

A systematic review and meta-analysis of serum cystatin C levels and acute ischemic stroke outcomes

Chenguang Hao^{1,A,D–F}, Shibao Chen^{2,B–C}

¹ The First Affiliated Hospital of Xinjiang Medical University, Urumqi, China

² Bayingolin Mongolian Autonomous Prefecture People's Hospital, Korla, China

A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

Advances in Clinical and Experimental Medicine, ISSN 1899–5276 (print), ISSN 2451–2680 (online)

Adv Clin Exp Med. 2025;34(2):153–163

Address for correspondence

Chenguang Hao

E-mail: chenguang1232022@163.com

Funding sources

None declared

Conflict of interest

None declared

Acknowledgements

We would like to thank Guosen Bu who provided advice when there were conflicts in the literature search.

Received on September 11, 2023

Reviewed on October 31, 2023

Accepted on February 20, 2024

Published online on March 21, 2024

Abstract

Acute ischemic stroke (AIS) has a high rate of death and causes long-term disability, leading to a global economic burden annually. Therefore, discovering biomarkers to improve AIS patient prognosis is critical. Previous studies reported an association between serum cystatin C (CysC) levels and outcomes in AIS patients, but the results remain controversial. This systematic review and meta-analysis aimed to explore the relationship between serum CysC and AIS patient outcomes using currently available studies. The literature search included PubMed, Embase, Web of Science, Cochrane Library, China National Knowledge Infrastructure (CNKI), VIP, and Wan Fang databases. Outcomes included poor functional recovery, cognitive dysfunction and death. Weighted mean difference (WMD) with 95% confidence interval (95% CI) was used as an effect index for measurement data. Results demonstrated that serum CysC was significantly higher in AIS patients with poor functional recovery (WMD = 0.18, 95% CI: 0.08–0.28), cognitive dysfunction (WMD = 0.16, 95% CI: 0.09–0.23) and death (WMD = 0.32, 95% CI: 0.02–0.62) than in the control groups when follow-up time was <1 month. These findings show that high serum CysC levels were associated with poor AIS patient outcomes. Further studies are needed to examine whether reducing serum CysC can prevent poor outcomes in AIS patients.

Key words: risk factors, biomarkers, cognitive dysfunction, cystatin C, ischemic stroke

Cite as

Hao C, Chen S. A systematic review and meta-analysis of serum cystatin C levels and acute ischemic stroke outcomes. *Adv Clin Exp Med.* 2025;34(2):153–163. doi:10.17219/acem/184641

DOI

10.17219/acem/184641

Copyright

Copyright by Author(s)

This is an article distributed under the terms of the Creative Commons Attribution 3.0 Unported (CC BY 3.0) (<https://creativecommons.org/licenses/by/3.0/>)

Introduction

Stroke has one of the highest global morbidity rates, with ischemic stroke accounting for approx. 87% of such events.¹ Acute ischemic stroke (AIS) refers to disorders of the cerebral circulation which cause irreversible damage to local brain tissues, leading to brain tissue ischemia and hypoxic necrosis in the acute stage.² Acute ischemic stroke has a high rate of death and causes long-term disability, resulting in a considerable annual economic burden worldwide.³

Acute ischemic stroke is caused by focal cerebral hypoperfusion, mainly from atherosclerotic diseases.² During a transient ischemic attack, arterial flow to brain tissue is temporarily interrupted, leading to focal neurologic symptoms (such as hemiparesis), but spontaneous flow recovery can alleviate symptoms without permanent tissue damage.² However, if arterial flow does not recover promptly, ischemia may develop into irreversible infarction, and patients may experience an AIS.²

Several neural substrates are thought to be involved in AIS, such as kynurenine, methylxanthine and N-methyl-D-aspartate,^{4–6} and have been shown to be associated with cognitive functions, motor skills and emotions.^{7–13} Post-stroke cognitive dysfunction is a common symptom affecting 20–80% of patients and impacting neurological function recovery.¹⁴ Depression is a common emotional syndrome after a stroke that substantially reduces patients' quality of life and occurs in approx. 30% of cases.¹⁵ Quantitative analyses of electroencephalogram data have identified the psychophysiological correlates of cognition. However, current international guidelines do not endorse the use of electroencephalogram biomarkers in neuropsychiatric disorders and depression.^{16,17} To improve the prognosis of AIS patients, it is necessary to identify other methods, such as simple and economical biochemical detection indicators, that may have additional clinical application value.

Serum cystatin C (CysC) is a member of the endogenous cysteine protease inhibitor family that can inhibit the activity of endogenous protein cysteine¹⁸; it is released from all nucleated cells at a constant rate, and can freely pass through the glomerular filtration membrane due to its low molecular weight.^{18,19} Previous studies demonstrated that CysC was an effective biomarker for assessing kidney function.¹⁹ Kidney disease is a crucial risk factor for cerebrovascular diseases, and the proposed underlying mechanisms for this association include cerebral hypoperfusion.²⁰ Recent studies found an association between CysC and cardiovascular diseases and showed its involvement in the pathophysiology of atherosclerosis in AIS patients.^{21,22}

Serum CysC levels were significantly elevated in patients with AIS.²³ Zeng et al. found it to be an independent prediction biomarker for ischemic stroke,²⁴ and a meta-analysis by Wang et al. reported an association between high serum CysC levels and increased ischemic stroke risk.²⁵ However, the correlation between CysC and AIS patient outcomes

also deserves attention, though the specific mechanisms by which CysC affects AIS patient outcomes remain unclear.

Cystatin C is an endogenous cathepsin inhibitor that plays a central role in regulating vascular wall proteases and antiproteases,²⁶ and unbalanced expression of CysC and cysteine cathepsin may lead to atherosclerosis.²⁶ In addition, increased serum CysC levels may indicate renal dysfunction in AIS patients,²⁷ and those with chronic renal failure generally experience oxidative stress and systemic inflammation, which accelerates the progression of atherosclerosis.²⁷

Cystatin C participates in inflammatory reactions and injures nervous system cells, creating a vicious cycle.²⁸ Existing studies show that CysC plays a role in neuronal damage and dysfunction, and may be related to clinical manifestations of cognitive impairment in neurodegenerative disorders.^{29,30} Meanwhile, other studies found that CysC can inhibit cerebral amyloid protein aggregation and potentially prevent cognitive dysfunction in neurodegenerative disorders.^{31,32} Previous studies reported an association between CysC and AIS patient outcomes, but the results are inconsistent.^{29,33–35} Zeng et al. found that higher serum CysC levels were associated with a higher risk of cognitive dysfunction,³⁶ whereas Guo et al. reported a protective effect of increased CysC levels in cognitive dysfunction.³³ The reason for this discrepancy may be the difference in serum CysC levels among the populations included in their studies (1.07 compared to 0.77).^{33,36}

Liu et al. found that a higher CysC level was related to an increased risk of recurrent stroke in AIS patients.³⁴ Dong et al. also found that the risk of recurrence was elevated with increasing serum CysC in AIS patients.³⁷ However, Zhu et al. found no association between CysC level and recurrence in AIS patients.³⁵ Such a discrepancy may be due to the difference in follow-up time of their studies (1 year compared to 2 years).^{34,35,37}

A meta-analysis is a powerful tool that combines the results of 2 or more separate studies to demonstrate good evidence strength and contribute to healthcare decision-making.^{38,39} Considering the controversial results in previously reported studies, we aimed to conduct a systematic review and meta-analysis to comprehensively explore the association between CysC level and AIS patient outcomes to guide unfavorable outcome management in AIS patients.

