REVIEW ARTICLE DOI: https://doi.org/10.18502/fem.v9i1.18069

Serum IGF-1 level as a prognostic marker for acute ischemic stroke: a systematic review

Shayan Roshdi Dizaji[1 a], Hamed Zarei[1 a], Sajjad Jabermoradi[1], Parsa Paridari[1], Mostafa Hosseini[2]*, Mahmoud Yousefifard[1]*

1. Physiology Research Center, Iran University of Medical Sciences, Tehran, Iran.
2. Pediatric Chronic Kidney Disease Research Center, Tehran University of Medical Sciences, Tehran, Iran; Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran.

[a] Both authors contributed equally to this work.

***Corresponding authors:** Mostafa Hosseini; **Email:** sepmhossein110@yahoo.com
Mahmoud Yousefifard; **Email:** yousefifard20@gmail.com

Published online: 2025-02-17

Abstract: **Objective:** Assessing the risk levels of patients with acute ischemic stroke (AIS) can assist in making informed choices about their treatment and rehabilitation. To assess the prognostic value of serum insulin-like growth factor-1 (IGF-1) in neurological deficit (National Institutes of Health Stroke Scale [NIHSS]), functional independence (Modified Rankin Scale [mRS]), and mortality following AIS.

Methods: The search encompassed Medline, Embase, Scopus, and Web of Science until June 2023. Two autonomous researchers incorporated articles by the established inclusion and exclusion criteria. The quality of the included studies were assessed using the quality assessment of prognostic accuracy studies (QUAPAS) tool.

Results: Ten articles were included, with evidence suggesting that IGF-1 may have prognostic value in AIS outcomes. Several studies reported positive associations between IGF-1 levels, reduced neurological deficits, improved functional independence, and lower mortality. Additionally, intraindividual fluctuations in IGF-1 after AIS were identified as a potential predictor of recovery in functional independence, though significant inconsistencies exist in the findings.

Conclusion: The available studies with a very low level of evidence are not sufficient to firmly endorse the applicability of IGF-1 as a prognostic factor for mortality, neurological disability, and functional independence.

Keywords: Ischemic Stroke; Insulin-Like Growth Factor I; Prognosis

Cite this article as: Roshdi Dizaji S, Zarei H, Jabermoradi S, Paridari P, Hosseini M, Yousefifard M. Serum IGF-1 level as a prognostic marker for acute ischemic stroke: a systematic review . Front Emerg Med. 2025;9(1):e7.

1. Introduction

Stroke is a major disabling neurological disease and stands for the second cause of death and the third cause of combined death and disability worldwide (1). In the United States, acute ischemic stroke (AIS) is the most prevalent form, accounting for about 87% of stroke incidence (2). Despite new advances in expanding our knowledge about the underlying pathophysiology of AIS, the available therapeutic modalities are still confined to rapid pharmacological thrombolysis and mechanical thrombectomy. Nonetheless, many patients cannot benefit from these therapeutic measures considering the golden time window defined for the efficacy of the treatments and limited access of some populations to the equipped medical centers. Consequently, many patients with stroke suffer from debilitating sensory and motor neurological impairments, which heavily compromise the patient's quality of life.

To mitigate post-stroke disabilities, detecting those who would benefit most from acute care and long-term rehabilitative programs is vital. Hence, great efforts have been devoted to identifying prognostic factors of functional recovery after stroke. With this aim, several blood biomarkers, including neuroinflammatory cytokines and structural compounds, have been introduced with conflicting prognostic values (3,4). In recent years, studies have demonstrated the adverse impact of impaired secretory function of the pituitary axis after stroke on the patient's outcome (5,6). Consequently, examining the intricate interrelationship between the endocrine system and stroke became an area of research interest for finding novel biomarkers concerning functional recovery among stroke patients.

As an endogenous somatotrophic hormone, insulin-like growth factor 1 (IGF-1) is a polypeptide with structural similarity to insulin. Under physiological circumstances, IGF-1 is mainly synthesized by hepatocytes under growth hormone stimulation and exerts multiple regulatory effects on various cell lines throughout the body (7). During embryonic development, IGF-1 participates in neuronal development, synaptogenesis, and myelination of the central nervous system (8, 9). In the post-natal period, IGF-1 levels decline with ag-

ing, lower physical activity levels, and malnutrition. Investigations on the link between IGF-1 level and risk of stroke yielded evidence that lower baseline serum concentration of IGF-1 is associated with an increased risk of stroke (10,11). Moreover, subsequent preclinical studies endorsed the neuroprotective and neuro-regenerative properties of IGF-1 in animal models of ischemic cerebral injuries (12).

In this line, several human studies assessed the correlation between IGF-1 and injury severity, functional recovery, and survival of stroke patients. However, the results obtained on the prognostic role of IGF-1 were conflicting and burdensome in drawing a firm conclusion.

Previously, a systematic review with a meta-analysis aimed to appraise and collate the studies investigating the value of IGF-1 for the incidence and outcome prediction of AIS patients (13). However, only four studies were included when assessing the value of IGF-1 in predicting post-stroke outcomes, among which one study has recently been retracted (14). Another drawback of the aforementioned review was that of the three remaining studies, the IGF-1 sampling time (day 8 vs. day 90) and follow-up duration (3 months vs. 2 years) were different among the two studies, which cast doubts on the reliability of the meta-analysis results. So, we designed this systematic review to comprehensively appraise all available reports in the literature regarding the prognostic role of IGF-1 in AIS and its association with stroke severity.

2. Methods

This systematic review was conducted and reported in adherence with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement (15).

2.1. Eligibility criteria

Our systematic search attempted to collate all evidence from observational studies evaluating the IGF-1 prognostic value measured after stroke incidence on the post-stroke outcomes. We opted for human cohort studies conducted on adult patients (age ≥18 years) with AIS evaluated for serum levels of IGF-1 and post-stroke outcomes, including neurological deficit, functional independence, and mortality. Regarding the type of stroke, we excluded patients with hemorrhagic stroke or subarachnoid hemorrhage as these entities have a more discrete pathophysiology than AIS. We selected the Modified Rankin Scale (mRS) and National Institutes of Health Stroke Scale (NIHSS), two universally accepted and validated tools for evaluating functional independence and neurological deficit severity, respectively. We adopted the most common dichotomization used for the mRS score, which designates patients into favorable (mRS:0-2) and unfavorable (mRS: 3-5) groups. Studies evaluating the relationship between IGF-1 and stroke incidence and those with simultaneous assessment of IGF-1 and our interest outcomes were not in conformance with our study question and thus excluded. Furthermore, studies measuring IGF-1 in cerebrospinal fluid, assessing the pre-stroke prognostic value of IGF-1, exogenous administration of IGF-1, duplicate reports, case studies, and reviews were excluded. We did not apply any restriction regarding the minimum duration of follow-up or the number of time points at which outcomes were evaluated.

