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Elevated Serum Aminotransferase Level as a Predictor of Intracerebral Hemorrhage

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Background and Purpose—Serum aminotransferase levels are known to be associated with cardiovascular risk factors, but the relation with stroke incidence is not well known. We investigated the relation between serum aminotransferase levels and the incidence of stroke.

Methods—We measured serum aspartate and alanine aminotransferase levels and traditional cardiovascular risk factors in 108 464 Korean men, aged 35 to 59 years, in 1990 and 1992. Serum aminotransferase levels were classified into 3 categories (<35, 35 to 69, and ≥70 IU/L). The outcomes were hospital admissions and deaths from stroke subtypes (ischemic stroke, intracerebral hemorrhage [ICH], and subarachnoid hemorrhage [SAH]) from 1993 to 2002.

Results—During the 10 years, 1728 ischemic, 1051 hemorrhagic (718 ICH and 222 SAH), and 243 unspecified stroke events occurred. After adjustment for age and other traditional risk factors and according to Cox proportional-hazards models, serum aminotransferase level had an independent positive associations with ICH. However, ischemic stroke and SAH were not associated with aminotransferase levels. Compared with the level <35 IU/L, the adjusted relative risks (95% confidence interval) of ICH for an aspartate aminotransferase level of 35 to 69 and ≥70 IU/L were 1.49 (1.21 to 1.83) and 4.21 (3.06 to 5.77), respectively. The corresponding risks for alanine aminotransferase were 1.34 (1.09 to 1.65) and 2.89 (2.09 to 4.01), respectively. These associations were consistent regardless of the level of obesity, blood pressure, fasting glucose, alcohol intake, and follow-up length.

Conclusions—These findings suggest that an elevated aminotransferase level is a predictor of ICH. The biologic significance of aminotransferase level for the development of ICH merits further study. **(*Stroke*. 2005;36:1642-1647.)**

Key Words: alanine aminotransferase ■ aspartate aminotransferase ■ epidemiology ■ intracerebral hemorrhage ■ risk factors

Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) assays are common laboratory tests that are used for the screening of liver diseases. Epidemiologic studies have reported positive associations between serum aminotransferase levels and various conventional cardiovascular risk factors.[1–8] Nevertheless, a direct association between serum aminotransferase levels and the risk of cardiovascular disease has not been fully studied. Some patient studies reported a positive association between hemorrhagic stroke and a history of liver dysfunction, which was defined by elevated liver enzymes.[9–11] However, there are no data on the association between aminotransferase levels and the incidence of stroke. Therefore, we prospectively investigated the relation between serum aminotransferase levels and the 10-year incidence of stroke by subtypes.

Methods

Study Population

The Korea Medical Insurance Corporation (KMIC) provides health insurance to government employees, private school employees, and their dependents. All insured workers are required to participate in biennial health examinations, which are conducted by the KMIC. In 1990 and 1992, 95% and 94%, respectively, of workers completed the examinations. The KMIC Study cohort therefore consisted of 115 200 male (25% random sample) and 67 932 female (100% sample) workers, aged 35 to 59 years, who underwent the health examinations in 1990 and 1992. We restricted these analyses to men because the frequencies of abnormal aminotransferase levels (3.5%) and the incidence of stroke (1.1% in 10 years) were very low for women. We had data on major cardiovascular risk factors and serum aminotransferase assays for 108 637 men. We excluded 173 men who died before 1993 and enrolled 108 464 men for the analyses. Because of missing data on smoking and/or alcohol consumption for 4170 men, 104 294 men were enrolled for the multivariate analysis.

