



BMJ Open Relationship between serum insulin-like growth factor 1 levels and ischaemic stroke: a systematic review and meta-analysis

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ABSTRACT

Objective To assess the association of insulin-like growth factor 1 (IGF-1) with the risk of incident ischaemic stroke and outcome after ischaemic stroke.

Design A systematic review of primary studies.

Setting Hospitals in Western Sweden, Italy, China and Denmark.

Methods A search was carried out in eligible studies in electronic databases (PubMed, Scopus, Embase, China National Knowledge Infrastructure and Web of Science) updated to 29 December 2020. The relevant data were extracted in order to conduct the meta-analysis. Review Manager V.5.2 was used to pool data and calculate the mean difference (MD) and its 95% CI. Heterogeneity, subgroup analysis, sensitivity analysis and publication bias were also performed in this meta-analysis.

Results A total of 2277 patients were included in 17 studies. This meta-analysis indicated that higher serum IGF-1 levels were significantly correlated with less risk of ischaemic stroke (MD=-45.32 95% CI -63.70 to -26.94], $p < 0.00001$, $I^2=99%$) and better improvement of outcome after ischaemic stroke (MD=27.52, 95% CI 3.89 to 51.14, $p=0.02$, $I^2=96%$). According to subgroup analysis, heterogeneity comes from country, sample size, male and the time from symptom onset to blood collection. Sensitivity analysis showed that there was no significant influence of any individual study on the pooled MD. The effect of high heterogeneity on result credibility was eliminated when four included studies were merged (MD=-30.32, 95% CI -36.52 to -24.11, $p < 0.00001$, $I^2=0%$). Moreover, no potential publication bias was discovered in this meta-analysis.

Conclusion Higher serum IGF-1 was significantly correlated with a lower risk of ischaemic stroke. In view of the high degree of heterogeneity, it may need more studies to confirm the prognostic value of serum IGF-1 levels in ischaemic stroke and explore the sources of heterogeneity.

INTRODUCTION

Insulin-like growth factors (IGFs), confirmed as peptide hormones, share similar structural homology with insulin. IGF-1 protects cells from apoptosis and functions as a vital regulator in cell survival.^{1 2} A growing body of evidence has established that IGF-1 influenced

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This is a meta-analysis of 17 published studies comprising a total of 2277 patients in this study.
- ⇒ The included studies were heterogeneous in the time from symptom onset to blood collection and follow-up duration at the end of the study.
- ⇒ Study populations were limited to not less than 25 cases and no more than 1000 cases to prevent large samples from affecting the overall results.
- ⇒ A thorough systematic review and meta-analysis provide confidence in the findings.
- ⇒ Begg's test of publication bias was not performed on the relationship between serum insulin-like growth factor 1 and poststroke functional independence due to insufficient included studies.

vascular function in many different ways, possessing anti-inflammatory properties and inducing vasodilation by promoting nitric oxide production.^{3 4} Recently, substantial evidence has accrued to demonstrate that IGF-1 plays a significant role in many cerebral diseases, for example, depression in ischaemic stroke, cerebrovascular disease and Alzheimer's disease.⁵⁻⁷

Stroke is a leading cause of death and disability worldwide, especially in the current ageing society.⁸ Animal studies and observational studies on humans have been trying to establish an association between IGF-1 and the risk of ischaemic stroke. However, the association of IGF-1 with the risk of incident ischaemic stroke still remains unclear. Seven previous studies are exploring the association manifested inconsistent conclusions. On the one hand, five studies showed that IGF-1 possessed a protective effect against ischaemic stroke.⁹⁻¹³ On the other hand, no association between incident ischaemic stroke and IGF-1 was uncovered in two studies.^{14 15} Moreover, IGF-1 is widely disseminated and highly expressed in the nervous system,¹⁶

which exerts neuroprotective effects and accelerates proliferation of neurons. According to some studies, circulating serum IGF-1 is correlated with improvement of functional outcome after ischaemic stroke and might predict outcome after ischaemic stroke.^{13 14 17–19} Actually, the outcome after ischaemic stroke relies on complex interactions of multiple factors, and it still needs more studies to disclose whether the association is causative.

This meta-analysis was conducted in order to evaluate the association of IGF-1 with the risk of incident ischaemic stroke and the outcome after ischaemic stroke.

