Cross-sectional study	Metabolomics(lipidomics)	UHPLC-HRMS	supervised statistical methods	IS 49, control 82	NO	NO	131	4.5h	Plasma	27	No
Kimberly 2013(28)	Prospective study + animal experimental study	Metabolomics; targeted	LC-MS/MS	Principal component analysis (PCA), partial least-squares discriminant analysis (PLS-DA)	Rat	IS 32, control (TIA + non-stroke) 52	NO	84	2h; 9h	Plasma	18	Yes
Turek-Jakubowska 2022 (4)	Case control study	Proteomics	LC-MS	Diffprot software	IS 32, control 28	NO	NO	60	24h	Plasma	1	No
Song 2019(68)	Case control study + animal experimental study	Proteomics	LC-MS/MS, ELISA	Principal component analysis (PCA)	Mouse	IS 70, control (healthy) 70	NO	140	24h	Serum	2	No
Sharma 2015(73)	Case control study	Proteomics	iTRAQ-Based LC-MS	None	IS 50, control (healthy) 35	NO	NO	85	24h	Serum	3	No
Rico Santana 2014(79)	Case control study	Proteomics	MALDI-TOF MS	None	IS 45, control (TIA+ HS+ SM+ head injury) 18, control (healthy) 56	NO	NO	119	6h	Serum	1	No
Penn 2018 (88)	Prospective study	Proteomics ; targeted	LC/MS-MS, ELISA	None	IS 20, control (outpatient neurology clinic) 20	NO	NO	40	24h	Plasma	30	Yes
O'Connell 2019 (95)	Case control study	Proteomics	Custom-fabricated high-density peptide array	Random forest	IS 19, HS 17, SM 20	NO	NO	56	12h	whole blood	17	Yes
Nahan 2017 (102)	Case control study	Proteomics (targeted metalloprotein)	MS	Principal component analysis (PCA)	IS 14, paired control 14; HS(ICH) 23, paired control 23	NO	NO	74	12h	Plasma	36	No

Kodali 2013 (127)	Case control study	Proteomics ; targeted	Nano-LC-ESIMS	None	IS 10, HS 9, SM 10	NO	NO	29	12h	Plasma	8	No
Kodali 2012 (128)	Case control study	Proteomics (metals and metalloproteins)	ICP-MS followed by ESIMS	None	IS 10, HS 9, SM 10	NO	NO	29	12h	Plasma	6	No
Gawryś 2022 (9)	Case control study	Proteomics (platelet)	LC-MS	None	IS 32, control 29	NO	NO	61	24h	platelet	8	No
Simats 2018 (70)	Case control study + animal experimental study	Proteomics	SOMAscan proteomic assay, ELISA	None	Rat	IS 38, control 8	NO	46	6h	Plasma	2	No
Yang 2022 (3)	Case control study	Transcript omics	CircRNA microarray, qRT-PCR	Volcano plot and heatmap	IS 10, control 10	NO	NO	20	12h	plasma; exosome	4	No
Tian 2022 (5)	Case control study	Transcript omics	RNA microarray, qRT-PCR	Heatmap and hierarchical clustering	IS 39, control 39	NO	NO	78	6h	whole blood	1	No
Tiedt 2017 (59)	Prospective study	Transcript omics	RNA Sequencing	None	IS 20, control (healthy) 20	IS 40, control (healthy) 40	IS 200, control (healthy) 100, TIA 72	492	24h	Plasma	3	Yes
Tian 2016 (62)	Prospective study	Transcript omics	miRNAs microarrays, qRT-PCR	Clustering heatmap	IS 7, control (healthy) 4	IS 33, control (healthy) 23	NO	67	6h	Plasma	1	No
Stamova 2019 (67)	Case control study	Transcript omics	RNA microarray	None	IS 33, HS (ICH) 33, control (risk factors) 33	NO	NO	99	24h	not stated	not exactly	No
Sepramaniam 2014 (75)	Prospective study + animal experimental study	Transcript omics	microRNA microarray, qRT-PCR	None	IS 68, control (healthy) 24	IS 101	Metabolic syndrome patients 94 At last, validation in rats	287	24h	whole blood	5	No
Nguyen 2020 (101)	Prospective study	Transcript omics	Small RNA-sequencing	LASSO (least absolute shrinkage and selection operator)	IS 9, HS(ICH)8, SM 9	IS 20, control (healthy) 20	NO	66	6h	Plasma	3	Yes
Lu 2020 (112)	Case control study + animal	Transcript omics	CircRNA Microarray, RT-qPCR	None	Mouse		NO	16	24h; 3h	whole blood	2	No

