Serum Iron for Prognosis of Acute Ischemic Stroke by Endovascular Treatment

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Abstract

Background Iron, as an import micronutrient, is related to many diseases in a human body. Although the function of iron in acute ischemic stroke is yet debatable, there are few reports from clinical data on serum iron for the prognosis of acute ischemic stroke by endovascular treatment. The current retrospective study aimed to investigate the correlation between serum iron and acute ischemic stroke prognosis by endovascular treatment.

Methods This study was carried out retrospectively and 84 patients participated from March 2016 to April 2019 who suffered acute ischemic stroke and were treated by endovascular treatment at this stroke center. The laboratory test and clinical data were assessed for the prognosis of acute ischemic stroke by endovascular treatment. An independent relationship was analyzed through binary logistic analysis and receiver operating characteristic curves for the accuracy of the test.

Results This retrospective study was carried out at Harbin Medical University's Second Affiliated Hospital, and enrolled 84 patients from March 2018 to September 2019, including 32 patients in whom the outcomes were clinically favorable and 52 patients with unfavorable clinical outcomes. The groin puncture to recanalization time significantly varied between patients with favorable as well as unfavorable clinical outcomes (45.0 min vs 72.5 min, $p = 0.001$), serum iron (10.87 μmol/L vs 4.07 μmol/L, $p < 0.001$) and thrombin time (13.40 s vs 14.25 s, $p = 0.034$) from univariable analysis. Serum iron ($p < 0.001$; adjusted OR [95% CI]:70.765 [9.904 - 505.636]) was associated independently with acute ischemic stroke prognosis by endovascular treatment, and receiver operating characteristic showed area under the curve of 0.926 ($p < 0.001$, 95% CI: 0.872 - 0.979).

Conclusions The outcomes of this study reveal that serum iron level was associated independently with acute ischemic stroke prognosis, and high serum iron level could predict favorable clinical outcomes with a significantly accurate ability. Thus, serum iron could be a marker for acute ischemic stroke prognosis through endovascular treatment.

Introduction

Acute ischemic stroke (AIS) is lethal worldwide and is also the primary cause of death in China among people greater than 60 years. Acute ischemic stroke causes a high rate of morbidity and mortality. Treatments of acute ischemic stroke involve intravenous medical treatment (IVT) and endovascular treatment (EVT). EVT is confirmed as a prior method for acute ischemic stroke in recent years, which significantly improves the recanalization rate of occlusive intracranial large artery and prognosis of acute ischemic stroke [1–3]. No matter what therapy for acute ischemic stroke is advocated, an early evaluation marker for acute ischemic stroke is always important for improving clinically functional outcomes.

Iron is an essential nutrient as an enzyme cofactor in the mitochondrial respiratory chain, in the synthesis of DNA, and as a primary molecule for oxygen binding and transport by myoglobin and hemoglobin [4]. Peculiarly, both iron excess and deficiency may enhance the risk of causing thromboembolic events [5].

The focus is also on the level of serum iron in association with acute ischemic stroke. However, previous studies on the correlation between iron and acute ischemic stroke prognosis adopted IVT rather than EVT [6, 7]. This study aimed to investigate the correlation between serum iron and acute ischemic stroke prognosis through EVT.

Methods

Enrollment of Patients and Collection of Data

Acute ischemic stroke patients who had undergone EVT beginning from March 2018 until September 2019 at Harbin Medical University's Second Affiliated Hospital were enrolled retrospectively. The ethics committee of Second Affiliated Hospital of Harbin Medical University approved this study, and each patient gave a written consent. The authors had access to information that could identify individual participants.

Each patient followed the indications of acute ischemic stroke and associated EVT for: (1) a positive diagnosis of acute ischemic stroke; (2) age ≥ 18 years; (3) a large occlusion of intracranial artery; (4) the score of < 2 for premorbid modified Rankin Scale (mRS); (5) a score ≥ 6 for pretreatment National Institutes of Health Stroke Scale (NHISS) and score ≥ 6 for Alberta Stroke Program Early Computed Tomography Score (ASPECTS); (6) received a treatment within 6 hours of stroke onset, or in between 6 to 16 hours to be eligible for DEFUSE 3 or DAWN criteria [8, 9]; (7) having no concomitant potential cerebral hemorrhagic disease, such as arteriovenous malformation or aneurysm. We excluded patients with iron-related diseases for ensuring relative iron homeostasis.

