SUPPLEMENTAL MATERIAL

Low Serum Albumin Levels Predict Poor Outcome in Patients with Acute Ischemic Stroke or Transient Ischemic Attack

Catalogs

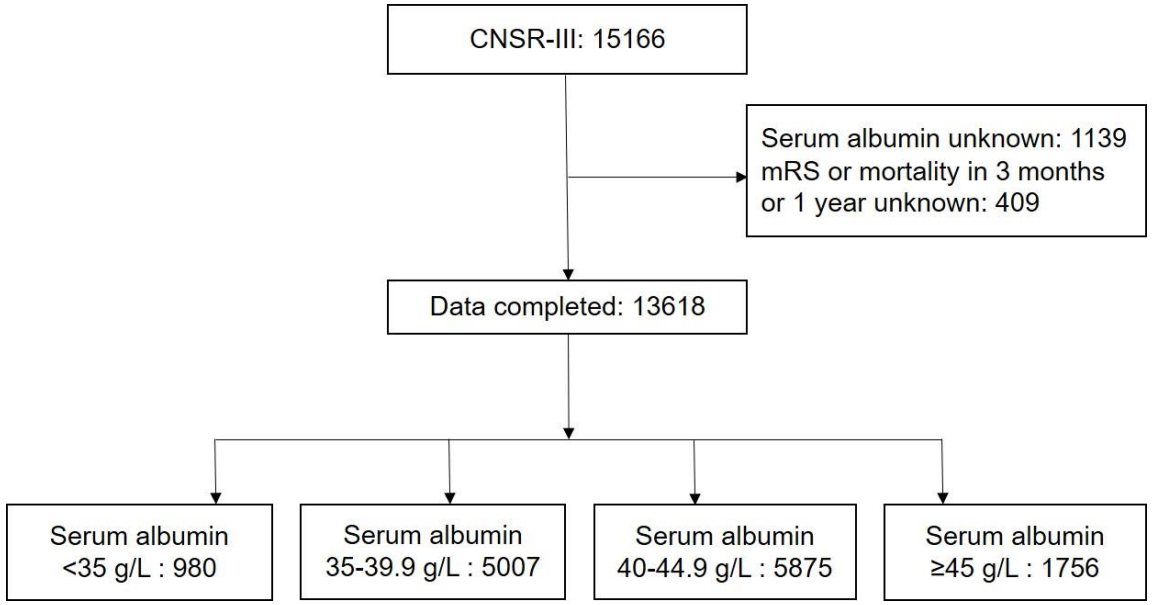
Supplementary Methods

Statistical analysis for the meta-analysis

Details of the included studies were shown in online supplementary table 6 and 7. Including our study, there was five research with poor functional outcome, and three research with mortality. Two studies had to convert serum albumin unit to g/L.[1] Only one paper needed to be converted into the continuous scale (g/L) based on the previous literature.[2, 3] The OR/HR per 1g/L serum albumin increase was converted to per 1g/L serum albumin decrease by reverse calculation.[4-6] In our study, the risk of poor functional outcome and mortality increased 3% and 4% for every 1 g/L decrease in serum albumin levels (adjusted OR, 1.03; 95%CI, 1.02-1.05; adjusted HR, 1.04, 95%CI, 1.02-1.07) (online supplementary table 5). We combined the odds ratio (OR) and hazard ratio (HR) for prospective studies for a risk ratio (RR_{pooled}). The poor functional outcome was analysed by the fixed-effect model, while mortality by the random-effect model according to heterogeneity assessed with the I^2 statistic and the Q statistic.[7] Furthermore, we evaluated potential publication bias by the funnel plots, the Begg's tests and the Egger's tests.

Supplementary Figures

Figure 1. Study flowchart and numbers of eligible patients in each group



mRS, modified Rankin Scale.