	experimental study					IS 8, control 8						
Li 2015 (120)	Case control study	Transcript omics	miRNA microarray, qRT-PCR	None	IS 117, control (healthy) 82	IS 53, control 50	NO	199	24h	Serum	4	No
Abe 2020 (182)	Prospective study	Transcript omics	miRNA Array	Principal component analysis (PCA)	IS 22, controls (without stroke symptoms) 22	NO	NO	44	12h	whole blood	5	No
Kalani 2020 (135)	Prospective study	Transcript omics	RNA sequencing	LASSO (least absolute shrinkage and selection operator)	IS 21, HS 36 (ICH 19, SAH 17)	NO	NO	57	24h	Plasma	13	Yes
Simats 2020 (69)	Case control study + animal experimental study	Transcript omics + Proteomics	Whole-genome microarray, BCA Protein Assay, LC-MS, ELISA	Ingenuity Pathway Analysis (IPA), Principal Component Analysis (PCA), Multiple Co-Inertia Analysis (MCIA), regularized Canonical Correlation Analysis (rCCA), Multiple Factor Analysis	Mouse	IS 71, SM 36	NO	107	6h	Plasma	1	NO

IS: ischemic stroke; HS: haemorrhagic stroke; SM: stroke mimics; TIA: transient ischemic attack

Supplementary list 5: Biomarkers pooled from high-throughput omics studies

103 Genes:

ABCA1, AMN1, ANKRD28, ANTXR2, ARG1, ASTN2, BCL6, BST1, RPF1, CA4, CCDC144A, CCR7, ACKR4, CD163, CHMP1B, CKAP4, CKLF, CLEC4E, CPEB2, CSPG2, CTSZ, CXADR, DLX6, EGR2, ELAVL2, ELL2, ENTPD1, ETS2, F5, FAR2, FAT3, FCHO2, FCRL4, FGD4, FOXA2, FPR1, GAB1, GABRB2, GADL1, GLYATL1, GRAP, GYPA, H2AC18, HNRNPH2, HNRNPUL2, ID3, IFRD1, IQGAP1, KIAA0319, KIF1B, LAMP2, LDB3, LECT2, PPFIBP1, LTB4R, LY96, MAL, MCTP1, MMP9, NPL, ORM1, OSBPL1A, OVOL2, PDK4, PGM5, PHTF1, PLXDC2, PRTG, PTPRD, PYGL, QKI, RBM25, RBMS3, REM2, RNASE2, RNF141, RPL22, RRAGD, S100A12, S100A9, S100P, SCD5, SH3GL3, SHOX, SLC16A6, SNIP1, SNRPN, SPIB, SPTLC3, ST3GAL6, STK3, TBX5, THBD, THSD4, TIMM8A, TIMP2, UBR5, UBXN2B, UNC5B, VAPA, VSNL1, VNN3, ZNF608

79 proteins (or peptides):