The data acquired from the study center included primarily laboratory and clinical data. The information in clinical data pertained to age, sex (male), a medical history of disease including hypertension, diabetes mellitus (DM), atrial fibrillation (AF), coronary artery disease (CAD) and history of ischemic stroke, smoking status interpreted as a patient who smoked ≥1 cigarette each day continuously for six months. Severity assessment in patients, such as admission NIHSS by physical examination and ASPECTS by cranial computed tomography (CT) scan or magnetic resonance imaging (MRI). Further, IVT prior to EVT, number of patients treated between 6 to 16 h, symptom onset to groin puncture time (OTP), sites of occlusion judged by computed tomography angiography (CTA) or magnetic resonance angiography (MRA), and confirmed by digital subtraction angiography (DSA) including internal carotid artery (ICA), middle cerebral artery (MCA) and basilar artery (BA), groin puncture to recanalization time (GTR) and stroke causes judged by TOSAT classification were also included. After 90 days of EVT, assessment of mRS for patients' clinical outcomes was done through telephonic follow-up. The favorable and unfavorable clinical outcomes in terms of mRS were 0-2 and 3-6 [10]. The data for blood tests conducted at Harbin Medical University's Second Affiliated Hospital primarily contained serum calcium, prothrombin time (PT), prothrombin activity (PTA), prothrombin ratio (PTR), activated partial thromboplastin time (APTT), international normalized ratio (INR), fibrinogen (FIB), D-dimer, and thrombin time (TT). All the

patients were then grouped into two on the basis of mRS, with favorable clinical outcomes (mRS: 0-2) and unfavorable clinical outcomes (mRS: 3-6).

Endovascular Treatment Procedure and Post-procedure

Local or general anesthesia was given for EVT in patients with acute ischemic stroke. The enrolled patients were treated within 4.5 hours of the onset of symptom with IVT, and in some patients, beyond 4.5 hours from the onset of symptom, direct EVT with no IVT was performed. All patients with IVT were treated with recombinant tissue-type plasminogen activator (rt-PA). The SOLUMBRA technique was used for EVT [11].

Measurement of Serum Iron

Blood samples of all participants were collected before EVT within two hours. Blood samples were centrifuged immediately, aliquoted, and preserved at -80°C until further use. Measurement of serum iron levels was done by colorimetric method using 2,2-dipyridine-bipyridine (Solarbio, Beijing, China) as previously reported [12].

Statistical Analysis

Analyses of statistical data were done by SPSS 22.0 from IBM (Armonk, NY).

All categorical variables are represented as frequency (%) and number, and continuous variables were mentioned in terms of interquartile range (IQR) and median. Mann-Whitney U test or Student's T-test were used for continuous variables. Further, Fisher exact or $\chi 2$ tests were applied for categorical variables on univariate analysis. For independent relationships, multivariate binary logistic regression analysis was carried out, and variables with a possible association ($p < 0.1$) were included in the univariate analysis. The accuracy of blood biomarkers as a prognosis for acute ischemic stroke was assessed by the receiver operating characteristic curves (ROC), and the criterion for test accuracy was assessed by area under the curve (AUC). $p<0.05$ was deemed statistically significant with adjusted odds ratio (OR) and 95 % confidence interval (CI).

Results

A total of 84 patients with acute ischemic stroke participated in this study from March 2018 to September 2019 at Harbin Medical University's Second Affiliated Hospital. Each enrolled patient was tended using SOLITAIRE FR (Medtronic, USA) for EVT. There were 32 patients in the favorable clinical outcomes group and 52 patients in the unfavorable clinical outcomes group. Table 1 presents the collected data of all enrolled patients.

Clinical data and laboratory test were assessed with univariable analysis and presented in Table 2. No difference was observed among patients treated by mechanical thrombectomy and rescue therapy, no difference was observed on considering age (62 years vs 65 years, $p = 0.086$), male (65.63 % vs 76.92 %,

