Higher serum lactate dehydrogenase level predicts poor outcome of aneurysmal subarachnoid hemorrhage after microsurgery

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Abstract

We explored the clinical significance of serum LDH level in aSAH patients after microsurgical clipping in our single institution, to test the hypothesis that higher serum LDH level predicts the outcome of aSAH patients at 3 months. A total of 2054 aSAH patients were collected, and 874 patients treated by microsurgical clipping were enrolled. And the serum LDH level within 24 hours after aSAH were recorded. The median serum LDH level (U/L) in the good outcome group (180.096±50.237) was obviously lower than that in the poor outcome group (227.554±83.002)(p=0.000). The area under the receiver operating characteristic (ROC) curve was 0.702(95% confidence interval [CI], 0.650 - 0.754; p=0.000). The optimal cutoff value for serum LDH level as a predictor for 3-month poor outcome (mRS>2) was determined as 201.5U/L in the ROC curve. Our finding showed that that higher serum LDH level correlated with Hunt & Hess grade, Fisher grade and neurological functional outcome, and predicted the outcome of aSAH at 3 months, which was involved in the related mechanisms of early brain injury and showed its great clinical significance in aSAH patients.

Background

Several risk factors, such as hypertension, poor Hunt & Hess grade, higher Fisher grade, hydrocephalus, pneumonia and treatment modalities, contributed to the poor prognosis for aSAH [19-21] . However, few reports have explored the clinical significance of serum LDH level in patients with aneurysmal subaracrhnoid hemorrhage(aSAH), and the role of LDH in aSAH were not fully established. It was conceivable that there were at least the following two factors contributed to higher serum LDH level in aSAH patients: (1)LDH originated from apoptotic/necrotic/damaged neuron or glial cells. (2) LDH from lytic red blood cells(RBC) after being released into cerebrospinal fluid(CSF). As Lu Y reported, the amount of apoptotic/necrotic/damaged cells positively correlated to clinical condition of aSAH patients and their Hunt& Hess grade[22]. Similarly, the amount of RBC in cerebra cisterna, sulcus and/or ventricle correlated to Fisher grade. Frontera JA found that early brain ischaemia injury associated with worse Hunt-Hess grade, which is related to poor acute neurological status and correlated with worse functional outcomes after SAH[23]. Claassen J's study showed that SAH completely filling cistern or fissure and intraventricular hemorrhage (IVH) on CT were risk factors for delayed ischemic neurological deficit (DIND)[24], which correlated with the poor outcomes after SAH. However, few reports have explored the relation between serum LDH level and the extent of cerebral tissue injury in aSAH patients. Here, we explored the clinical significance of serum LDH in aSAH patients treated by microsurgical clipping in our single institution, to test the hypothesis that higher serum LDH level, which could correlate with Hunt & Hess grade and Fisher grade, and predicted the outcome of aSAH patients at 3 months.

Methods

Inclusion and exclusion criteria. Patients were enrolled in the study based on the following criteria: 1) Diagnosis of subarachnoid hemorrhage was confirmed by Computed Tomography (CT). Computerized tomography angiography (CTA) or digital subtraction angiography (DSA) was used to confirm the presence of the intracranial aneurysm. 2) All aneurysms treated by microsurgical clipping, and CTA and/or DSA were performed postoperatively. The exclusion criteria were: 1) aSAH was detected over 1 day; 2) The patients with the other cerebrovascular diseases (such as cerebral arteriovenous malformations, intracranial arteriovenous fistula, and moyamoya syndrome/disease) and intracranial tumors. 3) The patients with myocardial infarction, hepatitis, malignant tumor, pulmonary infarction, leukemia, hemolytic anemia, kidney disease or progressive muscular atrophy, etc. The aSAH patients in our institution between 2010 and 2018 were collected. Age, sex, history of smoking, drinking, medical history(hypertension、diabetes、coronary heart disease、cerebral stroke), Hunt-Hess and Fisher grade, aneurysm location, delayed ischemic neurological deficit (DIND), intracranial infection, hydrocephalus, pneumonia and the serum LDH level within 24 hours after aSAH were recorded.

Treatment definition. After being confirmed, ruptured intracranial aneurysms were treated with microsurgical clipping. After surgical management, the patients were treated according to the current guidelines for aneurismal subarachnoid hemorrhage[25], including prevention or re-versal of the cerebral arterial narrowing, improving cerebral blood flow, neurotrophic treatment, stress ulcer prevention and nutritional support.