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TABLE 1. Baseline Characteristics by Serum Aminotransferase Level in 108 464 Men

Baseline Characteristics	All Participants (n=108 464)	Normal Aminotransferase* (n=89 173)	Elevated Aminotransferase (n=19 291)
Age, y	45.0 (6.7)	45.0 (6.7)	45.6 (6.7)
Body mass index, kg/m^2	23.5 (2.4)	23.3 (2.3)	24.3 (2.6)
Systolic blood pressure, mm Hg	125.5 (14.3)	124.8 (14.0)	128.5 (14.8)
Diastolic blood pressure, mm Hg	82.1 (9.6)	81.7 (9.5)	84.1 (9.9)
Fasting blood glucose, mmol/L	5.2 (1.2)	5.1 (1.2)	5.4 (1.4)
Total cholesterol, mmol/L	5.0 (0.9)	5.0 (0.8)	5.1 (1.0)
AST, IU/L	26.0 (14.6)	22.3 (5.1)	43.5 (26.6)
ALT, IU/L	25.7 (17.9)	20.7 (5.8)	49.1 (31.2)
No. (%)			
Cigarette smoking			
Nonsmoker	22 119 (21.2)	18 479 (21.5)	3640 (19.7)
Ex-smoker	22 207 (21.3)	18 312 (21.4)	3895 (21.0)
Current smoker	59 968 (57.5)	48 981 (57.1)	10 987 (59.3)
Average alcohol consumption			
Nondrinker	26 103 (24.8)	21 881 (25.3)	4222 (22.6)
<50 g/d	69 292 (65.8)	57 314 (66.2)	11 978 (64.1)
≥50 g/d	9900 (9.4)	7398 (8.5)	2502 (13.4)

Values are mean and (SD). Abbreviations are as defined in text.
*AST <35 IU/L and ALT <35 IU/L.

Institutional review board approval of the Severance Hospital at Yonsei University was obtained for the study design.

Data Collection

Baseline information was obtained from the health examinations in 1990 and 1992, and averages of the 2 measurements were used. The examinations were conducted in a standardized manner by trained medical staff at 416 hospitals nationwide. The participants' weight, height, and blood pressure were measured at each examination. Systolic and diastolic blood pressure was measured in the seated position with a mercury sphygmomanometer or automatic manometer. Fasting serum specimens were analyzed for total cholesterol, glucose, and aminotransferase levels.

Data on smoking and alcohol consumption were available for 1992 only. The participants were asked to describe their smoking status, duration, and amount. The participants were asked whether they consumed alcoholic beverage or not, how frequently (times per week on average) they consumed alcoholic beverage, and how much alcohol they consumed at once. The amount of alcohol was expressed as the number of bottles of "soju," which was the most popular alcoholic beverage in Korea. One bottle of soju contains ≈72 g of ethanol. For drinkers, daily alcohol intake was calculated from the frequency and the amount of alcohol consumption. The participants were also asked whether they had any previously known disease, but detailed information on diagnosis was not available.

The outcome variable was the incidence of stroke and its subtypes (ischemic stroke, hemorrhagic stroke, intracerebral hemorrhage [ICH] and subarachnoid hemorrhage [SAH]). The follow-up period was the 10 years from 1993 to 2002. For individuals who had >1 stroke, we used only the first event in our analyses. We ascertained nonfatal outcomes from health insurance claim data and fatal outcomes from death certification data.

Statistical Analysis

Body mass index was classified into quartiles. Blood pressure level was classified into 6 categories: optimal (systolic/diastolic <120/80 mm Hg), normal (120 to 129/80 to 84 mm Hg), high-normal (130 to 139/85 to 89 mm Hg), and hypertension stages 1 (140 to 159/90 to 99 mm Hg), 2 (160 to 179/100 to 109 mm Hg), and 3 (≥180/110 mm Hg).[12] When systolic and diastolic blood pressures fell into different categories, the higher category was selected. The categories for fasting glucose level were <6.1, 6.1 to 6.9, and ≥7.0 mmol/L. The categories for serum cholesterol level were <5.2, 5.2 to 6.1, and ≥6.2 mmol/L. AST and ALT levels were classified into 3 categories: <35, 35 to 69, and ≥70 IU/L. AST and ALT levels were also analyzed as continuous variables. Smoking was classified into 3 categories: current smokers, ex-smokers, and nonsmokers. Based on the average daily alcohol intake, participants were classified into nondrinkers, moderate drinkers (<50g/d), and heavy drinkers (≥50g/d). Cox's proportional-hazards models were used to estimate the relative risks of stroke subtypes according to the serum aminotransferase level, after adjustments for age and the aforementioned variables.

