Association between blood IGF-1 levels and functional prognosis in hyperacute ischemic stroke patients undergoing thrombolytic therapy

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Approval No R-12-7J

Characters: 1,966 words (Abstract 254words), 24 References, 3 figures, 3 tables

Running title: IGF-1 levels and prognosis of hyperacute ischemic stroke patients

Abstract

Insulin-like growth factor-1 (IGF-1) is associated with the functional prognosis in cerebral infarction patients. However, no studies have been performed on patients who underwent intravenous thrombolytic therapy with recombinant tissue-type plasminogen activator (rt-PA). Fifty-five patients with hyperacute ischemic stroke within six hours of onset who were admitted to our hospital and underwent intravenous thrombolytic therapy and gave consent were included in this study. Serum IGF-1 levels were measured within 24 hours of stroke onset, and their association with the following data was assessed: age, sex, body mass index (BMI), medical history, blood D-dimer level, BNP level, blood glucose level, renal function, stroke subtype, infarct size, National Institutes of Health Stroke Scale (NIHSS) at stroke onset, and modified Rankin Scale (mRS) at three months. The good outcome group (mRS 0-1) had significantly higher serum IGF-1 levels than the poor outcome group (mRS $\geq$ 2, median 83 ng/mL vs. 62 ng/mL, p 0.032). Furthermore, the good outcome group was significantly younger than the poor outcome group ($p<0.001$) and had higher BMI ($p=0.021$), had lower D-dimer ($p=0.032$) and BNP ($p=0.026$) levels. There was no difference in NIHSS at onset, and the IGF-1 correlation was eliminated by age-adjustment. Serum IGF-1 levels may correlate with prognosis at three months after stroke in patients with hyperacute ischemic stroke treated with intravenous thrombolytic therapy, but the effect of age is also strong. Further studies

that focus on specific age groups, include large number of patients, and evaluate mechanical thrombectomy at multiple institutions are needed.

Key words: Insulin-like growth factor-1, hyperacute ischemic stroke, recombinant tissue-type plasminogen activator

Introduction

Insulin-like growth factor 1 (IGF-1) is a small protein with a molecular weight of 7649 Da that contains 70 amino acids and mediates the growth-promoting effects of growth hormones [1,2]. It was identified by Salmon and Daughday in 1957 [3], and subsequent studies have revealed that it has multiple roles in the central nervous system. IGF-1 is now known to play many important roles in neuronal development, differentiation, plasticity, and survival, and its neuroprotective effects and involvement in the pathogenesis of neurodegenerative diseases have been widely reported [4]. In patients with cerebral infarction, those with high serum IGF-1 levels at onset have shown better improvement in neurological symptoms and significantly better functional prognosis after three months, compared with patients with low serum IGF-1 levels [5]. Furthermore, an association between cerebral infarct expansion and low serum IGF-1 levels and a decreased mortality related to cerebrovascular disease was observed in a high serum IGF-1 group[6], which indicates a strong association between serum IGF-1 levels and cerebral infarction outcomes.

Intravenous alteplase, a recombinant tissue-type plasminogen activator (rt-PA), was approved in Japan in 2005 as a treatment for hyperacute ischemic stroke within 4.5 hours of onset and is now widely used as a treatment for hyperacute ischemic stroke [7]. Furthermore, rt-PA has been reported to amplify IGF-1 bioavailability [8] and that serum IGF-1 levels may influence functional improvement and prognosis after intravenous thrombolytic therapy, although this has not been

verified further. We hypothesize that high serum IGF-1 levels at stroke onset correlate with better functional outcomes in patients treated with intravenous thrombolytic therapy (rt-PA intravenous therapy, IV-tPA) for hyperacute ischemic stroke.

