Supplementary Table 2. Cohort studies: thrombus composition and TOAST stroke etiology or underlying pathology

Study	Sample size (clots/ patients)	Analysis	Thrombus composition items	Etiology groups (patients)	Association composition-etiology or underlying pathology
Ahn et al. (2016) Int J Stroke[57]	36	Histopathology	RBC and FBR proportions	LAA (8), CE (22), and CRY (6)	RBCs most abundant (56.9%±12.2%) in LAA, higher than CE. FBR most abundant (39.5%±13.5%) in CE, higher than LAA. Similar composition in CRY and CE
Baek et al. (2018) Ann Clin Transl Neurol[112]	82	Biomolecular RTqPCR	Expression of inflammatory mediators	LAA (9), CE (51), and CRY (22)	Higher IL-1β expression in LAA than in both CE and CRY. Similar expression in CRY and CE
Berndt et al. (2018) World Neurosurg[126]	137	Histopathology	FP/RBC ratio	LAA (22), CE (67), ODC (11), and CRY (36)	Higher FP/RBC in CE+CRY than non-CE (LAA+ODC)
Bhaskar et al. (2019) Eur J Neurol[127]	85	Histopathology	RBC, FP, and WBC proportions	CE, non-CE, and CRY	RBC (26%), FP (61%) and WBC (11%) proportions in CE similar to RBC (28%), FP (64%) and WBC (9%) proportions in CRY. Different proportions in non-CE
Boeckh-Behrens et al. (2016) Clin Neuroradiol[89]	34	Histopathology	RBC, FP, and WBC proportions	LAA (3), CE (16), ODC (6), and CRY (9)	Higher proportion of WBCs in CE than in LAA or CRY
Boeckh-Behrens et al. (2016) Stroke[122]	137	Histopathology	RBC, FP, and WBC proportions	LAA (22), CE (67), ODC (11), and CRY (36)	Different composition in CE (RBC 38.3%±20.0%, FP 52.6%±18.6% and WBC 9.1%±6.4%) and in non-CE (LAA+ODE) (RBC 52.7%±25.2%, FP 40.9%±23.3%, and WBC 6.5%±3.8%). Similar composition in CRY (RBC 42.0%±21.4%, FP 50.8%±20.8%, and WBC 7.1%±4.5%) and in CE
Brinjikji et al. (2020) Stroke[59]	1,022	Histopathology	PLT proportion	LAA and CE	Higher PLT content in LAA (PLT-rich clots [55.0%], PLT-area [22.1%]) than in CE (PLT-rich clots [21.2%], PLT-area [13.9%])
Dargazanli et al. (2016) PLOS One[90]	54	Histopathology	CD3+ T-cell count	LAA (10), CE (25), and other causes (ODC+CRY, 19)	Higher T-cell count in LAA (53.60±28.78) than in both CE (20.08±15.66) or other causes (21.77±18.31)
Dargazanli et al. (2020) Front Neurol[115]	60	Biomolecular Proteomics	Relative protein	LAA (28) and CE (32)	Coagulation factor XIII associated with CE
Deng et al. (2020) Neurosci Lett[94]	46	Histopathology	NETs (H3Cit) proportion	NG (28), AHG (9), and DM (9)	Higher NETs proportion in both AHG and DM than in NG
Di Meglio et al. (2020) Stroke[118]	250	Biochemical	GP (glycoprotein) VI, heme, and DNA contents	CE (142), non-CE (33), and ESUS (75)	CE richer in DNA (35.8 ng/mg), i.e., more leukocytes, and poorer in GP VI (0.104 ng/mg), i.e., less PLTs, than non-CE (DNA 13.8 ng/mg; GP VI 0.117 ng/mg)
Essig et al. (2020) Int J Mol Sci[76]	37	Histopathology	Neutrophil count and FBR proportion	CE (21), non-CE (7), and CRY (9)	Higher neutrophil counts in both CE (799.1±477.6 cells/mm^2) and CRY (734.1±329.1 cells/mm^2) compared to non-CE (376±128.5 cells/mm^2). Higher FBR proportion in both CE (46.1%±29.9%) and CRY (46.6%±21.8%) compared to non-CE (25.9%±12.1%)