2.2. Search strategy

To investigate the prognostic role of serum IGF-1 for the post-stroke outcomes, we explored four main bibliographic databases encompassing Medline (via PubMed), ESMBASE, Scopus, and Web of Science from their inception until the end of June 2023. The related key terms for drafting search queries were adapted by consultations from experts in the field, relevant MeSH terms and Emtree terms and corresponding synonyms, and reviewing the related studies' titles, abstracts, and subject indexing. Although the search strategy was not formally peer-reviewed using structured tools such as the PRESS checklist, we ensured its comprehensiveness and relevance through expert opinion. Exhaustive search strings ran in each aforementioned database were presented in the supplementary material. We applied no date of publication filters or language restrictions through our search. Moreover, to avert missing potentially related records, we conducted a manual search on Google and Google Scholar search engines and forward and backward citation tracking of included studies. Full Record citations of results obtained by searching each database were imported to Endnote version 20.0 software (Clarivate Analytics, Philadelphia, PA, USA), and duplicates were automatically removed.

2.3. Selection and data collection process

Two independent reviewers (SJ and PP) screened the title and abstract of entire records and identified potentially eligible studies for full-text retrieval. Afterward, the retrieved full-text articles were reviewed independently by the same two reviewers based on inclusion and exclusion criteria. In each step, when there were disagreements, discrepancies were resolved through discussion or consultation with the third author (MY). As for non-English manuscripts, we utilized the Google Translate application for content translation to English. Finally, the two reviewers (SJ and PP) independently extracted the data from the included studies and entered them into a predesigned checklist. Sought data included study features (first author, study design, location, and publication year), target population characteristics (sample size and demographics), patients' comorbidities (smoking, hypertension, and diabetes mellitus), stroke severity on admission (measured by NIHSS), serum IGF-1 measurement time and assessment technique, follow-up duration, and reported outcomes. Whenever data on variables of interest was only presented visually, PlotDigitizer software was used to extract numerical data from graphs and figures. When desired information was unavailable or questionable, the study's corresponding author(s) were contacted by email and asked for relevant data. For studies with overlapping populations, the

study with the larger sample size was prioritized for inclusion.

Gleaned data were compared for consistency, and any discordance was resolved by re-examining the article or consultation with the third author (MY). Meta-analyses could not be undertaken due to the heterogeneity of IGF-1 sampling time, reported IGF-1 values (e.g., crude IGF-1 or its alteration level), and outcome assessment timing.

2.4. Risk of bias assessment and certainty of the evidence

Two independent authors (SRD, HZ) rated each study based on the quality assessment of prognostic accuracy studies (QUAPAS) tool (16). Using the tool, the risk of bias is determined in five distinct domains: 1) participants: the techniques for enrolling participants and preventing unwarranted exclusions, 2) index test: definition, measuring, or interpreting the index test, 3) outcome: definition, measurement method, or interpretation of the outcome, 4) flow and timing: the timing of the tests and the time horizon to capture the outcome. 5) analysis: the data itself, including handling missing data. Each item is labeled with high, moderate, or low risk of bias. The raters were well trained and adept at using the QUAPAS tool and resolved disagreements by discussing or arbitration with the third expert (MY). The grades of recommendation, assessment, development, and evaluation (GRADE) approach was utilized to determine the level of evidence for each outcome by assessing four domains of publication bias, risk of bias assessments, inconsistency, imprecision, and indirectness with the overall rating as high, moderate, low, and very low (17).

3. Results

3.1. Study selection and characteristics

The systematic search yielded 3610 records, and after removing duplications, 2074 studies entered the primary screening stage. Following the title and abstract screening, the full text of 59 studies was retrieved and reviewed comprehensively. Ultimately, 10 published studies met the eligibility criteria (18-28) (Figure 1). All studies were observational in design. Later, we performed a manual search based on the included studies' citation and reference tracking and results of search engines; however, no extra eligible article meeting our inclusion and exclusion criteria was found. A total of 1630 participants diagnosed with AIS were included, with a mean age of 78.04 years and 76.6% of them being male. Nine of ten studies were designed prospectively with follow-up duration ranging from 1 month to 7 years. Table 1 summarizes the characteristics of the included studies. Among the five studies that reported NIHSS at baseline, median values ranged from 4 to 15.44. Regarding the comorbidities, all studies except three provided information on enrolled patients' medical conditions (Table 2).

3.2. Risk of bias assessment

In five studies, the risk of bias was classified as unclear within the patient selection domain due to a lack of information regarding the utilization of either random or consecutive sampling methods (24-28). In the domain of the index test, six articles were found to have a high risk of bias because they used thresholds or quantiles for IGF-1 (or ΔIGF-1) that were not predetermined (12,19,20,22,23,25,27). For the outcome domain, all articles received an unclear risk of bias rating because it was not clear whether the outcomes were assessed while blinded to the IGF-1 assessment or not.

In the flow and timing domain, all articles were judged to have a high risk of bias as none of the studies avoided treatment after the index test was performed. Given that the avoidance of treatment or the implementation of uniform treatment for all patients is not feasible in the context of stroke, we recommend excluding this signaling question when evaluating the overall risk of bias for the study.

Six studies were identified as having a high risk of bias in the analysis domain due to the loss to follow-up patients (18-20, 23-25), while three studies had an unclear risk of bias due to a lack of a patient flow diagram (26-28). In all other domains of risk of bias assessment, the studies were rated as having a low risk of bias. Concerning applicability, one study had unclear applicability because the exclusion criteria were not clearly described (24). However, there were no concerns about applicability in other domains (Table 3).