Materials and methods

This was a single-center prospective study of patients with hyperacute ischemic stroke who were treated at Dokkyo Medical University Hospital. Of 503 patients (72.4 ± 13.2 years) with hyperacute ischemic stroke within six hours of onset who were admitted to our hospital between July 1, 2018 and March 31, 2022, 55 patients who underwent IV-tPA and gave written consent to participate in this study were included (Fig. 1). Consent was obtained from the patient's family if the patient had difficulty in making decisions due to impaired consciousness or higher brain dysfunction. In addition, patients with ischemic lesions with signal changes on diffusion-weighted (DWI) head magnetic resonance imaging (MRI) on admission who did not show signal changes on fluid-attenuated inversion recovery (FLAIR) images (DWI-FLAIR mismatch) were considered eligible for thrombolytic therapy, even if the onset time was more than 4.5 hours, and were included in the study [9]. Patients who met the exclusion criteria for IV-tPA, who underwent concurrent endovascular treatment, or whose consent could not be obtained from the patient or his/her family were excluded. Serum IGF-1 levels were measured at the time of admission. All the samples were assayed by

trained staff at a single laboratory (The SRL, Inc., Hachioji, japan). The serum levels of IGF-1 were measured by immuno-radiometric assay using commercially available kits (TFB, INC. Tokyo). The range of reliable measurement was 4-1,990 ng/mL for IGF-1. Their association with patient age, sex, body mass index (BMI), medical history, D-dimer level in blood tests at the time of admission, BNP level, blood glucose level, renal function, stroke subtype and infarct size, National Institutes of Health Stroke Scale (NIHSS) at stroke onset, and modified Rankin Scale (mRS) three months after stroke onset were assessed. We defined mRS 0-1 as a good outcome and mRS ≥ 2 as a poor outcome.

SPSS ver 28.0 statistical software was used for statistical analysis. The statistics used were the unpaired t-test, Pearson χ^2 test, Spearman rank correlation coefficient, and logistic regression analysis. Statistical significance was defined as $p < 0.05$. This study was approved by the Bioethics Committee of Dokkyo Medical University Hospital (approval No. R-12-7J) and was conducted with the informed consent of patients, in accordance with the Declaration of Helsinki.

Results

The background of the 55 patients who were included in this study is shown in Table 1. There were 32 males (62%), the median patient age was 72 years (range: 41-91 years old), cardiac emboli was the most common type of stroke, at 38.4% (20 patients), followed by large-artery atherosclerosis

at 21.2% (11 patients), small-vessel occlusion at 23.1% (12 patients), paradoxical emboli at 13.5% (7 patients), and embolic stroke of undetermined source at 3.8% (2 patients).

The individuals of the good outcome group (mRS 0-1) at three months after onset were significantly younger than those of the poor outcome group (mRS ≥2), with higher serum IGF-1 and BMI, lower D-dimer and BNP levels, and no significant differences in NIHSS at onset or rt-PA start time (onset to needle) (Table 2).

The serum IGF-1 level was significantly high, at 83 ng/mL (median, range 23-189 ng/mL), in the good outcome group compared to its level of 62 ng/mL (21-127 ng/mL) in the poor outcome group ($p = 0.032$) (Fig. 2). Meanwhile, IGF-1 was not identified to be a significant factor in univariate logistic regression analysis that examined factors associated with better outcomes ($p = 0.242$, 95% confidence interval [0.135 -1.657]). There was also no correlation after adjustment for age, D-dimer, BNP or BMI (Table 3). On the other hand, there was a negative correlation between age and serum IGF-1 level (correlation coefficient -0.688, $p<0.0001$) (Fig. 3).

Discussion

The results from the present study suggest that high serum IGF-1 levels were associated with better outcomes at three months after onset in stroke patients treated with hyperacute thrombolytic therapy, although the multivariate analysis did not show significant results.

It has previously been reported that high serum IGF-1 levels within six hours after the onset of cerebral infarction correlate with subsequent symptomatic improvement and good functional prognosis three months after onset; however, the associated study did not examine treatment for cerebral infarction [5]. Meanwhile, it has been reported that IGF-1 bioavailability is amplified by rt-PA[8]. Since IGF-1 has neuroprotective effects, as described below, serum IGF-1 levels were expected to influence functional improvement and prognosis after intravenous thrombolytic therapy. Notably, the association has never been verified in actual clinical practice.

