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 (180.09±50.237) was obviously lower than that in the poor outcome group (227.55±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 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. However, few reports have explored the clinical significance of serum LDH level in patients with aneurysmal subarachnoid 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. Similarly, the amount of RBC in cerebra cisterna, sulcus and/or ventricle correlated to Fisher grade. Frionera 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. 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), 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, including prevention or re-erson 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 neurological 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.
Fisher grade, delay ischemic neurological deficit, pneumonia, higher serum LDH level could also be indicators of poor outcome. Hunt-Hess grade was shown to be a significant predictor of poor outcome in the multivariate analysis (OR 2.426, 95% CI 1.378-4.271, p = 0.002). Serum LDH level (>201.5 U/L) was still considered as an independent risk factor of poor outcome in the logistic regression model (table 2). After PSM, there were no significant differences in Hunt-Hess grade among the matched groups (p > 0.05). 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 was associated with Hunt-Hess grade in the univariate analysis. The results revealed that age, hypertension, Hunt-Hess grade, Fisher grade, delay ischemic neurological deficit, hydrocephalus, pneumonia, serum LDH (>201.5 U/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 (>201.5 U/L) were associated with 3-month poor outcome (p < 0.05). In multivariate analysis, however, Hunt-Hess grade, Fisher grade, delay ischemic neurological deficit, pneumonia, serum LDH (>201.5 U/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 >201.5 U/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 (>201.5 U/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 grade 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 < 0.001), 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 (shown 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 (shown 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, which were major players in the mechanism of early brain injury after SAH and contributed to the clinical condition of aSAH patients. Frontera JA's study 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. 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, 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. Therefore, serum LDH level reflects the severity of brain tissue injury. Yu W's study 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, and inhibition of LDH release might reduce neuronal apoptosis. Rao C'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. 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.

It was suggested that serum LDH level were correlated with the prognosis of adult T-cell leukemia-lymphoma, prostate cancer, acute myeloid leukemia, melanoma, neuroblastoma, glioblastoma multiforme, acute encephalopathy, and mycoplasma pneumoniae pneumonia. 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, and cerebral ischemia would caused an anaerobic shift of metabolism with lactic acidosis and upregulation of serum LDH level. 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. Shimoda M's report 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 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. 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, LDH from lytic RBC was absorbed into blood after being released into CSF. 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.

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

Competing Interests: The authors declare no competing interests.

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**Tables**

Table 1 Basic clinical characteristics of patients with aneurysmal subarachnoid hemorrhage before and after propensity-score matching.
| General Information          | Before propensity-score matching | After propensity-score matching |
|-----------------------------|----------------------------------|---------------------------------|
|                             | Good outcome (n=753)             | Poor outcome (n=121)            | Good outcome (n=101) | Poor outcome (n=101) | P value |
| Age                         | 0.043                            | 0.128                           |
| ≤65yrs                      | 645                              | 95                              | 74                  | 83                  |
| >65yrs                      | 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                     | 0.593                            | 11                              | 6                   | 0.205               |
| Drink                       | 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

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