3.3. Relationship between serum IGF-1 and post-stroke neurological deficit

Three studies investigated the relationship between serum IGF-1 and post-stroke neurological deficit measured by NIHSS (22,24,28). These studies collected blood samples from patients within a short time window (< 6 hours to 5 days) after the onset of AIS. They recorded patients' NIHSS scores from one to three months after the stroke. The results obtained were not conclusive as only one study supported an independent association between IGF-1 and 3-month NIHSS (adjusted OR=0.824, SE =0.019, P=0.001) (22). De Smedt et al. (255 patients) found that those with serum IGF-1 >76 ng/mL measured within 6 hours post-injury showed significantly better neurological recovery starting on day 3, with improvements lasting throughout the three-month study period (22). In contrast, the remaining two studies (24,28) with comparatively smaller sample sizes (96 patients combined) and a wide interval of sampling acquisition times (from <24 hours up to 5 days) could not confirm a similar association in either univariate or multivariate regression analysis. Table 4 summarizes the findings of the studies as mentioned above.

3.4. Relationship between serum IGF-1 and post-stroke functional independence

Overall, eight studies investigated the association between serum IGF-1 and functional independence by employing diverse methodologic and statistical approaches (Table 5) (18-

Table 1 Characteristics of the included studies

Study	Country	Sampling period	Study design	Sample size	Serum IGF-1 measurement times[a]	Serum IGF-1 assessment technique	Commercial kit	Outcome measurement times	Outcome
Aberg, 2011 (18)	Sweden	1998 – 2003	Prospective	407	< 10 days, 3 months	RIA	Mediagnost	3 months, 2 years	mRS
Aberg, 2018 (19)	Sweden	1998 – 2003	Prospective	354	< 19 days, 3 monthsb	RIA	Mediagnost	3 months, 2 years	mRS
Aberg, 2020 (20)	Sweden	1998 – 2003	Prospective	324	3 months	RIA	Mediagnost	3 months, 2 years, 7 years	mRS, mortality
De Smedt, 2011 (22)	Belgium	NR	Prospective	255	< 6 h	RIA	Nichols Institute Diagnostics	3 months	NIHSS, mRS, mortality
Denti, 2004 (23)	Italy	1998 – 2000	Prospective	85	< 24 h	IRMA	DSL-Chematil	6 months	mortality
Fan, 2019 (24)	New Zealand	NR	Prospective	28	< 72 h, day 7	ELISA	Crystal Chem	3 months	NIHSS, mRS
Lee, 2021 (25)	South Korea	2014 – 2017	Retrospective	379	< 24 h	CLIA	LIAISON, DiaSorin	3 months	mRS
Mehrpour, 2016 (26)	Iran	2014 – 2015	Prospective	60	< 24 h	CLIA	NR	1 year	NIHSS, mRS
Tao, 2018 (27)	China	2016 - 2017	NR	105	< 3 days	CLIA	Immulite 1000, Siemens	3 months	mRS
Yasar, 2015 (28)	Turkey	NR	Prospective	68	< 24 h, day 5	NR	Immulite 2000, Siemens	1 month	NIHSS, mortality

IGF-1: Insulin-like growth factor 1; RIA: Radioimmunoassay; CLIA: Chemiluminescent immunoassay; IRMA: Immunora diometric assay; ELISA: Enzyme-linked immunoassay; mRS: Modified Rankin scale; NIHSS: National Institutes of Health Stroke Scale; NR: Not reported

a : Interval from admission to blood sampling

b: ΔIGF-1

Table 2 Patients' characteristics among the included studies

Study	Age, years, mean±sd	Male, n (%)	NIHSS score at admission	Diabetes mellitus	Hypertension	Current smoking	Dyslipidemia/ hyperlipidemia	Atrial fibrillation	Previous stroke
Aberg, 2011	55±NR	259 (64)	NR	74 (18)	258 (63)	157 (39)	NR	NR	NR
Aberg, 2018	55.4±NR	229 (65)	5.3 (0.7, 10.2) *	67 (19)	188 (53)	136 (38)	NR	NR	NR
Aberg, 2020	55.3±11	211 (65)	5.1 (0.74, 8.5) *	61 (19)	179 (55)	117 (36)	NR	NR	NR
De Smedt, 2011	71.34±NR	139 (55)	15.44 [NR]	54 (21)	159 (62)	NR	NR	69 (27)	NR
Denti, 2004	83±7	29 (34)	NR	23 (27)	66 (77)	11 (13)	NR	32 (37)	NR
Fan, 2019	66.79±14.64	19 (56)	4 [NR]	6 (17.6)	15 (44.1)	4 (11.8)	12 (35.3)	9 (26.5)	NR
Lee, 2021	67.2±12.6	230 (55.9)	5 [2-11]	119 (31.4)	233 (61.5)	131 (34.6)	134 (35.4)	101 (26.6)	74 (19.5)
Mehrpour, 2016	71.1±9	28 (46.7)	NR	NR	NR	NR	NR	NR	NR
Tao, 2018	60.49±NR	70 (66.67)	NR	NR	NR	NR	NR	NR	NR
Yasar, 2015	60.07±15.65	34 (54.41)	NR	NR	NR	NR	NR	NR	NR

Data are reported for all patients enrolled in each study. Data are presented as mean ± standard deviation, median [interquartile range], or n (%) values, unless otherwise specified.

NR: Not reported

*: Mean (20, 80%)

Table 3 Risk of bias assessment based on QUAPAS tool

Study	Risk of bias					Applicability			
	Participants	Index test	Outcome	Flow and timing	Analysis	Participants	Index test	Outcome	Flow and timing
Aberg, 2011	☺	☺	?	☹	☹	☺	☺	☺	☺
Aberg, 2018	☺	☹	?	☹	☹	☺	☺	☺	☺
Aberg, 2020	☺	☹	?	☹	☹	☺	☺	☺	☺
De Smedt, 2011	☺	☹	?	☹	☺	☺	☺	☺	☺
Denti, 2004	☺	☹	?	☹	☹	☺	☺	☺	☺
Fan, 2019	?	☺	?	☹	☹	?	☺	☺	☺
Lee, 2021	?	☹	?	☹	☹	☺	☺	☺	☺
Mehrpour, 2016	?	☺	?	☹	?	☺	☺	☺	☺
Tao, 2018	?	☹	?	☹	?	☺	☺	☺	☺
Yasar, 2015	?	☺	?	☹	?	☺	☺	☺	☺

☹: High risk; ☺: Low risk; ?: unclear

Table 4 Summary of studies evaluating the association of serum IGF-1 levels and NIHSS scores in acute ischemic stroke patients