2155-Da peptide, ADAMTS13, AEQREFNKHLSA, Alpha-1B-glycoprotein, Amyloid-like protein 2, Antithrombin-III, APFGQKDALGL, ApoC-I, ApoC-III, Apolipoprotein D, AWQKSKGVALSG, Beta-amyloid protein A4, calpain-15, Calponin, Coagulation factor XII, CKB, Clusterin, CMPK, coactosin-like protein, Coagulation factor V, Coagulation factor XI, Collagen alpha-1(IV) chain, Complement C3, Complement component 4b (C4b and C4a), CRP, CTNND2, cystatin C (CST3), E-selectin, EKLYYHDSQEKH, Epidermal growth factor receptor (EGFR), Fatty acid binding protein 3 (FABP3), Fibrinogen alpha chain, Fibrinogen beta chain, Fibrinogen gamma chain, GASVHDGVALSG, GDRRPLGVALSG, GEYFRWNWDSVA, Guanylate cyclase A(NPR1) (ANPR1), histone proteins (H2A type 1 and 1-A, H2A types 2B and J, H2Av, -z, and -x), IGF-1, IL-6, Insulin-like growth factor-binding protein 3 (IBP 3), interferon regulatory factor 7 (IRF7), KGQRGYHLKHDA, KPEKLNGVALSG, L-selectin, metalloproteins Cu, metalloproteins Mg, metalloproteins Mn, metalloproteins Mo, metalloproteins Pb, metalloproteins Se, Methylenetetrahydrofolate reductase, NNYWANVASGLG, NSLKENGVALSG, NVAVAQDENLAG, PEFRELSKHDVA, PKPHGFPGQEYV, Plasma protease C1 inhibitor (C1 inhibitor), Plasma serine protease inhibitor (Protein C inhibitor), Plasminogen/plasmin/angiostatin, platelet basic protein, Platelet endothelial cell adhesion molecule (PECAM 1), Prolactin, Protein kinase C eta type, Prothrombin/thrombin, QRPDPKDGQAKD, QSLKPKGVALSG, S100A12 (CGRP), S100A7, Serum paraoxonase/aryl esterase 1 (Paraoxonase- PON1), Serum paraoxonase/lactonase 3 (Paraoxonase- PON3), thymidine phosphorylase 4 (TYMP-4), titin Isoform 3, tropomyosin alpha-4 chain, Vitamin K-dependent protein C (Protein C), Vitamin K-dependent protein S (Protein S), Vitamin K-dependent protein Z (Protein Z), VLGPRHEPDSGA, vWF

97 metabolites:

(0+2+3+16+18:1)/Cit, (0+2+3016+18:1)/Cit, 5-adenosylhomocysteine, Adenosine, Aldosterone, Arg, Asparagine, asymmetrical dimethylarginine (ADMA), BCAA isoleucine, BCAA leucine, BCAA valine, Betanin, C10, C10:2, C12, C14, C14:2, C16, C16-OH, C16-OH/C16, C16:1-OH, C18, C18-OH, C18:1, C22, C3/Met, C3DC, C3DC/C10, C4, C4-OH, C4DC, C5, C5/C3, C5DC, C5DC/C16, C5DC/C5-OH, Carnitine, cis/trans hydroxyproline, creatinine, cysteamine, cysteine, Deoxocathasterone, FA (16:1), FA (17:1), FA (20:2), FA (20:3), FA (20:4), FA (20:5), FA (22:4), FA (22:5), FA (22:6), FAHFA (14:0/16:2), FAHFA (16:1/18:3), FAHFA (18:1/20:3), FAHFA (18:2/20:4), FAHFA (20:4/18:3), folic acid, glucose, glycine, hexadecanedioate, histidine, Hydroxy eicosatetraenoic acid, Hydroxy octadecadienoic acid, isoleucine, betaine, LPC (20:5), LPC (22:5), LPC (22:6), LPE (18:2), LPE (20:4), LPE (22:6), LPI (18:1), LPI (18:2), Lysine, LysoPE (18:2), Methionine, N-carbamoyl-beta-alanine, oxidized glutathione, PC (5:0/5:0), pregnenolone sulphate, Pro, Proline, S-adenosyl-homocysteine, Serine, Sucrose 6-phosphate, symmetrical dimethylarginine (SDMA), tetradecanedioate, Tetrahydrofolate, TG (14:0_16:1_20:3), TG (16:0_16:1_18:0), TG (16:0_18:2_18:3), TG (16:0_18:2_22:6), TG (17:1_17:2_19:0), Thr, Threonine, Tyr/Cit, Uridine, Val/Phe

41 transcripts:

circ-BBS2, circ-PHKA2, circ_0041685, circ_0066867, circ_0093708, circ_0112036, lncRNA NR_120420, miR-106-5p, miR-1246, miR-1255b-5p, miR-125a-5p, miR-125b-2*, miR-125b-5p, miR-132-3p, miR-134-5p, miR-143-3p, miR-150-3p, miR-16, miR-186-5p, miR-21-3p, miR-27a*, miR-27b-3p, miR-30e-3p, miR-32-3p, miR-338-3p, miR-342-3p, miR-422a, miR-4286, miR-4523, miR-485-5p, miR-488, miR-5010-5p, miR-505-5p, miR-532-5p, miR-550b-2-5p, miR-627, miR-6795-3p, miR-7c-5p, tRNA-ThrCGT, tRNA-TyrGTA, tRNA-ValCAC