METHODS

Patient and public involvement

This article did not involve patients and or public.

Study protocol

This meta-analysis was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (online additional file 1).

Literature search strategy

PubMed, Scopus, Embase, China National Knowledge Infrastructure (CNKI) and Web of Science were searched for studies published or presented on or before December 29, 2020. Publications are not restricted to English. To achieve maximum sensitivity in the search strategy and to include more extensive studies, Medical Subject Headings (MeSH) terms and the keywords that were retrieved in the field of Title/Abstract were used in combination. “IGF-1” was selected in the MeSH term and “Insulin-Like Somatomedin Peptide I”, “Insulin Like Somatomedin Peptide I”, “Somatomedin C”, “IGF-I-SmC”, “IGF-I” and “Insulin Like Growth Factor I” were retrieved in the field of Title/Abstract. All the above are connected by “OR”. “Stroke” was selected in the MeSH term. Ultimately, “AND” was utilised to connect the two parts. All relevant articles were found first, and then irrelevant articles were manually excluded through title and abstract screening and full-text assessment. To avoid selection bias, all work was carried out independently by two authors.

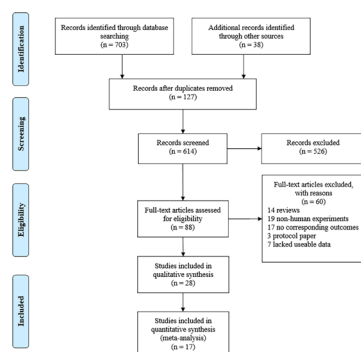


Figure 1 Study search and selection flow diagram.

Eligibility criteria

Studies were included if they fulfilled the following criteria:

- ▶ Studies were confined to those involving human subjects.
- ▶ There were no restrictions on the information of language, year of the study, patient age, imaging criteria, body mass index (BMI) and the National Institutes of Health Stroke Scale score.
- ▶ Study populations had no fewer than 25 cases and no more than 1000 cases.
- ▶ Study had a definite inclusion criterion for acute ischaemic stroke.
- ▶ Patients who suffered from stroke were confirmed by CT or MRI before treatment.
- ▶ Studies reported the complete outcomes.
- ▶ Study used a prospective or retrospective cohort design, or nested case–control design.
- ▶ If duplicate studies with an accumulating number of patients or something else were published, only the most complete studies were included in the analysis performed in this study.

Data extraction and quality assessment

All data were extracted independently from the tables and figures of included studies by two authors in an unblinded fashion or adjudicated by the third author in case of disagreement. Moreover, another author took responsibility for the accuracy and reliability of all of the extracted data. The modified Rankin Scale (mRS) is a clinical poststroke functional independence assessment tool. For each study, the study characteristics (author, publication year, study period, country), main characteristics of the patients (age gender and BMI) and outcomes (the number of ischaemic stroke patients, the number of people in control, serum IGF-1 and mRS at 90 days) were extracted independently by two authors. The quality of the included studies was assessed by two other authors using the modified Newcastle-Ottawa Scale, while 6 points or more was considered to be of high quality.

Outcome measure

The Mean, SD, total of serum IGF-1 (ng/mL) in case and control groups is a main indicator of stroke risk assessment. The mRS is an evaluation tool to assess the clinical poststroke functional independence (detailed grades of mRS: 0—no symptoms; 1—no significant disability; 2—slight disability; 3—moderate disability; 4—moderately severe disability; 5—severe disability; 6—dead). The prespecified primary outcome measures were the mRS score of 0–2 and the mRS score 3–6.

