Article

Extremely Low Alanine Aminotransferase Level Increases All-Cause Mortality Rate in the Elderly after Ischemic Stroke

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Abstract: (1) Background: Extremely low alanine aminotransferase (ALT) levels are being recognized as a risk factor of increasing mortality in the elderly in relation to frailty. In the elderly, both frailty and ischemic stroke are not only common, but also associated with mortality. This study aimed to investigate whether extremely low ALT levels increase the all-cause mortality rate in the elderly after ischemic stroke. (2) Methods: A retrospective review was performed on 901 patients with ischemic stroke admitted to a university-affiliated hospital between February 2014 and April 2019. The multivariate Cox proportional hazard analysis was performed to determine whether extremely low ALT levels are an independent risk factor of mortality in elderly patients after ischemic stroke. (3) Results: This study enrolled 323 older adults (age ≥65 years) who were first diagnosed with ischemic stroke. The mean age of the participants was 76.5 ± 6.6 years, mean survival time was 37.1 ± 20.4 months, and the number of deaths was 96 (29.7%). The multivariate Cox proportional hazard analysis revealed that the risk factors for all-cause mortality in the elderly after ischemic stroke were age, initial National Institutes of Health Stroke Scale score, serum creatinine, and extremely low ALT level (<10 U/L) at the time of diagnosis (adjusted hazard ratio: 3.243, 95% confidence interval: 1.945–5.408; P < 0.001) (4) Conclusions: Extremely low ALT level at the time of diagnosis (<10 U/L) is an independent risk factor that increases the mortality rate in the elderly after ischemic stroke.

Keywords: Aged; Alanine Transaminase; Brain infarction; Frailty; Mortality

1. Introduction

Serum alanine aminotransferase (ALT) activity has been used as a predictor of overall health status as well as for liver function monitoring [1]. ALT is an enzyme synthesized in the liver; high serum ALT levels are indicative of liver diseases such as cirrhosis or hepatitis. However, recent studies have shown that extremely low ALT levels increase the all-cause mortality rate in elderly individuals [2,3]. A meta-analysis study found that mortality increases with every 5 U/L decrement of the serum ALT level [4]. Thus, extremely low ALT levels could be a result of frailty [2,5]. In elderly individuals with frailty, multiple organ failure may occur. Moreover, sarcopenia may occur due to decreased muscle synthesis, and the synthesis of body-controlled substances may decrease due to decreased liver function. Albumin is synthesized in the liver, and studies have

shown an association of low serum albumin levels with frailty and mortality [6,7]. ALT is also an enzyme synthesized in the liver that decreases with aging [8].

The term "frailty" refers to a condition of vulnerability to external stress, wherein the physical function is reduced to maintain homeostasis; however, frailty itself does not increase the mortality rate [9]. Frailty can occur due to illness, but about 32% of elderly individuals without any disease are known to be frail [10]. Frail individuals cannot recover from severe stress situations, which can lead to death [11]. Ischemic stroke is one of the most physically stressful diseases. Patients with stroke experience extreme physical stress, even if they have fully recovered without complications [12].

Frailty and ischemic stroke are common among the elderly. To our knowledge, no study has investigated the relationship between extremely low ALT levels and mortality in them after ischemic stroke. We hypothesized that extremely low ALT levels are associated with frailty and may increase the all-cause mortality rate after ischemic stroke. This study aimed to investigate whether extremely low ALT levels increase the all-cause mortality rate in the elderly after ischemic stroke.

2. Materials and Methods

Participants

We retrospectively reviewed 901 patients with ischemic stroke admitted to a university-affiliated hospital between February 2014 and April 2019. A retrospective review of the medical records of these patients diagnosed using magnetic resonance imaging or computed tomography was performed. The exclusion criteria and number of patients excluded were as follows: suspected liver injury (serum ALT level >40 U/L; n = 92); not the first episode of acute ischemic stroke (n = 244); incomplete medical records or missing laboratory data (n = 8); and age <65 years (n =234).

Finally, 323 participants were enrolled in this study (Figure. 1), which was approved by the Institutional Review Board of the university-affiliated hospital.