p = 0.259) and smoking (59.38 % vs 51.92 %, p = 0.505). There was also no variation in medical history of patients, including hypertension (53.13 % vs 59.62 %, p = 0.559), DM (21.88 % vs 23.08 % , p = 0.898), AF (28.13 % vs 23.08 %, p = 0.604), CAD (15.63 % vs 21.15 %, p = 0.531), history of ischemic stroke (15.63 % vs 15.38 %, p = 1.000). Endovascular treatment and its pre-procedure assessment were also non-significant between both groups in terms of admission NIHSS (14 vs 14, p = 0.933), ASPECTS (9 vs 8, p = 0.622) and OTP (243.5 min vs 261.5 min, p = 0.484). Here, a few patients received EVT beyond the window of standard time, being 6 hours of onset of symptoms, and these patients met eligibility criteria DEFUSE 3 or DAWN [8, 9]. We thus assessed this group of patients according to beyond time window, and this also showed insignificant effect on prognosis of acute ischemic stroke (18.75 % vs 23.08 %, p = 0.639). Insignificant difference was seen among favorable and unfavorable clinical outcomes in patients treated by IVT prior to EVT (31.25 % vs 26.92 %, p = 0.639). The primary judgement based on MRA or CTA and confirmed finally from DSA, in both groups the occlusion sites mainly contained the ICA (25.00 % vs 32.69 %), MCA (53.13 % vs 30.77 %), and BA (12.50 % vs 25.00 %). The occlusion sites between patients were not of significance (p = 0.110), and tandem occlusion was not significant (9.38 % vs 11.54 %, p = 1.000). GTR showed significant difference on prognosis of acute ischemic stroke (45.0 min vs 72.5 min, p = 0.001). A significant difference was observed in few laboratory tests between both groups, such as serum iron (10.87 μmol/L vs 4.07 μmol/L, p < 0.001), TT (13.40 s vs 14.25 s, p = 0.034], but serum calcium (2.24 μmol/L vs 2.21 μmol/L, p = 0.522), PT (10.95 s vs 10.90 s, p = 0.593), PTA (93.00 % vs 93.50 %, p = 0.423), PTR (1.02 vs 1.01, p = 0.605), INR (1.02 vs 1.01, p = 0.596), APTT (31.95 s vs 31.65 s, p = 0.728), FIB (3.12g/L vs 2.86 g/L, p = 0.064), D-dimer (223.00 ng/L vs 216.50 ng/L, p = 0.343) showed no difference.

In multivariate binary logistic regression analysis, each factor was analyzed after univariate analysis and exhibiting a potential association was mentioned in Table 3. Serum iron (p < 0.001, adjusted OR: 70.765, 95 % CI: 9.904 - 505.636) was independently associated with favorable clinical outcomes instead of age (p = 0.070, adjusted OR: 0.238, 95 % CI: 0.050 - 1.126), GTR (p = 0.082, adjusted OR: 0.270, 95 % CI: 0.062 - 1.182), FIB (p = 0.131, adjusted OR: 0.314, 95 % CI: 0.070 - 1.410) and TT (p = 0.168, adjusted OR: 0.336, 95 % CI: 0.071 - 1.584).

Sex difference and blood collection time directly influence serum iron levels in congruence with previous reports [13, 14]. In this study, we respectively divided all patients into two subgroups based on sex difference and iron in blood collection. The results showed that serum iron was still significantly associated with favorable clinical outcomes in male subgroup (11.18 μmol/L vs 4.67 μmol/L, p < 0.001) (Figure 1A) as well as in female subgroup (8.93 μmol/L vs 3.97 μmol/L, p < 0.001) (Figure 1B). We divided those patients based on blood collection time into 8:00 am to 15:00 pm and 15:00 pm to 8:00 am the next day, and we found that serum iron was also significantly associated with favorable clinical outcomes in 8:00 am to 15:00 pm (10.83μmol/L vs 5.21 μmol/L, p< 0.001) (Figure 1C) and 15:00 pm to 8:00 am (10.91 μmol/L vs 3.97 μmol/L, p < 0.001) (Figure 1D). This suggested that serum iron was not affected by sex difference and blood collection iron in the aspect of predicting acute ischemic stroke prognosis.

As an index to prognosis of the outcome, the serum iron level optimal cutoff value was projected based on the ROC curve to be 6.86 μmol/L, with 96.9 % sensitivity and 71.2 % specificity, and AUC of 0.926 ($p < 0.001$, 95 % CI: 0.872 - 0.979). serum iron showed a significantly accurate ability for prognosis of acute ischemic stroke by EVT.

Discussion

In humans, iron, as a necessary microelement, is associated with many diseases, and the exact function of iron in acute ischemic stroke is still debatable. However, a point worth confirming is that iron plays a role in the unfavorable prognosis of acute ischemic stroke and hemorrhage transmission [15, 16]. Nevertheless, those studies mainly adopted intravenous medicine treatment, and the actual recanalization was unclear, besides, the research on iron focused mainly on neurological protection and medical treatment after acute ischemic stroke. We evaluated serum iron for the prognosis of acute ischemic stroke again this time, it was different from the previous studies because we adopted EVT, which significantly enhanced the rate of recanalization of the occlusive intracranial arteries, as the primary treatment for acute ischemic stroke. In addition, the thrombi may be the main reason for the difference in the recanalization rate between IVT and EVT, so we mainly analyzed the common laboratory test related to the formation of thrombi or the structure of thrombi.