Statistical analyses

Statistical analysis was implemented using Review Manager V.5.2 (The Nordic Cochrane Centre, the Cochrane Collaboration, Copenhagen, Denmark). The combined effect of mean difference (MD) and 95% CI was defined by a random-effect model or a fixed-effect

Table 1 Basic characteristics of included studies in the meta-analysis

Study	Study period	Country	The time from symptom onset to blood collection	Age (year)* †	Male (%)	BMI (kg/m ²)* †	Follow-up duration	IGF-1 (ng/mL)			
								Risk (mean, SD or IQR, Total)		mRS (mean, SD, Total)	
								Case	Control	mRS 0–2	mRS 3–6
Fu <i>et al</i> (2001) ²²	Not stated	China	NA	57–74	55.00	NA	NA	205.7, 125.8, 20	472.6, 317.9, 20	NA	NA
Sun <i>et al</i> (2001) ²⁷	1998.9–1999.10	China	≤24hours	67	70.00	26.45±2.51	NA	91.1, 51.30	175.49, 30	NA	NA
Liu <i>et al</i> (2002) ²⁵	1999.2–2002.3	China	3 days	63.85±8.74	63.33	27±5	NA	94.27, 60	185.30, 30	NA	NA
Denti <i>et al</i> (2004) ¹⁰	1998.1–2000.6	Italy	≤24hours	83±7	34.12	25±5	6 months	69.45, 85	102.67, 88	NA	NA
Zhang <i>et al</i> (2004) ²⁹	2000.12–2001.6	China	NA	64±11	66.67	NA	NA	99.48, 33.76, 57	179.9, 35.47, 26	NA	NA
Johnsen <i>et al</i> (2005) ¹²	1993.12–1997.5	Denmark	NA	50–64	61.00	26.5±4.0	NA	107.1, 33.3, 254	112.9, 33.2, 254	NA	NA
Geng <i>et al</i> (2006) ²³	2003.6–2004.1	China	≤48hours	65.08±10.93	70.27	NA	NA	153.22, 64.56, 56	196.1, 33.43, 10	NA	NA
Peng <i>et al</i> (2009) ²⁶	2006.12–2008.6	China	≤48hours	NA	NA	NA	NA	10.4, 1.6, 22	28.2, 7.8, 30	NA	NA
Chen <i>et al</i> (2010) ²¹	2009.1–2009.12	China	≤24hours	65.64±7.59	55	NA	NA	73.5, 28.40	103.3, 5.8, 20	NA	NA
Åberg <i>et al</i> (2011) ¹⁴	1998.8–2003.12	Western Sweden	4 days	55.5±0.86	56.65	26.2±0.43	3 months	172.3, 388	145.9, 40	NA	NA
Dong <i>et al</i> (2014) ¹¹	2011.8–2013.8	China	≤24hours	66 (57–77)	58.75	23.9 (22.6–26.8)	NA	129.44, 221	140.34, 200	NA	NA
Tang <i>et al</i> (2014) ¹³	2012.8–2013.8	China	≤24hours	72 (62–83)	53.57	25.3 (21.8–28.4)	3 months	127.50, 168	155.38, 100	114, 29, 113	146, 43, 55
Zhang <i>et al</i> (2016) ³⁰	2013.2–2015.9	China	NA	65.2±8.6	56.00	26.28±1.59	3 months	87.92, 25.31, 50	152.21, 23.32, 50	NA	NA
Li <i>et al</i> (2016) ²⁴	2014.5–2015.6	China	3 days	51.9±9.6	56.41	23.9±6.1	NA	98.66, 20.91, 39	153.01, 26.35, 43	NA	NA
Armbust <i>et al</i> (2017) ¹⁹	NA	NA	≤24hours	72.9±9.5	55.1	26.8±4.4	3 months	NA	NA	131.7, 55.7, 315	114.2, 55.3, 89
Tao and Wang (2018) ²⁸	2016.1–2017.3	China	3 days	60.30±9.75	66.67	NA	3 months	106.54, 48.84, 60	199.2, 53.15, 30	145.81, 49.89, 57	85.56, 32.16, 48
Åberg <i>et al</i> (2019) ²⁰	1998–2003	Western Sweden	≤24hours	55.3±11	65.12	NA	7 years	NA	NA	151.5, 6.6, 256	148.3, 12.3, 67

*Median (IQR).

†Mean (SD).

BMI, body mass index; IGF-1, insulin-like growth factor 1; mRS, modified Rankin Scale; NA, not available.