Supplementary Table 6: Quality assessment results using QUADAS-2

STUDY ID	Risk of bias				Concerns of applicability		
	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD	FLOW AND TIMING	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD
Zhou 2021 (1)	Unclear	Low	Low	Low	Low	Low	Low
Zhang 2022 (2)	Unclear	High	Unclear	Unclear	Low	Low	Unclear
Yang 2022 (3)	Unclear	Low	Unclear	Unclear	Unclear	Low	Unclear
Turek-Jakubowska 2022 (4)	Unclear	Low	Low	Low	Low	Low	Low
Tian 2022 (5)	Unclear	Low	Unclear	Unclear	Low	Low	Unclear
Rahmati 2021 (6)	Low	Low	Low	Low	Low	Low	Low
Li 2021 (7)	Unclear	Low	Low	Low	Low	Low	Low
Induruwa 2022 (8)	Low	Low	Unclear	Unclear	Low	Low	Unclear
Gawryś 2022 (9)	Low	Low	Low	Low	Low	Low	Low
Cho 2022 (10)	Unclear	Low	Unclear	Unclear	Low	Low	Low
Intiso 2004 (11)	Low	Low	Low	Low	Low	Low	Low
Perini 2001(12)	Low	Low	Low	Low	Low	Low	Low
Pedersen 2004 (13)	Unclear	Low	Low	Low	Low	Low	Low
Nayak 2011 (14)	Unclear	Low	Low	Low	Low	Low	Low
Senes 2007 (15)	Low	Low	Unclear	Unclear	Low	Low	Unclear
Feng 2019 (16)	High	Low	Low	Low	Low	Low	Low
Blann 1999 (17)	Low	Low	Unclear	Low	Low	Low	Unclear
Shyu 1997 (18)	Low	Low	Low	Low	Low	Low	Low
Liu 2015 (19)	Low	Low	Low	Low	Low	Low	Low
Supanc 2011 (20)	Low	Low	Low	Low	Low	Low	Low
Wunderlich 2005(21)	Low	Low	Low	Low	Low	Low	Low
Hu 2016 (22)	High	Low	Unclear	Unclear	Unclear	Low	Unclear

Uno 2003 (23)	Low	Low	Low	Low	Low	Low	Low
Sun 2019 (24)	Unclear	Low	Low	Low	Low	Low	Low
Song 2006 (25)	Low	Low	Low	Low	Low	Low	Low
Zitnanova 2016 (26)	Low	Low	Low	Low	Low	Low	Low
Can 2015 (27)	Low	Low	Low	Low	Low	Low	Low
Kimberly 2013 (28)	Low	Low	Low	Low	Low	Low	Low
Abboud 2007 (29)	Low	Low	Low	Low	Low	Low	Low
Tang 2006 (30)	Unclear	Low	High	Low	Low	Low	Low
Rainer 2007 (31)	Low	Low	Low	Low	Low	Low	Low
Tiedt 2018 (32)	Low	Low	Low	Low	Low	Low	Low
Zhu 2019 (33)	Low	Low	Low	Low	Low	Low	Low
Zhu 2018 (34)	Unclear	Low	Low	Low	Low	Low	Low
Zhou 2016 (35)	Unclear	Low	High	Low	Low	Low	Unclear
Zhou 2018 (36)	Unclear	Low	Low	Low	Low	Low	Low
Zhou 2022 (37)	Low	Low	Low	Low	Low	Low	Low
Zhao 2016 (38)	Low	Low	Unclear	Unclear	Low	Low	Unclear
Zhao 2017 (39)	High	Low	Low	Low	Low	Low	Low
Zhao 2016 (40)	Unclear	Low	Low	Low	Low	Low	Low
Zhang 2017 (41)	Unclear	Low	Low	Low	Low	Low	Low
Zhang 2020 (42)	Low	Low	Low	Low	Low	Low	Low
Zaremba 2006 (43)	Unclear	Low	Low	Low	Low	Low	Low
Yuan 2020 (44)	Unclear	Low	Low	Low	Low	Low	Low
Yigit 2017 (45)	Unclear	Low	Unclear	Unclear	Low	Low	Unclear
Yang 2016 (46)	Unclear	Low	Low	Low	Low	Low	Low
Xiong 2015(47)	Low	Low	Low	Low	Unclear	Low	Low
Wu 2020 (48)	Unclear	Low	Low	Low	Low	Low	Low
Williams 2007 (49)	Low	Low	Low	Low	Low	Low	Low
Wang 2017 (50)	Low	Low	Low	Low	Low	Low	Low
Wang 2014 (51)	Low	Low	Low	Low	Low	Low	Low