Objectives

The study analyzed the association between CysC levels and outcomes in AIS patients.

Methods

The meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement (PRISMA) guidelines.⁴⁰

Literature search

The literature search included 4 English-language (PubMed, Web of Science, Cochrane Library, and Embase) and 3 Chinese databases (VIP, China National Knowledge Infrastructure (CNKI) and Wan Fang) from inception to August 21, 2023. Supplementary File 1 shows the search terms. The literature search was conducted by 2 independent researchers (CGH and SBC), and the 3rd person (Guosen Bu) provided consultation if conflicts arose.

Study selection

The inclusion criteria were 1) patients: patients with AIS, 2) reporting: serum CysC levels (at baseline); 3) outcomes: functional recovery, cognitive dysfunction, death, hemorrhagic transformation, vascular events, depression, and recurrence; 4) cohort studies or case-control studies; and 5) language: published in Chinese or English. Studies meeting 1 of the following criteria were excluded: 1) duplicated publication; 2) animal studies; 3) incomplete or inaccessible data; 4) not matching the topic; and 5) reviews or meta-analyses, conference abstracts, case reports, and letters.

Functional recovery was evaluated using the modified Rankin Scale (mRS)⁴¹ and the National Institute of Health Stroke Scale (NIHSS).⁴² According to the mRS, patients were divided into good recovery (mRS ≤ 2 points) and poor recovery (mRS > 2 points) groups.⁴¹ Based on the NIHSS, patients were divided into basic recovery (91–100% decrease in NIHSS score), significant improvement (46–90% decrease in NIHSS score), improvement (18–45% decrease in NIHSS score), and ineffective/deterioration ($\leq 17\%$ decrease in NIHSS score) groups.⁴²

The Montreal Cognitive Assessment (MoCA) evaluated cognitive function from a total score of 30 points, with < 26 points defined as cognitive dysfunction.²⁹

Data extraction and quality assessment

Two researchers (CGH and SBC) independently conducted data extraction, including the study authors, publication year, country, study design, patients, treatments, groups, sample size, gender, age, body mass index (BMI), comorbidities (hypertension, diabetes mellitus and hyperlipidemia), smoking, CysC levels, and follow-up time.

The Newcastle–Ottawa Scale (NOS) was used to assess the quality of cohort studies and case-control studies⁴³ on a 9-point scale, with 0–3 points indicating poor quality, 4–6 points fair quality and 7–9 points good quality.⁴³

Statistical analyses

Weighted mean difference (WMD) acted as an effect index for measurement data, with effect size expressed as 95% confidence intervals (95% CIs). The choice between using a fixed-effect or random-effect meta-analysis

was performed a priori, with a random-effect model selected to analyze the association between CysC levels and functional recovery assessed using mRS, functional recovery assessed using NIHSS, cognitive dysfunction, and death. Heterogeneity was assessed for each outcome using Cochrane I² statistics, with I² ranging 0–100%, and divided into $< 50\%$ (low heterogeneity) and $\geq 50\%$ (high heterogeneity). Subgroup analysis was performed based on follow-up time to explore the source of heterogeneity for outcomes (functional recovery assessed using mRS) with high heterogeneity. The robustness of the pooled results for each outcome was assessed using sensitivity analysis by excluding each study independently. Publication bias was assessed using Begg's test when the outcome included 10 or more studies.⁴⁴ Funnel plots were provided for each outcome (functional recovery assessed using mRS, functional recovery assessed using NIHSS, cognitive dysfunction, and death). All statistical analysis employed Stata v. 15.1 software (StataCorp, College Station, USA), with $p < 0.05$ regarded as statistically significant.

Results

Selection and characteristics of studies

There were 535 studies identified from English-language databases and 410 from Chinese databases, with 232 duplicates excluded and 653 excluded due to being reviews or meta-analyses ($n = 38$), conference abstracts ($n = 47$), case reports ($n = 4$), letters ($n = 4$), animal experiments ($n = 34$), articles not in English or Chinese ($n = 2$), or the topic not meeting the requirements ($n = 524$). After screening full texts, 36 studies were excluded for not having access to the full text ($n = 2$) and the topic not meeting the requirements ($n = 34$). Finally, 24 eligible studies were included (Fig. 1). Table 1 describes the characteristics of these studies, of which 23 were cohort studies^{15,26,29,33,34,42,45–61} and 1 was a case-control study.³⁶ A total of 7,567 AIS patients were assessed.

Risk of bias assessment

The NOS evaluated the risk of bias by evaluating 3 methodological domains, including selection, comparability and outcomes (for cohort studies)/exposure (for case-control studies) assessment. In this meta-analysis, 1 study was assessed as having poor quality, 17 fair quality and 6 good quality (Supplementary Table 1).

Meta-analysis of the association between CysC levels and AIS patient outcomes

Functional recovery assessed by mRS showed no significant difference in CysC levels between the poor and