Table 2 Newcastle-Ottawa Scale for quality assessment

Study	Exposed cohort	Non-exposed cohort	Ascertainment of exposure	Outcome of interest	Control factor	Assessment of outcome	Follow-up long enough	Adequacy of follow-up	Total score
Fu <i>et al</i> (2001) ²²	*	*	*	†	†	*	*	*	6
Sun <i>et al</i> (2001) ²⁷	*	*	*	†	†	*	*	*	6
Liu <i>et al</i> (2002) ²⁵	*	*	*	†	†	*	*	*	6
Denti <i>et al</i> (2004) ¹⁰	*	*	*	†	†	*	*	*	8
Zhang <i>et al</i> (2004) ²⁹	*	*	*	†	†	*	*	*	6
Johnsen <i>et al</i> (2005) ¹²	*	*	*	†	†	*	*	*	6
Geng <i>et al</i> (2006) ²³	*	*	*	†	†	*	*	*	7
Peng <i>et al</i> (2009) ²⁶	*	*	*	†	†	*	*	*	6
Chen <i>et al</i> (2010) ²¹	*	*	*	†	†	*	*	*	7
Åberg <i>et al</i> (2011) ¹⁴	*	*	*	†	†	*	*	*	8
Dong <i>et al</i> (2014) ¹¹	*	*	*	†	†	*	*	*	6
Tang <i>et al</i> (2014) ¹³	*	*	*	†	†	*	*	*	8
Zhang <i>et al</i> (2016) ³⁰	*	*	*	†	†	*	*	*	8
Li <i>et al</i> (2016) ²⁴	*	*	*	†	†	*	*	*	6
Armbrust <i>et al</i> (2017) ¹⁹	*	*	*	†	†	*	*	*	8
Tao <i>et al</i> (2018) ²⁸	*	*	*	†	†	*	*	*	8
Åberg <i>et al</i> (2019) ²⁰	*	*	*	†	†	*	*	*	9

*The study scored one point in the project;

†The study scored two points in the project.

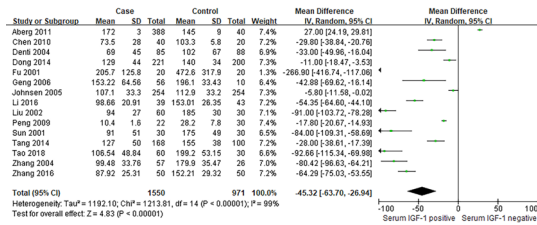


Figure 2 Forest plot of the relationship between serum IGF-1 and ischaemic stroke risk. IGF-1, insulin-like growth factor 1.

model. The heterogeneity among included studies was tested using the inconsistency index (I^2). A random-effect model was used when there was a high level of heterogeneity (I^2 values > 50%). A $p < 0.05$ was considered statistically significant. For indicators with higher heterogeneity, sensitivity analysis and subgroup analyses were carried out to identify the reliability of the meta-analysis and meta-regression was used to explore the sources of heterogeneity. Publication bias was evaluated qualitatively by visual observation of funnel graphs and was assessed quantitatively by the Begg's test (Stata V.12.0), which manifests a publication bias with $p < 0.05$. The number, MD, SD of the experimental group and control group of the included studies and country, sample size, male, the time from symptom onset to blood collection of 17 included studies were imported into Stata V.12.0 software.

RESULTS

Study selection and characteristics

Detailed steps of the inclusion and exclusion criteria of the study are shown in figure 1. Briefly, a total of 703 studies were retrieved through 5 electronic database searches. Thirty-eight additional studies were identified from the references of included studies after removing the duplicates. On the basis of extraneous titles and abstracts, 526 studies were excluded. Several studies were excluded because they were reviews, non-human experiments; did not present the corresponding outcomes and lack usable data. Ultimately, the final meta-analysis was conducted after a complete evaluation of 17 studies that met the inclusion criteria.^{10-14 20-30} The basic characteristics and quality score of the included studies are presented in table 1. The quality score of studies was proven to be acceptable (table 2).

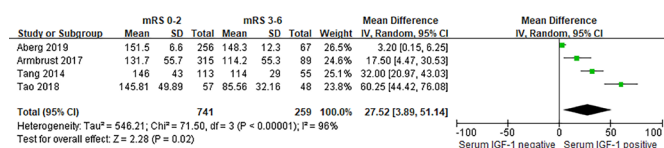


Figure 3 Forest plot of the relationship between serum IGF-1 and poststroke functional independence. IGF-1, insulin-like growth factor 1.