Study	Crude or ΔIGF-1	Sampling to injury interval	NIHSS measurement time	Summary of results
De Smedt, 2011	Crude	< 6h	3M	After adjustment for baseline NIHSS levels and admission glucose, higher baseline IGF-1 levels were independently associated with lower NIHSS scores at 3M (OR=0.824, SE=0.019, P=0.001)
Fan, 2019	Crude	< 72h	3M	After adjustment for baseline NIHSS levels and age, baseline IGF-1 levels were not independently associated with NIHSS scores at 3M (multivariate, P =0.11)
Yasar, 2015	Crude	< 24h	1M	Baseline IGF-1 levels were not associated with NIHSS at 1M (statistics were not reported)
Yasar, 2015	Crude	D5	1M	IGF-1 on D5 was weakly and negatively correlated with NIHSS at 1M (r=-0.35, P value was not reported)

IGF-1: Insulin-like growth factor 1; NIHSS: National Institutes of Health Stroke Scale; h: Hours; D: Days; M: Months; Y: Years

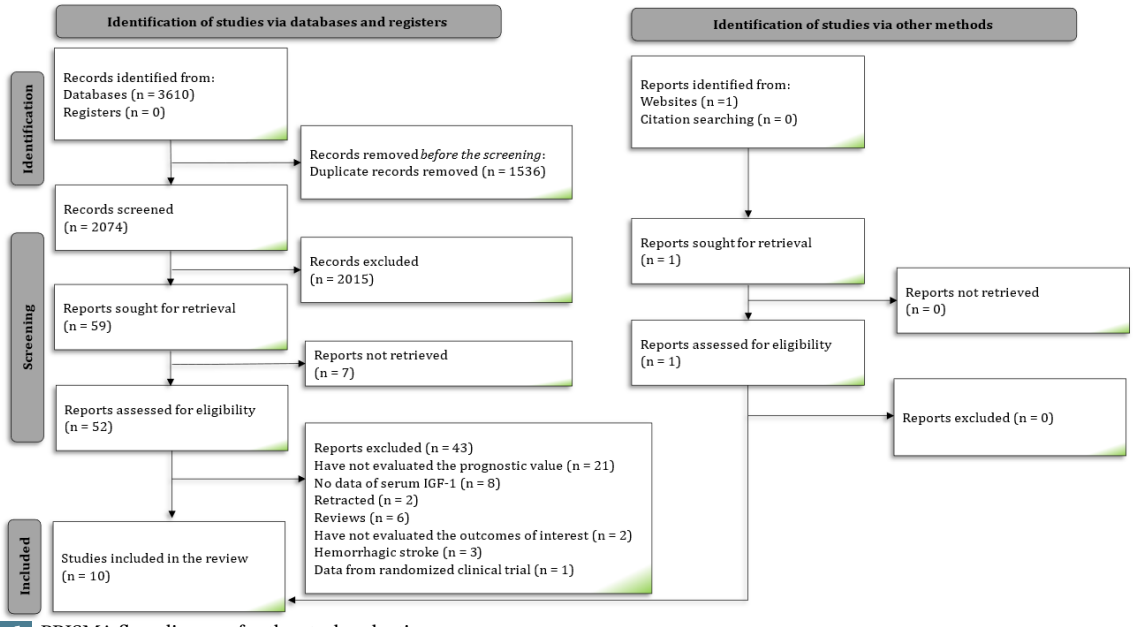

Figure 1 PRISMA flow diagram for the study selection process

20,22,24-27). Five studies examined the association between early IGF-1 (obtained up to 72 hours following stroke) and subsequent functional independence. Among them, two studies demonstrated no independent association between IGF-1 levels and the mRS score after adjusting for confounding variables (24, 25). Conversely, the remaining three stud-

Table 5 Summary of studies evaluating the association of serum IGF-1 levels and modified Rankin scale in acute ischemic stroke patients

Study	Type of IGF-1	Sampling to injury interval	Outcome	Outcome measurement time	Summary of results
Fan, 2019	Crude	< 72h	mRS	3M	Baseline IGF-1 level was not associated with mRS score at 3M (multivariate, P=0.72)
Lee, 2021	Crude	< 24h	mRS	3M	There was no significant correlation between acute IGF-1 levels and 3-month functional outcome (adjusted OR=0.62 [0.27- 1.43])
De Smedt, 2011	Crude	< 6h	mRS	3M	The distribution of the mRS score was more favorable in the group with high IGF-1 (> 76 ng/ml) compared to low IGF-1 level group (multivariate shift analysis, P=0.031)
Mehrpour, 2016	Crude	< 24h	mRS	1Y	There was a weak negative correlation between baseline IGF-1 levels and mRS scores at 1Y (P=0.025, correlation coefficient =-0.329)
Tao, 2018	Crude	< 3D	mRS	3M	Univariate analysis showed that the level of IGF-1 in the favorable group was significantly higher than that in the unfavorable group (P<0.01)
Aberg, 2020	Crude	3M	mRS	2Y, 7Y	There was an independent association between 3M IGF-1 and mRS shift categories between 3M and 2Y (partial r=0.142, P=0.036). Similar association was not found for mRS shift categories between 3M and 7Y (partial r=0.064, P=0.33)
Aberg, 2011	Crude	< 10D, 3M	mRS	3M, 2Y	Acute level of IGF-1 was not associated with either 3M or 24M value of mRS while it was independently associated with better recovery (ΔmRS) between 3M and 24M (P=0.017, β=0.134, adjusted). Likewise, 3-month IGF-1 was independently associated with better recovery between 3M and 2Y (P=0.002, r=0.175, adjusted) while it did not have association with final mRS score at 2Y (P=0.47, r=0.04)
Aberg, 2018	ΔIGF-1	< 19D, 3M	mRS	2Y	Multivariate regression analysis revealed that decreased serum IGF-1 between the acute phase and after 3 months post-stroke was independently associated with better functional independence after 2 years (adjusted OR=3.63, 95% CI: 1.40,9.38)

IGF-1: Insulin-like growth factor 1; mRS: Modified Rankin scale; H: Hours, D: Days, M: Months, Y: Years

Table 6 Summary of studies evaluating the association of serum IGF-1 levels and mortality in acute ischemic stroke patients

Study	Type of IGF-1	Sampling to injury interval	Outcome measurement time	Summary of results
De Smedt, 2011	Crude	< 6h	3M	The risk of mortality is 1.7 times higher in patients with higher IGF-1 (> 76 ng/ml) levels (adjusted HR=1.7 [1.01,2.86], P=0.045)
Denti, 2004	Crude	< 24h	6M	Each 20-ng/mL increase in IGF-1 was independently associated with lower mortality risk at 6 months (adjusted HR=0.7 [0.5,0.9], P=0.008)
Yasar, 2015	Crude	< 24h, D5	1M	First-day IGF-1 level was not associated with mortality (P=0.179, unadjusted HR=0.992, SE=0.006) while the risk of mortality was 2% lower in patients with higher fifth-day IGF-1 levels (unadjusted HR=0.983, SE=0.008, P=0.026)
Aberg, 2020	Crude	3M	7Y	3-month serum IGF-1 levels were not associated with the risk of mortality at 7 years (adjusted HR=1.01 [0.55,1.84], P=0.97).