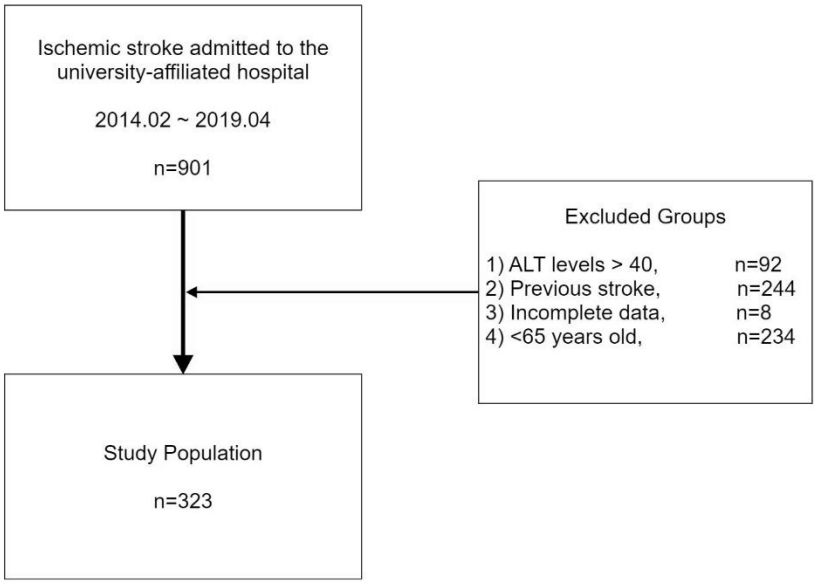

Figure 1. Strengthening the reporting of observational studies in epidemiology (STROBE) diagram of the study population

From the 901 patients, 92 patients whose serum ALT level greater than 40 were excluded. 244 patients were excluded because they had a history of previous stroke. Among the remaining stroke patients, 8 patients with incomplete medical record and laboratory data and 234 patients under 65 years old were excluded. Finally, 323 subjects were enrolled in the study.

Data collection

Age, sex, and body mass index (BMI) data were evaluated. The investigated medical data related to ischemic stroke included lesions of ischemic stroke and etiology as per the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification and history of atrial fibrillation, diabetes, hypertension, coronary artery occlusive disease, cancer, alcohol, and smoking. The initial National Institutes of Health Stroke Scale (NIHSS) score was used to adjust the ischemic stroke severity. Laboratory data of albumin, ALT, creatinine (Cr), erythrocyte sedimentation rate (ESR), glucose, total cholesterol, and hemoglobin (Hb) were collected from the time of diagnosis. Mortality surveillance was investigated using the National Health Insurance database as of September 28, 2020.

Data preprocessing

Factors known to be linearly associated with mortality, such as age, initial NIHSS score, Cr, total cholesterol, and ESR, were used as continuous variables [13-20].

Based on previous studies, albumin, Hb, BMI, glucose, and ALT were categorized into the risk group and control group. Serum albumin levels <3.5 g/dL, serum glucose levels >7.3 or <3.7 mmol/L, and serum Hb levels <11 g/dL are considered risk factors for increased mortality [6,21,17]. Both extremes of underweight and obesity are known to be associated with mortality. Therefore, BMI (kg/m2) was used as a categorical variable and divided into four groups: underweight (<18.5), normal weight (18.5–24.9), overweight (25.0–29.9), and obese (≥30) [22,23]. A meta-analysis study found that mortality increases with every 5 U/L decrement of the serum ALT level [4]. Based on previous studies, the criterion for extremely low ALT was set as <10 U/L.

Statistical analyses

Statistical analysis was performed using Statistical Package for the Social Sciences, version 22.0 (IBM Corp., Armonk, NY, USA). The participants were divided into the expired group and surviving group; the differences between the groups were compared statistically. Independent t-test for continuous variables and Fisher's exact test or chi-square test with post-hoc Bonferroni test for categorical variables were used. Categorical variables were described as frequency and percentage and continuous variables as mean ± standard deviation for normally distributed variables. The multivariate Cox proportional hazard analysis was used to assess the association between extremely low ALT levels and all-cause mortality while controlling for potential confounding factors. A P-value ≤0.05 was considered statistically significant.

3. Results

This study enrolled 323 older adults aged ≥65 years. Their mean age was 76.5 ± 6.6 years and mean survival time was 37.1 ± 20.4 months; death was reported in 96 (29.7%) cases. The variables with statistically significant differences between the two groups were age, initial NIHSS score, survival time, hemispheric localization, low albumin (<3.5 g/dL), low Hb (<11 g/dL), Cr, ESR, BMI, and extremely low ALT level (<10 U/L) (Table 1.)