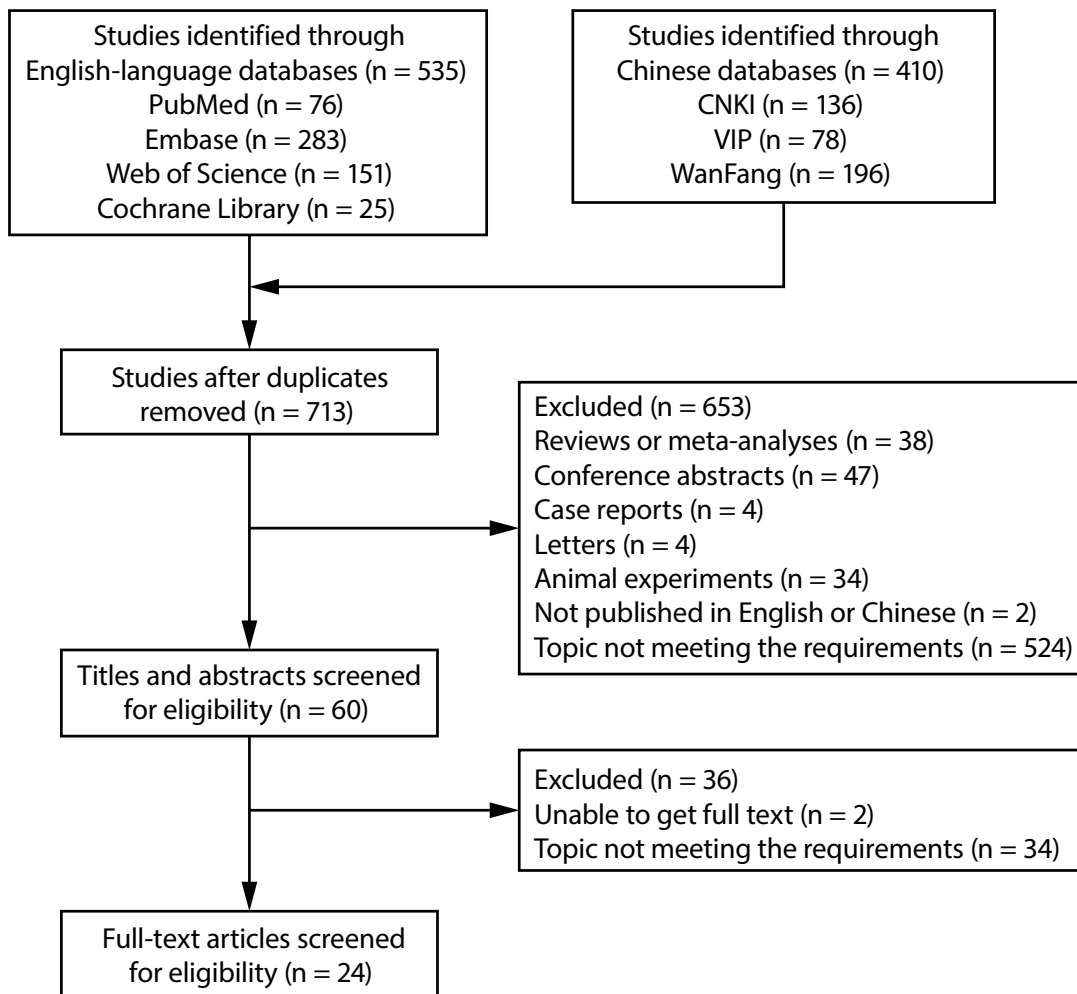


Fig. 1. Flowchart of study selection

good functional recovery groups (WMD = 0.36, 95% CI: -0.18–0.91, $I^2 = 99.9\%$) (Fig. 2A). Follow-up time was identified as the source of heterogeneity (follow-up time <1 month: WMD = 0.18, 95% CI: 0.08–0.28; follow-up time \geq 1 month: WMD = 0.43, 95% CI: -0.29–1.14). For functional recovery assessed with the NIHSS, compared to the basic recovery group, the CysC levels were higher in the significant improvement group (WMD = 0.15, 95% CI: 0.06–0.24), improvement group (WMD = 0.27, 95% CI: 0.16–0.37) and ineffective/deterioration group (WMD = 0.37, 95% CI: 0.27–0.47) (Fig. 2B). Furthermore, CysC was higher in AIS patients with cognitive dysfunction (WMD = 0.16, 95% CI: 0.09–0.23) (Fig. 2C). In addition, high CysC levels were found in the death group (WMD = 0.32, 95% CI: 0.02–0.62) (Fig. 2D). The results of the meta-analysis are summarized in Table 2.

Systematic review of the association between CysC levels and AIS patient outcomes

Dong et al. divided the CysC level by quartile and found no statistical difference between the CysC and functional recovery in the 4 groups.⁴⁷ Regarding cognitive

dysfunction, Guo et al. reported no association between CysC and cognitive dysfunction,³³ while Li et al. found that high CysC was a risk factor for cognitive dysfunction.⁵⁰ We also observed hemorrhagic transformation, vascular events, depression, and recurrence, with 1 study showing that AIS patients with hemorrhagic transformation had higher CysC levels than those without hemorrhagic transformation (1.28 ± 0.27 mg/L compared to 1.13 ± 0.27 mg/L, $p < 0.01$).⁵⁶ Xing et al. reported high CysC levels as an independent risk factor for depression in AIS patients.¹⁵ For stroke recurrence, Ding et al. found that CysC was higher in the recurrence group than in the non-recurrence group.⁴⁶ Meanwhile, Liu et al. reported no association between CysC and recurrence but found a higher risk of vascular events in patients with increased CysC.³⁴

Sensitivity analysis and publication bias

The influence of a single study on the effect estimate was assessed using sensitivity analysis by removing each study in turn. The results showed no significant influence of any individual study on the results of the meta-analysis. Begg's test was used to evaluate the publication bias for functional recovery assessed with the mRS, showing no

Table 1. Characteristics of included studies

Author, year	Study design	Patients	Treatments	Groups	Sample size, n	Male, n	Age [years]	BMI [kg/m ²]	Hyper-tension, n	Diabetes mellitus, n	Hyper-lipidemia, n	Smoking, n	Cystatin C [mg/L]	Follow-up	Quality
Xing et al., 2020 ¹⁵	cohort	AIS	N/A	non-PSD	64	49	61.56 ± 8.30	N/A	39	22	28	21	0.662 ± 0.110	1 month	6
				mild PSD	19	4	65.89 ± 10.36	N/A	6	4	6	3	0.717 ± 0.075		
				moderate-severe PSD	18	10	64.67 ± 11.20	N/A	4	7	7	8	0.928 ± 0.084		
				non-CMBs	74	43	59.43 ± 10.80	N/A	30	12	20	11	0.79 ± 0.23		
Zuo et al., 2020 ²⁶	cohort	AIS	endovascular therapy	mRS > 2	66	36	66.9 ± 13.0	N/A	41	10	N/A	18	1.08 ± 0.22	3 months	6
Yan et al., 2022 ²⁹	cohort	AIS	without endovascular therapy or intravenous thrombolysis	mRS ≤ 2	59	40	59.8 ± 16.4	N/A	38	9	N/A	24	0.95 ± 0.24	3 months	7
				with PSCI	164	117	62.31 ± 13.78	N/A	102	41	N/A	59	1.2 ± 0.39		
Guo et al., 2019 ³³	cohort	AIS	receiving immediate blood pressure reduction or use of hypoglycemic treatment	without PSCI	117	77	57.74 ± 12.2	N/A	73	43	N/A	41	1 ± 0.38	3 months	6
				high CysC	582	405	60.5 ± 10.4	24.9 ± 3.1	448	97	42	220	0.77 (0.65–0.91)		
Liu et al., 2021 ³⁴	cohort	AIS	receiving antihypertensive medications or lipid-lowering medications	low CysC	1528	1022	64.8 ± 11.0	24.9 ± 3.2*	1246	260	96	571	≥ 0.78	24 months	6
				VCI	1946	1196	59.6 ± 10.1	24.9 ± 3.1**	1490	349	149	706	< 0.78		
Zeng et al., 2019 ³⁶	case-control	AIS	N/A	CIND	71	45	76.28 ± 15.16	N/A	61	30	N/A	20	1.07 ± 0.28	N/A	5
Zhang and Wang, 2013 ⁴²	cohort	AIS	N/A	–	81	61	71.40 ± 11.32	N/A	61	38	N/A	29	0.97 ± 0.27	N/A	3
				–	112	71	66.96 ± 12.90	N/A	N/A	N/A	N/A	N/A	1.07 ± 0.32		
Chen et al., 2017 ⁴⁵	cohort	AIS	antihypertensive drugs, antiplatelet drugs, anticoagulants, and statins	mild stroke	120	37	64.3 ± 9.15	N/A	95	46	77	41	1.21 ± 0.23	2 weeks	6
				moderate and severe stroke	68	58	65.8 ± 9.43	N/A	60	38	41	21	1.36 ± 0.29		
Ding et al., 2020 ⁴⁶	cohort	AIS	anti-platelet aggregation, improve cerebral blood supply, nutritional brain cells and other symptomatic treatment	recurrence	38	21	61.25 ± 8.12	27.12 ± 3.08	25	19	35	34	3.95 ± 1.07	12 months	8
				no recurrence	153	82	59.98 ± 8.04	26.58 ± 2.94	84	88	162	167	2.78 ± 0.86		
Dong and Nao, 2018 ⁴⁷	cohort	AIS	without intravenous thrombolysis	–	109	69	63.25 ± 12.99	N/A	80	34	N/A	48	1.33 ± 0.52	3 months	7
Hu et al., 2020 ⁴⁸	cohort	AIS	N/A	–	95	44	75.0	N/A	N/A	N/A	N/A	N/A	1.25 ± 0.45	10 days	5
Li et al., 2019 ⁴⁹	cohort	AIS	without intravenous thrombolysis or arterial thrombectomy	–	235	126	63.9 ± 14.8	N/A	170	98	175	135	1.24 ± 0.42	3 months	6

Table 1. Characteristics of included studies – cont.