Figure 2. Flowchart on the selection of eligible articles

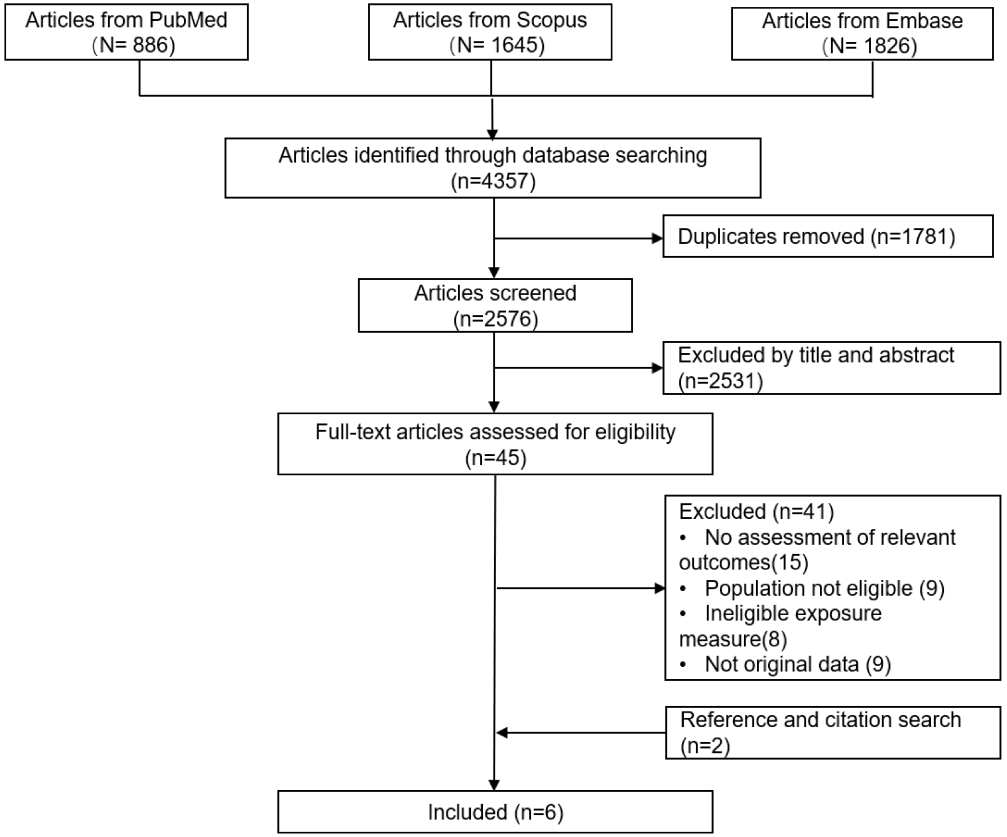


Figure 3. Forest plot of the meta-analysis showed relative risk and 95% CI of mortality in every 1 g/L decreased serum albumin (excluding Idicula, 2009)