Wang 2018 (52)	Unclear	Low	Low	Low	Low	Low	Low
Wang 2017 (53)	Unclear	Low	Low	Low	Low	Low	Low
Walsh 2016 (54)	Low	Low	Unclear	Unclear	Low	Low	Unclear
Vukasovic 2006 (55)	Unclear	Low	Low	Low	Low	Low	Low
von Recum 2015 (56)	Low	Low	Unclear	Unclear	Low	Low	Unclear
Unden 2009 (57)	Low	Low	Low	Low	Unclear	Low	Low
Tunç 2018 (58)	Unclear	Low	Low	Low	Low	Low	Low
Tiedt 2017 (59)	Low	Low	Low	Low	Low	Low	Low
Tiedt 2020 (60)	Low	Low	Low	Low	Low	Low	Low
Tian 2015 (61)	Low	Low	Low	Low	Low	Low	Low
Tian 2016 (62)	Low	Low	Unclear	Unclear	Low	Low	Unclear
Taema 2014 (63)	Unclear	Low	High	Low	Low	Low	High
Stejskal 2011 (64)	High	Low	Low	Low	Low	Low	Low
Stanca 2015 (65)	Low	Low	Low	Low	Low	Low	Low
Stamova 2010 (66)	Unclear	Low	Unclear	Unclear	Unclear	Low	Unclear
Stamova 2019 (67)	Unclear	Low	Low	Low	Low	Low	Low
Song 2019 (68)	Unclear	Low	Low	Low	Low	Low	Low
Simats 2020 (69)	Unclear	Low	Unclear	Unclear	Low	Low	Unclear
Simats 2018 (70)	Unclear	Low	Unclear	Unclear	Unclear	Low	Unclear
Simats 2018 (71)	Unclear	Low	Unclear	Unclear	Low	Low	Unclear
Sharma 2014 (72)	Low	Low	Low	Low	Low	Low	Low
Sharma 2015 (73)	Unclear	Low	Low	Low	Low	Low	Low
Shaker 2020 (74)	Unclear	Low	Low	Low	Low	Low	Low
Sepramaniam 2014 (75)	Unclear	Low	Low	Low	Low	Low	Low
Sayan 2016 (76)	Low	Low	Low	Low	Low	Low	Low
Rozanski 2017 (77)	Low	Low	Low	Low	Low	Low	Low
Roudbary 2011 (78)	High	Low	Low	Low	Low	Low	Low
Rico Santana 2014 (79)	Unclear	Low	Low	Low	Low	Low	Low
Richard 2016 (80)	Unclear	Low	Low	Low	Low	Low	Low

Reynolds 2003 (81)	Low	Low	Low	Low	Low	Low	Low
Ren 2016 (82)	High	Low	Low	Low	Low	Low	Low
Ranga 2016 (83)	High	Low	Low	Low	High	Low	Low
Rahmati 2020 (84)	Unclear	Low	Low	Low	Low	Low	Low
Qi 2021 (85)	Unclear	Low	Low	Low	Low	Low	Low
Peycheva 2021 (86)	Low	Low	Low	Low	Low	Low	Low
Perovic 2017 (87)	Low	Low	Low	Low	Low	Low	Low
Penn 2018 (88)	Unclear	Low	Low	Low	Low	Low	Low
Park 2013 (89)	Low	Low	Low	Low	Low	Low	Low
Park 2018 (90)	Low	Low	Low	Low	Low	Low	Low
Pan 2020 (91)	High	Low	Unclear	Low	High	Low	Unclear
Palm 2018 (92)	Low	Low	Low	High	Low	Low	Low
Oraby 2019 (93)	High	Low	Low	Low	Low	Low	Low
O'Connell 2019 (94)	Unclear	Low	Low	Low	Low	Low	Low
O'Connell 2019 (95)	Unclear	Low	Low	Low	Low	Low	Low
O'Connell 2016 (96)	Unclear	Low	Low	Low	Low	Low	Low
O'Connell 2017 (97)	Unclear	Low	Low	Low	Low	Low	Low
O'Connell 2017 (98)	High	Low	Unclear	Unclear	Low	Low	Unclear
O'Connell 2020 (99)	Unclear	Low	Low	Low	Low	Low	Low
Nielsen 2020 (100)	Low	Low	Low	Low	Low	Low	Low
Nguyen 2020 (101)	Low	Low	Low	Low	Low	Low	Low
Nahan 2017 (102)	High	Low	Unclear	Unclear	Low	Low	Unclear
Montaner 2012 (103)	Low	Low	Low	Low	Low	Low	Low
Menon 2018 (104)	Low	Low	Unclear	Unclear	Low	Low	Unclear
Mattila 2021(105)	Low	Low	Unclear	Unclear	Low	Low	Unclear
Matsuo 2013 (106)	Low	Low	Low	Low	Low	Low	Low
Matsumori 2002 (107)	Low	Low	Low	Unclear	Low	Low	Low
Maly 2021 (108)	Low	Low	Unclear	Unclear	Low	Low	Unclear
Mahovic 2013 (109)	High	Low	Low	Low	Low	Low	Low