The risk factors that increased the mortality rate were investigated by the Cox proportional hazard analysis. The factors found to control the confounders were age, sex, TOAST classification, stroke location, hemispheric localization, extremely low ALT level (<10 U/L), low albumin level (<3.5 g/dL), low Hb level (<11 g/dL), abnormal glucose level (>7.3 or <3.7 mmol/L), serum Cr, ESR, total cholesterol levels, BMI, and history of diabetes, hypertension, atrial fibrillation, coronary artery occlusive disease, cancer, smoking, and alcohol consumption. Table 2 shows the results of univariate regression analysis for predicting mortality.

The multivariate Cox proportional hazard analysis revealed that the risk factors for all-cause mortality in the elderly after ischemic stroke were age, initial NIHSS score, extremely low ALT level (<10 U/L) (adjusted hazard ratio: 3.243, 95% confidence interval: 1.945–5.408; P<0.001), and serum Cr levels at diagnosis (Table 3).

The Cox proportional model was constructed according to the ALT level, and it was confirmed that there was a difference in the survival rate of the elderly after ischemic stroke despite controlling for confounders. In this study, log minus log functions did not intersect with each other; hence, it was appropriate to apply the Cox proportional hazard model (Figure. 2).

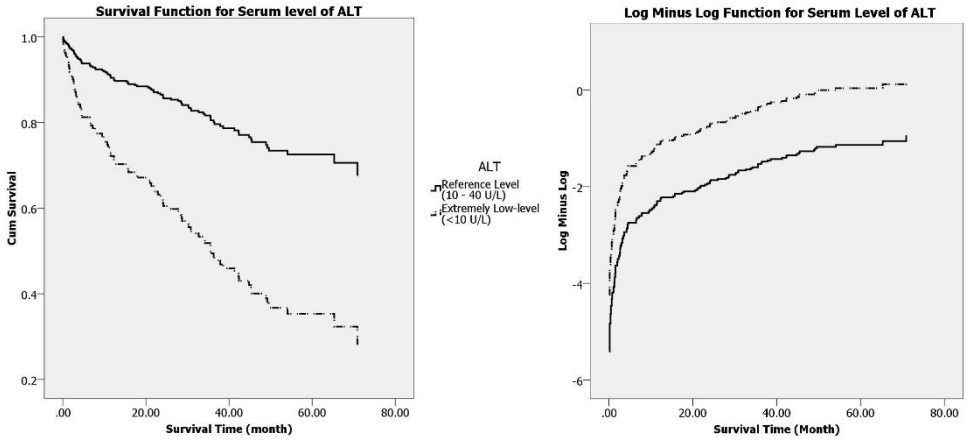

Figure 2. Cumulative survival and log minus log curve for Serum level of ALT

The Cox proportional model showed that the extremely low ALT level (<10 U/L) at the time of ischemic stroke had a higher mortality rate than those with reference ALT levels (10-40 U/L) in elderly population.Since the log minus log functions did not cross each other in this study, the application of the Cox proportional hazard model is appropriate.

4. Discussion

This study aimed to confirm whether extremely low ALT levels (<10 U/L) affect mortality in the elderly after ischemic stroke. Patients with ALT level >40 U/L were excluded. The results showed that the factors that increase the mortality rate in the elderly after ischemic stroke were age, initial NIHSS score (indicator of stroke severity), high Cr level, and extremely low ALT (<10 U/L). It is noteworthy that laboratory tests at diagnosis have a significant association with mortality, even though statistically controlled confounding factors are known to be risk factors. Survival analysis using the multivariate Cox proportional hazard analysis revealed that elderly individuals with an extremely low ALT level (<10 U/L) had a significantly higher mortality rate after ischemic stroke; this difference in mortality rate was observed shortly after the onset and increased over time.

Totaled Health Risks in Vascular Events (THRIVE) and Acute Stroke Registry and Analysis of Lausanne (ASTRAL) are models predicting the mortality outcomes using acute ischemic stroke states [24]. THRIVE is a tool for predicting mortality and prognosis with NIHSS, age, and other risk factors (hypertension, diabetes, and hyperlipidemia). ASTRAL is also a tool for predicting mortality with NIHSS, age, and abnormal glucose level at admission [17]. Similar to these well-known mortality prediction tools, age and initial NIHSS score were the major mortality predictors in our study. It is obvious that stroke severity and age are related to mortality. The significant association of initial NIHSS score with stroke mortality suggests that it is not only an indicator of stroke severity, but also a strong predictor of ischemic stroke mortality.