IGF-1: Insulin-like growth factor 1; H: Hours; D: Days; M: Months; Y: Years

ies indicated that elevated levels of early IGF-1 were associated with more favorable outcomes (mRS 0-2) (22,26,27). Notably, the last three studies had comparatively smaller sample sizes (420 compared to 811 patients), with only one study by De Smedt et al. utilizing multivariate analyses to control for potential confounding factors (multivariate shift analysis, P=0.031) (22). Among the other two studies, Tao et al. demonstrated that the level of IGF-1 in the favorable group was significantly higher than that in the unfavorable group (P< 0.01) (27), and Mehrpour and colleagues reported a weak negative correlation between baseline IGF-1 levels and mRS scores at 1 year (P=0.025, correlation coefficient= -0.329) (26). Regarding delayed sampling, only one study investigated the association between IGF-1 measured at 8- and 10-days post-stroke and three-month mRS scores. Aberg and colleagues found no association between the IGF-1 value measured on day 10 and three months of functional independence (18).

While studies have been controversial regarding the relationship between single serum IGF-1 and crude mRS values, there is consistent evidence linking IGF-1 to the recovery pro-

Table 7 The certainty of evidence using the grades of recommendation, assessment, development, and evaluation (GRADE)

Outcome	Sample size	Risk of bias	Inconsistency	Imprecision	Indirectness	Publication bias	Judgment	Level of evidence
Neurological deficit	351	Serious	Serious	Not serious	Not serious	Can not be determined	Level of evidence was down rated three grades due to possible risk of bias, inconsistency, and publication bias	Very low ⊕⊖⊖⊖
Functional independence	1912	Serious	Serious	Not serious	Not serious	Can not be determined	Level of evidence was down rated three grades due to possible risk of bias, inconsistency, and publication bias	Very low ⊕⊖⊖⊖
Mortality	732	Serious	Serious	Not serious	Not serious	Can not be determined	Level of evidence was down rated three grades due to possible risk of bias, inconsistency, and publication bias	Very low ⊕⊖⊖⊖

cess. Aberg and colleagues conducted two studies with serial mRS assessments (18,20). Through their research comprising an overall 731 AIS patients, they revealed that higher IGF-1 values measured early during the first 10 days (P=0.017, β=0.134, adjusted) or later at 3 months post-stroke (P=0.002, r=0.175, adjusted) were independently associated with functional improvement (ΔmRS) between 3 to 24 months, while no association was found between serum IGF-1 levels and final mRS values at these time points. However, when the follow-up was extended to 7 years, the 3-month IGF-1 measurement lost its significant association with better recovery between the 3-month and 7-year visits (P=0.33) (20).

Ultimately, regarding the intra-individual changes in IGF-1 levels, the only study by Aberg et al. found that a decrease in IGF-1 levels between the acute phase (<19 days) and 3 months post-stroke was independently associated with improved functional independence after 2 years (adjusted OR=3.63, 95% CI: 1.40,9.38) (19).

3.5. Relationship between serum IGF-1 and post-stroke mortality

Studies have reported conflicting findings regarding the predictive role of IGF-1 in mortality (Table 6). Measured within the first 24 hours after admission, Denti and colleagues observed a reduced risk of 6-month mortality with each 20 ng/mL increase in IGF-1 (adjusted HR=0.7 [0.5-0.9], P=0.008) (23). In contrast, De Smedt et al. identified an increased 3-month mortality risk (adjusted HR=1.7 [1.01,2.86], P=0.045) in individuals with elevated acute IGF-1 values (> 76 ng/mL) (22). Yasar et al. could not establish an association between acute IGF-1 values and 1-month mortality (P=0.179, unadjusted HR=0.992, SE=0.006). Meanwhile, higher IGF-1 levels in delayed samples taken 5 days after a stroke were shown to decrease mortality risk by 2% (unadjusted HR=0.983, SE=0.008, P=0.026), although no adjustments were made for confounding factors (28). Only one study evaluated subacute 3-month IGF-1 levels and did not find an association with mortality risk during a 7-year follow-up (adjusted HR=1.01 [0.55,1.84], P=0.97) (20).

3.6. Certainty of evidence

The included articles were designed as observational studies, and according to GRADE guidelines, the initial level of evidence was classified as low. However, studies displayed notable risk of bias and high heterogeneity, each reducing the level of evidence by one. Additionally, publication bias could not be assessed via standard quantitative tests. As a result, the level of evidence for the outcomes related to the predictive value of the IGF-1 serum levels in AIS was classified as very low (Table 7).

4. Discussion

Through the current review, we demonstrated that the available evidence regarding the prognostic value of IGF-1 following AIS remains inconclusive in terms of its predictive capacity for neurological deficits and mortality. About functional independence, although inconsistencies were noted regarding the significance of crude IGF-1 levels, existing studies indicated that intraindividual fluctuations of IGF-1 after AIS may have a role in predicting subsequent recovery of functional independence. While the present evidence does not sufficiently support or refute the prognostic significance of IGF-1 following AIS, a comprehensive understanding of its pathophysiological role in ischemic brain injury, along with the inherent limitations associated with its assessment, may provide valuable insights for the design of future studies aimed at elucidating its role in predicting outcomes for AIS patients.