Table 3 Regression of heterogeneity sources

Item	No of studies	95% CI	P value
Country	15	(-41.50 to 78.27)	0.516
Sample size	15	(0.05 to 0.28)	0.008
Male	14	(-4.42 to 1.57)	0.320
The time from symptom onset to blood collection	14	(-18.71 to 83.61)	0.192

Relationship between serum IGF-1 and ischaemic stroke risk

The relationship between serum IGF-1 and ischaemic stroke patients was evaluated, and there was a high degree of heterogeneity among these included fifteen studies ($I^2=99%$). Thus, the random-effects model was used to pool MDs. The consequence manifested a significant difference (MD=-45.32, 95% CI -63.70 to -26.94, $p < 0.00001$, $I^2=99%$, random effect) (figure 2).

Relationship between serum IGF-1 and poststroke functional independence

Poststroke functional independence was identified by mRS at 90 days. The relationship between serum IGF-1 and poststroke functional independence was evaluated, and the random-effects model was used to pool MDs. The result showed a significant difference (MD=27.52, 95% CI 3.89 to 51.14, $p=0.02$, $I^2=96%$, random effect) (figure 3).

Regression of heterogeneity sources

There is high heterogeneity in analyses so we use meta-regression to explore heterogeneity. From the analysis results, we can see that the sample size may be the primary source of heterogeneity (table 3).

Subgroup analysis of heterogeneity sources

In view of enormous heterogeneity, subgroup analysis of heterogeneity sources was performed to explore heterogeneity sources. The heterogeneity of each subgroup decreased modestly to varying degrees. Notably, the heterogeneity of the time from symptom onset to blood collection presented a significant decrease in parallel with other subgroup results (table 4).

Sensitivity analysis and adjusted relationship between serum IGF-1 and ischaemic stroke

Sensitivity analysis was performed by omitting one study by turn, which showed that there was no significant influence of any individual study on the pooled MDs (figure 4). Moreover, in pursuit of a low degree of heterogeneity and to uncover low degree of heterogeneity sources, the included studies were randomly merged. It was discovered that heterogeneity reached its minimum when four included studies were merged (MD=-30.32, 95% CI -36.52 to -24.11, $p < 0.00001$, $I^2=0%$) (figure 5A).^{10 13 21 23} The other eleven included studies, in the other hand, remained high degree of heterogeneity (MD=-50.34, 95% CI -72.82 to -27.87, $p < 0.00001$,

Table 4 Subgroup analysis of heterogeneity sources

Item	Subgroup	No of studies	MD	95% CI	P value	Heterogeneity (I ²)
Country	Asian	12	-55.44	(-72.07 to 38.82)	<0.00001	97%
	Non-Asian	3	-2.92	(-32.42 to 26.58)	0.85	99%
Sample size	≥100	6	-18.84	(-45.77 to 8.08)	0.17	99%
	<100	9	-65.16	(-88.48 to 41.83)	<0.00001	97%
Male	≥60%	6	-65.89	(-107.51 to 24.26)	0.02	98%
	<60%	8	-35.21	(-65.91 to 4.52)	0.2	99%
The time from symptom onset to blood collection	≤48 hours	7	-30.04	(-40.05 to 20.03)	<0.00001	86%
	>48 hours	4	-52.40	(-120.79 to 15.99)	0.13	99%
	≤24 hours	5	-33.76	(-49.51 to 18.01)	<0.0001	89%

MD, mean difference.

I²=99%) (figure 5B).^{11 12 14 22 24-30} Taken together, high degree of heterogeneity seemed not to discredit the final merged result.

Publication bias analysis

According to Begg’s test (p=0.092>0.05) and the funnel plot (figure 6), no potential publication bias among the 17 included studies was noted in this meta-analysis.