IGF-1 is known to prevent brain damage after cerebral ischemia through its anti-apoptotic effects [10], and the improvement of the prognosis of patients with cerebral infarction by IGF-1 preparations and the prediction of prognosis after cerebral infarction based on serum IGF-1 levels at onset have been investigated. IGF-1 is a small protein with a molecular weight of 7649 Da that is comprised of 70 amino acids and is also known as somatomedin C. It is a member of the insulin-like peptide superfamily, which is one type of factors that mediate the growth-promoting effects of growth hormones [1,2]. In the central nervous system, IGF-1 is associated with various pathways via six types of binding proteins (IGF binding proteins; IGFBP1-6) and two types of receptors (IGF-1R, IGF-2R) and acts in a neuroprotective manner [11]. IGF-1 protects neurons including glutamate decarboxylase (GAD), an enzyme that converts glutamate to γ-aminobutyrate (GABA) and also protects neurons from excitotoxicity by promoting the expression of GAD in neurons [12]. IGF-1 also alleviates

neuronal damage caused by inflammation [13], oxidative stress [14], and hypoglycemia [15]. Astrocytes survive longer under ischemic conditions than neurons and reduce ischemia-induced changes in ionic gradients, glucose metabolism, and oxidative stress [16]. IGF-1 has also been reported to increase astrocyte survival [14] and further enhance these effects. Microglia are divided into the M1-type and M2-type, which are known to be injurious and protective, respectively, to brain tissues when activated. IGF-1 promotes the phenotypic change of microglia to M2 type and acts in a brain protective manner by reducing the production of tissue injurious factors, such as TNF-α, IL-1β, iNOS, and ROS [17].

The above mechanisms suggest that high serum IGF-1 level is associated with good outcomes at three months after onset in patients with hyperacute ischemic stroke treated with IV-tPA. Notably, the univariate analysis revealed that IGF-1levels correlate with patient outcomes. On the other hand, IGF-1 was not predictive of outcome in the multivariate analysis. One reason is that the serum IGF-1 level is known to decrease by 14% every 10 years in healthy elderly individuals [18]. As such, neuroprotection by IGF-1 is expected to be significantly affected by age. In fact, in our study, a significant negative correlation was observed between age and serum IGF-1 levels. It has also been reported that the incidence of lifestyle-related diseases, such as hypertension and diabetes mellitus, increases with decreasing serum IGF-1 levels [19]. This observation suggests that the risk of vascular injury may influence clinical outcome after cerebral infarction. Furthermore, serum D-dimer and

BNP levels often reflect the presence of atrial fibrillation, which is known to be suggestive of cardiac emboli [20]. Cardiac emboli has a poor prognosis compared to other stroke subtypes, but in this study, although D-dimer and BNP values were high in the poor outcome group, no difference was observed between stroke subtypes. This suggests that not only the type of cerebral infarction, but also other clinical factors such as infection and heart failure, may be involved in and influence prognosis. Although there was a difference in BMI between the good outcome group and the poor outcome group, multivariate analysis shows no significant differences. Some reports showed a positive correlation between body weight and serum IGF-1 levels in patients with BMI <25[21], while other showed no significant correlation was found between BMI and serum IGF-1 levels in age-corrected comparisons[22]. Therefore, no consensus has been reached.

Clinicians hope that IGF-1 preparations will improve the prevention and acute treatment of cerebral infarction; however, clinical studies have thus far not yielded positive results, and the introduction of IGF-1 preparations in clinical practice has not progressed. The reasons for this include the fact that young, healthy animal models are often used in experimental studies, whereas in clinical practice, the influence of background factors and response to treatment differ among elderly patients. Furthermore, in animal studies, evaluations after cerebral infarctions are often based on infarct size, whereas in clinical practice, efficacy is often judged on the basis of symptoms [23]. In addition, the effects of effective blood concentration and central transition are considered, and

studies are ongoing to determine the method of administration (transdermal, nasal, etc.), dosage, and timing of administration. Currently, endovascular therapy is used along with intravenous thrombolytic therapy in an increasing number of patients, and animal studies have shown that IGF-1 administration in combination with mechanical thrombectomy can reduce brain tissue damage [24]. Notably, further verification of this finding is needed.

There are several limitations of this study. First, since all patients in this study had disorders of the anterior circulation system, clinical outcomes may differ in patients with lesions in the posterior circulation system. Second, as serum IGF-1 levels were measured only once at the time of presentation, we could not examine the relationship between changes in serum IGF-1 levels over time and clinical outcome. Third, IGFBP3 values were not measured in this study. As mentioned above, IGFBP is involved in the action of IGF-1 as well as its receptors (IGF-1R, IGF-2R) in the central nervous system. In particular, it is possible that different results could have been obtained by measuring IGFBP3, which is greatly related to the action of IGF-1, and by examining the ratio of IGFBP3 to IGF-1.