Results

At baseline, 19 291 men (17.8%) had elevated aminotransferase levels, which were defined as an AST or ALT ≥35 IU/L (Table 1).[13] An elevated aminotransferase level was positively associated with body mass index, blood pressure, fasting glucose, total cholesterol, smoking, and alcohol consumption ($P<0.001$).

During the 10 years of follow-up, 3022 stroke (1728 ischemic, 1051 hemorrhagic, and 243 unspecified) events were found to have occurred (Table 2). Of the 3022 strokes, 534 cases (17.7%) were fatal events.

Body mass index, blood pressure, fasting glucose, total cholesterol, aminotransferase level, current smoking, and heavy drinking were associated with the age-adjusted stroke incidence. Blood pressure had positive associations with all stroke subtypes, but some risk factors showed different associations according to stroke subtypes. Body mass index

TABLE 2. Incidence of Stroke During 10-Year Follow-Up by Serum Aminotransferase Level

Stroke Subtype	ICD-10 Codes	All Participants (n=108 464)	Normal Aminotransferase* (n=89 173)	Elevated Aminotransferase (n=19 291)
All stroke	I60–67	288.1 (3022)	268.8 (2331)	379.7 (691)
Ischemic	I63, 65, 66	164.7 (1728)	159.0 (1379)	191.8 (349)
Hemorrhagic	I60–62	100.2 (1051)	88.2 (765)	157.2 (286)
ICH	I61	68.4 (718)	58.9 (511)	113.8 (207)
SAH	I60	21.2 (222)	21.0 (182)	22.0 (40)
Other hemorrhage	I62	10.6 (111)	8.3 (72)	21.4 (39)
Unspecified	I64, 67	23.2 (243)	21.6 (187)	30.8 (56)

ICD indicates International Classification of Diseases. Other abbreviations are as defined in text. Unit is the incidence per 100 000 person-years (No. of events).

*AST <35 IU/L and ALT <35 IU/L.

was positively associated with ischemic stroke but negatively associated with SAH. Total cholesterol level was significantly associated with ischemic stroke only. Alcohol consumption was significantly associated with ICH only. Aminotransferase level was positively associated with all strokes and ICH, but not with ischemic stroke or SAH (data not shown).

Even after adjustment for age and other traditional risk factors, the serum aminotransferase level was independently associated with the incidence of stroke. For the different subtypes of stroke, serum aminotransferase level was strongly associated with ICH but not with ischemic stroke or SAH. Also, when treated as continuous variables, both AST and ALT levels had positive associations with the incidence of ICH (Table 3).

To examine the possible confounding effects, we evaluated the relation between aminotransferase level and the risk of ICH by the level of other major risk factors. The positive association between aminotransferase level and ICH risk could be observed at any level of other risk factors, although the association was somewhat stronger in men with a lower body mass index and in heavy drinkers (Figure).

Discussion

In this prospective study of Korean men, we found an independent positive association between serum aminotransferase level and the 10-year incidence of ICH.

Aminotransferase and Traditional Risk Factors

Liver enzymes are known to be associated with several cardiovascular risk factors.[1–8,14–16] Obesity is a frequently reported factor associated with both liver enzymes and cardiovascular disease.[1,3,5–8] However, in our analyses, body mass index was not an important risk factor for ICH, and the association between aminotransferase level and ICH was also observed in men with a low body mass index. Aminotransferase levels are also known to be influenced by alcohol intake,[1,4,6,7] and heavy drinking can increase the risk of ICH.[17,18] If alcohol intake is a strong confounder between aminotransferase level and ICH risk, then the aminotransferase level may be an indicator of alcohol-related liver damage rather than an independent risk factor for ICH. In our data, ICH risk was more closely related with aminotransferase level than with alcohol consumption; age-adjusted and multivariate-adjusted risk ratios for heavy drinking were 1.83