Author, year	Study design	Patients	Treatments	Groups	Sample size, n	Male, n	Age [years]	BMI [kg/m ²]	Hyper-tension, n	Diabetes mellitus, n	Hyper-lipidemia, n	Smoking, n	Cystatin C [mg/L]	Follow-up	Quality
Li and Yuan, 2019 ⁵⁰	cohort	AIS	N/A	–	297	168	68.24 ± 6.33	N/A	64	96	N/A	N/A	1.49 ± 0.31	10 days	5
Liu et al., 2018 ⁵¹	cohort	AIS	N/A	mRS > 2	150	96	60.5 (54.0, 71.0)	N/A	37	50	84	78	0.9 (0.82, 1.00)	3 months	8
				mRS ≤ 2	114	62	74.0 (60.0, 80.3)	N/A	30	36	56	49	1.03 (0.92, 1.10)		
Luan et al., 2019 ⁵²	cohort	AIS	N/A	–	40	23	63.52 ± 2.04	N/A	N/A	N/A	N/A	N/A	1.24 ± 0.27	3 months	5
Lv, 2019 ⁵³	cohort	AIS	intravenous thrombolysis	–	60	35	65.78 ± 3.33	N/A	N/A	N/A	N/A	N/A	1.46 ± 0.31	2 weeks	4
Sun et al., 2021 ⁵⁴	cohort	AIS	intravenous thrombolysis	mRS > 2	189	99	70.50 ± 14.76	25.05 ± 2.12	90	78	N/A	55	1.84 ± 0.20	1 month	7
				mRS ≤ 2	255	156	68.95 ± 14.90	24.80 ± 2.05	135	54	N/A	57	0.27 ± 0.07		
Wang and Tan, 2018 ⁵⁵	cohort	AIS	N/A	with PSCI	43	25	64.37 ± 6.24	N/A	32	21	N/A	17	1.02 ± 0.39	2 weeks	5
				without PSCI	60	37	61.82 ± 5.95	N/A	46	17	N/A	25	0.82 ± 0.22		
Wang, 2017 ⁵⁶	cohort	AIS	without anticoagulants or thrombolysis and anticoagulation	hemorrhagic transformation	65	31	62.09 ± 10.49	N/A	30	25	N/A	27	1.28 ± 0.27	2 weeks	5
				non-hemorrhagic transformation	127	63	58.54 ± 10.01	N/A	55	41	N/A	57	1.13 ± 0.27		
Wei and Wang, 2016 ⁵⁷	cohort	AIS	N/A	–	76	44	64.1 ± 11.9	N/A	N/A	N/A	N/A	N/A	1.06 ± 0.31	N/A	4
Wu et al., 2022 ⁵⁸	cohort	AIS	intravenous thrombolysis	–	67	45	57.93 ± 12.96	N/A	N/A	12	N/A	N/A	1.12 ± 0.17	3 weeks	5
Wang and Li, 2022 ⁵⁹	cohort	acute cerebral infarction	rt-PA intravenous thrombolysis	mRS > 2	33	20	63.03 ± 6.90	23.12 ± 2.41	18	N/A	N/A	9	1.16 ± 0.32	3 months	6
				mRS ≤ 2	67	37	61.30 ± 6.01	23.43 ± 2.10	47	N/A	N/A	26	0.88 ± 0.29		
Wang et al., 2023 ⁶⁰	cohort	acute cerebral infarction	N/A	–	100	73	64.18 ± 3.51	N/A	52	48	N/A	N/A	1.82 ± 0.15	3 months	5
Dong et al., 2023 ⁶¹	cohort	acute cerebral infarction	rt-PA intravenous thrombolysis	mRS > 2	45	26	64.24 ± 5.18	22.46 ± 2.02	18	15	7	13	1.16 ± 0.38	1 month	7
				mRS ≤ 2	60	36	61.55 ± 4.78	21.97 ± 1.95	21	18	9	10	0.79 ± 0.26		

Continuous variables were expressed as mean ± standard deviation (mean ± SD), or as median (interquartile range (IQR)); AIS – acute ischemic stroke; BMI – body mass index; END – early neurological deterioration; VC – vascular cognitive impairment; CIND – cognitive impairment no dementia; CysC – cystatin C; PSCI – post-stroke cognitive impairment; mRS – modified Rankin Scale; CMBs – cerebral microbleeds; rt-PA – recombinant tissue plasminogen activator; PSD – post stroke depression; N/A – not available.