Conclusion

In this study, we found that high serum IGF-1 level was associated with good outcomes at three months after stroke in patients who underwent intravenous thrombolytic therapy in the hyperacute

phase. In actual clinical practice, it is necessary to take into account the high possibility that serum IGF-1 levels affect clinical outcomes. This report is based on a small number of patients who received only intravenous thrombolytic therapy at a single institution, and future studies are warranted to examine a larger number of patients at other institutions or in combination with mechanical thrombectomy.

Reference

1) Rinderknecht E, Humbel RE: The amino acid sequence of human insulin-like growth factor I and its structural homology with proinsulin. J Biol Chem 253: 2769–2776, 1978. https://doi.org/10.1016/S0021-9258(17)40889-1

2) Bianchi VE, Locatelli V, Rizzi L: Neurotrophic and Neuroregenerative Effects of GH/IGF1. Int. J. Mol. Sci. 18: 244, 2017. https://doi.org/10.3390/ijms18112441

3) Salmon WD Jr, Daughaday WH: A hormonally controlled serum factor which stimulates sulfate incorporation by cartilage in vitro. J Lab Clin Med 49: 825–36, 1957.

4) Benarroch EE: Insulin-like growth factors in the brain and their potential clinical implications. Neurology. 79: 2148-2153, 2012. https://doi.org/10.1212/WNL.0b013e3182752eef

5) Smedt AD, Brouns R, Uyttenboogaart M, et al: Insulin-Like Growth Factor I Serum Levels Influence Ischemic Stroke Outcome. Stroke. 42: 2180-2185, 2011. https://doi.org/10.1161/STROKEAHA.110.600783

6) Sohrabji F: Estrogen-IGF-1 interactions in neuroprotection: Ischemic stroke as a case study. Front Neuroendocrinol 36: 1-14, 2015. http://dx.doi.org/10.1016/j.yfrne.2014.05.003

7) Yamaguchi T, Mori E, Minematsu K, et al: Alteplase at 0.6 mg/kg for Acute Ischemic Stroke Within 3 Hours of Onset. Japan Alteplase Clinical Trial (J-ACT). Stroke 37: 1810-1815, 2006. https://doi.org/10.1161/01.STR.0000227191.01792.e3

8) Wilczak N, Elting JW, Chesik D, et al: Intravenous Tissue Plasminogen Activator in Patients With Stroke Increases the Bioavailability of Insulin-Like Growth Factor-1. Stroke. 37: 2368-2371, 2006. https://doi.org/10.1161/01.STR.0000236496.30106.4b

9) Thomalla G, Simonsen CZ, Simonsen F, et al: MRI-Guided Thrombolysis for Stroke with Unknown Time of Onset. N Engl J Med 379: 611-622, 2018. DOI: 10.1056/NEJMoa1804355

10) Guan J, Bennet L, Gluckman PD, et al: Insulin-like growth factor-1 and post-ischemic brain injury. Prog. Neurobiol. 70: 443–462, 2003. https://doi.org/10.1016/j.pneurobio.2003.08.002

11) Czech, M.P: Signal transmission by the insulin-like growth factors. Cell 59: 235–238, 1989. https://doi.org/10.1016/0092-8674(89)90281-X

12) Guan J, Bennet L, George S, et al: Selective neuroprotective effects with insulin-like growth factor-1 (IGF-1) in phenotypic striatal neurons following ischemic brain injury in fetal sheep. Neuroscience 95: z831–839, 2000. https://doi.org/10.1016/S0306-4522(99)00456-X

13) Rodriguez-Perez AI, Borrajo A, Diaz-Ruiz C, et al: Crosstalk between insulin-like growth factor-1 and angiotensin-II in dopaminergic neurons and glial cells: role in neuroinflammation and aging. Oncotarget 7: 30049–30067, 2016. https://doi.org/10.18632/oncotarget.9174

14) Genis L, Dávila D, Fernandez S, et al: Astrocytes require insulin-like growth factor I to protect neurons against oxidative injury. F1000Res 3: 28, 2014. https://doi.org/10.12688/f1000research.3-28.v2

15) Cheng B, Mattson MP: IGF-I and IGF-II Protect Cultured Hippocampal and Septal Neurons against Calcium-mediated Hypoglycemic Damage. J Neurosci 12: 1558–1566, 1992. https://doi.org/10.1523/JNEUROSCI.12-04-01558.1992