Under the physiological state, the IGF-1 level is mainly regulated through hepatic synthesis stimulated by the growth hormone, physical activity, and metabolic condition (29,30). Following acute stress, such as brain ischemic insults, animal studies revealed a surge in serum IGF-1 level (31). Regarding the sources of IGF-1 release, two main sources of cere-

bral and extra-cerebral could be suspected. Along with the liver, IGF-1 is expressed abundantly in the brain and plays a role in the autocrine/paracrine signaling (32). Human studies demonstrated that 30-35% of patients suffer from growth hormone deficiency following stroke (33). Weak correlation between growth hormone and IGF-1 in stroke patients with growth hormone deficiency and increasing IGF-1 levels after brain insult in animal studies strengthened the alternative hypothesis that the observed surge in blood concentration of IGF-1 may have resulted from local brain synthesis with subsequent leakage to serum (31,34,35). We initially hypothesized that the extent of brain damage after stroke reflected by severity scores like the NIHSS scale would correlate with serum IGF-1 level.

We selected neurological deficit, functional independence, and mortality as the key outcome domains in our systematic review due to their critical importance in evaluating stroke prognosis. These outcomes were chosen based on their consistent identification as primary prognostic indicators in the stroke literature. Specifically, as highlighted by Gao et al. (2020), data-driven models consistently identified NIHSS, preadmission mRS, and age as the primary predictors of functional outcomes, confirming their intuitive recognition by clinicians as key factors in stroke prognosis (36). NIHSS and mRS are widely accepted, standardized tools that measure neurological severity and functional recovery, respectively, making them essential for assessing post-stroke outcomes. Mortality, being the ultimate adverse outcome, remains a fundamental measure of disease severity and intervention efficacy. Thus, by focusing on these critical outcomes, our review aligns with well-established prognostic frameworks in stroke research and enhances the applicability of findings to clinical practice.

Contrary to our expectation, most included studies indicated that the magnitude of IGF-1 at admission following stroke was not correlated with the severity of stroke assessed by NIHSS, and the remaining reported conflicting results. In a subgroup analysis of patients with quantitative infarct size evaluation by MRI, Zhang et al. reported an inverse correlation between IGF-1 and infarct size (37). Regarding the dynamics of IGF-1 and stroke severity, one study by Aberg et al. demonstrated that patients with decreasing levels of IGF-1 from the acute phase to 3 months post-stroke had suffered from less severe stroke (19). This result highlights the demand for future experiments with concomitant measurement of IGF-1 in serum and cerebrospinal fluid and quantitative volumetric measurement of infarct lesions to illuminate the potential releasing and uptaking sources of IGF-1 after brain injury.

IGF-1 is present in the circulation predominantly in a complex with the insulin-like growth factor binding proteins (IGFBP) such as IGFBP3 and, to a lesser extent, as an unbound form (28). The latter is the bioavailable form for cellular uptake with a short half-life of 15 minutes (38).

Although our review did not investigate the value of IGFBP3, there is convincing evidence that the IGF-1/IGFBP3 ratio, which reflects bioavailable IGF-1, significantly affects patient outcomes (22,23). Since the IGFBP3 is not consistently bound with the IGF-1, as a surrogate of bioactive IGF-1 level, Fan et al. recently proposed cGP, an N-terminal cleaved of unbounded IGF-1 to be more accurate than IGF-1/IGFBP3 ratio as an indicator of bioavailable IGF-1 (23). Overall, it is implicated that the estimation of bioavailable IGF-1 using surrogate markers would be more accurate and informative in understanding its role in the pathogenesis and outcome prediction after stroke.

Respecting the predictive value of IGF-1 for functional recovery after stroke, studies showed inconsistent results for the admission value of IGF-1 and crude mRS score evaluated in both short-term and long-term follow-ups. During the acute phase of stroke, IGF-1 level shows instability, and serial sampling may reveal increasing or decreasing levels. Hence, the temporal profile and dynamics of IGF-1 may provide a more reliable perspective on the patient's prognosis rather than an absolute single measurement unless a definite time point after stroke onset was determined. Concordantly, a study evaluating the changing rate of IGF-1 revealed that decreasing IGF-1 (IGF-1) levels over a specified time window was associated with a more favorable outcome (19). While IGF-1 overcomes the intra-individual variance of IGF-1 and is more informative on the patient's outcome, absolute IGF-1 level is not completely futile. Two studies by Aberg et al. showed that a higher 3-month IGF-1 level was associated with functional improvement in the two-year follow-up (18,20). Therefore, it can be deduced that altered IGF-1 level is in tandem with the progression of neural recovery processes. In other words, although unchanged or high IGF-1 after the subacute phase of stroke is associated with poorer functional outcomes at that time point, there is still promise that functional improvement will be ensured in longer follow-up assessments.

The complex mechanisms underlying the role of IGF-1 in ischemic brain damage evolution are not yet fully known and are under investigation. Most of our current knowledge on the pathophysiological role of IGF-1 in ischemic brain damage has been derived from animal experiments. In these studies, IGF-1 has been shown to have anti-apoptotic effects mainly through the phosphoinositide 3-kinase (PI3K)–Akt pathway, which contributes to neuronal viability at ischemic penumbra following stroke (39). Respecting vascular structures, IGF-1 was shown to promote vasodilation, plaque stability, and blood-brain barrier integrity which are crucial in alleviating ischemic damages (40). Moreover, preclinical studies showed IGF-1 to have effects against excitotoxicity and oxidative damage after brain ischemic insults (41,42). Aside from its neuroprotective properties, IGF-1 contributes to functional recovery through neural regeneration, plasticity, and myelin expression (32,43). In a study by Chang et al., the decline in the blood concentration of IGF-1 over time after ischemic brain damage was credited partly to the neuronal uptake stimulated by physical activity, supported by

the increasing level of cerebral IGF-1 and decreasing peripheral levels (44). In this line, intraventricular administration of recombinant IGF-1 in rats with ischemic cerebral injury models has been shown to reduce the infarct size (45). Although ample evidence in animal studies shed light on the pathways through which IGF-1 exerted desired outcomes in ischemic damages, one should note that most animal models used in such studies were hypertension and diabetes-free.