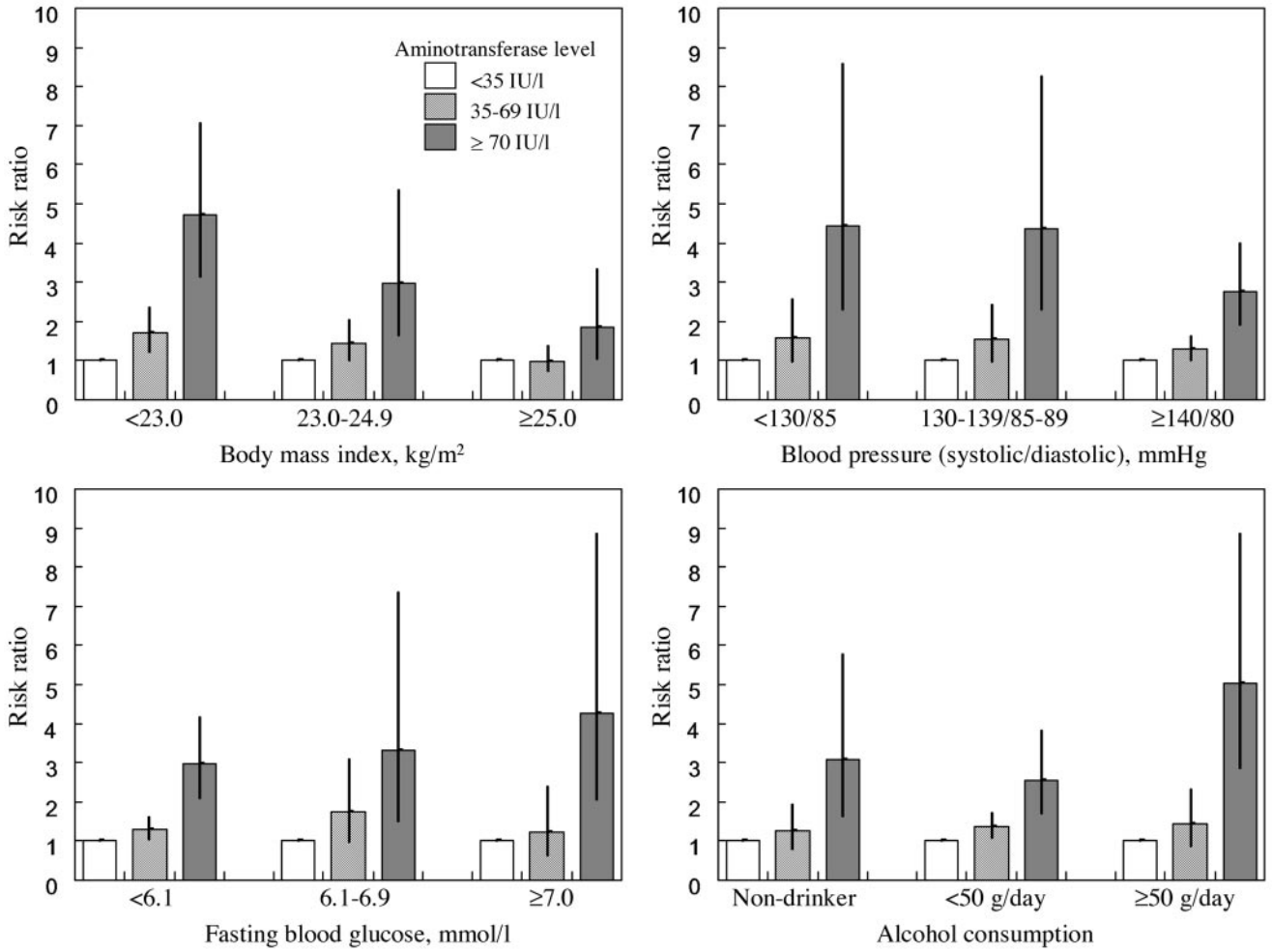
TABLE 3. Risk Ratio (95% CI) of Stroke Subtypes by Serum Aminotransferase Level at Baseline