DISCUSSION

The mechanism of serum IGF-1 in evaluating the risk and prognosis of ischaemic stroke

This meta-analysis merged 17 studies comprising 2277 patients to evaluate the association of serum IGF-1 with the risk of incident ischaemic stroke and the prognostic value of serum IGF-1 in ischaemic stroke. The results demonstrated that serum IGF-1 could be used to evaluate the risk of incident ischaemic stroke (MD=-45.32, 95% CI-63.70 to -26.94, p<0.00001, I²=99%, random effect) and the outcome after ischaemic stroke (MD=27.52, 95% CI 3.89 to 51.14, p=0.02, I²=96%, random effect). The main mechanism is as follows: Serum IGF-1 mainly comes from the liver, a small part comes from the kidneys and peripherals.³¹ In body fluids, IGF-1 has a high affinity with IGF binding proteins (IGFBPs). IGFBPs regulate the biological activity and bioavailability of IGF-1, and the intake of serum IGF-1 enters the cerebrospinal fluid through the blood-brain barrier.³² IGF-1 binds to the

widely distributed receptor IGF-1 receptor (IGF-1R) in the brain to activate the two main signal pathways of PI3K/Akt and MAPK, thereby inhibiting neuronal apoptosis,³³ promoting the survival of oligodendrocytes³⁴ and protecting the hippocampus.³⁵

Discussion on the causes of heterogeneity

However, there was an inevitable high degree of heterogeneity among the included studies in this meta-analysis. In order to make the conclusion more persuasive and scientific, subgroup analysis was performed to explore the heterogeneity sources. As the results suggested, the time from symptom onset to blood collection appeared to be part of the source of heterogeneity, while heterogeneity decreased modestly to varying degrees. A study reported that stroke severity was related to decreased IGF-1 in rats as well as humans, which meant that the different stroke severity of recruited patients may also cause heterogeneity.^{11 36} Besides, insufficient follow-up duration may be the heterogeneity source. Due to the inability to obtain the original data, the heterogeneity from the time of symptom onset to blood collection, follow-up duration and stroke severity of recruited patients cannot be explored further. By scrutinising the included studies, it was found that ischaemic stroke patients who were recruited were subjected to the WHO criteria in some included studies,^{10 12 13} whereas others included studies were not subjected to the criteria. In addition to different patient recruitment criteria, the nutritional status of the



Figure 4 Forest plot in the sensitivity analysis of serum IGF-1 and ischaemic stroke risk. IGF-1, insulin-like growth factor 1.

Figure 5 Forest plot of the adjusted relationship between serum IGF-1 and ischaemic stroke risk in (A) four included studies and (B) eleven included studies. IGF-1, insulin-like growth factor 1.

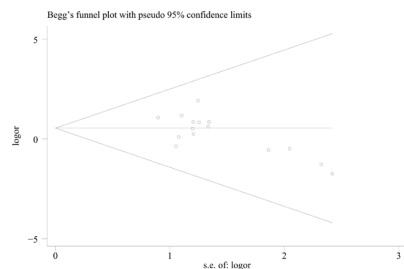


Figure 6 Begg's funnel plot for publication bias test of the relationship between serum IGF-1 and ischaemic stroke risk. IGF-1, insulin-like growth factor 1.

patient may cause heterogeneity, which can be indirectly reflected by BMI. Many ischaemic stroke patients are followed by accelerated catabolism and decreased food intake, which results in a decrease in body muscle mass and BMI. The current study cannot rule out the possible effect of malnutrition on serum IGF-1. Moreover, forest plots in the sensitivity analysis (figure 4) and of the adjusted relationship between serum IGF-1 and ischaemic stroke risk (figure 5) both demonstrate that the exclusion of any included study and a high degree of heterogeneity do not affect the final combined result.

The relationship between growth hormone and IGF-1 in cerebrovascular diseases

Growth hormone (GH) exerts much of its biological activity by promoting the production of IGF-1, and IGF-1 can also mediate the effects of GH in turn. The majority of circulating serum IGF-1 is completed with IGFBPs and acid labile subunits, which prevent IGF-1 from binding to the insulin receptor or modulate IGF-1's binding to the IGF-1R.³⁷ It is universally acknowledged that the bioavailability of IGF-1 is regulated by IGFBPs and that only unbound or free IGF-1 possesses biological activity. As part of the body's ageing process, IGF-1 decreases sharply. Some human studies demonstrate that the effects of circulating serum IGF-1 on cerebrovascular events may be induced by metabolic syndrome.^{38 39} Furthermore, patients with GH deficiency may have lower circulating IGF-1 levels, which raises the risk of cerebrovascular diseases significantly.⁴⁰ Notably, it was reversible with GH replacement.⁴¹