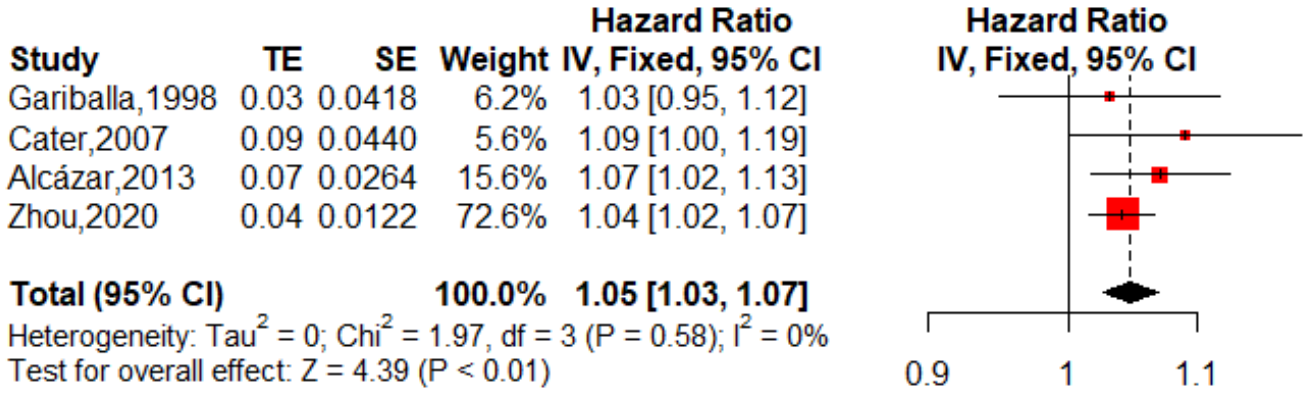
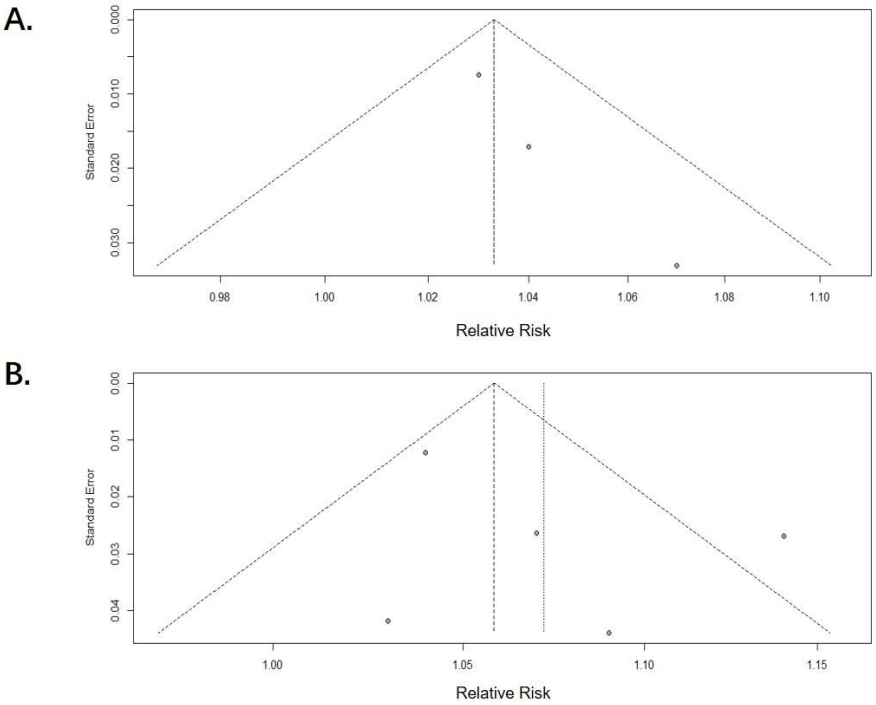


Figure 4. Funnel plots of studies reporting on the association of serum albumin level with (A) poor functional outcome and (B) mortality



Supplementary Tables

Table 1. Baseline characteristics of patients between included and excluded patients

Variable	Included	Excluded	P Value
	n=13618	n=1548	
Age, y, mean (SD)	62.2±11.3	62.7±11.6	0.07
Men, n (%)	9276(68.1)	1088(70.3)	0.08
BMI, kg/m^2, mean (SD)	24.7±3.3	24.9±3.5	0.16
Medical history, n (%)			
Hypertension	8503(62.4)	991(64.0)	0.22
Diabetes mellitus	3135(23.0)	375(24.2)	0.29
Dyslipidemia	1070(7.9)	121(7.8)	0.96
Stroke or TIA	3005(22.1)	350(22.6)	0.63
Coronary heart disease	1432(10.5)	176(11.4)	0.30
Atrial fibrillation/ flutter	911(6.7)	108(7.0)	0.67
Peripheral vascular disease	90(0.7)	28(1.8)	<0.0001
Index event, n (%)			
Ischemic stroke	12690(93.2)	1456(94.1)	0.19
TIA	928(6.8)	92(5.9)	
TOAST types, n (%)			
Large-artery atherosclerosis	3441(25.3)	415(26.8)	0.12