Follow-up visit and definition of outcome. Postoperative complications were evaluated with CT scanning within 24 hours after surgical treatment. The neurological outcome was assessed at the 3-month follow-up and classified according to the modified Rankin Scale (mRS) score: a good clinical outcome was defined as mRS 0–2, a poor outcome as mRS 3–6. We divided the functional outcome into four levels according to mRS namely no symptoms (mRS 0), no significant to slight disability (mRS 1-2), moderate to serious disability (mRS 3-4) and severe disability to death (mRS 5-6). To define the relation between serum LDH level and clinical outcome of aSAH patients, we investigated the whether the serum LDH level was associated with Hunt-Hess grade, Fisher grade and the upper four functional outcome.

Standard protocol approvals and patient consents. All procedures performed in this retrospective study involving human participants were on the basis of the 1964 Helsinki declaration and approved by the ethics committee of First Affiliated Hospital of Fujian Medical University. Informed consent was obtained from all individual participants enrolled in the study.

Statistical analysis. All the statistical analyses were performed utilizing SPSS for windows version 25.0 (IBM Corp., Armonk, NY, USA). One-way analysis of variance (ANOVA) or Student's t test was used to determine the significance of differences in continuous data. Chi-squared test ($\chi 2$ test) or Fisher's exact test was used to determined the significance of differences in qualitative data. Multivariable analysis logistic regression model included all variables whose p value was less than 0.10 in univariate analysis. For inclusion in the multivariable analysis model, age was divided into “less than 65 years” and “more than 65 years”[26], Hunt-Hess grade divided into “low grade (Grade Ⅰ-Ⅱ)” and “high grade (Grade Ⅲ-V)”, Fisher grade divided into “low grade (Grade 1,2,3)” and “high grade (Grade 4)” , serum LDH level as “≤ optimal cutoff value ” and “ optimal cutoff value ”. P<0.05 was deemed statistically significant. Receiver operating curve (ROC) (MedCalc for windows version 15.2.2 , Mariakerke, Belgium)was generated to analyze the specificity, sensitivity of serum LDH level for mRS. Propensity-score matching (PSM) analysis was performed to remove imbalances in basic clinical characteristics between good outcome and poor outcome groups, which was also performed between pneumonia and non-pneumonia groups. Conditional probability was estimated with the logistic regression model. The good outcome and poor outcome groups were matched at a ratio of 1:1 using the nearest neighboring matching algorithm.

Results

A total of 2054 aSAH patients in our institution between 2010 and 2018 were collected, and 874 patients treated by microsurgical clipping were enrolled based on the upper criteria (figure 1). Incidence of poor outcome following aSAH was 13.8%(121/874). Basic clinical characteristics of patients with aneurysmsal subarachnoid hemorrhage were shown on table 1 and 2. The median serum LDH level(U/L) in the good outcome group (180.096±50.237) was obviously lower than that in the poor outcome group (227.554±83.002)(p=0.000). The receiver operating characteristic (ROC) curve of serum LDH level for poor outcome of aSAH patients at the 3-month follow-up is shown in Figure 2. The area under the ROC curve (AUC) was 0.702(95% confidence interval [CI], 0.650 - 0.754; p=0.000). The optimal cutoff value for serum LDH level as a predictor for 3-month poor outcome (mRS>2) was determined as 201.5U/L in the ROC curve. On this level, the sensitivity was 59.5%, the specificity was 76.4%.

In order to analyze the predictors for poor outcome of aSAH patients, the variables significance level at p < 0.10 including age、hypertension、diabetes、Hunt-Hess、Fisher、anterior communicating artery aneurysm, basilar artery aneurysm, delay ischemic neurological deficit(DIND), hydrocephalus, pneumonia, serum LDH(>201.5U/L) were included in the univariate analysis. The results revealed that age, hypertension, Hunt-Hess grade、Fisher grade, delay ischemic neurological deficit, hydrocephalus, pneumonia, serum LDH(>201.5U/L) were associated with 3-month poor outcome(table 2, p < 0.05). In multivariate analysis, however, Hunt-Hess grade、Fisher grade, delay ischemic neurological deficit, pneumonia, serum LDH(>201.5U/L) were still significantly associated with outcome, whereas, age、hypertension, diabetes, anterior communicating artery aneurysm, basilar artery aneurysm and hydrocephalus were not. Patients with Hunt-Hess grade IV-V had a 1.6-fold increased risk of developing poor outcome (OR 1.637, 95% CI 1.266-2.118, p=0.000). Fisher grade 4 had a 1.5-fold increased risk of developing poor outcome(OR 1.517, 95% CI 1.182-1.946, p=0.001). DIND had a 4.2-fold increased risk of developing poor outcome(OR 4.234, 95% CI 2.412-7.432, p=0.000). Pneumonia had a 3.8-fold increased risk of developing poor outcome(OR 3.848, 95% CI 2.386-6.206, p=0.000). Serum LDH level greater than >201.5U/L was associated with a 2.7-fold increase risk of developing poor outcome(OR 2.702, 95% CI 1.645-4.440, p=0.000) (table 2). After PSM, there were no significant differences in Hunt-Hess grade、Fisher grade, delay ischemic neurological deficit, pneumonia between good outcome and poor groups (table 1 and 2). In the logistic regression model (table 2), serum LDH(>201.5U/L) was still considered as an independent risk factor of poor outcome (OR 2.426, 95% CI 1.378-4.271, p = 0.002).