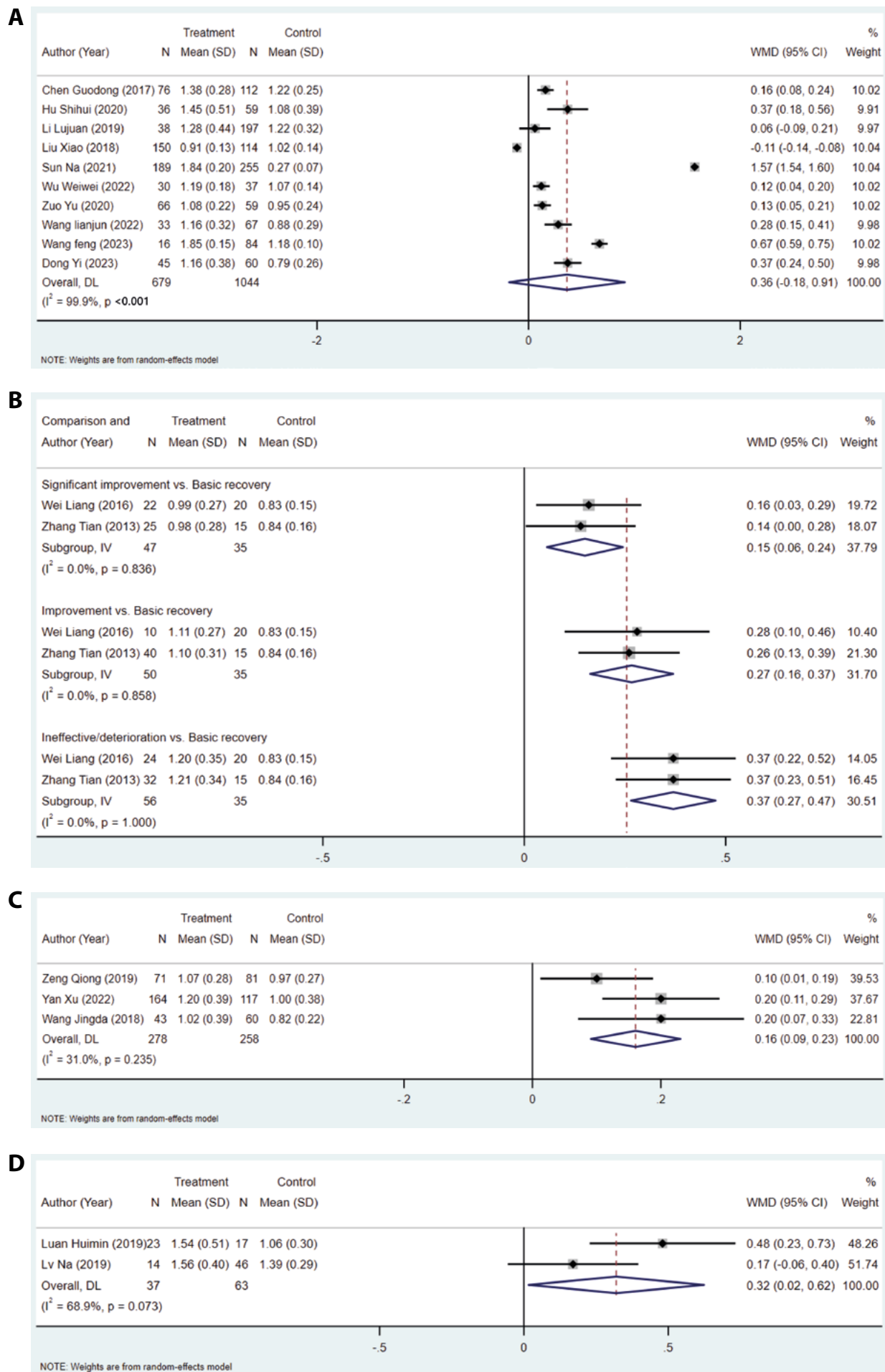


Fig. 2. Forest plots for the association between cystatin C (CysC) level and functional recovery assessed using the modified Rankin Scale (mRS) (A), function recovery assessed with the National Institute of Health Stroke Scale (NIHSS) (B), cognitive dysfunction (C), and death (D)

Table 2. Association between CysC level and outcomes of AIS patients

Outcomes		Number of studies	WMD (95% CI)	p-value	I ²
Function recovery assessed with mRS	sensitivity analysis	10	0.36 (−0.18, 0.91)	0.194	99.9
	publication bias		Z = 0.18	0.858	–
	follow-up, <1 month	3	0.18 (0.08, 0.28)	<0.001	63.5
	follow-up, ≥1 month	7	0.43 (−0.29, 1.14)	0.241	99.9
Function recovery assessed with NIHSS	significant improvement, sensitivity analysis	2	0.15 (0.06, 0.24)	0.002	0.0
	improvement, sensitivity analysis	2	0.27 (0.16, 0.37)	<0.001	0.0
	ineffective/deterioration, sensitivity analysis	2	0.37 (0.27, 0.47)	<0.001	0.0
Cognitive dysfunction, sensitivity analysis		3	0.16 (0.09, 0.23)	<0.001	31.0
Death, sensitivity analysis		2	0.32 (0.02, 0.62)	0.039	68.9

95% CI – 95% confidence interval; WMD – weighted mean difference; mRS – modified Rankin Scale; NIHSS – National Institute of Health Stroke Scale.

publication bias ($Z = 0.18$, $p = 0.858$) (Table 2). Also, funnel plots indicated no evidence of publication bias for functional recovery assessed using the mRS (Supplementary Fig. 1A), functional recovery assessed with the NIHSS (Supplementary Fig. 1B), cognitive dysfunction (Supplementary Fig. 1C), and death (Supplementary Fig. 1D).

Discussion

Acute ischemic stroke is a cause of long-term disability and has a high mortality rate, which leads to a significant annual economic burden globally.³ Previous studies reported controversial results on the association between CysC and AIS patient outcomes. Therefore, this systematic review and meta-analysis comprehensively explored the association between CysC and AIS outcomes based on currently available studies. Results showed that CysC level was higher in AIS patients with cognitive dysfunction, significant improvement of function recovery, improvement of function recovery and ineffective/deterioration of function recovery, and in patients who died. Although there was no significant difference between CysC levels and functional recovery assessed using mRS in the total population, subgroup analysis showed a significant difference during follow-up time <1 month. For the systematic review, we found that high CysC levels were associated with hemorrhagic transformation,⁵⁶ vascular events,³⁴ depression,¹⁵ and recurrence.⁴⁶ The overall results suggest that high CysC levels may be one of the risk factors for poor outcomes in AIS patients.

Cystatin C has been reported to influence endogenous neuroprotection and may be a candidate drug for treating stroke through lysosomal membrane integrity maintenance.⁶² However, some studies reported CysC as a risk factor for stroke.^{25,27} Compared to patients without stroke, CysC was higher in AIS patients, indicating that CysC may be an AIS risk prediction factor.²⁵ Cognitive dysfunction is a common symptom after stroke, and the incidence reaches up to 56.6% in China within 3 months after stroke,^{63,64} though current studies on the association

between CysC and cognitive dysfunction remain inconsistent.^{29,33,36,65} Nonetheless, our meta-analysis found higher CysC in AIS patients with cognitive dysfunction. Some pathways may explain the mechanisms by which CysC affects cognitive function after AIS. The stroke event may elevate serum CysC level, and a high CysC level is associated with dementia and cognitive dysfunction.^{29,36} Furthermore, there is an association between CysC and symptomatic common carotid artery stenosis, which is related to cognitive impairment in patients with or without stroke.^{21,66–68} Moreover, CysC is involved in the pathogenesis of cerebral amyloidosis, which may result in early cerebral hemorrhage.⁶⁹ Previous research indicated higher serum CysC in AIS patients complicated with cerebral microbleeds than in those without, highlighting CysC as a risk factor for cerebral microbleeds.⁷⁰ Cerebral microbleeds are closely associated with cognitive dysfunction, resulting in damage to memory, abstract thinking and visual, spatial and executive functions.⁷¹

Functional recovery is of substantial concern to patients. The 7-level mRS covers a range of functional outcomes, from no symptoms to death, and the categories are intuitive and easy for clinicians and patients to understand.⁴¹ Results of our meta-analysis showed that, although there was no association between CysC levels and functional recovery assessed using mRS in the total AIS population, a significant association was found with a follow-up time <1 month. There are no studies on serum CysC levels at different time points, and the mechanism behind this finding remains unclear. Further studies are needed to explore the relationship between serum CysC and functional recovery at different time points to help understand the mechanisms underlying these associations.

Cystatin C was higher in significant improvement, improvement and ineffective/deterioration groups than the basic cure group, and there are several explanations for this. Cystatin C participated in the inflammatory reaction, destroyed nerve cells and aggravated nervous system damage, which affected the recovery of patients with cerebral infarction.⁷² In addition, CysC was involved in blood vessel

wall remodeling and aggravated atherosclerosis, causing cerebral infarction.⁷³ These mechanisms are supported by our finding that high CysC levels were associated with vascular events.³⁴

Stroke is the 2nd leading cause of death and the primary reason for long-term disability worldwide.³ Our results showed that serum CysC was higher in the death group than in the survival group. Luan et al. and Li et al. reported that serum CysC was higher in the death group than in the AIS patient survival group.^{52,53} Serum CysC level may increase in AIS patients with disease aggravation,⁵³ as it may cause neuronal cell apoptosis and neuron loss, leading to delayed neuronal damage and resulting in death.⁵³

We included available studies on the relationship between CysC levels and AIS patient outcomes, and found consistent and meaningful results through the meta-analysis. Publication bias was not found, and sensitivity analyses showed stable overall effect sizes. To minimize factors that may affect the results and explore potential sources of heterogeneity, we applied subgroup analyses and found that follow-up time may be a source of heterogeneity. Furthermore, high CysC levels in AIS patients with cognitive dysfunction, unfavorable functional recovery and death suggest that it may be related to AIS patient outcomes. Our meta-analysis highlighted the importance of early monitoring and management of CysC and provided evidence for improving AIS patient outcomes. Future studies should explore whether decreasing serum CysC is a therapeutic target for preventing poor outcomes in AIS patients.