The TOAST classification and tentorial location were not associated with mortality. However, in hemispheric localization, the proportion of the bilateral injury group was higher in the expired group; in univariate analysis, the unilateral injury group had a lower mortality rate than the bilateral injury group. This could be attributed to the difference in severity according to the extent of the infarction area.

The post-hoc test results for the four BMI categories in our study showed a significant difference in the mortality between the overweight and underweight groups; there were more expired cases in the latter. Previous studies have shown that BMI and mortality are inversely related. Elderly individuals with a higher BMI had a lower mortality rate than those with underweight BMI, which was interpreted as sarcopenia. Thus, the mortality risk due to frailty in patients who are underweight is higher than that in those who are overweight [25,26].

In our study, the laboratory findings of the two groups showed that the proportion of extremely low ALT level (<10 U/L), low albumin level (<3.5 g/dL), and low Hb level (<11 g/dL) was significantly higher in the expired group than in the surviving group. Furthermore, Cr and ESR levels were significantly higher in the expired group. Albumin and Hb levels reflect the whole-body nutritional status, high ESR indicates systemic inflammatory response, and high Cr indicates renal dysfunction. All these parameters were significantly associated with mortality in previous studies [6,21,7,18,20,3].

Extremely low ALT level is a risk factor for all-cause mortality in the elderly population [6,8,7,2,4,3]. A meta-analysis found that the mortality rate increased with every 5 U/L decrement of the serum ALT level [4]. According to previous studies, extremely low ALT levels may reflect frailty. In elderly individuals with frailty, the hepatic organ degenerates, thereby reducing the production of ALT in the liver, resulting in an extremely low serum concentration [27,2]. In this study, the Cox proportional model was constructed according to the ALT level (10 U/L), and despite controlling for confounding factors, there were significant differences in the mortality rates in the elderly after ischemic stroke. This result is consistent with those of previous studies, and extremely low ALT levels (<10 U/L) have been found to be an independent risk factor of the all-cause mortality rate in the elderly after ischemic stroke. Notably, the laboratory results at diagnosis showed significant associations with mortality rate, even though other well-known risk factors were controlled.

The mechanism of death from frailty is due to damage accumulation in the body's organ system. Those affected by most diseases will recover without dying. However, those with frailty are susceptible to other diseases and slow to recover, and this damage continues to accumulate in the organs, leading to death [28]. Frailty can be improved through rehabilitation. There are clear theoretical reasons for using effective rehabilitation approach for frailty, and some studies have suggested its usefulness [19]. Therefore, if ALT levels in elderly patients with acute ischemic stroke are extremely low (<10 U/L)

and they are at a high risk of mortality associated with frailty; hence, an active rehabilitation approach for frailty would be required.

This study had some limitations. Since the cause of mortality was not investigated, it is not possible to determine whether it was the cause of the ischemic stroke. Therefore, when referring to mortality, it is considered as mortality caused by the all-causative cause. In the future, it is necessary to use cohort studies rather than cross-sectional studies to determine the association between extremely low ALT levels, frailty, and mortality. Further research is also needed to determine the effectiveness of rehabilitation in patients with extremely low ALT levels.

5. Conclusions

In conclusion, extremely low ALT level at diagnosis (<10 U/L) is an independent risk factor that increases the mortality rate in the elderly after ischemic stroke.

Supplementary Materials: None

Author Contributions: For research articles with several authors, a short paragraph specifying their individual contributions must be provided. The following statements should be used "Conceptualization, D.Y.Kim and S.J.An. ; methodology, S.J.An. and D.Y.Kim.; software, Y.-P.Hong.; validation, Y.-J.Yang.; formal analysis, D.Y.Kim.; investigation, Y-J.Yang.; resources, N.-M.Jeon.; data curation, N.-M.Jeon.; writing—original draft preparation, D.Y.Kim.; writing—review and editing, D.Y.Kim and S.J.An.; visualization, Y.-J.Yang.; supervision, D.Y.Kim.; project administration, S.J.An.; funding acquisition, None. All authors have read and agreed to the published version of the manuscript." Please turn to the CRediT taxonomy for the term explanation. Authorship must be limited to those who have contributed substantially to the work reported.

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Institutional Review Board Statement: This retrospective chart review study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Institutional Review Board of the Catholic Kwandong University International St Mary's Hospital (IRB No. IS19RISI0037). Our research was retrospective study and exempted from obtaining appropriate participants' informed consent

Informed Consent Statement: "Not applicable."
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