This retrospective study showed the potential use of serum iron as the marker for acute ischemic stroke, and a relatively high serum iron level was associated with favorable clinical outcomes without being affected by sex difference and blood collection time. It also showed greater accuracy for evaluating acute ischemic stroke prognosis from ROC curve. This study is the first to indicate a relationship between serum iron and the prognosis of acute ischemic stroke ensuring the recanalization of the occlusive arteries.

EVT is an effective method used currently for acute ischemic stroke, and this treatment can significantly improve recanalization rates. As we know, the most important factor that influences the prognosis of acute ischemic stroke is the recovery of blood flow in intracranial occlusive sites as soon as possible [17]. In a few recent studies, many neurologists focused on thrombi from patients with AIS after EVT [18, 19]. These studies suggested high erythrocyte fraction in thrombi seemed to indicate a certain correlation with favorable clinical outcomes by influencing number of attempts of stent retrieval in EVT from the later studies because more red blood cells in thrombi could increase friction between the thrombus and the stent so that the overall intracranial thrombus could be retrieved with stent retriever [20]. Thus, high erythrocyte fraction in thrombus may tend to minimize the procedure time of this treatment with first-pass complete reperfusion, and then better prognosis of acute ischemic stroke [21, 22].

It was traditionally thought that during thrombosis, the red blood cells in thrombi are associated with fibrin networks, and more dense fibrin networks could capture more red blood cells [23]. Because fibrin networks in thrombus might be related with coagulation factors, so we also analyzed the blood coagulation items in this study, including serum calcium, prothrombin time, prothrombin activity,

prothrombin ratio, D-dimer, activated partial thromboplastin time, international normalized ratio, fibrinogen, thrombin time, and tried to assess whether those items exited the relationship with prognosis of acute ischemic stroke. However, all of those did not indicate any positive findings. Results showed that only serum iron was independently associated with the prognosis of acute ischemic stroke. Maybe serum iron seemed to related to erythrocyte fraction or the fibrin networks in thrombi. Boguslaw Lipinski et al found that the increasingly high concentration of iron led to more dense fibrin networks as observed from scanning electron microscope in vitro[24, 25]. Etheresia Pretorius et al also found regulating iron-induced dense deposit formation could change the density of fibrin networks [26]. However, these studies could not explain the mechanism why serum iron-regulated erythrocyte fraction or fibrin networks in the thrombus. Thus, the relationship between serum iron and erythrocyte fraction must be explored in thrombi in vivo or in vitro. In addition, the previous evidences have suggested that brain iron homeostasis deregulation plays a part in carrying out neuronal damage post-acute ischemic stroke, and iron can be released from brain storage proteins after acute ischemic stroke [27]. However, we enrolled all patients without iron-related diseases to ensure serum iron maintained within the normal level in this study, and it might be explained because high serum iron level could predict a favorable clinical outcome by EVT under iron homeostasis.

There were some limitations to this retrospective study. First, all patients were enrolled from Harbin Medical University's Second Affiliated Hospital, thus, potentially may cause statistical bias because of the data was of a limited sample size from a single center. Meanwhile, we recognized there might be lots of biomarkers associated with prognosis of AIS, but we only concluded serum iron might be the markers in this study. It might be that we only analyzed the common laboratory test about the formation of thrombi or the structure of thrombi, and other biomarkers associated with prognosis of AIS might not influence the formation of thrombi or the structure of thrombi. Finally, although the results from this study were different from those of the previous studies, we did not intend to deny their conclusions. We investigated the correlation between serum iron and acute ischemic stroke prognosis again from other aspects.

To conclude, the results from this study showed that serum iron level was independently associated with the prognosis of acute ischemic stroke and that high serum iron could predict favorable clinical outcomes. Thus, serum iron could be used as a marker for the acute ischemic stroke prognosis by EVT.