16) Yamashita K, Vogel P, Fritze K, et al: Monitoring the temporal and spatial activation pattern of astrocytes in focal cerebral ischemia using in situ hybridization to GFAP mRNA: comparison with*sgp-2* and*hsp70* mRNA and the effect of glutamate receptor antagonists. Brain Res 735: 285–297, 1996. https://doi.org/10.1016/0006-8993(96)00578-1

17) Park SE, Dantzer R, Kelley KW, et al: Central administration of insulin-like growth factor-I decreases depressive-like behavior and brain cytokine expression in mice. J Neuroinflammation 8:12, 2011. https://doi.org/10.1186/1742-2094-8-12

18) Gasperi M, Castellano AE: Growth hormone/insulin-like growth factor 1 axis in neurodegenerative diseases. J Endocrinol Invest 33: 587-591, 2010. https://doi.org/10.1007/BF03346653

19) Hunt KJ, Lukanova A, Rinaldi S, et al: A potential inverse association between insulin- like growth factor I and hypertension in a cross-sectional study. Ann Epidemiol 16: 563–571, 2006. https://doi.org/10.1016/j.annepidem.2005.10.007

20) Lip GYH, Lip PL, Zarifis J, et al: Fibrin d-Dimer and β-Thromboglobulin as Markers of Thrombogenesis and Platelet Activation in Atrial Fibrillation. Circulation. 94: 425-431, 1996. https://doi.org/10.1161/01.CIR.94.3.425

21) Yamamoto H, Kato Y: Relationships between plasma insulin-like growth factor-1 (IGF-1) and body mass index (BMI) in adults. Endocr J. 40:41-45, 1993. https://doi.org/10.1507/endocrj.40.41

22) Sherlala RA, Kammerer CM, Kuipers Al, et al: Relationship Between Serum IGF-1 and BMI Differs by Age. J. Gerontol. A Biol. Sci. Med. Sci. 76:1303-1308, 2021. https://doi.org/10.1093/gerona/glaa282

23) Dirnagl U, Iadecola C, Moskowitz MA: Pathobiology of ischaemic stroke: an integrated view. Trends Neurosci. 22: 391–397, 1999. https://doi.org/10.1016/S0166-2236(99)01401-0

24) Parker K, Berretta A, Saenger S, et al: PEGylated insulin-like growth factor-I affords protection and facil- itates recovery of lost functions post-focal ischemia. Sci Rep 7: 241, 2017. https://doi.org/10.1038/s41598-017-00336-z

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Table1. Baseline characteristics

Number	52
Mean age (years)	72(41-91)
Gender (male)	32(62%)
BMI (kg/m^2)	22.9(15.5-44.7)
Stroke subtype	n(%)
Cardiac emboli	20(38.4%)
Large-artery atherosclerosis	11(21.2%)
Small-vessel occlusion	12(23.1%)
Paradoxical emboli	7(13.5%)
ESUS	2(3.8%)
Infarct size	n(%)
Small	29(56%)
Middle	18(35%)
Large	5(9%)
Insulin like growth factor-1 (ng/mL)	77(21-189)
Systolic blood pressure (mmHg)	161(102-236)
Blood glucose (mg/dL)	121(84-253)
Hypertension	33(63%)
Diabetes mellitus	9(17%)
Dyslipidemia	23(44%)
Atrial fibrillation	18(35%)
D-dimer (μg/mL)	0.8(0.3-26.9)
Brain natriuretic peptide (pg/mL)	94.4(2.4-742.4)
Creatinine (mg/dL)	0.74(0.39-1.49)
Injection time (minute)	178.5(23-775)
NIHSS onset	6(1-26)
mRS at 3months	1(0-6)

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Table 2. Comparison between good outcome group and poor outcome group