Interestingly, we found that serum LDH level was associated with Hunt-Hess and Fisher grade, it was revealed that serum LDH level(U/L) was 163.880±35.571 in Hunt-Hess grade Ⅰ group, which was lower than that in Ⅱ (174.981±49.616), Ⅲ (188.306±50.702), Ⅳ (225.609±69.509), and Ⅴ (252.851±93.302). There were statistically significant differences between groups (p=0.000), and there was obvious trend that serum LDH level will increase concomitantly with increasing grade of Hunt-Hess (shown in figure 3). Serum LDH level was 169.492±41.621 in Fisher grade 1 group, which was lower than that in grade 2 (177.097±42.621), grade 3(198.709±72.553) and grade 4 (210.811±68.962). There were statistically significant differences between grade 4 vs 3, 4 vs 2, 4 vs 1, 3 vs 2, 3 vs 1(p=0.000). There was obvious trend that serum LDH level will increase concomitantly with increasing Fisher grade(show in figure 4).

It was also shown that serum LDH level correlated with neurological functional outcome. Serum LDH level was 179.247±46.761 in no symptoms (mRS 0) group, which was lower than that in no significant to slight disability (mRS 1-2) (193.977±69.399), moderate to serious disability (mRS 3-4) (205.918±59.203) and severe disability to death (mRS 5-6) (234.188±108.336). There were statistically significant differences (p=0.000). There was obvious trend that serum LDH level would increase with deterioration of neurological function (show in figure 5).

Discussion

Our findings showed that there was obvious trend that serum LDH level will increase concomitantly with increasing Hunt & Hess and Fisher grade. And it was indicated that Hunt-Hess grade、Fisher grade, delay ischemic neurological deficit, pneumonia, higher serum LDH level could

predicted and contributed to the poor outcome of aSAH patients at 3 months. The optimal cutoff value for serum LDH level as a predictor for the 3-month poor outcome (mRS>2) was determined as 201.5U/L. It was also shown that serum LDH level correlated with neurological functional outcome. There was obvious trend that serum LDH level would increase with deterioration of neurological function. After PSM, Serum LDH(>201.5U/L) was still considered as an independent risk factor of poor outcome.

It was demonstrated that subarachnoid clots in sulci/fissures would induce spreading depolarizations and acute cerebral infarction of adjacent cortex[27], which were major players in the mechanism of early brain injury after SAH[28] and contributed to the clinical condition of aSAH patients. Frontera JA's study[23] indicated that the early ischemic brain injury was elated to worse Hunt-Hess grade, Glasgow Coma Scale(GCS) score, higher rates of death, severe disability/death (mRS 4-6) at the 3-month follow-up. And the increase in ischemic lesion volume was associated with the increase on the Hunt-Hess grade and the 3-month mRS[29]. In other words, Hunt-Hess grade correlates with the degree of early ischemic brain injury to some extent.

It was known that neuronal apoptosis and necrosis was present 24 h after SAH[27,30], which could result in cytolysis and cell membrane destruction. Then LDH will be released into the blood from damaged or dead cells and resulting in serum LDH increase[4]. Therefore, serum LDH level reflects the severity of brain tissue injury. Yu W's study[14] demonstrated that serum LDH activities were associated with the infarct volume and degree of middle cerebral artery occlusion in a dose-dependent manner. Study showed that LDH quantification were used to predict the neuronal damage[15,16], and inhibition of LDH release might reduce neuronal apoptosis[14]. Rao CJ's report showed that a significant rise of serum LDH level was a predictor of severe brain damage and the poor prognosis of traumatic brain injury[17]. In addition, Engelke S's study indicated that LDH was also significantly correlated with subsequent seizures, hydrocephalus and the adverse long-term outcome of neonatal intracranial hemorrhage[18].