Abbreviations

AIS: Acute Ischemic Stroke; IVT: Intravenous Medical Treatment; EVT: Endovascular Treatment; mRS: modified Rankin Scale; NIHSS: National Institute of Health Stroke Scale; APECTS: Alberta Stroke Program Early Computed Tomography Score; DM: Diabetes Mellitus; AF: Atrial Fibrillation; CAD: Coronary Artery Disease; CT: Computed Tomography; MRI: Magnetic Resonance Imaging; OTP: Symptom Onset to Groin Puncture Time; GTR: Groin Puncture to Recanalization Time; CTA: Computed Tomography Angiography; MRA: Magnetic Resonance Angiography; DSA: Digital Subtraction Angiography; rt-PA: recombinant tissue-type Plasminogen Activator; ICA: Internal Carotid Artery; MCA: Middle Cerebral Artery; BA: Basilar Artery; LAA: Large Artery Arteriosclerosis; CE: Cardiogenic Embolism; PT: Prothrombin Time; PTA:

Prothrombin Activity; PTR: Prothrombin Ratio; APTT: Activated Partial Thromboplastin Time; INR International Normalized Ratio; FIB Fibrinogen; TT Thrombin Time; IQR: Interquartile Range; OR: Odds Ratio; CI: Confidence Interval; ROC: Receiver Operating Characteristic Curves; AUC: Area Under the Curve.

Declarations

Ethical approval and consent to participate

This study was approved by the Ethics Committee of the Second Affiliated Hospital of Harbin Medical University (HMU). All patients received written consent before endovascular thrombectomy. This study conformed to the standards set by the Declaration of Helsinki and was approved by the medical ethics committee of HMU (KY2018-349). The study participants agreed to participate and provided written informed consent.

Consent for publication

Not applicable.

Conflict of interest statement:

The authors declare that they have no competing interests.

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Author Contributions

Chuanlu Jiang, Yongli Li, Mingli Liu designed the research study;

Mingli Liu, Zhongfei Hao collected the clinical data;

Mingli Liu, Zhongfei Hao analyzed the data;

Ruiyan Li, Yongli Li contributed to the procedure of operation and related clinical work;

Mingli Liu wrote the paper;

Jinquan Cai revised the paper.

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None

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Tables

Table 1. Clinical Data and Laboratory Data of All Enrolled Patients:

	All patients(N=84)
Age, median (IQR)	63(58.8-69)
Male sex, n (%)	61(72.62%)
Hypertension, n (%)	48(57.14%)
DM, n (%)	19(22.62%)
AF, n (%)	21(25.00%)
CAD, n (%)	16(19.05%)
History of ischemic stroke, n (%)	13(15.48%)
Smoking, n (%)	46(54.76%)
NIHSS score, median (IQR)	14(12-16)
ASPECTS, median (IQR)	9(8-10)
IVT, n (%)	24(28.57%)
EVT beyond time window, n (%)	18(21.43%)
OTP (min), median (IQR)	257.5(189.8-348.8)
Occlusion Sites, n (%)	
ICA	25(29.76%)
MCA	33(39.29%)
BA	17(20.24%)
Tandem Occlusion, n (%)	9(10.71%)
GTR (min), median (IQR)	67.5(43.8-90.0)
Stroke Cause, n (%)	
LAA	48(57.14%)
CE	21(25.00%)
Other	15(17.86%)
Preoperative blood test, median (IQR)	
Serum Iron (μmol/L)	7.06(3.29-10.42)
Serum Calcium (μmol/L)	2.23(2.14-2.32)
PT (sec)	10.90(10.40-11.50)
PTA (%)	93.00(85.00-102.25)
PTR	1.01(0.96-1.06)
INR	1.01(0.96-1.07)
APTT (sec)	31.80(29.35-35.20)
FIB (g/L)	2.90(2.58-3.43)
TT (sec)	13.90(13.00-14.70)

D-dimer (ng/mL)	221.0(128.00-440.50)

IQR Interquartile Range, DM Diabetes Mellitus, AF Atrial Fibrillation, CAD Coronary Artery Disease, NHISS National Institutes of Health Stroke Scale, ASPECTS Alberta Stroke Program Early Computed Tomography Score, IVT Intravenous Treatment, EVT Endovascular Treatment, OTP Symptom Onset to Groin Puncture Time, ICA Internal Carotid Artery, MCA Middle Cerebral Artery, BA Basilar Artery, GTR Groin Puncture to Recanalization Time, LAA Large Artery Atherosclerosis, CE Cardiogenic Embolism, PT Prothrombin Time, PTA Prothrombin Activity, PTR Prothrombin Ratio, APTT Activated Partial Thromboplastin Time, INR International Normalized Ratio, FIB Fibrinogen, TT Thrombin Time