Variable	Included	Excluded	P Value
	n=13618	n=1548	
Cardioembolism	824(6.1)	93(6.0)	
Small-vessel occlusion	2836(20.8)	329(21.3)	
Other determined etiology	173(1.3)	9(0.6)	
Undetermined etiology	6344(46.6)	702(45.4)	
Smoking status, n (%)			
Never	7674(56.4)	832(53.8)	0.005
Previous	1674(12.3)	234(15.1)	
Current	4270(31.4)	482(31.1)	
NIHSS score on admission, median (IQR)	3(1-6)	4(2-6)	<0.0001
Pre-stroke mRS 0~2, n (%)	13044(95.8)	1465(94.6)	0.04
Arterial stenosis, n (%)			
ICAS	3382/11689(28.9)	431/1323(32.6)	0.006
ECAS	529/11689(4.5)	67/1323(5.1)	0.37
Acute recanalization therapy, n (%)			
Intravenous thrombolysis	1146(8.4)	157(10.1)	0.02
Endovascular therapy	85(0.6)	10(0.7)	0.92
Inpatient medication, n (%)			
Antihypertensive agents	6237(45.8)	763(49.3)	0.009
Hypoglycemic agents	3374(24.8)	418(27.0)	0.06
Cholesterol-lowering agents	13033(95.7)	1473(95.2)	0.32
Antiplatelet agents	13142(96.5)	1471(95.0)	0.003
Anticoagulant agents	1372(10.1)	174(11.2)	0.15
Laboratory tests			

Variable	Included	Excluded	P Value
	n=13618	n=1548	
TC, mmol/L, mean (SD)	4.13±1.23	4.07±1.12	0.27
LDL, mmol/L, mean (SD)	2.45±1.08	2.40±1.00	0.40
HDL, mmol/L, mean (SD)	0.97±0.30	0.95±0.29	0.19
TG, mmol/L, mean (SD)	1.60±0.92	1.58±0.90	0.36
eGFR, mL/min/1.73 m^2, mean (SD)	92.0±33.7	92.0±37.7	0.37
ALT, U/L, median (IQR)	18.0(13.0-25.7)	18.0(13.6-27.0)	0.11
hs-CRP, mg/L, median (IQR)	1.7(0.8-4.6)	2.1(0.9-5.6)	<0.0001

BMI, body mass index; TIA, transient ischemic attack; TOAST, the Trial of Org 10172 in Acute Stroke Treatment; NIHSS, National Institute of Health Stroke Scale; mRS, modified Rankin Scale; ICAS, intracranial arterial stenosis; ECAS, extracranial arterial stenosis; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglyceride; eGFR, estimated glomerular filtration rate; ALT, alanine aminotransferase; hs-CRP, high-sensitivity C-reactive protein; IQR, interquartile range; SD, standard deviation.

Table 2. Association of plasma albumin with poor functional outcome (mRS of 3-6) at 3 months and 1 year in analyses stratified for risk factors