It was suggested that serum LDH level were correlated with the prognosis of adult T-cell leukemia-lymphoma[6], prostate cancer[7], acute myeloid leukemia[8], melanoma[9], neuroblastoma[10], glioblastoma multiforme[11], acute encephalopathy[12] and mycoplasma pneumoniae pneumonia[13].To our best knowledge, there were few reports investigating the relationship between LDH and aSAH. It was demonstrated that regional cerebral blood flow and arteriovenous difference of oxygen would be reduced due to the primary injury of aSAH[31], and cerebral ischemia would caused an anaerobic shift of metabolism with lactic acidosis and upregulation of serum LDH level[32]. It was reported that there was significant correlation between serum LDH and lactic acid levels, and both of them reflected the degree of tissue damage[31,33]. Shimoda M's report[34] indicated that World Federation of Neurosurgical Societies (WFNS) Grade III-V showed significantly higher lactic acidosis than Grade I-II. Therefore, we deduced that Hunt & Hess grade IV-V also showed higher serum LDH level than I-III. There was an obvious trend that serum LDH level will increase concomitantly with increasing Hunt & Hess grade in our study. Thus, we deduced that serum LDH level exactly did correlate with Hunt & Hess grade, which reflects the degree of early brain injury and clinical condition of aSAH patients.

The greater the amount of blood within subarachnoid space, the higher Fisher grade, which correlated with poor outcome of aSAH[35,36]. After cerebral aneurysm rupture, destruction of blood brain barrier occurred and RBC was released into the subarachnoid space from artery as a consequence of cerebral aneurysm rupture, the RBC in cerebrospinal fluid(CSF) would broke down[36], LDH from lytic RBC was absorbed into blood after being released into CSF[17]. The levels of serum LDH would increase. Our findings showed that there was also an obvious trend that serum LDH level will increase concomitantly with increasing Fisher grade. Thus, higher serum LDH level was associated with higher Fisher grade, which was closely related to poor outcome of aSAH consistent with the previous reports[35,37,38].

Our study has some limitations. First, LDH exists in all important human organs, and it lacks specificity to central nervous system. The LDH from CSF in our patients was not measured and collected, the serum LDH level does not reflect the true level in the brain tissue directly. Second, the imaging data were not available to confirm the relationship between serum LDH level and degree brain tissue damage, which can not be clarified intuitively. Third, the serum LDH level(>201.5U/L) in a proportion of patients was within normal range, and it can not be fully explained why these patients suffered from poor prognosis, the detailed mechanism needs further exploration.

Conclusions

Our finding showed that that higher serum LDH level correlated with Hunt & Hess grade, Fisher grade and neurological functional outcome, and predicted the outcome of aSAH patients at 3 months, which was involved in the related mechanisms of early brain injury and showed its great clinical significance in aSAH patients.

Declarations

Data availability

All data generated or analysed during this study are included in this published article.

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Author contributions

Acquisition of data and Critical revision of manuscript for intellectual content: S.F.Z., H.J.W., G.R.C., H.C.S.G., and L.H.Y.(These authors contributed equally to the manuscript).Study supervision: Y.X.L. Study concept and design: Z.Y.L, P.S.Y. and D.Z. K. Analysis and interpretation of data and Study supervision: P.S.Y. and D.Z.K. All authors reviewed the manuscript.

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Additional Information

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Tables

Table 1 Basic clinical characteristics of patients with aneurysmsal subarachnoid hemorrhage before and after propensity-score matching

	Before propensity-score matching			After propensity-score matching		
General information	Good outcome	Poor outcome	P value	Good outcome	Poor outcome	P value
	(n=753)	(n=121)		(n=101)	(n=101)	
Age			0.043			0.128
≤65yrs	645	95		74	83	
>65 yrs	108	26		27	18	
Age range(y)	10-86	22-85		10-85	22-85	
Sex			0.193			0.240
Male	302	41		40	32	
Female	451	80		61	69	
Smoking	115	7	0.593	11	6	0.205
Drink	75	7	0.144	9	5	0.268
Medical history						
Hypertension	327	73	0.001	61	59	0.774
Diabetes	40	11	0.100	8	7	0.788
Coronary heart disease	9	2	0.675	2	1	0.561
Cerebral stroke	13	2	0.954	2	1	0.561
Hunt-Hess grade			0.000			0.196
0-III	677	58		65	56	
IV-V	76	63		36	45	
Fisher			0.000			0.396
1–3	621	57		59	53	
4	132	64		42	48	
Location of Aneurysm						
Internal carotid artery	141	25	0.614	12	20	0.123
Anterior choroidal artery	25	4	0.994	2	3	0.651
Ophthalmic artery	18	2	0.615	0	2	0.155
Posterior communicating artery	160	24	0.723	25	19	0.306
Middle cerebral artery	171	33	0.271	23	29	0.334
Anterior communicating artery	230	47	0.069	37	41	0.563
Basilar artery	4	3	0.026	0	1	0.316
Anterior cerebral artery	49	6	0.515	8	3	0.121
Posterior cerebral artery	6	2	0.359	0	2	0.155
Delay ischemic neurological deficit	74	43	0.000	29	30	0.877
Hydrocephalus	117	54	0.000	38	40	0.773
Intracranial infection	53	13	0.152	12	11	0.825
Pneumonia	148	79	0.000	65	61	0.561
Serum Lactate dehydrogenase (>201.5U/L)	178	72	0.000	38	60	0.002