Limitations

Limitations of this meta-analysis include the small number of studies on some outcomes, which may affect the stability of the results. All included studies were conducted in China, meaning the results cannot be generalized to global populations. As such, the findings of this meta-analysis should be verified by studies in other countries. Cystatin C is a highly accurate measure of kidney decline, and since data on kidney function were not recorded in the included studies, we were unable to perform analysis based on renal function. In addition, patient age, AIS course and severity, and comorbidities may affect the prognosis, but current data are insufficient to support further analysis. As such, further meta-analyses with more studies are needed to explore the impact of these factors on the association between serum CysC and AIS patient outcomes.

Conclusions

The current systematic review and meta-analysis found that higher levels of serum CysC are associated with poor outcomes of patient with AIS. The results demonstrate that

higher serum CysC may be a risk factor for poor outcomes in patients with AIS, which provides a new direction for preventing such outcomes. However, more prospective studies are needed to confirm these findings and reduce study limitations.

Since AIS patient outcomes are affected by many factors, it is not clear whether CysC is an independent predictor. Additional research is needed to explore whether single or combined measurements of this biomarker, with or without other demographic, clinical and biochemical variables, can further increase early risk stratification and clinical decisions in this population. Close attention should also be paid to studies of CysC as a therapeutic target for preventing poor outcomes in patients with AIS. Further clinical studies are important for examining whether decreasing serum CysC can prevent or treat poor AIS patient outcomes.

Supplementary data

The Supplementary materials are available at <https://doi.org/10.5281/zenodo.10674816>. The package includes the following files:


Supplementary File 1. Search terms.

Supplementary Table 1 Risk of bias summary.

Supplementary Fig. 1. A. Funnel plot for publication bias regarding function recovery assessed with mRS; B. Funnel plot for publication bias regarding to function recovery assessed using NIHSS; C. Funnel plot for publication bias regarding cognitive dysfunction; D Funnel plot for publication bias regarding death.

ORCID iDs

Chenguang Hao  <https://orcid.org/0000-0002-3711-8729>

Shibao Chen  <https://orcid.org/0009-0003-9884-1333>

References

1. Saini V, Guada L, Yavagal DR. Global epidemiology of stroke and access to acute ischemic stroke interventions. *Neurology*. 2021;97 (20 Suppl 2). doi:10.1212/WNL.00000000000012781
2. Mendelson SJ, Prabhakaran S. Diagnosis and management of transient ischemic attack and acute ischemic stroke: A review. *JAMA*. 2021;325(11):1088. doi:10.1001/jama.2020.26867
3. Herpich F, Rincon F. Management of acute ischemic stroke. *Crit Care Med*. 2020;48(11):1654–1663. doi:10.1097/CCM.0000000000004597
4. Brouns R, Verkerk R, Aerts T, et al. The role of tryptophan catabolism along the kynurenine pathway in acute ischemic stroke. *Neurochem Res*. 2010;35(9):1315–1322. doi:10.1007/s11064-010-0187-2
5. Bath P, Bath F, Asplund K. Pentoxifylline, propentofylline and pentifylline for acute ischaemic stroke. *Cochrane Database Syst Rev*. 1996; 1996:CD000162. doi:10.1002/14651858.CD000162
6. Sperber PS, Gebert P, Broersen LHA, et al. Serum anti-NMDA-receptor antibodies and cognitive function after ischemic stroke (PROSCIS-B). *J Neurol*. 2022;269(10):5521–5530. doi:10.1007/s00415-022-11203-x
7. Tanaka M, Szabó Á, Vécsei L. Preclinical modeling in depression and anxiety: Current challenges and future research directions. *Adv Clin Exp Med*. 2023;32(5):505–509. doi:10.17219/acem/165944
8. Polyák H, Galla Z, Nánási N, et al. The tryptophan-kynurenine metabolic system is suppressed in cuprizone-induced model of demyelination simulating progressive multiple sclerosis. *Biomedicine*. 2023;11(3):945. doi:10.3390/biomedicine11030945