Fitzgerald et al. (2019) Stroke[50]	105	Histopathology	RBC, WBC, FBR, and PLTs+other proportions	LAA (20), CE (52), ODC (12), and CRY (21)	Higher PLT content in LAA (PLT-rich clots [55.0%], PLT-area [22.1%±18.6%]) than in CE (PLT-rich clots [21.2%], PLT-area [13.9%±14.3%]). More PLT-rich clots in both LAA (55.0%) and CRY (50.0%) than in CE (21.2%)
Fitzgerald et al. (2020) J NeuroInterv Surg[39]	612 / 441	Histopathology	ECA; RBC, WBC, FBR, PLTs+other, and collagen proportions	LAA (115), CE (209), ODC (16), and CRY (101)	Larger ECA in LAA (54.96 mm^2) than in CE (33.64 mm^2), ODC (39.60 mm^2), and CRY (32.28 mm^2). Higher RBC proportion in LAA (48.89%) than in CE (35.57%), ODC (42.82%), and CRY (39.08%). Highest proportion of both FBR (33.3%) and PLTs+other (28.53%) in CE
Fitzgerald et al. (2021) J Stroke Cerebrovasc Dis[40]	550	Histopathology	ECA. Number of clot fragments	LAA (110), CE (197), ODC (33), and CRY (143). Excluded (67)	Larger ECA in LAA (109 mm^2) than in CE (52 mm^2), ODC (52 mm^2), and CRY (47 mm^2). Greater number of fragments in LAA (5.36) than in CE (3.72), ODC (3.73), and CRY (3.52)

Supplementary Table 2. Continued

Study	Sample size (clots/ patients)	Analysis	Thrombus composition items	Etiology groups (patients)	Association composition-etiology or underlying pathology
Fu et al. (2020) Stroke[38]	152	Macroscopic. Histopathology	RBC, FP, and WBC proportions	AC (19), LAA (26), and CE (107)	White gross appearance in AC vs. darker/reddish in LAA or CE. Higher FP proportion in AC (85.7%) than in LAA (42.5%) or CE (43.9%). Lower RBC proportion in AC (8.1%) than in LAA (51.7%) or CE (52.2%). Lower WBC proportion in AC (1.9%) than in LAA (3.1%) or CE (3.7%)
Goebel et al. (2020) Am J Neuroradiol[67]	85	Histopathology	RBC, WBC (macrophages, lymphocytes, granulocytes), FBR, and PLTs proportions	LAA (16), CE (51), ODC (1), and ESUS (17)	Higher proportion (range) of macrophages in CE (0.9% [0.1%–3.3%]) than in LAA (0.3% [0.1%–3.8%]) or ESUS (0.4% [0.0%–5.2%]). Higher proportion of PLTs in CE (19.1% [3.6%–81.1%]) than LAA (10.3% [2.3%–25.1%])
Gong et al. (2019) Cell Transplant[125]	45	Histopathology	RBC and FBR proportions	LAA (9) and CE (36)	Higher RBC proportion in CE (69%) than in LAA (55.5%). Lower FBR proportion in CE (31%) than in LAA (44.5%)
Hernández-Fernández et al. (2017) Cardiovasc Intervent Radiol[109]	65	Histopathology. Bacteriological	Distribution of RBCs, PLTs, and WBCs. Bacteria presence	CE (38), non-CE or CRY (27)	Gram-positive bacteria in four thrombi: infective endocarditis (2), urinary tract infection (1), and pneumonia (1)
Itsekson Hayosh et al. (2020) J NeuroInterv Surg[121]	68	Biochemical	Eluted thrombin activity (ETA)	LAA (15), CE (18), ODC (18), and CRY (17)	Temporal profile of ETA similar in CRY and CE, and different from LAA
Juega et al. (2019) Stroke[120]	40	Flow cytometry	Leukocyte populations	LAA, CE, and ODC	Higher proportion of CD4 T lymphocytes in LAA (24.85%) than in CE (15.83%). Higher proportion of natural killer (NK) cells in LAA (21.08%) than in CE (17.04%). Lower proportion of CD8 T lymphocytes in LAA (13.56%) than in CE (20.24%)
Kim et al. (2020) J Clin Neurosci[51]	52	Histopathology	RBC, FBR, and PLTs proportions. PLT distribution pattern (PDP)	LAA (10), CE (31), and CRY (11)	Mostly peripheral PDP in LAA (70%). Mostly clustering PDP in CE (77.4%). Similar PDPs in CE and CRY.