Table 2 Predictors for poor outcome of aSAH in multivariate model

	univariate analysis				multivariate analysis				After propensity-score matching			
	OR(95%CI)				OR(95%CI)				OR(95%CI)			
Independent Variable	OR	lower	upper	P value	OR	lower	upper	P value	OR	lower	upper	P value
Age	1.025	1.008	1.043	0.004	1.019	0.998	1.040	0.075				
Hypertension	1.981	1.339	2.931	0.001	0.876	0.528	1.451	0.606				
Diabetes	1.782	0.888	3.578	0.104	1.056	0.436	2.557	0.904				
Hunt-Hess IV-V	2.746	2.244	3.360	0.000	1.637	1.266	2.118	0.000				
Fisher 4	2.445	1.994	2.998	0.000	1.517	1.182	1.946	0.001				
Anterior communicating artery aneurysm	1.444	0.971	2.148	0.070	1.048	0.636	1.727	0.855				
Basilar artery aneurysm	3.803	0.897	16.125	0.070	3.296	0.479	22.693	0.226				
Delay ischemic neurological deficit	5.058	3.248	7.877	0.000	4.234	2.412	7.432	0.000				
Hydrocephalus	4.381	2.910	6.596	0.000	1.043	0.612	1.778	0.877				
Pneumonia	7.689	5.076	11.646	0.000	3.848	2.386	6.206	0.000				
Serum Lactate dehydrogenase(>201.5U/L)	4.747	3.182	7.081	0.000	2.702	1.645	4.440	0.000	2.426	1.378	4.271	0.002