Variable	mRS 3-6 at 3 months (%)	Adjusted OR of per 10 g/L decrease	Adjusted *P* for interaction*	mRS 3-6 at 1 year (%)	Adjusted OR of per 10 g/L decrease	Adjusted *P* for interaction*
Age, Years			0.56			0.16
<70y	1088/10020 (10.9)	1.15(0.96-1.38)		942/10020 (9.4)	1.35(1.12-1.62)	
⩾70y	783/3598(21.7)	1.14(0.90-1.45)		843/3598(23.4)	1.48(1.17-1.87)	
Sex			0.76			0.84
Men	1145/9276(12.3)	1.19(0.99-1.42)		1108/9276(11.9)	1.46(1.21-1.75)	
Women	726/4342(16.7)	1.15(0.91-1.46)		677/4342(15.6)	1.39(1.09-1.77)	
BMI			0.88			0.36
<18.5 kg/m^2	76/295(25.8)	0.99(0.42-2.36)		77/295(26.1)	2.39(0.89-6.43)	
⩾18.5 kg/m^2	1795/13323 (13.5)	1.16(1.00-1.34)		1708/13323(12.8)	1.39(1.20-1.61)	
TOAST Types			0.89			0.94
Large-artery atherosclerosis	686/3441(19.9)	1.07(0.84-1.38)		631/3441(18.3)	1.35(1.05-1.75)	
Cardioembolism	156/824(18.9)	1.22(0.71-2.09)		161/824(19.5)	1.37(0.79-2.36)	
Small-vessel occlusion	200/2836(7.1)	1.34(0.88-2.04)		184/2836(6.5)	1.49(0.97-2.29)	
Other determined etiology	29/173(16.8)	0.92(0.24-3.59)		30/173(17.3)	0.89(0.22-3.70)	
Undetermined etiology	800/6344(12.6)	1.18(0.96-1.46)		799/6344(12.3)	1.47(1.19-1.82)	
NIHSS score on admission			0.42			0.13
≤3	372/7495(5.0)	1.22(0.92-1.62)		442/7495(5.9)	1.65(1.28-2.14)	

Variable	mRS 3-6 at 3 months (%)	Adjusted OR of per 10 g/L decrease	Adjusted *P* for interaction*	mRS 3-6 at 1 year (%)	Adjusted OR of per 10 g/L decrease	Adjusted *P* for interaction*
>3	1499/6123(24.5)	1.14(0.97-1.33)		1343/6123(21.9)	1.29(1.09-1.52)	
NIHSS score on admission			0.04			0.09
≤10	1320/12630(10.5)	1.22(1.05-1.42)		1284/12630(10.2)	1.46(1.25-1.70)	
>10	551/988(55.8)	0.92(0.65-1.31)		501/988(50.7)	1.13(0.79-1.62)	
eGFR			0.80			0.25
<60 mL/min/1.73 m^2	156/718(21.7)	1.11(0.70-1.78)		168/718(23.4)	1.83(1.18-2.84)	
⩾60 mL/min/1.73 m^2	1153/8896(13.0)	1.19(0.99-1.44)		1072/8896(12.1)	1.46(1.20-1.76)	
eGFR			0.56			0.13
<90 mL/min/1.73 m^2	669/3978(16.8)	1.13(0.89-1.43)		690/3978(17.4)	1.68(1.33-2.12)	
⩾90 mL/min/1.73 m^2	640/5636(11.4)	1.31(1.02-1.69)		550/5636(9.8)	1.40(1.08-1.82)	

*Adjustment model: age, sex, BMI, medical history (hypertension, DM, stroke or TIA, coronary heart disease and atrial fibrillation/fullter), index event, TOAST types, pre-stroke mRS 0~2, NIHSS scores on admission, intracranial arterial stenosis, extracranial arterial stenosis, intravenous thrombolysis, inpatient medication (antihypertensive agents, anticoagulant agents), serum TG, TC, LDL, HDL, ALT, eGFR, and hs-CRP.

BMI, body mass index; TOAST, the Trial of Org 10172 in Acute Stroke Treatment; NIHSS, National Institute of Health Stroke Scale; mRS, modified Rankin Scale; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglyceride; eGFR, estimated glomerular filtration rate; ALT, alanine aminotransferase; hs-CRP, high-sensitivity C-reactive protein; OR, odds ratio.