9. Baliellas DEM, Barros MP, Vardaris CV, et al. Propentofylline improves thiol-based antioxidant defenses and limits lipid peroxidation following gliotoxic injury in the rat brainstem. *Biomedicines*. 2023;11(6):1652. doi:10.3390/biomedicines11061652
10. Tanaka M, Diano M, Battaglia S. Editorial: Insights into structural and functional organization of the brain: Evidence from neuroimaging and non-invasive brain stimulation techniques. *Front Psychiatry*. 2023;14:1225755. doi:10.3389/fpsy.2023.1225755
11. Battaglia MR, Di Fazio C, Battaglia S. Activated tryptophan-kynurenine metabolic system in the human brain is associated with learned fear. *Front Mol Neurosci*. 2023;16:1217090. doi:10.3389/fnmol.2023.1217090
12. Battaglia S, Di Fazio C, Vicario CM, Avenanti A. Neuropharmacological modulation of N-methyl-D-aspartate, noradrenaline and endocannabinoid receptors in fear extinction learning: Synaptic transmission and plasticity. *Int J Mol Sci*. 2023;24(6):5926. doi:10.3390/ijms24065926
13. Tran KN, Nguyen NPK, Nguyen LTH, Shin HM, Yang JJ. Screening for neuroprotective and rapid antidepressant-like effects of 20 essential oils. *Biomedicines*. 2023;11(5):1248. doi:10.3390/biomedicines11051248
14. Sun JH, Tan L, Yu JT. Post-stroke cognitive impairment: Epidemiology, mechanisms and management. *Ann Transl Med*. 2014;2(8):80. doi:10.3978/j.issn.2305-5839.2014.08.05
15. Xing L, Li Y, Su D. Correction analysis of serum cystatin C and NIHSS, post-stroke depression in patients with first-ever acute cerebral infarction [in Chinese]. *Clinical Focus*. 2020;35(5):417–420. doi:10.3969/j.issn.1004-583x.2020.05.006
16. Di Gregorio F, La Porta F, Petrone V, et al. Accuracy of EEG biomarkers in the detection of clinical outcome in disorders of consciousness after severe acquired brain injury: Preliminary results of a pilot study using a machine learning approach. *Biomedicines*. 2022;10(8):1897. doi:10.3390/biomedicines10081897
17. Di Gregorio F, Battaglia S. Advances in EEG-based functional connectivity approaches to the study of the central nervous system in health and disease. *Adv Clin Exp Med*. 2023;32(6):607–612. doi:10.17219/acem/166476
18. Kim TJ, Kang MK, Jeong HG, et al. Cystatin C is a useful predictor of early neurological deterioration following ischaemic stroke in elderly patients with normal renal function. *Eur Stroke J*. 2017;2(1):23–30. doi:10.1177/2396987316677197
19. Ferguson TW, Komenda P, Tangri N. Cystatin C as a biomarker for estimating glomerular filtration rate. *Curr Opin Nephrol Hypertens*. 2015;24(3):295–300. doi:10.1097/MNH.0000000000000115
20. Kelly DM, Ademi Z, Doehner W, et al. Chronic kidney disease and cerebrovascular disease: Consensus and guidance from a KDIGO Controversies Conference. *Stroke*. 2021;52(7):e328–e346. doi:10.1161/STROKEAHA.120.029680
21. Ren J, Dong X, Nao J. Serum cystatin C is associated with carotid atherosclerosis in patients with acute ischemic stroke. *Neurol Sci*. 2020;41(10):2793–2800. doi:10.1007/s10072-020-04383-9
22. Zhang Y, Yang S, Chen J, et al. Associations of serum cystatin C and its change with new-onset cardiovascular disease in Chinese general population. *Nutr Metab Cardiovasc Dis*. 2022;32(8):1963–1971. doi:10.1016/j.numecd.2022.05.016
23. Huang GX, Ji XM, Ding YC, Huang HY. Association between serum cystatin C levels and the severity or potential risk factors of acute ischemic stroke. *Neurol Res*. 2016;38(6):518–523. doi:10.1080/01616412.2016.1187825
24. Zeng Q, Lin K, Yao M, Wei L. Significant correlation between cystatin C, cerebral infarction, and potential biomarker for increased risk of stroke. *Curr Neurovasc Res*. 2015;12(1):40–46. doi:10.2174/1567202612666150102150941
25. Wang Y, Li W, Yang J, et al. Association between cystatin C and the risk of ischemic stroke: A systematic review and meta-analysis. *J Mol Neurosci*. 2019;69(3):444–449. doi:10.1007/s12031-019-01373-1
26. Zuo Y, Gu Y, Zhu H. The correlation between cystatin C level and the effect of endovascular therapy on acute ischemic stroke patients [in Chinese]. *Stroke and Nervous Diseases*. 2020;27(6):738–742. doi:10.3969/j.issn.1007-0478.2020.06.008
27. Xiao D, Liu H, Zhang H, Luo Y. Impact of cystatin C levels on infarct size and hemorrhage volume in acute cerebral stroke. *J Neurol*. 2012;259(10):2053–2059. doi:10.1007/s00415-012-6453-2
28. Mathews PM, Levy E. Cystatin C in aging and in Alzheimer's disease. *Ageing Res Rev*. 2016;32:38–50. doi:10.1016/j.arr.2016.06.003
29. Yan X, Chen H, Shang X. Association between serum cystatin C level and post-stroke cognitive impairment in patients with acute mild ischemic stroke. *Brain Behav*. 2022;12(3):e2519. doi:10.1002/brb3.2519
30. Chen WW, Cheng X, Zhang X, et al. The expression features of serum cystatin C and homocysteine of Parkinson's disease with mild cognitive dysfunction. *Eur Rev Med Pharmacol Sci*. 2015;19(16):2957–2963. PMID:26367713.
31. Hu WD, Chen J, Mao CJ, et al. Elevated cystatin C levels are associated with cognitive impairment and progression of Parkinson disease. *Cogn Behav Neurol*. 2016;29(3):144–149. doi:10.1097/WNN.0000000000000100
32. Mi W, Pawlik M, Sastre M, et al. Cystatin C inhibits amyloid- β deposition in Alzheimer's disease mouse models. *Nat Genet*. 2007;39(12):1440–1442. doi:10.1038/ng.2007.29
33. Guo DX, Zhu ZB, Zhong CK, et al. Serum cystatin C levels are negatively correlated with post-stroke cognitive dysfunction. *Neural Regen Res*. 2020;15(5):922. doi:10.4103/1673-5374.268928
34. Liu H, Qian S, Zhong C, et al. Predictive value of cystatin C for stroke recurrence in patients with acute ischemic stroke. *Circ J*. 2021;85(2):213–219. doi:10.1253/circj.CJ-20-0771
35. Zhu Z, Zhong C, Xu T, et al. Prognostic significance of serum cystatin C in acute ischemic stroke patients according to lipid component levels. *Atherosclerosis*. 2018;274:146–151. doi:10.1016/j.atherosclerosis.2018.05.015
36. Zeng Q, Huang Z, Wei L, Fang J, Lin K. Correlations of serum cystatin C level and gene polymorphism with vascular cognitive impairment after acute cerebral infarction. *Neurol Sci*. 2019;40(5):1049–1054. doi:10.1007/s10072-019-03777-8
37. Dong X, Nao J. Cystatin C as an index of acute cerebral infarction recurrence: One-year follow-up study. *Int J Neurosci*. 2019;129(1):36–41. doi:10.1080/00207454.2018.1503180
38. Schünemann H, Oxman A, Vist G, et al; on behalf of the Cochrane Applicability and Recommendations Methods Group. Chapter 12: Interpreting results and drawing conclusions. In: Higgins JPT, Thomas J, Chandler J, et al., eds. *Cochrane Handbook for Systematic Reviews of Interventions*. 2nd ed. Chichester, UK: Wiley & Sons; 2019. doi:10.1002/9781119536604
39. Deeks J, Higgins J, Altman D; on behalf of the Cochrane Statistical Methods Group. Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins JPT, Thomas J, Chandler J, et al., eds. *Cochrane Handbook for Systematic Reviews of Interventions*. 2nd ed. Chichester, UK: Wiley & Sons; 2019. doi:10.1002/9781119536604
40. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: Elaboration and explanation. *BMJ*. 2015;349:g7647. doi:10.1136/bmj.g7647
41. Broderick JP, Adeoye O, Elm J. Evolution of the Modified Rankin Scale and its use in future stroke trials. *Stroke*. 2017;48(7):2007–2012. doi:10.1161/STROKEAHA.117.017866
42. Zhang T, Wang T. Correlation analysis of serum cystatin C with the incidence and short-term prognosis of acute cerebral infarction [in Chinese]. *Journal of Apoplexy and Nervous Diseases*. 2013;30(10):935–936. doi:10.19845/j.cnki.zfysjzbz
43. Wells G, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa, Canada: Ottawa Hospital Research Institute; 2021. https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed September 10, 2022.
44. Sterne JAC, Sutton AJ, Ioannidis JPA, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ*. 2011;343:d4002. doi:10.1136/bmj.d4002
45. Chen G, Xiao J, Liu B. Correlations of serum cystatin C level with severity of stroke and short-term outcome in patient with acute ischemic stroke [in Chinese]. *International Journal of Cerebrovascular Diseases*. 2017;25(11):996–1001. doi:10.3760/cma.j.issn.1673-4165.2017.11.006
46. Ding B, Hu C, Meng L. Analysis of the predictive value of serum cystatin C on the risk of stroke recurrence in patients with acute cerebral infarction within 1 year [in Chinese]. *Progress in Modern Biomedicine*. 2020;20(11):2174–2178. doi:10.13241/j.cnki.pmb.2020.11.038
47. Dong X, Nao J. Analysis of the correlation between serum cystatin C levels and acute ischemic infarction [in Chinese]. *Journal of Brain and Nervous Diseases*. 2018;26(1):13–16.