	Age Adjusted (n=108 464)			Multivariate Adjusted* (n=104 294)		
Aminotransferase Level	Ischemic Stroke	ICH	SAH	Ischemic Stroke	ICH	SAH
AST, IU/L						
<35	1.00	1.00	1.00	1.00	1.00	1.00
35–69	1.22 (1.05–1.42)	1.94 (1.59–2.37)	1.03 (0.66–1.60)	0.99 (0.85–1.15)	1.49 (1.21–1.83)	0.96 (0.62–1.50)
≥70	1.16 (0.77–1.73)	5.68 (4.20–7.70)	1.83 (0.75–4.45)	0.86 (0.56–1.32)	4.21 (3.06–5.77)	1.31 (0.48–3.54)
Continuous†	1.03 (1.01–1.06)	1.10 (1.08–1.12)	1.00 (0.92–1.10)	1.00 (0.96–1.03)	1.09 (1.07–1.11)	0.97 (0.87–1.08)
ALT, IU/L						
<35	1.00	1.00	1.00	1.00	1.00	1.00
35–69	1.47 (1.29–1.68)	1.64 (1.35–2.00)	0.72 (0.45–1.15)	1.09 (0.95–1.25)	1.34 (1.09–1.65)	0.68 (0.42–1.10)
≥70	0.69 (0.44–1.08)	3.73 (2.75–5.07)	1.84 (0.91–3.72)	0.51 (0.32–0.81)	2.89 (2.09–4.01)	1.57 (0.73–3.35)
Continuous†	1.03 (1.01–1.05)	1.07 (1.06–1.09)	1.01 (0.94–1.08)	0.99 (0.97–1.02)	1.07 (1.05–1.09)	0.99 (0.91–1.08)

Abbreviations are as defined in text.

*Adjusted for age, body mass index, blood pressure, fasting glucose, total cholesterol, smoking, and alcohol consumption.

†Per 10 IU/L elevation of aminotransferase level.



Relation between aminotransferase level and ICH by the presence of other risk factors. Risk ratios are adjusted for age, total cholesterol, smoking, and other variables in the figure. Vertical lines indicate 95% CIs. Abbreviations are as defined in text.

(95% confidence interval [CI], 1.43 to 2.34) and 1.21 (95% CI, 0.93 to 1.58), respectively. Moreover, the association between aminotransferase level and ICH was observed even in nondrinkers. However, alcohol consumption still should be considered a potential confounder, because alcohol consumption was measured with a simple self-administered questionnaire, and past drinking was not considered. Blood pressure and fasting glucose level were also associated with elevated aminotransferase levels, but they did not seriously affect the relation between aminotransferase level and ICH in our data (Figure).

Preexisting Disease

In observational studies, undetected preexisting disease may cause a false relation between the independent variable and outcome events. We asked the participants whether they had any previously diagnosed disease or not, but we had no detailed information on the diagnoses. We further analyzed the association between serum aminotransferase level and ICH only for men without known disease and observed similar results. Compared with the <35 IU/L level, the adjusted relative risks of ICH for an AST level of 35 to 69 and ≥70 IU/L were 1.45 (95% CI, 1.08 to 1.95) and 3.69 (95% CI, 2.27 to 6.01), respectively. The corresponding relative risks for the ALT level were 1.36 (95% CI, 1.02 to 1.82) and 2.63 (95% CI, 1.60 to 4.33), respectively. We also assessed the possible confounding effects of unknown preexisting disease by comparing the results from different follow-up periods, but we observed no difference by follow-up period (data not shown).

Possible Mechanisms

The mechanism for the development of ICH in men with abnormal liver enzymes is not fully understood. Several previous studies reported dose-response relations between liver dysfunction and abnormalities of almost all major hemostatic parameters.[9–11] Abnormal hemostasis may partially contribute to the adverse effects of liver dysfunction on ICH. However, it is likely that nonhemostatic mechanisms are also involved, because impairment of the hemostatic system in men with abnormal liver enzymes is too modest to cause bleeding.[11]

A low cholesterol level has been suggested as another mechanism of ICH in patients with liver disorders.[19–21] However, a low cholesterol level does not seem to be a major cause of the association. In our data, men with elevated

aminotransferase levels had relatively high cholesterol levels. Moreover, we previously reported that low cholesterol is not an independent risk factor for ICH in the same population.[22]

Aminotransferase levels are highly correlated with the γ-glutamyltransferase level, which has been reported to be associated with ischemic heart disease and stroke.[14–16,23–25] Several studies proposed that γ-glutamyltransferase may be a marker of oxidative stress, or perhaps it is involved in the generation of reactive oxygen species.[16,25,26] However, in our results, the serum aminotransferase level was associated only with ICH, but not with ischemic heart disease or ischemic stroke. This, a specific association with ICH cannot be fully explained by oxidative stress.