Table 3. Association of plasma albumin with mortality at 3 months and 1 year in analyses stratified for risk factors

Variable	Mortality at 3 months (%)	Adjusted HR of per 10 g/L decrease	Adjusted *P* for interaction*	Mortality at 1 year (%)	Adjusted HR of per 10 g/L decrease	Adjusted *P* for interaction*
Age, Years			0.35			0.35
<70y	82/10020(0.8)	1.61(0.93-2.78)		185/10020(1.9)	1.75(1.23-2.49)	
⩾70y	113/3598(3.14)	1.87(1.16-3.04)		245/3598(6.8)	1.33(0.96-1.84)	
Sex			0.72			0.65
Men	115/9276(1.2)	1.75(1.11-2.77)		270/9276(2.9)	1.50(1.11-2.02)	
Women	80/4342(1.8)	2.00(1.12-3.56)		160/4342(3.7)	1.56(1.03-2.35)	
BMI			0.48			0.19
<18.5 kg/m^2	16/295(5.4)	2.43(0.30-19.55)		27/295(9.2)	5.23(1.18-23.22)	
⩾18.5 kg/m^2	179/13323(1.3)	1.09(0.99-1.21)		403/13323(3.0)	1.49(1.16-1.91)	
TOAST Types			0.80			0.21
Large-artery atherosclerosis	62/3441(1.8)	1.91(1.01-3.61)		135/3441(3.9)	1.43(0.91-2.24)	
Cardioembolism	25/824(3.0)	2.38(0.77-7.41)		57/824(6.9)	1.53(0.72-3.26)	
Small-vessel occlusion	9/2836(0.3)	0.96(0.18-5.19)		32/2836(1.1)	1.02(0.42-2.49)	
Other determined etiology	3/173(1.7)	-		11/173(6.4)	0.54(0.09-3.36)	
Undetermined etiology	96/6344(1.5)	1.78(1.07-2.96)		195/6344(3.1)	1.70(1.20-2.41)	
NIHSS score on admission			0.40			0.11
≤3	57/7495(0.8)	1.64(0.85-3.16)		131/7495(1.8)	1.26(0.82-1.93)	
>3	138/6123(2.3)	1.89(1.24-2.88)		299/6123(4.9)	1.64(1.23-2.19)	

Variable	Mortality at 3 months (%)	Adjusted HR of per 10 g/L decrease	Adjusted *P* for interaction*	Mortality at 1 year (%)	Adjusted HR of per 10 g/L decrease	Adjusted *P* for interaction*
NIHSS score on admission			0.02			0.18
≤10	116/12630(0.92)	2.45(1.56-3.85)		296/12630(2.34)	1.60(1.20-2.13)	
>10	79/988(8.00)	1.03(0.59-1.78)		134/988(13.56)	1.15(0.75-1.75)	
eGFR			0.34			0.87
<60 mL/min/1.73 m^2	24/718(3.34)	0.98(0.30-3.20)		60/718(8.36)	1.33(0.72-2.45)	
⩾60 mL/min/1.73 m^2	119/8896(1.34)	1.94(1.21-3.10)		248/8896(2.79)	1.46(1.05-2.02)	
eGFR			0.37			0.93
<90 mL/min/1.73 m^2	92/3978(2.31)	1.82(1.10-3.02)		206/3978(5.18)	1.53(1.09-2.15)	
⩾90 mL/min/1.73 m^2	51/5636(0.90)	1.62(0.76-3.44)		102/5636(1.81)	1.66(0.98-2.83)	

*Adjustment model: age, sex, BMI, medical history (hypertension, DM, stroke or TIA, coronary heart disease and atrial fibrillation/fullter), index event, TOAST types, pre-stroke mRS 0~2, NIHSS scores on admission, intracranial arterial stenosis, extracranial arterial stenosis, intravenous thrombolysis, inpatient medication (antihypertensive agents, anticoagulant agents), serum TG, TC, LDL, HDL, ALT, eGFR, and hs-CRP.

BMI, body mass index; TOAST, the Trial of Org 10172 in Acute Stroke Treatment; NIHSS, National Institute of Health Stroke Scale; mRS, modified Rankin Scale; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglyceride; eGFR, estimated glomerular filtration rate; ALT, alanine aminotransferase; hs-CRP, high-sensitivity C-reactive protein; HR, hazard ratio.