Table 2. Univariate Analysis on Prognosis of Acute Ischemic Stroke:

	mRS (0-2) (N=32)	mRS (3-6) (N=52)	p value
Age, median (IQR)	62(54.8-65.2)	65(59.0-70.3)	0.086
Male sex, n (%)	21(65.63%)	40(76.92%)	0.259
Hypertension, n (%)	17(53.13%)	31(59.62%)	0.559
DM, n (%)	7(21.88%)	12(23.08%)	0.898
AF, n (%)	9(28.13%)	12(23.08%)	0.604
CAD, n (%)	5(15.63%)	11(21.15%)	0.531
History of ischemic stroke, n (%)	5(15.63%)	8(15.38%)	1.000
Smoking, n (%)	19(59.38%)	27(51.92%)	0.505
NIHSS score, median (IQR)	14(12-17)	14(13-16)	0.933
ASPECTS, median (IQR)	9(8-10)	8(8-10)	0.622
IVT, n (%)	10(31.25%)	14(26.92%)	0.670
EVT beyond time window	6(18.75%)	12(23.08%)	0.639
OTP (min), median (IQR)	243.5(187.3-348.8)	261.5(198.5-338.3)	0.484
Occlusion Sites, n (%)			0.110
ICA	8(25.00%)	17(32.69%)	
MCA	17(53.13%)	16(30.77%)	
BA	4(12.50%)	13(25.00%)	
Tandem Occlusion, n (%)	3(9.38%)	6(11.54%)	1.000
GTR (min), median (IQR)	45.0(30.0-80.0)	72.5(57.5-100)	**0.001**
Stroke Cause, n (%)			0.838
LAA	18(56.25%)	30(57.69%)	
CE	9(28.13%)	12(23.08%)	
Other	5(15.63%)	10(19.23%)	
Preoperative blood test, median (IQR)			
Serum Iron (μmol/L)	10.87(8.89-12.32)	4.07(2.31-7.16)	**<0.001**
Serum Calcium (μmol/L)	2.24(2.17-2.28)	2.21(2.10-2.33)	0.522
PT (sec)	10.95(10.40-11.83)	10.90(10.40-11.5)	0.593
PTA (%)	93.00(83.75-101.00)	93.50(85.75-103)	0.423
PTR	1.02(0.96-1.09)	1.01(0.96-1.06)	0.605
INR	1.02(0.96-1.09)	1.01(0.96-1.07)	0.596
APTT (sec)	31.95(29.55-34.52)	31.65(29.35-35.40)	0.728
FIB (g/L)	3.12(2.67-3.68)	2.86(2.56-3.39)	0.064
TT (sec)	13.40(12.78-14.33)	14.25(13.38-14.9)	**0.034**

D-dimer (ng/mL)	223.00(110.75-338.75)	216.50(139.75-475.50)	0.343

IQR Interquartile Range, DM Diabetes Mellitus, AF Atrial Fibrillation, CAD Coronary Artery Disease, NHISS National Institutes of Health Stroke Scale, ASPECTS Alberta Stroke Program Early Computed Tomography Score, IVT Intravenous Treatment, EVT Endovascular Treatment, OTP Symptom Onset to Groin Puncture Time, ICA Internal Carotid Artery, MCA Middle Cerebral Artery, BA Basilar Artery, GTR Groin Puncture to Recanalization Time, LAA Large Artery Atherosclerosis, CE Cardiogenic Embolism, PT Prothrombin Time, PTA Prothrombin Activity, PTR Prothrombin Ratio, APTT Activated Partial Thromboplastin Time, INR International Normalized Ratio, FIB Fibrinogen, TT Thrombin Time

Table 3. Multivariate analysis on Prognosis of Acute Ischemic Stroke:

	Multivariate Analysis	
	p value	adjusted OR (95%CI)
Age	0.070	0.238 (0.050-1.126)
GTR	0.082	0.270 (0.062-1.182)
Serum Iron	**<0.001**	70.765 (9.904-505.636)
FIB	0.131	0.314 (0.070-1.410)
TT	0.168	0.336 (0.071-1.584)

OR Odds Ratio, CI Confidence Interval, GTR Groin Puncture to Recanalization Time, FIB Fibrinogen, TT Thrombin Time.