Overall, the serum aminotransferase level is likely to be a marker of liver dysfunction rather than a causal factor of ICH. Actually, the serum aminotransferase level is a sensitive marker of liver damage, but it does not provide information on the underlying causes of liver damage. Although the causal relation between aminotransferase level and ICH risk is still unclear, serum aminotransferase levels can be used as a predictor of ICH. The role of serum aminotransferase levels in the development of ICH needs to be further studied.

Age and Sex Effects

The KMIC cohort members were relatively young (35 to 59 years) at baseline; thus, we could not test for an effect modification by age group. It was reported that blood pressure was strongly and directly associated with the risk of ICH throughout middle and old age, but the association was weakened in the older age group.[27,28] However, the effect modifications by age in other risk factors than blood pressure are not established yet. The association between serum aminotransferase level and the risk of ICH needs to be further studied in wider age groups.

In a further analysis of women, we did not observe any significant difference of ICH incidence between those with normal versus elevated aminotransferase values. The age-adjusted risk ratios for elevated (≥35 IU/L) AST and ALT were 0.87 (95% CI, 0.28 to 2.75) and 1.06 (95% CI, 0.39 to 2.86), respectively. The sex difference in our findings could be explained in several ways. First, sex difference in the absolute risk of ICH may be a possible cause. A recent meta-analysis reported that men were at 3.73 (95% CI, 3.28 to 4.25) times higher risk for ICH than women.[29] Also, in our data, men had a 3.3 times higher incidence of ICH. However, the underlying mechanism of the sex difference is not yet established. Second, underlying causes of aminotransferase elevation may differ by sex. For example, if alcohol intake is a main cause of aminotransferase elevation in men but not in women, the relation between aminotransferase and ICH risk can be different by sex. Thus, there is a need to examine the underlying causes of aminotransferase elevations and their effects on the risk of ICH. Third, the negative finding in our further analysis of women might be due to low statistical power. We observed only 5 cases of ICH in women with elevated aminotransferase levels; thus, the estimated risk ratios had wide CIs. The relation between aminotransferase level and ICH risk in women needs to be further investigated.

Strengths and Limitations

Our study has several important strengths. First, our study had a large sample size (108 464 men) and a long follow-up period (10 years). Some previous studies have reported a high frequency of liver dysfunction for patients with ICH.[9–11] However, those studies had relatively small sample sizes and case-control designs, and they failed to investigate the temporal relation and possible confounding effects. Second, our study cohort was recruited from a nationwide general population, whereas previous studies were performed with selected patient data.[9–11] Third, we repeatedly measured major independent variables over 2 years; thus, we could decrease the possibility of measurement errors.

The study has potential limitations. First, we had no objective information on medical history. Thus, we performed further analysis for men who reported that they had not had any previously diagnosed disease, and we discovered similar trends. We also assessed the effects of preexisting disease by comparing the results according to follow-up period, and we found no significant difference. Second, the serum aminotransferase assay was not standardized. All hospitals, however, followed internal and external quality control procedures, as stipulated by the Korean Society of Quality Control in Clinical Pathology. The indexes of variation for the scores were acceptable: 107 for AST and 109 for ALT. The misclassification bias, if any, was likely to be a nondifferential reduction of relative risks. Third, we measured smoking status and alcohol consumption with a single self-reported questionnaire. Alcohol consumption was associated with both aminotransferase elevation and the risk of ICH, and the measurement error in alcohol consumption might be a cause of residual confounding. Finally, we could not verify the diagnosis from hospitalization and death certificate data. In Korea, computed tomography and magnetic resonance imaging are routinely used in the diagnosis of stroke, and a radiologists' reading is required for insurance claims. According to a nationwide survey of 152 representative hospitals, computed tomography and/or magnetic resonance imaging were used for 89% of hospital admissions for stroke in 2000.[30]

Conclusions

Our findings suggest that an elevated serum aminotransferase level may be an independent predictor of ICH. Men with elevated serum aminotransferase levels could be regarded as a high-risk group for ICH; they should be assessed for other vascular risk factors and strongly recommended to control those that are modifiable. Further studies are required on the role of an elevated aminotransferase level in the development of ICH.

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