Table 4. Serum albumin levels in different TOAST types

Variable	Large-artery atherosclerosis	Cardioembolism	Small-vessel occlusion	Other determined etiology	Undetermined etiology	*P* for trend
	n= 3441	n= 824	n= 2836	n=173	n=6344	
Serum albumin, g/L, mean (SD)	40.3±2.0	39.3±3.8	41.0±3.9	40.2±4.9	40.6±4.1	<0.0001

TOAST, the Trial of Org 10172 in Acute Stroke Treatment.

Table 5. The association of serum albumin with outcomes (poor functional outcome and mortality) in 1 year : HR/OR（95%CI）

Outcomes	N of events, %	Every 1 g/L decrease after adjustment*
mRS 3-6 at 1 year	1785(13.1)	1.03(1.02-1.05)
Mortality in 1 year	430(3.2)	1.04(1.02-1.07)

*Adjustment model: age, sex, BMI, medical history (hypertension, DM, stroke or TIA, coronary heart disease and atrial fibrillation/fullter), index event, TOAST types, pre-stroke mRS 0~2, NIHSS scores on admission, intracranial arterial stenosis, extracranial arterial stenosis, intravenous thrombolysis, inpatient medication (antihypertensive agents, anticoagulant agents), serum TG, TC, LDL, HDL, ALT, eGFR, and hs-CRP.

mRS, modified Rankin Scale; HR, hazard ratio; OR, odds ratio.

Table 6. Summary of the studies exploring an association between serum albumin and poor functional outcome or mortality

Author, year	Country	N0. of subjects	Participants	Age, years	Men,%	Follow-up time	NOS score	Albumin comparison	Study outcome(no.)	Adjustments	Effect estimate (95% CI)	Unified effect estimate (95% CI)
Gariballa SE *et al*[5] 1998	UK	225	Acute ischemic stroke	77.6±9.4	96(42.7)	3 months	9	Per +1 g/L	Mortality	Age, sex, mRS, previous illnesses, drugs, smoking	HR:0.91(0.84-0.99)	HR:1.03(1.01-1.19)
Dziedzic T *et al*[6], 2004	Poland	759	Acute ischemic stroke	68.3±12	372(49.0)	3 months	9	Per +1g/L	Poor outcome (mRS 4~6)	Age, sex, atrial fibrillation, ischemic heart disease, smoking, SSS score on admission, infarct size, TC	OR:0.96(0.93-0.99)	OR:1.04(1.01-1.08)
Carter AM *et al*[2],2007	UK	545	Acute ischemic stroke	-	274(50.3)	7.4 years(median)	9	>43 g/L vs <38 g/L	Mortality	Age, stroke subtype, previous stroke/TIA, atrial fibrillation, creatinine, haemoglobin, fibrinogen, FVIII, FXIIIA, β-TG, vWF, tPA	HR:0.65(0.44-0.96)	HR:1.09(1.01-1.20)
Idicula TT *et al*[4], 2009	Norway	444	Acute ischemic stroke	70.3±14.4	250(56.3)	2 years	8	Per +1g/L	Mortality	Age, sex and NIHSS score on admission	OR:0.88(0.83-0.93)	OR:1.14(1.08-1.20)
Alcázar Lázaro V *et al*[1], 2013	Spain	260	Acute ischemic stroke	-	127 (48.8)	5 years	9	Per -1 g/dL	Mortality	Age, BMI, cardiopathy, atrial fibrillation, urea, calcemia, total proteins, cholesterol, glycemia, embolic	OR:2.00(1.12-3)	OR:1.07(1.01-1.12)