	Group1 mRS 0-1	Group2 mRS ≥2	p value
Number	37	15	
Mean age (years)	69(41-90)	79(64-91)	＜0.001*
Gender (male)	32(62%)	23(38%)	0.885
BMI (kg/m^2)	23.4(17.3-44.7)	20.7(15.5-29.4)	0.021*
Stroke subtype			0.533
Cardiac emboli	15(40.5%)	5(33.3%)	
Large-artery atherosclerosis	7(18.9%)	4(26.7%)	
Small-vessel occlusion	8(21.6%)	4(26.7%)	
Paradoxical emboli	2(5.3%)	0(0%)	
ESUS	5(13.5%)	2(13.3%)	
Infarct size			0.499
Small	22(59%)	7(47%)	
Middle	11(30%)	7(47%)	
Large	4(11%)	1(7%)	
Insulin like growth factor-1 (ng/mL)	83(23-189)	62(21-127)	0.032*
Systolic blood pressure (mmHg)	161(102-236)	159(108-236)	0.936
Blood glucose (mg/dL)	121(84-253)	116(93-179)	0.762
Hypertension	21(57%)	12(80%)	0.115
Diabetes mellitus	7(19%)	2(13%)	0.63
Dyslipidemia	18(49%)	5(33%)	0.314
Atrial fibrillation	12(32%)	6(40%)	0.603
D-dimer (μg/mL)	0.5(0.3-26.9)	1.3(0.3-10.4)	0.032*
Brain natriuretic peptide (pg/mL)	48.7(2.7-742.4)	143.8(27.4-529.1)	0.026*
Creatinine (mg/dL)	0.73(0.45-1.40)	0.77(0.39-1.49)	0.137
Injection time (minute)	179(23-775)	178(130-255)	0.739
NIHSS onset	5(1-26)	7(2-26)	0.096
mRS at 3months	1(0-1)	3(2-6)	＜0.004*

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Table 3. Univariate and multivariate analysis of IGF-1 value in good outcome group

	Odds ratio	95%CI	p value
univariate analysis	0.474	0.135-1.657	0.242
Adjusted by			
Age	0.908	0.218-3.779	0.894
D-dimer	0.597	0.161-2.217	0.441
BNP	0.597	0.161-2.217	0.441
BMI	0.988	0.965-1.011	0.302
Age and D-dimer	0.958	0.225-4.069	0.953
Age and BNP	0.947	0.222-4.44-1	0.941
Age and BMI	1.013	0.982-1.045	0.403
D-dimer and BNP	0.723	0.184-2.833	0.641
D-dimer and BMI	0.988	0.964-1.013	0.358
BNP and BMI	0.989	0.965-1.013	0.366
Age, D-dimer and BNP	1.022	0.234-4.455	0.977
Age, BNP and BMI	1.015	0.983-1.048	0.253
D-dimer, BNP and BMI	0.988	0.964-1.013	0.350
Age, D-dimer, BNP and BMI	1.016	0.982-1.051	0.361

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Figure 1. Patients recruitment flow chart