Kim et al. (2015) Am J Neuroradiol[72]	37	Histopathology	RBC, FBR, PLTs, and WBC proportions	LAA (8), CE (22), and CRY (7)	Higher RBC proportion in CE (37.8%) than in LAA (16.9%). Lower FBR proportion in CE (32.3%) than in LAA (48.5%)
Laridan et al. (2017) Ann Neurol[93]	68	Histopathology	NETs (H3Cit) proportion	LAA (7), CE (40), ODC (6), and CRY (15)	Nearly double amount of NETs in CE (3.07%±2.21%) than non-CE (LAA+ODC; 1.57%±1.23%)
Liao et al (2020) Front Neurol[123]	88	Histopathology	RBC, FBR, and PLTs proportions. WBC count	LAA (25), CE (46), ODC (6), and CRY (11)	Higher RBC proportion (range) in LAA (53.44% [49.91%–56.97%]) than in CE (35.70% [32.04%–39.36%]) or CRY (38.18% [31.01%–45.35%]). Higher FBR proportion in both CE (35.91% [31.44%–40.39%]) and CRY (39.73% [27.97%–51.49%]) than in LAA (22.96% [17.81%–28.11%]) or ODC (26.33% [12.31%–40.36%]).
Maekawa et al. (2018) Cerebrovasc Dis Extra[82]	43	Histopathology	RBC, FBR, and WBC proportions	LAA (5), CE (30), ODC (1), and CRY (7)	Lower RBC proportion in CE (29.5%±26.2%) than in non-CE (49.6%±26.1%). Higher FBR proportion in CE (66.2%±25.8%) than in non-CE (46.4%±25.5%).
Marder et al. (2006) Stroke[7]	25	Histopathology	Distribution of RBCs, PLTs, and WBCs. Fungi presence	LAA (4), CE (16), ODC (3), and CRY (2)	One mycotic thrombus. Aortic valve infective endocarditis
Mereuta et al. (2020) Stroke[100]	79	Histopathology	VWF proportion	LAA (13), CE (39), ODC (12), and CRY (15)	Higher VWF proportion in CRY when compared to CE

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Supplementary Table 2. Continued

Study	Sample size (clots/ patients)	Analysis	Thrombus composition items	Etiology groups (patients)	Association composition-etiology or underlying pathology
Niesten et al. (2014) PLOS One[64]	22	Histopathology	RBC, FBR, and PLTs proportions	LAA (8), CE (6), ODC (3), and CRY (5)	Higher RBC proportion (range) in both LAA (50% [35%–90%]) and ODC (35% [20%–40%]), than in CE (35% [5%–45%]) or CRY (25% [2%–40%])
Nouh et al. (2020) BMC Neurology[73]	33	Histopathology	RBC and PLTs proportions. RBC/PLTs ratio	LAA (9), CE (14), ODC (4), and ESUS (6)	RBC/PLTs ratio in ESUS (0.36±0.33) similar to CE (0.78±0.65), and different from LAA (1.73±2.38) or ODC (1.44±0.70)
Novotny et al. (2020) Neurology[66]	71	Histopathology	FBR and PLTs proportions. WBC subtypes counts. NETs and H3Cit counts	LAA (15), CE (35), and CRY (21)	Lower NETs count and netting neutrophils rate in LAA than in CE or CRY.