5. Limitations

In the current review, we presented all relevant studies on the prognostic value of IGF-1 after stroke through a concise literature exploration. Nevertheless, we acknowledge some limitations in our study that one should exercise caution in interpreting the presented results. IGF-1 level is influenced by multiple variables, including age, sex, body mass index, liver function, diabetes, metabolic syndrome, malnutrition, and, most importantly, fasting status. Hormones that regulate serum IGFBP-3 (testosterone, estrogen, and thyroxine (T4)) can also have major effects on IGF-1 concentrations (46). IGF-1 level is also influenced by the treatments for stroke, with thrombolytic therapy resulting in increased bioavailability (47). Additionally, a vast range of assay methods has been employed in various studies to quantify IGF-1, including radioimmunoassay, chemiluminescent Immunoassay, and enzyme-linked immunoassay, each employing distinct reagent kits. Consequently, comparing quantitative IGF-1 values between studies and establishing a solid recommended cut-off value that can be confidently relied upon seems unfeasible. Although some included studies applied specific exclusion criteria and performed multiple logistic regression to adjust the covariates, the number of incorporated potential confounding factors differed among the studies, and defined cutoff values varied widely. Furthermore, the included studies in our review merely encompassed patients with AIS, and there were inconsistencies regarding recurrency and its severity among enrolled patients. It highlights the demand for future studies with a more robust and consistent methodology, taking into consideration the aforementioned factors.

6. Conclusion

Our study has determined that inconsistent findings with very low level of evidence suggest no firm association between a single IGF-1 value and a stroke patient's prognosis.

7. Declarations

7.1. Acknowledgement

None.

7.2. Authors' contribution

Ideation and design: MY, MH. Data collection: SRD, HZ. Interpretation of the results: SRD, HZ, SJ, PP, MY. Drafting the work: SRD, HZ. Revising draft critically for important intellectual content: All authors. The authors read and approved the final manuscript.

7.3. Conflict of interest

All of the authors declare no conflict of interest.

7.4. Funding

None.

7.5. Availability of data

The dataset extracted from the included studies are available upon a reasonable request from the corresponding authors.

References

1. Wang X. Correlation between serum neuron specific enolase level and neuron injury index and neuron apoptosis index in patients with brain injury. ACTA MEDICA MEDITERRANEA. 2021;37(2):791-4.
2. Tsao CW, Aday AW, Almarzooq ZI, Anderson CAM, Arora P, Avery CL, et al. Heart disease and stroke statistics-2023 update: a report from the American Heart Association. Circulation. 2023;147(8):e93-e621.
3. Whiteley W, Wardlaw J, Dennis M, Lowe G, Rumley A, Sattar N, et al. The use of blood biomarkers to predict poor outcome after an acute transient ischemic attack or ischemic stroke. Stroke. 2012;43(1):86-91.
4. Xu Q, Tian Y, Peng H, Li H. Copeptin as a biomarker for prediction of prognosis of acute ischemic stroke and transient ischemic attack: a meta-analysis. Hypertens Res. 2017;40(5):465-71.
5. El Husseini N, Laskowitz DT. The role of neuroendocrine pathways in prognosis after stroke. Expert Rev Neurother. 2014;14(2):217-32.
6. Bondanelli M, Ambrosio MR, Zatelli MC, Basaglia N, Degli Uberti EC. Prevalence of hypopituitarism in patients with cerebrovascular diseases. J Endocrinol Invest. 2008;31(9 Suppl):16-20.
7. Yakar S, Liu JL, Stannard B, Butler A, Accili D, Sauer B, et al. Normal growth and development in the absence of hepatic insulin-like growth factor I. Proc Natl Acad Sci U S A. 1999;96(13):7324-9.
8. Wrigley S, Arafa D, Tropea D. Insulin-like growth factor 1: at the crossroads of brain development and aging. Front Cell Neurosci. 2017;11:14.
9. Trejo JL, Piriz J, Llorens-Martin MV, Fernandez AM, Bolós M, LeRoith D, et al. Central actions of liver-derived insulin-like growth factor I underlying its pro-cognitive effects. Mol Psychiatry. 2007;12(12):1118-28.
10. Johnsen SP, Hundborg H, Sørensen H, Ørskov H, Tjønneland A, Overvad K, et al. Insulin-like growth factor (IGF) I,-II, and IGF binding protein-3 and risk of ischemic stroke. J Clin Endocrinol Metab. 2005;90(11):5937-41.