Figures

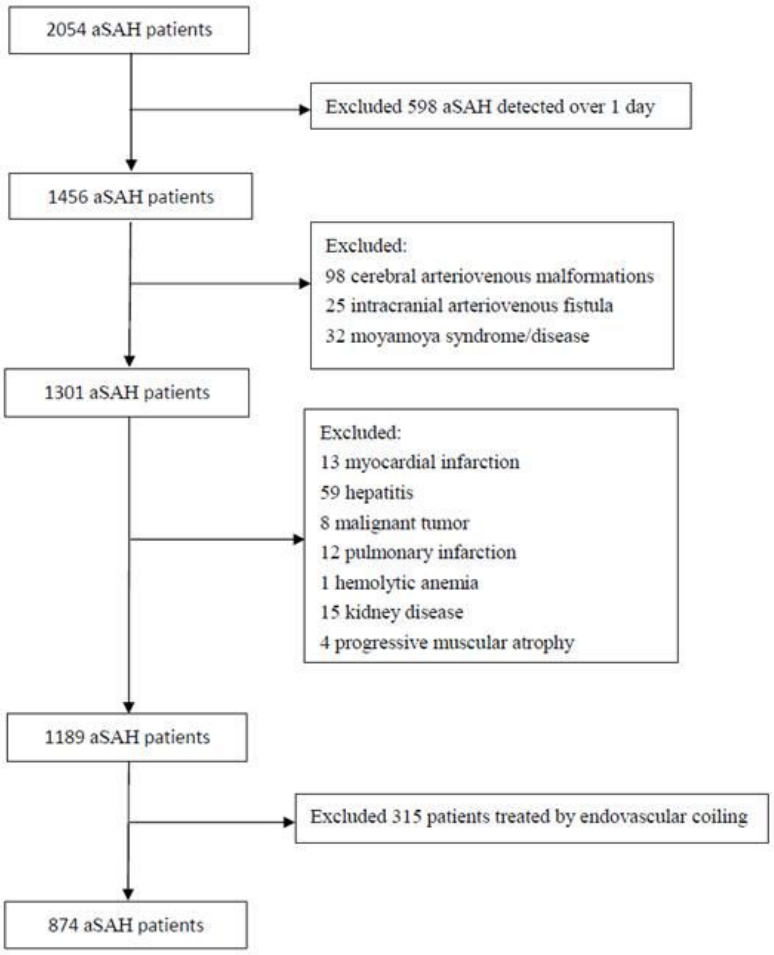

Figure 1

Flowchart of patient inclusion

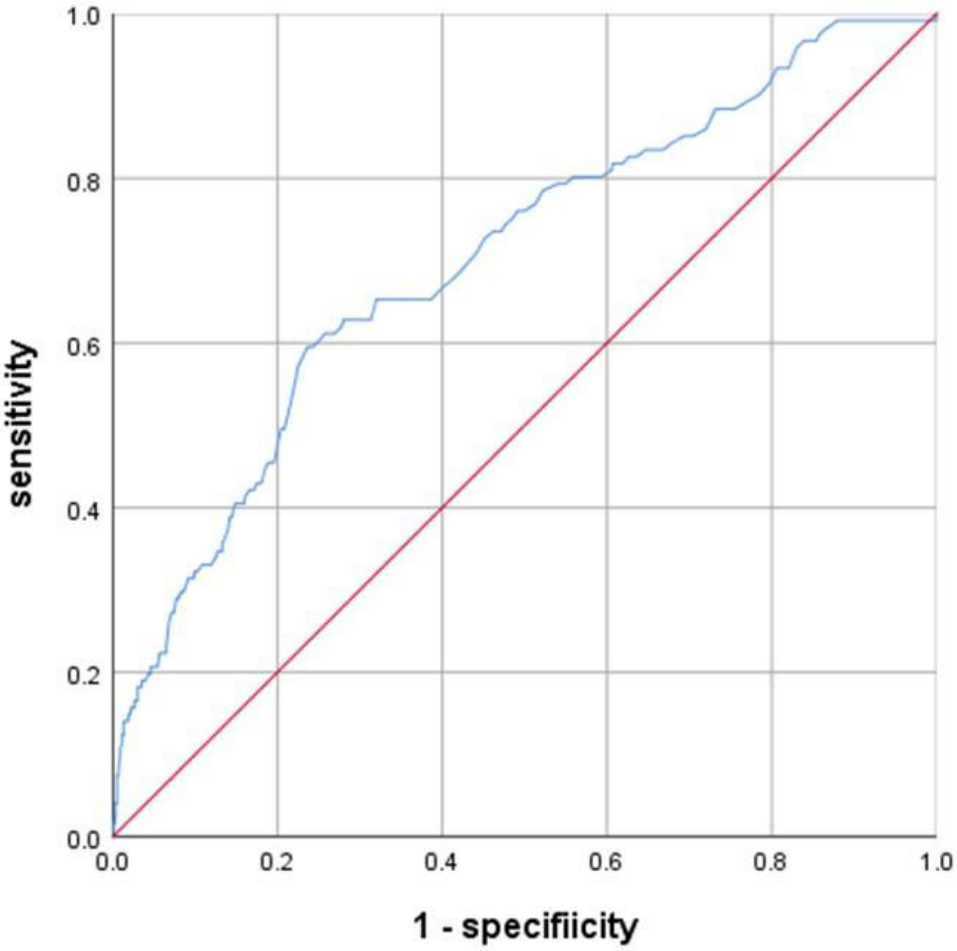

Figure 2

Predictive values of LDH for 3- month modified Rankin Scale (mRS) >2 area under curve 0.702(95% confidence interval [CI], 0.650 - 0.754; p=0.000).