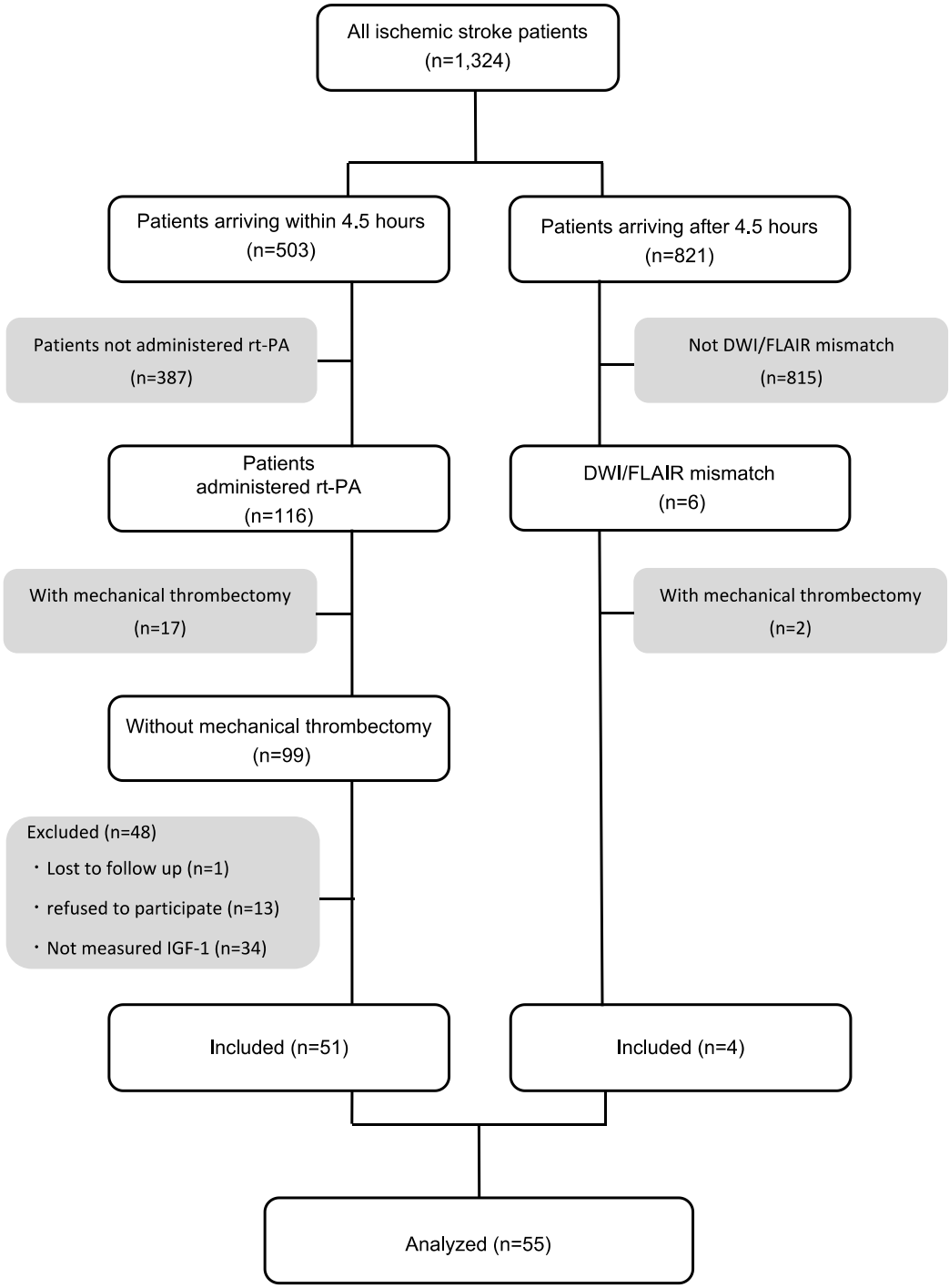

Figure 2. Comparison of IGF-1 values between good outcome group and poor outcome group