Park et al. (2019) Ann Neurol[65]	48	Histopathology	RBC, FBR, and PLTs proportions. Neutrophil and NETs counts	Control (16), AC (16), and IC (16)	Higher PLT proportion in AC (43.2%) than in IC (12.9%) or control (14.1%). Lower RBC proportion in AC (3.4%) than in IC (43.5%) or control (40.7%)
Sgreccia et al. (2019) J NeuroIntervent Surg[36]	255	Macroscopic	Visual aspect: red/black or white	LAA (53), CE (127), ODC (13), CRY (45), and atypical (17)	Atypical etiologies (AC, IE, etc.) more frequent in white clots (27.3%) than red/black clots (4.7%)
Shin et al. (2018) PLOS One[84]	93 / 37	Histopathology	RBC, FP, and WBC proportions	LAA (7), CE (22), and CRY (8)	Higher RBC proportion in CE (38%) than in LAA (23%) or CRY (26%). Lower WBC proportion in CE (3%) than in LAA (6%) or CRY (5%)
Sporns et al. (2017) Stroke[96]	187	Histopathology	RBC, FBR, and WBC proportions	LAA (35), CE (77), ODC (11), and CRY (64)	Composition (range) in both CE (RBC 28.0% [11.0%–53.0%], FBR 60.0% [40.0%–80.0%], and WBC 8.0% [5.0%–12.5%]) and CRY (RBC 26.0% [10.5%–43.5%], FBR 63.5% [45.5%–77.8%], and WBC 10.0% [5.0%–14.5%]) different from non-CE (LAA+ODE) (RBC 42.0% [20.9%–71.8%], FBR 51.5% [19.5%–68.5%], and WBC 5.0% [4.0%–10.0%]). Similar composition in and in CE and CRY
Wolpert et al. (2020) Eur J Neurol[129]	32	Histopathology	Tumor cell presence	AC: LAA (4), CE (8), ODC (1), and CRY (19)	Tumor cells in one out of 32 with AC (3.1%)
Xue et al. (2018) Natl Med J China[124]	58	Histopathology	RBC and FBR proportions	LAA (17), CE (31), and CRY (10)	Higher RBC proportion in LAA (58%) than in CE (46%), and higher FBR proportion in CE (54%) than in LAA (42%). Similar composition in CE (RBC 46%, FBR 54%) and CRY (RBC 47%, FBR 53%)
Ye et al. (2020) Interv Neuroradiol[55]	52	Histopathology	RBC, FBR, and PLT proportions. VWF content	LAA (12), CE (34), and CRY (6). NG (26) and DM (26)	Lower RBC proportion in DM (26.0%) than in NG (42.9%). Higher FBR proportion in DM (44.2%) than in NG (28.3%)

TOAST, Trial of Org 10172 in Acute Stroke Treatment; RBC, red blood cell; FBR, fibrin; LAA, large-artery atherosclerosis (TOAST 1); CE, cardioembolism (TOAST 2); CRY, cryptogenic stroke of undetermined etiology (TOAST 5); RTqPCR, reverse transcriptase quantitative polymerase chain reaction; IL-1β, interleukin-1β; FP, fibrin+platelet; ODC, stroke of other determined cause (TOAST 4); WBC, white blood cell; PLT, platelet; NET, neutrophil extracellular trap; NG, normoglycemia; H3Cit, citrullinated histone H3; AHG, acute hyperglycemia; DM, diabetes mellitus; ESUS, embolic stroke of undetermined cause; ECA, extracted clot area; AC, active cancer; VWF, von Willebrand factor; IC, inactive cancer; IE, infective endocarditis.