Ma 2019 (110)	Unclear	Low	Low	Low	Low	Low	Low
Luger 2017(111)	Low	Low	Low	Low	Low	Low	Low
Lu 2020 (112)	High	Low	Low	Low	Low	Low	Low
Long 2013 (113)	High	Low	Unclear	Unclear	Low	Low	Unclear
Llombart 2016 (114)	High	Low	Low	Low	Low	Low	Low
Liu 2015 (115)	Low	Low	Low	Low	Low	Low	Low
Liu 2017 (116)	High	Low	Low	Low	Low	Low	Low
Liu 2020 (117)	High	Low	Low	Low	Low	Low	Low
Liswati 2009 (118)	High	Low	Low	Low	Low	Low	Low
Li 2021 (119)	Unclear	Low	Low	Low	Low	Low	Low
Li 2015 (120)	High	Low	Low	Low	Low	Low	Low
Li 2018 (121)	Low	Low	Low	Low	Low	Low	Low
Leung 2014 (122)	Low	Low	Low	Low	Low	Low	Low
Laterza 2006 (123)	High	Low	Unclear	Unclear	Unclear	Low	Unclear
Laskowitz 2009 (124)	Low	Low	Low	Low	Low	Low	Low
Kokocinska 2007 (125)	High	Low	Low	Low	Low	Low	Low
Kokocinska 2005 (126)	High	Low	Low	Low	Low	Low	Low
Kodali 2013 (127)	High	Low	Unclear	Unclear	Unclear	Low	Unclear
Kodali 2012 (128)	High	Low	Unclear	Unclear	Unclear	Low	Unclear
Kochanowski 2012 (129)	High	Low	Low	Low	High	Low	Low
Kavalci 2011 (130)	Low	Low	Unclear	Unclear	Low	Low	Unclear
Katsanos 2017 (131)	Low	Low	Unclear	Unclear	Low	Low	Unclear
Kashyap 2009 (132)	High	Low	Low	Low	Low	Low	Low
Kara 2014 (133)	Low	Low	Low	Low	Low	Low	Low
Kalra 2021 (134)	Low	Low	Low	Low	Low	Low	Low
Kalani 2020 (135)	Low	Low	Low	Low	Low	Low	Low
Jin 2017 (136)	High	Low	Low	Low	Low	Low	Low
Jiang 2011 (137)	High	Low	Low	Low	Low	Low	Low