48. Hu S, Zhou J, Wang G. Changes of serum cystine-C and hypersensitive C-reactive protein levels in patients with acute cerebral infarction [in Chinese]. *Contemporary Medicine*. 2020;26(15):19–21. doi:10.3969/j.issn.1009-4393.2020.15.008
49. Li L, Sun L, Yang Y. Association between serum cystatin C levels and severity or prognosis of acute ischemic stroke [in Chinese]. *Chinese Journal of Neuroimmunology and Neurology*. 2019;26(5):331–333. doi:10.3969/j.issn.1006-2963.2019.05.005
50. Li W, Yuan Y. Relationship between peripheral serum cystatin C level and cognitive dysfunction in elderly patients with acute cerebral infarction [in Chinese]. *Zhongguo Shiyong Neike Zazhi*. 2019;39(8):705–707. doi:10.19538/j.nk2019080111
51. Liu X, Wang L, Ren H. Predictive value of cystatin C on the prognosis in patients with acute ischemic stroke [in Chinese]. *Journal of Hebei Medical University*. 2018;39(4):387–390. doi:10.3969/j.issn.1007-3205.2018.04.004
52. Luan H, Wang W, Li H. The value of serum cystatin C and high-sensitivity C-reactive protein in early diagnosis and prognosis evaluation of acute cerebral infarction [in Chinese]. *World Latest Medicine Information*. 2019;19(66):192–195. doi:10.19613/j.cnki.1671-3141.2019.66.105
53. Lv N. The application value of serum cystatin C and coagulation function in diagnosis and prognosis of patients with acute cerebral infarction [in Chinese]. *Contemporary Medical Symposium*. 2019;17(19):165–166.
54. Sun N, Zhong L, Zhao H. The value of cystatin C, C-reactive protein and homocysteine in predicting short-term prognosis of patients with acute cerebral infarction [in Chinese]. *Cardio-Cerebrovasc Diseases Prevention Treatment*. 2021;21(6):567–570. doi:10.3969/j.issn.1009-816x.2021.06.013
55. Wang J, Tan H. Relationship between serum cystatin C and cognitive impairment in patients with acute cerebral infarction [in Chinese]. *Chinese Journal of Behavioral Medical and Brain Science*. 2018;27(8):712–716. doi:10.3760/cma.j.issn.1674-6554.2018.08.008
56. Wang N. Association between serum cystatin C and hemorrhagic transformation in acute cerebral infarction [in Chinese]. *Chinese Journal of Urban and Rural Industrial Hygiene*. 2017;12(12):22–25. doi:10.16286/j.1003-5052.2017.12.009
57. Wei L, Wang W. Study on the correlation between serum cystatin C and the incidence and prognosis of acute cerebral infarction [in Chinese]. *World Latest Medicine Information*. 2016;16(67):81. doi:10.3969/j.issn.1671-3141.2016.67.059
58. Wu W, Xie H, Shao X. Correlation between serum cystatin C, hs CRP, Lp PLA2 and severity of acute cerebral infarction and its prognostic value [in Chinese]. *Chinese Journal of Integrative Medicine on Cardio and Cerebrovascular Disease*. 2022;20(1):149–151. doi:10.12102/j.issn.1672-1349.2022.01.032
59. Wang L, Li S. Effects of atrial fibrillation, serum CysC and Hcy levels on the prognosis of patients with acute cerebral infarction treated with rt-PA intravenous thrombolysis [in Chinese]. *Clinical Research and Practice*. 2022;7(4):17–20. doi:10.19347/j.cnki.2096-1413.202204005
60. Wang F, Zhang H, Chen Y. Relationship between lipoprotein-associated phospholipase A2, cystatin c, interleukin-6 on the degree of neurological deficit and short-term prognosis in patients with acute cerebral infarction [in Chinese]. *Journal of Clinical and Experimental Medicine*. 2023;22(1):15–19. doi:10.3969/j.issn.1671-4695.2023.01.005
61. Dong Y, Bao Y, Hu C. The prognostic factors of recombinant tissue plasminogen activator intravenous thrombolysis for acute cerebral infarction and the predictive value of serum cystatin C levels for prognosis [in Chinese]. *Clinical Journal of Medical Officer*. 2023;22(11):15–19. doi:10.16680/j.1671-3826.2023.04.19
62. Fang Z, Deng J, Wu Z, et al. Cystatin C is a crucial endogenous protective determinant against stroke. *Stroke*. 2017;48(2):436–444. doi:10.1161/STROKEAHA.116.014975
63. Rost NS, Brodtmann A, Pase MP, et al. Post-stroke cognitive impairment and dementia. *Circ Res*. 2022;130(8):1252–1271. doi:10.1161/CIRCRESAHA.122.319951
64. Qu Y, Zhuo L, Zhan S. Epidemiological characteristics of poststroke cognitive impairment in China: A systemic review [in Chinese]. *Chinese Journal of Geriatric Heart Brain and Vessel Diseases*. 2013;15(12):1294–1301. doi:10.3969/j.issn.1009-0126.2013.12.018
65. Kono S, Adachi H, Enomoto M, et al. Impact of cystatin C and microalbuminuria on cognitive impairment in the population of community-dwelling Japanese. *Atherosclerosis*. 2017;265:71–77. doi:10.1016/j.atherosclerosis.2017.08.022
66. Umemura T, Kawamura T, Mashita S, Kameyama T, Sobue G. Higher levels of cystatin C are associated with extracranial carotid artery steno-occlusive disease in patients with noncardioembolic ischemic stroke. *Cerebrovasc Dis Extra*. 2016;6(1):1–11. doi:10.1159/000443338
67. Li X, Ma X, Lin J, He X, Tian F, Kong D. Severe carotid artery stenosis evaluated by ultrasound is associated with post stroke vascular cognitive impairment. *Brain Behav*. 2017;7(1):e00606. doi:10.1002/brb3.606
68. Yue W, Wang A, Zhu R, et al. Association between carotid artery stenosis and cognitive impairment in stroke patients: A cross-sectional study. *PLoS One*. 2016;11(1):e0146890. doi:10.1371/journal.pone.0146890
69. Levy E, Jaskolski M, Grubb A. The role of cystatin C in cerebral amyloid angiopathy and stroke: Cell biology and animal models. *Brain Pathol*. 2006;16(1):60–70. doi:10.1111/j.1750-3639.2006.tb00562.x
70. Zhang JB, Jü XH, Wang J, Sun HR, Li F. Serum cystatin C and cerebral microbleeds in patients with acute cerebral stroke. *J Clin Neurosci*. 2014;21(2):268–273. doi:10.1016/j.jocn.2013.04.014
71. Yang J, Lyu Y, Ma Y, Chen Y. Relationship between cerebral microbleeds location and cognitive impairment in patients with ischemic cerebrovascular disease. *NeuroReport*. 2018;29(14):1209–1213. doi:10.1097/WNR.0000000000001098
72. Angelidis C, Deftereos S, Giannopoulos G, et al. Cystatin C: An emerging biomarker in cardiovascular disease. *Curr Top Med Chem*. 2013;13(2):164–179. doi:10.2174/1568026611313020006
73. Zou J, Chen Z, Wei X, et al. Cystatin C as a potential therapeutic mediator against Parkinson's disease via VEGF-induced angiogenesis and enhanced neuronal autophagy in neurovascular units. *Cell Death Dis*. 2017;8(6):e2854. doi:10.1038/cddis.2017.240