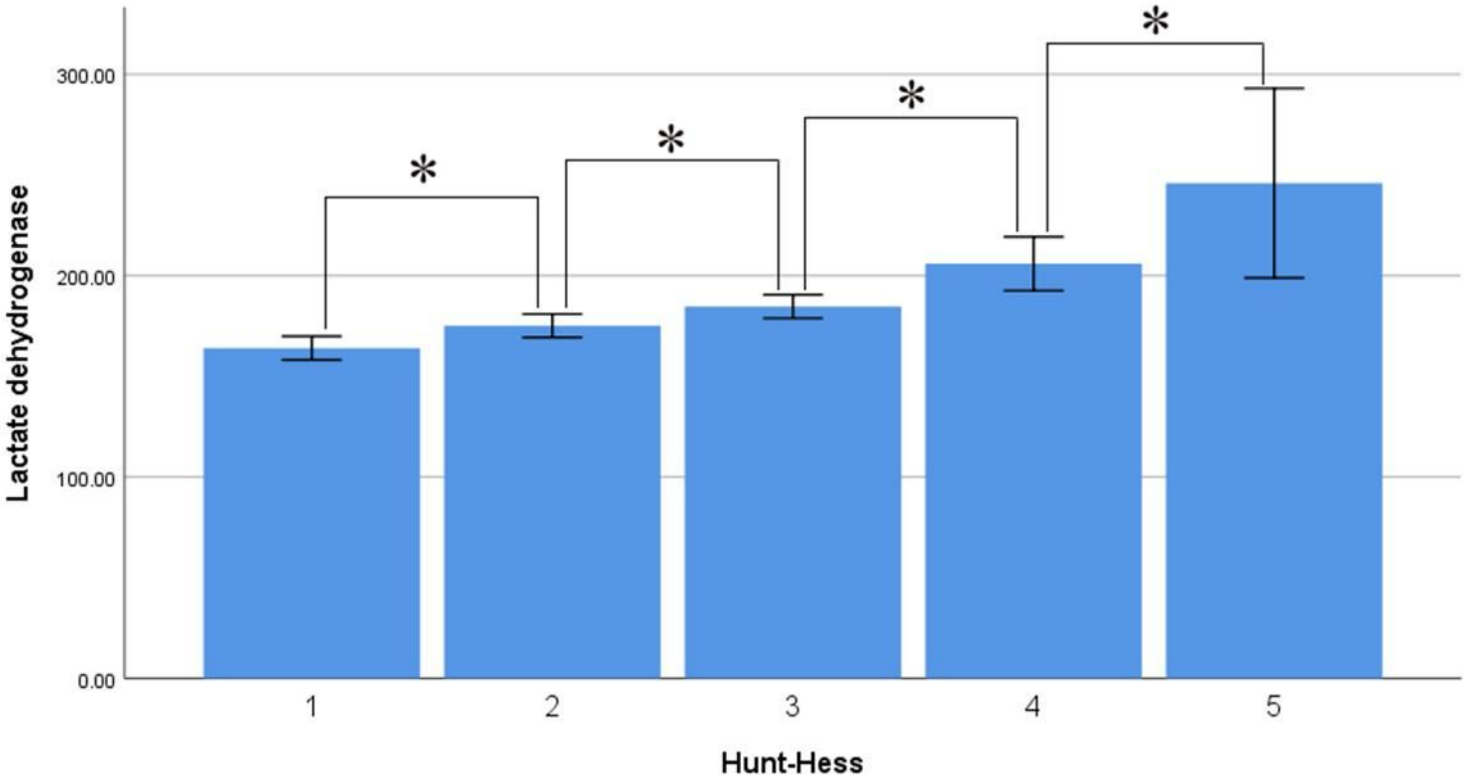

Figure 3

Average level of serum LDH in different Hunt-Hess grade(asterisk represent statistically significant differences).