Figures

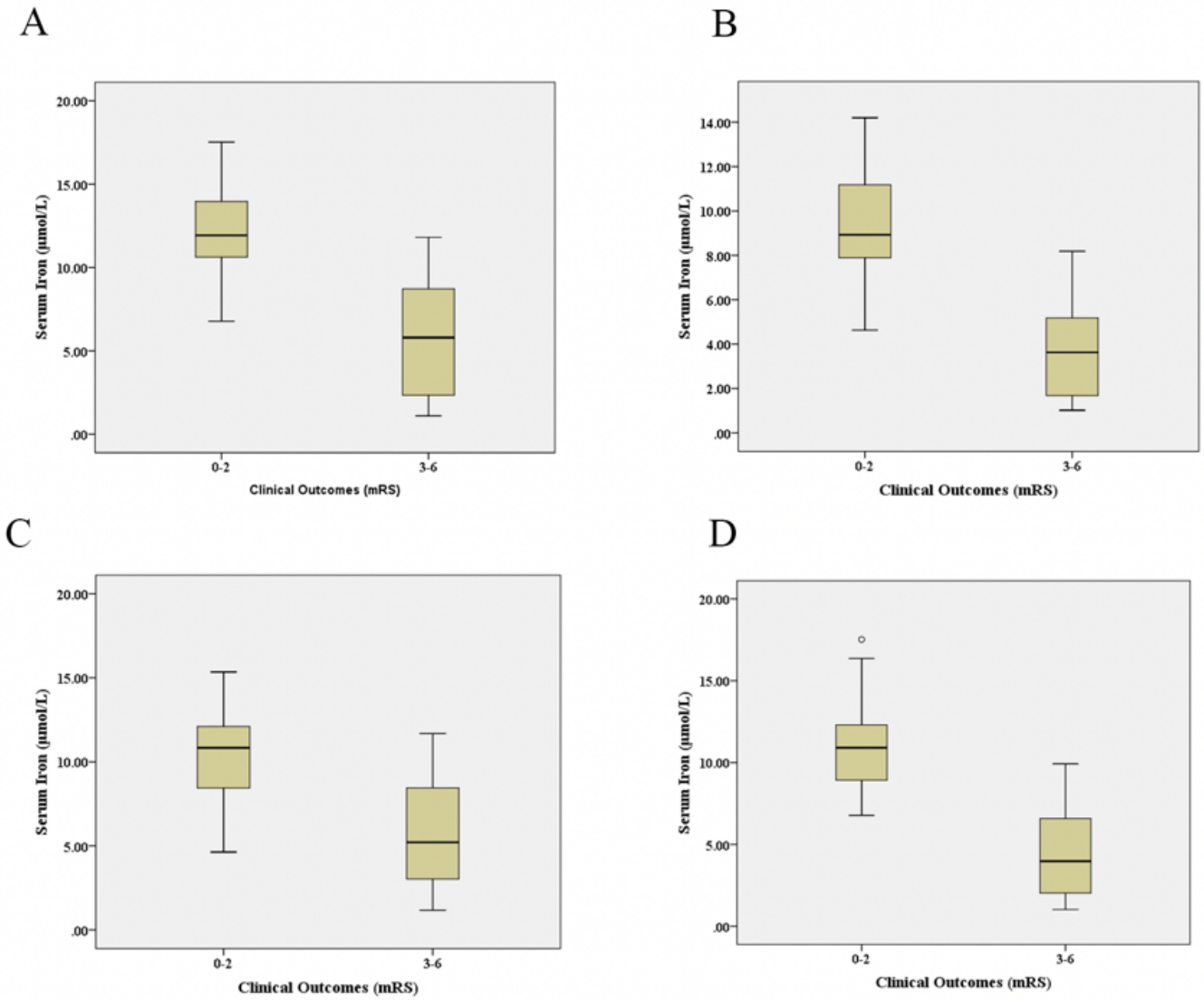

Figure 1

Serum Iron for Prognosis of Acute Ischemic Stroke in Sex Subgroup and Blood Collection Time Subgroup: Serum iron was significantly associated with favorable clinical outcomes in male subgroup [11.18 μmol/L (10.42 - 13.54 μmol/L) vs 4.67 μmol/L (2.33 - 7.68 μmol/L), p < 0.001] (A) as well as in female subgroup [8.93 μmol/L (7.89 - 11.18 μmol/L) vs 3.97 μmol/L (2.19 - 5.48 μmol/L), p < 0.001] (B). Serum iron was also significantly associated with favorable clinical outcomes in 8:00 am to 15:00 pm [10.83 μmol/L (8.44 - 12.11 μmol/L) vs 5.21 μmol/L (3.08 - 8.31 μmol/L), p < 0.001] (C) and 15:00 pm to 8:00 am [10.91 μmol/L (8.93 - 12.30 μmol/L) vs 3.97 μmol/L (2.05 - 6.58 μmol/L), p < 0.001] (D).