Jia 2015 (138)	Low	Low	Low	Low	Low	Low	Low
Ji 2016 (139)	Unclear	Low	Low	Low	Low	Low	Low
Inoue 2019 (140)	Low	Low	Low	Low	Low	Low	Low
Iltumur 2006 (141)	High	Low	Low	Low	Low	Low	Low
Herisson 2010 (142)	Low	Low	Low	Low	Low	Low	Low
Han 2012 (143)	High	Low	Low	Low	Low	Low	Low
Gunduz 2008 (144)	High	Low	Low	Low	Low	Low	Low
Gunaydin 2014 (145)	Low	Low	Low	Low	Low	Low	Low
Glickman 2011 (146)	High	Low	Low	Low	Low	Low	Low
Giannopoulos 2008 (147)	High	Low	Low	Low	Low	Low	Low
Garlichs 2003 (148)	High	Low	Low	Low	Low	Low	Low
Foerch 2012 (149)	Low	Low	Low	Low	Low	Low	Low
Foerch 2006 (150)	Low	Low	Low	Low	Low	Low	Low
Fiszer 1998 (151)	High	Low	Low	Low	Low	Low	Low
Fassbender 1997 (152)	Low	Low	Low	Low	Low	Low	Low
Fang 2018 (153)	Low	Low	Unclear	Unclear	Low	Low	Unclear
Ewida 2021 (154)	Low	Low	Low	Low	Low	Low	Low
Ekingen 2017 (155)	Low	Low	Unclear	Unclear	Low	Low	Unclear
Dvorak 2009 (156)	Low	Low	Low	Low	Unclear	Low	Low
Duan 2015 (157)	Low	Low	Low	Low	Low	Low	Low
De Marchis 2018 (158)	Low	Low	Low	Low	Low	Low	Low
Dassan 2012 (159)	Low	Low	Low	Low	Low	Low	Low
Dambinova 2003 (160)	High	Low	Low	Low	Low	Low	Low
Dambinova 2012 (161)	Low	Low	Low	Low	Low	Low	Low
Cheng 2018 (162)	Low	Low	Low	Low	Low	Low	Low
Chen 2018 (163)	Low	Low	Low	Low	Unclear	Low	Low
Cavrak 2021 (164)	High	High	Low	Low	Low	Low	Low
Cano 2003 (165)	Low	Low	Low	Low	Low	Low	Low

Cakmak 2014 (166)	Low	Low	Low	Low	Low	Low	Low
Büttner 1997 (167)	High	Low	Low	Low	High	Low	Low
Bustamante 2021 (168)	Low	Low	Low	Low	Low	Low	Low
Bustamante 2017 (169)	Low	Low	Low	Low	Low	Low	Low
Bolayir 2019 (170)	Low	Low	Low	Low	Low	Low	Low
Bibl 2012 (171)	Unclear	Low	Low	Low	Low	Low	Low
Barr 2010 (172)	High	Low	Low	Low	Low	Low	Low
Azarpazhoooh 2010 (173)	High	Low	Low	Low	Low	Low	Low
Atik 2016 (174)	Low	Low	Low	Low	Low	Low	Low
Alvarez-Perez 2011 (175)	Low	Low	Unclear	Unclear	Low	Low	Unclear
Allard 2004 (176)	Low	Low	Low	Low	Low	Low	Low
Allard 2005 (177)	Low	Low	Low	High	Low	Low	Low
Algin 2019 (178)	Low	Low	Low	Low	Low	Low	Low
Algawwam 2021 (179)	Low	Low	Unclear	Unclear	Low	Low	Unclear
Ahn 2011 (180)	Low	Low	Low	Low	Low	Low	Low
Sadik 2021 (181)	Low	Low	Low	Low	Low	Low	Low
Abe 2020 (182)	Low	Low	Low	Unclear	Low	Low	Unclear

Supplementary Table 7: Characteristics of included 10 studies for diagnostic meta-analysis