Insufficiency of previous related research

Previous studies assessing the association of IGF-1 with the risk of incident ischaemic stroke and the prognostic value of serum IGF-1 in ischaemic stroke reported controversial findings. A study performed by Dong *et al*¹¹ suggested that lower IGF-1 levels are significantly related to risk of stroke and stroke severity, but IGFBPs levels were not obtained in that biologically active IGF-1 was not fully represented.¹¹ Johnsen *et al*¹² found inverse associations between levels of IGF-1 and IGFBP-3 and the risk of ischaemic stroke. However, another study showed no association with incident ischaemic stroke.¹⁵ Meanwhile, Åberg *et al*¹⁴¹⁴ suggested that serum IGF-1 levels were closely

related to improvements in the mRS and Scandinavian Stroke Scale tested at 3 and 24 months. However, the widespread variation of sampling may have influenced conclusions. Mattlage *et al*¹²⁴² reported the potential importance of the change in IGF-1 and IGF-1 ratio to IGFBP-3 during the first week of stroke in understanding recovery. The limitation of the study was that serum IGF-1 levels were not supplemented with the levels of IGF-1 in the cerebral spinal fluid (CSF). Because in ischaemic stroke, IGF-1 transfers from the blood to the CSF. Nevertheless, another study showed an inconsistent conclusion that higher serum IGF-1 levels were modestly associated with better outcomes after ischaemic stroke.²⁰

Strengths and limitations

To our knowledge, this meta-analysis is the first one to investigate the relationship between serum IGF-1 levels and ischaemic stroke. Shaheen *et al*⁴³⁴³ have found that serum IGF-1 was an independent risk factor for ischaemic stroke in the Egyptian population which is consistent with our study. This research has geographical limitations so this meta-analysis included both English and Chinese studies so that publication bias was avoided to a great extent. Besides, the eligibility criteria that study populations were not less than 25 cases and not more than 1000 cases to prevent large samples from affecting the overall results. Åberg *et al*²⁰⁴⁴ have proved that levels of serum IGF-1 are associated with near 3-month outcomes. However, the study only included 354 patients, meaning that the sample size is too small. Otherwise, a comprehensive database search was performed in this meta-analysis, and as a result, 17 studies comprising a total of 2277 patients were included. Despite the shining points of this meta-analysis, its limitations and shortcomings should be emphasised. A high degree of heterogeneity may cause the unreliability of the results. Meanwhile, Begg's test of publication bias was not performed on the relationship between serum IGF-1 and post-stroke functional independence due to insufficient included studies. Ultimately, a data-feasible study¹⁵ was excluded because of oversize cases, ambiguous patient recruitment criteria and no mention of stroke confirmed by imaging examination.

The clinical significance and future prospects of the study

Because the majority of serum IGF-1 binds to IGFBPs, the current measured serum IGF level cannot accurately represent the biological activity of IGF in circulation. It is hoped that the future meta-analysis will use the data obtained by the IGF-1-specific tyrosine kinase receptor activation analysis method³² as much as possible. This method indirectly measures the actual biological activity by accurately assessing the activity of the official receptor. This meta-analysis significantly analysed that higher IGF-1 correlated with a lower risk of ischaemic stroke. It provides a basis for in-depth clinical research on the relationship

between the level of IGF-1 and the neurological score³⁰ of stroke patients, poststroke depression⁴⁵ dementia⁴⁶ and so on. In addition, it is also of great significance to the prevention of stroke (identification of high-risk groups and chemoprevention), early diagnosis, clinical treatment and prognosis.

CONCLUSIONS

This meta-analysis analysed all the available interrelated information in the published studies and found that higher serum IGF-1 was significantly correlated with a lower risk of ischaemic stroke. Concerning the relationship between serum IGF-1 and outcome after ischaemic stroke, it may need more studies to confirm the prognostic value of serum IGF-1 levels.

Contributors YL and WY are cofirst authors. YL and WY designed the study. WY, YiZ and HL performed the literature search. WY, YL and LZ selected the studies for inclusion in the meta-analysis. SC and YL extracted the data. WY performed the statistical analysis. YL, WY and JL wrote the manuscript. LH and YuZ revised the manuscript. YuZ provided the funding and is a guarantor. All authors read and approved the final manuscript.

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