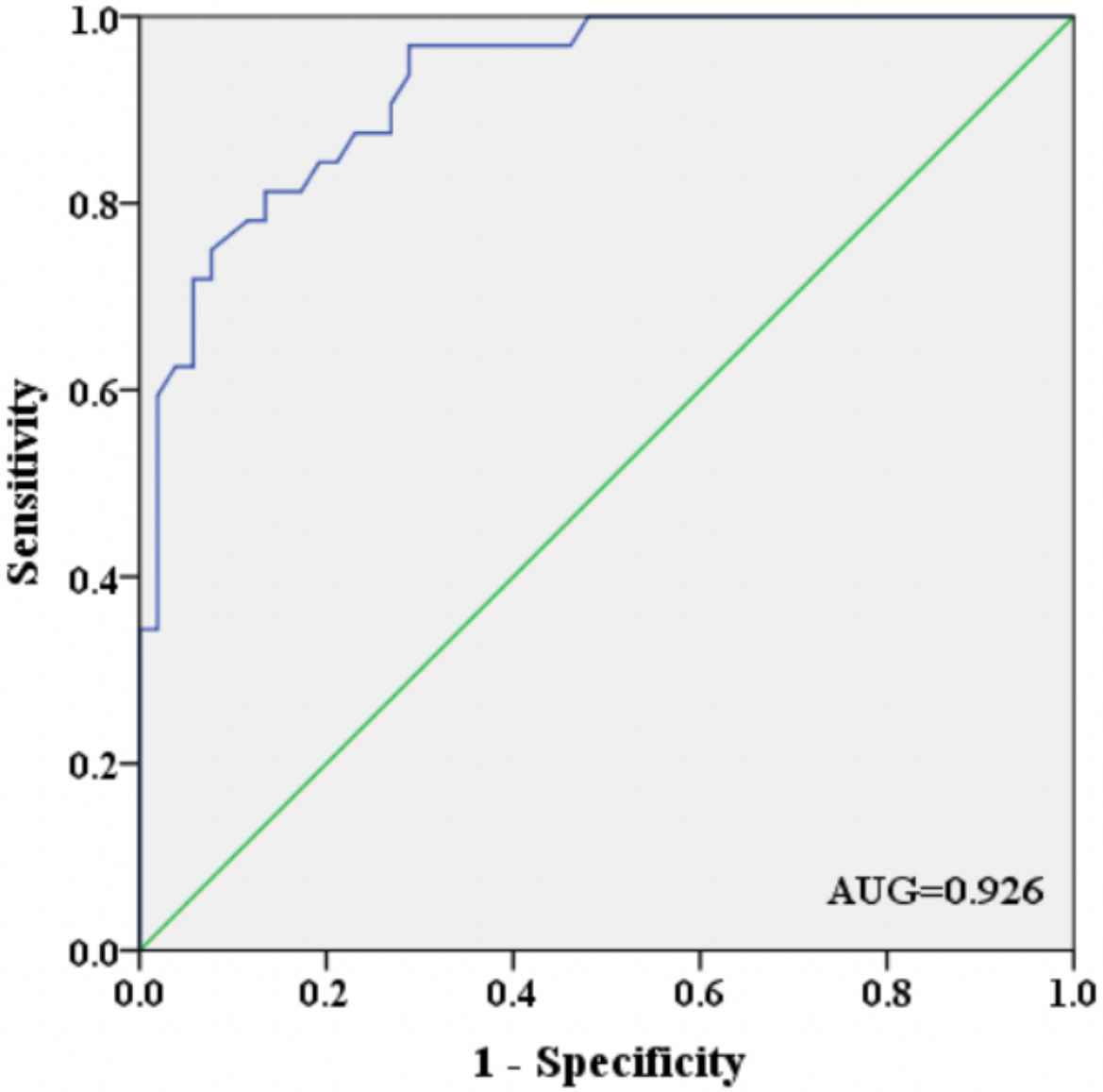

Figure 2

Accuracy of Serum Iron on Acute Ischemic Stroke Prognosis: Serum iron on acute ischemic stroke prognosis exhibited 96.9 % sensitivity and 71.2 % specificity, with an AUC of 0.926 [$p < 0.001$, 95 % CI: 0.872 - 0.979] from ROC curve.