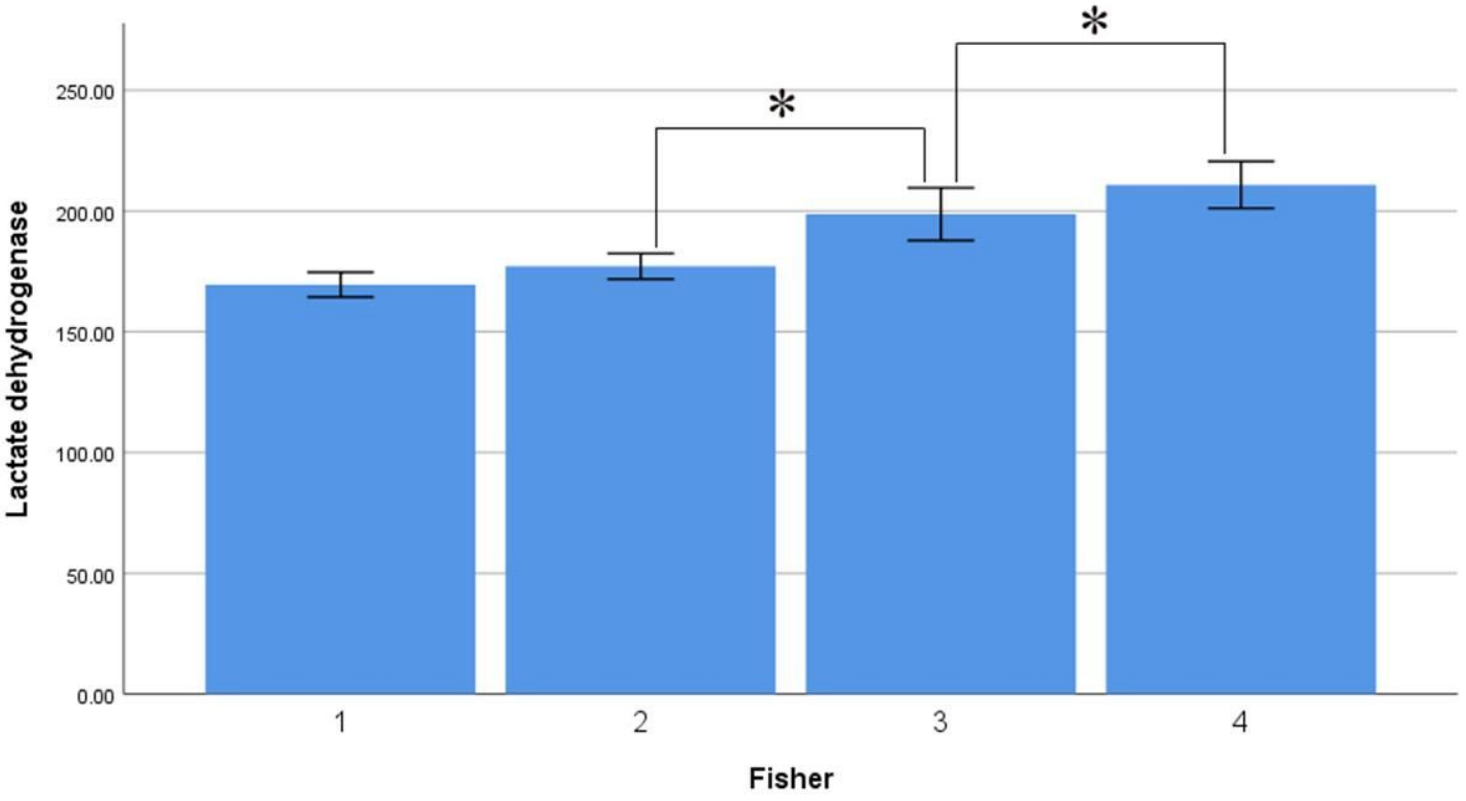

Figure 4

Average level of serum LDH in different fisher grade(asterisk represent statistically significant differences).

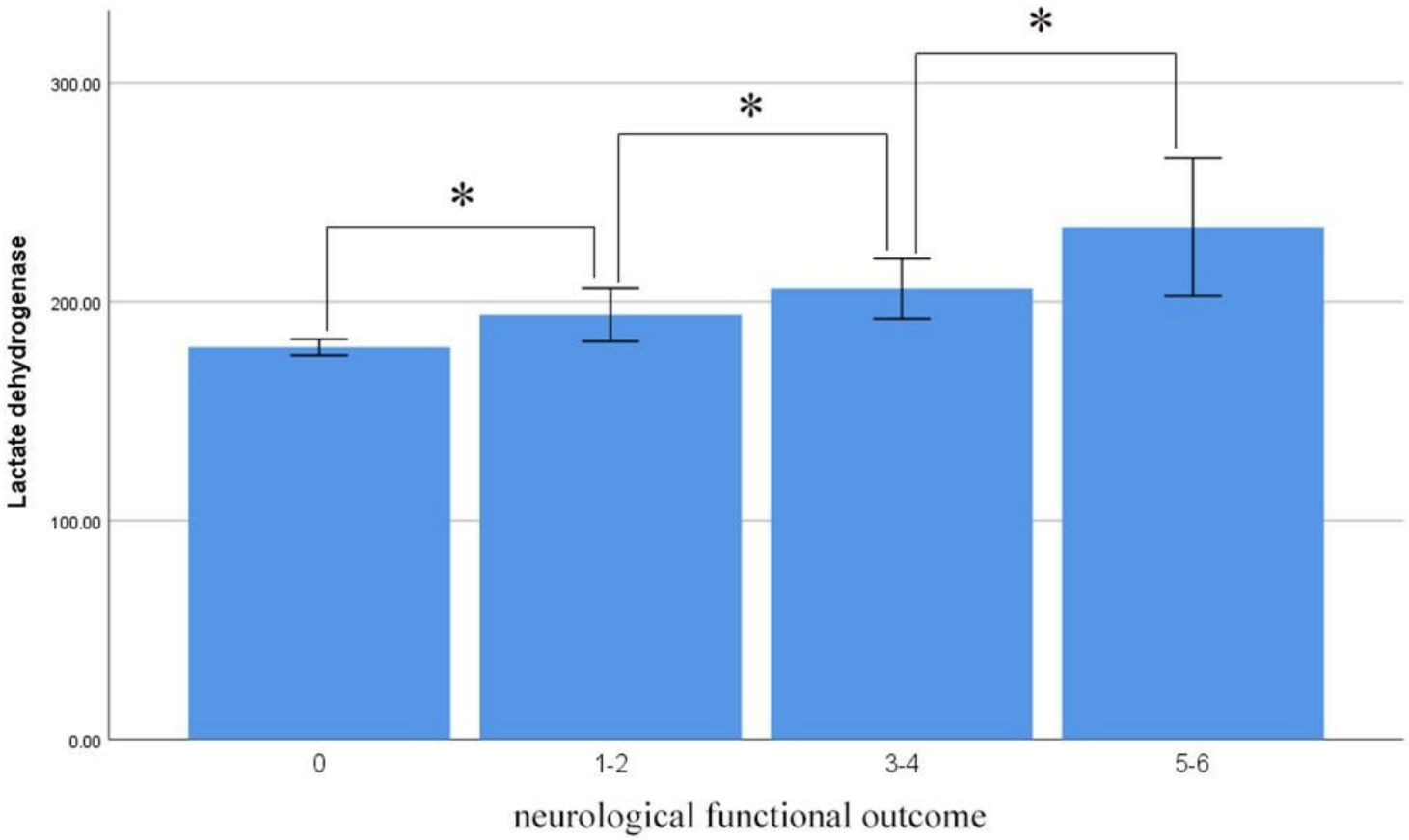

Figure 5

Average level of serum LDH in different neurological functional outcome(asterisk represent statistically significant differences).