Study ID	Study design	Group	Sample size	Age mean±SD/IQR	Sex male (%)	Setting	Reference	Specimen	Assay	Time point	Comparison	HS medium (IQR)	IS medium (IQR)	TP	FP	FN	TN	Sensitivity	Specificity	Cut-off value	Unit
Dvorak 2009(156)	Prospective study	IS 22, HS 17	39	HS 62 (60-70), IS 75 (61- 83)	HS 10 (55.6%), IS 25(55.6%)	NA	CT; MRI	serum	ELISA	3h	HS vs. IS	0.1 (0-0.47)	0 (0-0)	11	0	6	22	65%	100%	0.03	ug/l
Rozanski 2017(77)	Prospective study	IS 49, HS (ICH) 25	74	IS 75±10, HS 69±11	not stated	Stroke Emergency Mobile	CT	plasma	ELISA	3h	HS vs. IS	0.057 (0-1.426)	0 (0-0)	9	0	16	49	36%	100%	0.29	ng/ml
Mattila 2021(105)	Prospective study	IS 178, HS 59	237	IS 70 (61-80), HS 67 (57-76)	IS 111 (54.7), HS 38 (63.3)	ED	NA	plasma	Single-molecule array	3h	HS vs. IS	0.4681 (0.1977-1.1882)	0.1782 (0.0997-0.2951)	57	57	2	121	96.6%	68%	410	pg/ml
Foerch 2012(149)	Prospective study	IS 163, HS 39	202	IS 75.3±13.4, HS 70.7±17.4	IS 79 (48.5%), HS 21 (55.3%)	Stroke centre	CT; MRI	plasma	Electrochemiluminescent immunoassay	4.5h	HS vs. IS	1.91 (0.41-17.66)	0.08 (0.02-0.14)	33	6	6	157	84.2%	96.3%	0.29	ug/l
Foerch 2012(149)	Prospective study	IS 163, HS 39	202	IS 75.3±13.4, HS 70.7±17.4	IS 79 (48.5%), HS 21 (55.3%)	Stroke centre	CT; MRI	plasma	Electrochemiluminescent immunoassay	4.5h	HS vs. IS	1.91 (0.41-17.66)	0.08 (0.02-0.14)	29	2	10	161	73.7%	98.8%	0.5	ug/l
Foerch 2012(149)	Prospective study	IS 163, HS 39	202	IS 75.3±13.4, HS 70.7±17.4	IS 79 (48.5%), HS 21 (55.3%)	Stroke centre	CT; MRI	plasma	Electrochemiluminescent immunoassay	4.5h	HS vs. IS	1.91 (0.41-17.66)	0.08 (0.02-0.14)	24	0	15	163	60.5%	100%	1	ug/l
Bustamante 2021(168)	Prospective study	IS 154, HS 35	189	IS 81 (70-85), HS 82 (72-85.5)	IS 64 (41.6), HS 20 (57.1)	ED	CT; MRI	plasma	ELISA	4.5h	HS vs. IS	0.045 (0.045-0.059)	error	34	97	1	57	99.4%	37.1%	0.05	ng/ml
Ren 2016(82)	Case control study	ICH 45, IS 79	124	ICH 58.91±12.18, IS 61.1±13.33	ICH 36 (80%), IS 49 (62.02%)	ED	CT; MRI	serum	ELISA	4.5h	HS (ICH) vs. IS	0.81 (0.18-3.31)	0.02 (0.004-0.08)	27	3	18	76	61%	96%	0.34	ng/ml
Dvorak 2009(156)	Prospective study	IS 39, HS 14	53	HS 62 (60-70), IS 75 (61- 83)	HS 10 (55.6%), IS 25(55.6%)	NA	CT; MRI	serum	ELISA	6h	HS vs. IS	0.55 (0-1.3)	0 (0-0)	10	4	4	35	71%	95%	0.11	ug/l

Foerch 2006(150)	Prospective study	HS 42, IS 93	135	HS 67±11, IS 70±12	HS 28 (66.7%), IS 57 (61.3%)	stroke unit or NICU	CT; MRI	serum	ELISA	6h	HS vs. IS	0.011 (range 0-3.096)	0 (0-0.014)	33	2	9	91	79%	98%	2.9	ng/l
Katsanos 2017(131)	Prospective study	IS 121, ICH 31	152	IS 77.3±9.1, ICH 74.0±9.6	IS 62 (51.2%), ICH 17 (50.0%)	ED	NA	plasma	BAT GFAP assay	6h	HS (ICH) vs. IS	2.17 (0.55-10.12)	0.11 (0-0.27)	24	4	7	117	91%	97%	0.43	ng/ml
Xiong 2015(47)	Prospective study	IS 65, HS (ICH) 43	108	HS 68.7 ±11.2, IS 70.9 ±9.6	HS 28 (65.1%), IS 44 (67.7%)	NA	CT; MRI	serum	ELISA	6h	HS (ICH) vs. IS	1.6±0.8 (mean±SD)	0.6±0.4 (mean±SD)	37	15	6	50	86.0 %	76.9 %	0.7	ng/ml
Uden 2009(57)	Prospective study	IS 83, HS (ICH) 14	97	IS 75 (63.80), HS 64 (60.75)	not stated	NA	CT	NA	ELISA	24h	IS vs. HS (ICH)	0.055 (0.040-0.160)	<0.030 (<0.030-0.070)	11	30	3	53	79%	64%	40	ng/l
Ren 2016(82)	Case control study	ICH 45, IS 79	124	ICH 58.91 ±12.18, IS 61.1 ±13.33	ICH 36 (80%), IS 49 (62.02%)	ED	CT; MRI	serum	ELISA	24h	HS (ICH) vs. IS	0.81 (0.18-3.31)	0.02 (0.004-0.08)	30	7	15	72	67%	91%	0.34	ng/ml

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