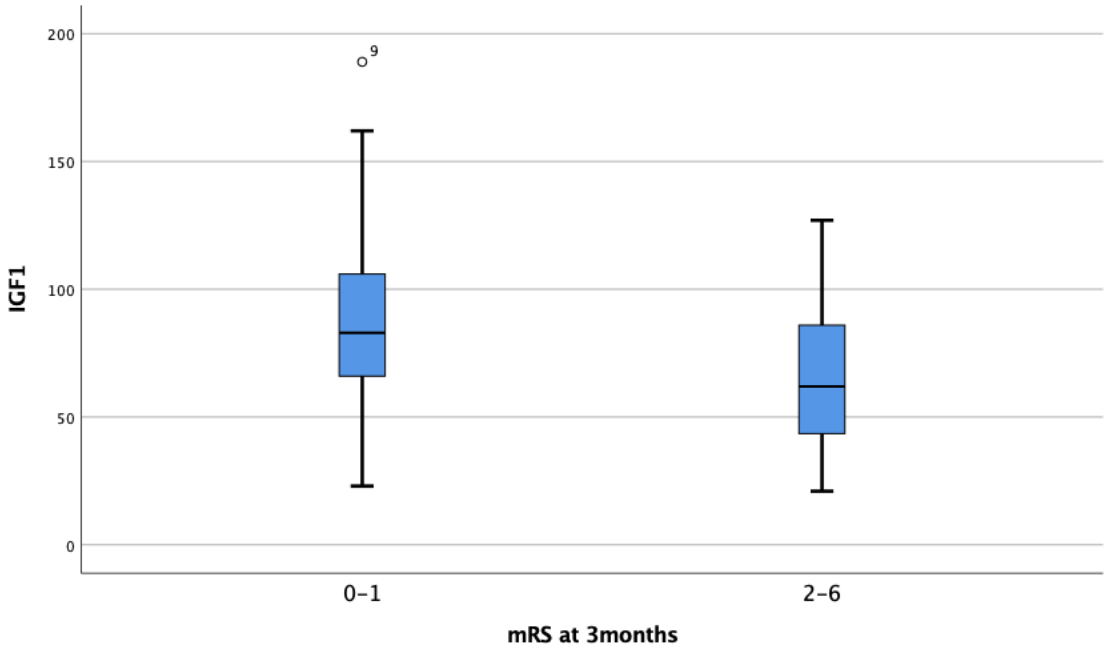

Figure 3. Scatter plot between age and serum IGF-1 levels

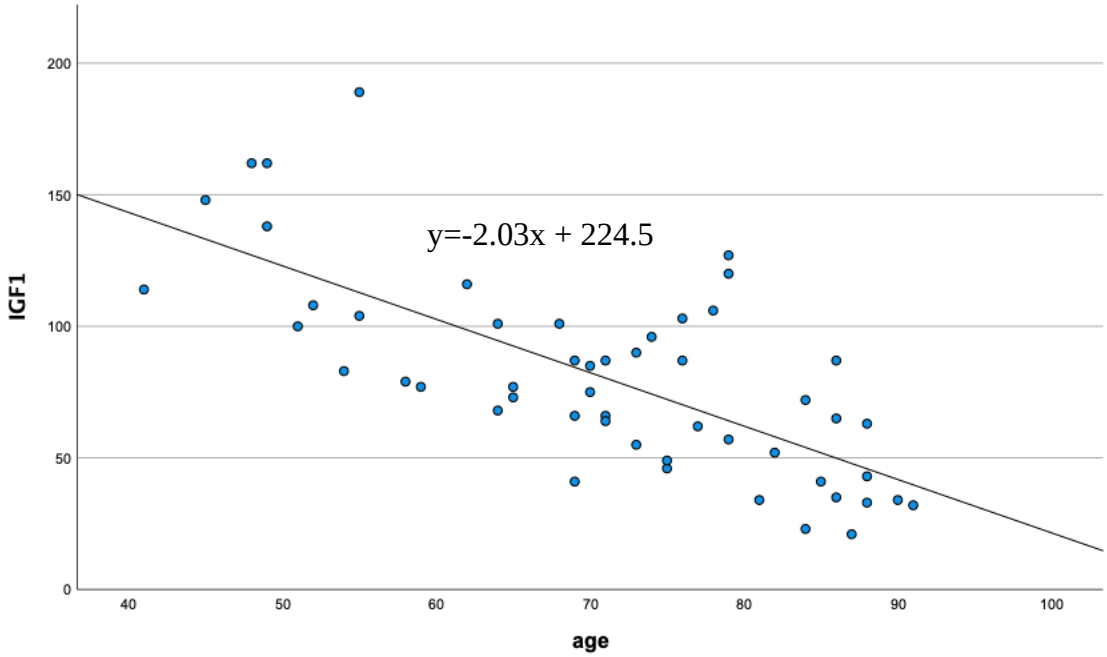

Figure Legends

Table 1. Baseline characteristics

Abbreviation: BMI, body mass index; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.

Table 2. Comparison between good outcome and poor outcome groups.

Three months after disease onset, patients with good outcomes (mRS 0-1) were significantly younger, had higher serum IGF-1, lower D-dimer, and lower BNP levels than those with poor outcomes (mRS ≥2), but there were no significant differences in NIHSS or rt-PA start time at disease onset.

Abbreviation: BMI, body mass index; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.

Table 3. Univariate and multivariate analysis of IGF-1 values in the good outcome group.

The serum IGF-1 levels in the good outcome group at three months after onset were investigated. Univariate logistic regression analysis showed that IGF-1 was not a significant factor (p 0.242, 95% confidence interval [0.135 -1.657]). The multivariate analysis adjusted for age, D-dimer, BNP and BMI also showed no association.

Abbreviation: BNP, brain natriuretic peptide; BMI, body mass index; CI, confidence interval.

Figure 1. Patient recruitment flow chart.

Figure 2. Comparison of IGF-1 values between good and poor outcome groups.

Comparison of serum IGF-1 levels between the good outcome group (mRS 0-1) and the poor outcome group (mRS≥2) at three months after disease onset showed significantly higher levels in the former ($p = 0.032$). Specifically, the good outcome group had a level of 83 ng/mL (median, range, 23- 189 ng/mL), while the poor outcome group had a level of 62 ng/mL (21-127 ng/mL).

Figure 3. Scatter plot between age and serum IGF-1 levels

There was a negative correlation between age and serum IGF-1 level (correlation coefficient -0.688, $p<0.0001$).