Author, year	Country	N0. of subjects	Participants	Age, years	Men,%	Follow-up time	NOS score	Albumin comparison	Study outcome(no.)	Adjustments	Effect estimate (95% CI)	Unified effect estimate (95% CI)
										mechanism, coma, DBP, Canadian scale score on admission		
Babu MS *et al*[8], 2013	India	560	Acute ischemic stroke	-	401(71.6)	3 months	9	Per -1 g/dL	Poor outcome (mRS 4~6)	Age, sex, smoking, diabetes, hypertension, alcoholism, TC, HDL-C, LDL-C and TG	OR:1.972(1.103- 4.001)	OR:1.07(1.01-1.15)
Zhou HY *et al, 2020*	China	13618	Acute ischemic stroke or transient ischemic attack	62.17±11.26	9276(68.12)	1 year	9	Per -1g/L	Poor outcome (mRS 3~6)	Age, sex, BMI, medical history (hypertension, diabetes mellitus, stroke or TIA, coronary heart disease and atrial fibrillation/flutter), diagnosis type, TOAST type, NIHSS score on admission, Pre-stroke mRS 0~2 on admission, intracranial arterial stenosis, extracranial arterial stenosis, intravenous thrombolysis, inpatient medication (antihypertensive agents, anticoagulant agents), TG, TC, LDL, HDL, ALT, eGFR, hs-CRP	OR:1.03(1.02-1.05)	OR:1.03(1.02-1.05)
									Mortality		HR:1.04(1.02-1.07)	HR:1.04(1.02-1.07)

BMI, body mass index; TOAST, the Trial of Org 10172 in Acute Stroke Treatment; NIHSS, National Institute of Health Stroke Scale; mRS, modified Rankin Scale; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglyceride; eGFR, estimated glomerular filtration rate; ALT, alanine aminotransferase; hs-CRP, high-sensitivity C-reactive protein; DBP, diastolic blood pressure; vWF, von Willebrand factor; tPA, tissue-type plasminogen activator; OR, odds ratio; HR, hazard ratio; NOS, the Newcastle-Ottawa Scale.

Table 7. The Newcastle-Ottawa Quality Scale (NOS) for prospective studies

	Selection				Comparability	Outcome			Total
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome not present at baseline	Adjustments i) age ii) additional factors	Assessment of outcome	Length of follow-up	Adequate follow-up	
Gariballa SE *et al*[5]	✸	✸	✸	✸	✸✸	✸	✸	✸	9
Dziedzic T *et al*[6]	✸	✸	✸	✸	✸✸	✸	✸	✸	9
Carter AM *et al*[2]	✸	✸	✸	✸	✸✸	✸	✸	✸	9
Idicula TT *et al*[4]	✸	✸	✸	✸	✸✸	✸		✸	8
Alcázar Lázaro V *et al*[1]	✸	✸	✸	✸	✸✸	✸	✸	✸	9
Babu MS *et al*[8]	✸	✸	✸	✸	✸✸	✸	✸	✸	9

Table 8. PRISMA Checklist

PRISMA Checklist	#	Checklist item	Reported on page #
TITLE			
title	1	Identify the report as a systematic review, meta-analysis, or both.	Because the meta-analysis was added after the original analysis, and the title had a word limit, it was not reflected in the title.
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page 6 Paragraph 3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 3 Paragraph 2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 6 Paragraph 3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	None

Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 6 Paragraph 3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 6 Paragraph 3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Page 6 Paragraph 3
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 6 Paragraph 3
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 6 Paragraph 3
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 6 Paragraph 3
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Online supplementary Page 3 Paragraph 1
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Page 6 Paragraph 3
Synthesis of results	14	Describe the methods of handling data and combining results of	Online supplementary Page 3

		studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.	Paragraph 1
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Online supplementary Page 3 Paragraph 1
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Online supplementary Page 3 Paragraph 1
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Online supplementary figure 2
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations	Online supplementary table 6
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Online supplementary table 7
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Online supplementary table 8 figure 4
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	figure 4
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	figure 4 Page 10 Paragraph 1

			Online supplementary figure 4
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	None.
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Page 10 Paragraph 2
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Page 14 Paragraph 1
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 14 Paragraph 2
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Complete draft Page 14 Paragraph 5

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