11. Saber H, Himali JJ, Beiser AS, Shoamanesh A, Pikula A, Roubenoff R, et al. Serum insulin-like growth factor 1 and the risk of ischemic stroke: the Framingham study. Stroke. 2017;48(7):1760-5.
12. Aberg ND, Brywe KG, Isgaard J. Aspects of growth hormone and insulin-like growth factor-I related to neuroprotection, regeneration, and functional plasticity in the adult brain. ScientificWorldJournal. 2006;6:53-80.
13. Li Y, Yang W, Li J, Zhang Y, Zhang L, Chen S, et al. Relationship between serum insulin-like growth factor 1 levels and ischaemic stroke: a systematic review and meta-analysis. BMJ Open. 2022;12(6):e045776.
14. Guan X, Peng Q, Wang J. Sevoflurane activates MEF2D-mediated Wnt/β-catenin signaling pathway via microRNA-374b-5p to affect renal ischemia/reperfusion injury. Immunopharmacology and immunotoxicology. 2022;44(4):603-12.
15. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.
16. Lee J, Mulder F, Leeflang M, Wolff R, Whiting P, Bossuyt PM. QUAPAS: an adaptation of the QUADAS-2 tool to assess prognostic accuracy studies. Ann Internl Med. 2022;175(7):1010-8.
17. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336(7650):924-6.
18. Åberg D, Jood K, Blomstrand C, Jern C, Nilsson M, Isgaard J, et al. Serum IGF-I levels correlate to improvement of functional outcome after ischemic stroke. J Clin Endocrinol Metab. 2011;96(7):E1055-E64.
19. Åberg ND, Åberg D, Jood K, Nilsson M, Blomstrand C, Kuhn HG, et al. Altered levels of circulating insulin-like growth factor I (IGF-I) following ischemic stroke are associated with outcome-a prospective observational study. BMC neurology. 2018;18:1-12.
20. Åberg ND, Åberg D, Lagging C, Holmegaard L, Redfors P, Jood K, et al. Association between levels of serum insulin-like growth factor I and functional recovery, mortality, and recurrent stroke at a 7-year follow-up. Experimental and clinical endocrinology & diabetes. 2020;128(05):303-10.
21. Armbrust M, Worthmann H, Dengler R, Schumacher H, Lichtinghagen R, Eschenfelder CC, et al. Circulating insulin-like growth factor-1 and insulin-like growth factor binding protein-3 predict three-months outcome after ischemic stroke. Exp Clin Endocrinol Diabetes. 2017;125(07):485-91.
22. De Smedt A, Brouns R, Uyttenboogaart M, De Raedt S, Moens M, Wilczak N, et al. Insulin-like growth factor I serum levels influence ischemic stroke outcome. Stroke. 2011;42(8):2180-5.
23. Denti L, Annoni V, Cattadori E, Salvagnini MA, Visioli S, Merli MF, et al. Insulin-like growth factor 1 as a predictor of ischemic stroke outcome in the elderly. Am J Med. 2004;117(5):312-7.
24. Fan D, Krishnamurthi R, Harris P, Barber PA, Guan J. Plasma cyclic glycine proline/IGF-1 ratio predicts clinical outcome and recovery in stroke patients. Ann Clin Transl Neurol. 2019;6(4):669-77.
25. Lee J, Lee J, Lee M, Lim J-S, Kim JH, Yu K-H, et al. Association between serum insulin-like growth factor-1 and neurological severity in acute ischemic stroke. J Clin Neurol (Seoul, Korea). 2021;17(2):206.
26. Mehrpour M, Rahatlou H, Hamzehpur N, Kia S, Safdarian M. Association of insulin-like growth factor-I with the severity and outcomes of acute ischemic stroke. Iranian Journal of Neurology. 2016;15(4):214.
27. yan T, WANG X. Studies of serum insulin-like growth factor-1 level in the patients with acute ischemic stroke and relative influence factors. CAJ. 2018;39(6):412-6.
28. Yasar H, Tombul T, Milanlioglu A. The association between insulin-like growth factor-1 and insulin-like growth factor binding protein-3 levels and clinical prognosis in patients with ischemic stroke. Turkish Journal of Cerebrovascular Diseases. 2015;21:30-5.
29. Landin-Wilhelmsen K, Wilhelmsen L, Lappas G, Rosén T, Lindstedt G, Lundberg PA, et al. Serum insulin-like growth factor I in a random population sample of men and women: relation to age, sex, smoking habits, coffee consumption and physical activity, blood pressure and concentrations of plasma lipids, fibrinogen, parathyroid hormone and osteocalcin. Clin Endocrinol (Oxf). 1994;41(3):351-7.
30. Lioutas VA, Alfaro-Martinez F, Bedoya F, Chung CC, Pimentel DA, Novak V. Intranasal insulin and insulin-like growth factor 1 as neuroprotectants in acute ischemic stroke. Transl Stroke Res. 2015;6(4):264-75.
31. Wang J, Tang Y, Zhang W, Zhao H, Wang R, Yan Y, et al. Insulin-like growth factor-1 secreted by brain microvascular endothelial cells attenuates neuron injury upon ischemia. FEBS J. 2013;280(15):3658-68.
32. Kooijman R, Sarre S, Michotte Y, De Keyser J. Insulin-like growth factor I: a potential neuroprotective compound for the treatment of acute ischemic stroke? Stroke. 2009;40(4):e83-8.
33. Bondanelli M, Ambrosio MR, Carli A, Bergonzoni A, Bertocchi A, Zatelli MC, et al. Predictors of pituitary dysfunction in patients surviving ischemic stroke. J Clin Endocrinol Metab. 2010;95(10):4660-8.
34. Beilharz EJ, Russo VC, Butler G, Baker NL, Connor B, Sirimanne ES, et al. Co-ordinated and cellular specific induction of the components of the IGF/IGFBP axis in the rat brain following hypoxic-ischemic injury. Brain Res Mol Brain Res. 1998;59(2):119-34.
35. Bondanelli M, Ambrosio MR, Onofri A, Bergonzoni A, Lavezzi S, Zatelli MC, et al. Predictive value of circulating insulin-like growth factor I levels in ischemic stroke

outcome. J Clin Endocrinol Metab. 2006;91(10):3928-34.
36. Gao MM, Wang J, Saposnik G. The art and science of stroke outcome prognostication. Stroke. 2020;51(5):1358-60.
37. Zhang W, Wang W, Kuang L. The relation between insulin-like growth factor 1 levels and risk of depression in ischemic stroke. Int J Geriatr Psychiatry. 2018;33(2):e228-e33.
38. Frystyk J, Hussain M, Skjaerbaek C, Pørksen N, Froesch ER, Orskov H. The pharmacokinetics of free insulin-like growth factor-I in healthy subjects. Growth Horm IGF Res. 1999;9(2):150-6.
39. Sun X, Yao H, Douglas RM, Gu XQ, Wang J, Haddad GG. Insulin/PI3K signaling protects dentate neurons from oxygen-glucose deprivation in organotypic slice cultures. J Neurochem. 2010;112(2):377-88.
40. Hayes CA, Valcarcel-Ares MN, Ashpole NM. Preclinical and clinical evidence of IGF-1 as a prognostic marker and acute intervention with ischemic stroke. J Cereb Blood Flow Metab. 2021;41(10):2475-91.
41. Vincent AM, Mobley BC, Hiller A, Feldman EL. IGF-I prevents glutamate-induced motor neuron programmed cell death. Neurobiol Dis. 2004;16(2):407-16.
42. Heck S, Lezoualc'h F, Engert S, Behl C. Insulin-like growth factor-1-mediated neuroprotection against oxidative stress is associated with activation of nuclear factor kappaB. J Biol Chem. 1999;274(14):9828-35.
43. Chesik D, De Keyser J, Wilczak N. Insulin-like growth factor system regulates oligodendroglial cell behavior: therapeutic potential in CNS. J Mol Neurosci. 2008;35(1):81-90.
44. Chang HC, Yang YR, Wang PS, Kuo CH, Wang RY. Insulin-like growth factor I signaling for brain recovery and exercise ability in brain ischemic rats. Med Sci Sports Exerc. 2011;43(12):2274-80.
45. Guan J, Williams C, Gunning M, Mallard C, Gluckman P. The effects of IGF-1 treatment after hypoxic-ischemic brain injury in adult rats. J Cereb Blood Flow Metab. 1993;13(4):609-16.
46. Clemmons DR, Snyder P, Martin K. Physiology of insulin-like growth factor I. In: Conner RF, ed. UpToDate. Wolters Kluwer. Updated Jan, 2024.
47. Wilczak N, Elting JW, Chesik D, Kema IP, De Keyser J. Intravenous tissue plasminogen activator in patients with stroke increases the bioavailability of insulin-like growth factor-1. Stroke. 2006;37(9):2368-71.