Original Article

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Association between Serum Liver Enzymes and Cardiovascular Diseases: A Case-control Study among Adults with Cardiovascular Disease

Biochemistry Section

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ABSTRACT

Introduction: Cardiovascular Diseases (CVDs) are the leading cause of global morbidity and mortality. However, their prevalence is disproportionately distributed, with the highest rate in low-income countries, moderate in middle-income countries, and the lowest in high-income countries. Several studies conducted elsewhere, have identified that certain liver enzymes in serum could predict incident CVDs in adults.

Aim: To explore the association between liver enzymes and CVDs in adults.

Materials and Methods: This was a hospital-based case-control study conducted at Manipal Teaching Hospital, Pokhara, Kaski, Nepal, from January 2018 to December 2021 among 400 adult subjects (200 healthy controls and 200 CVD patients). Socio-demographic, physiological, and biochemical variables were collected with structured questionnaires and appropriate standardised and validated measurement methods. The p-value (two-tailed) <0.05 was considered statistically significant.

Results: The frequency of smoking (p<0.001) and drinking habits (p<0.001), and mean values of Body Mass Index (BMI) (p<0.001), and Systolic Blood Pressure (SBP) (p=0.006), Waist Hip Ratio (WHR), Aspartate Aminotransferases (AST), Alanine Aminotransferases (ALT), Alkaline Phosphatase (ALP), Fasting Blood Sugar (FBS), Glycated Haemoglobin (HbA1c), Creatine Kinase-MB (CK-MB), Troponin I (TpI), Total Cholesterol (TC), and Triglyceride (TG) were significantly higher (p<0.001) in CVD patients than in healthy controls. The High Density Lipoprotein-Cholesterol (HDL-C), on the other hand, was significantly lower in CVD patients. Only the AST showed significant correlation with the cardiac markers CK-MB and TpI. Logistic regression analysis revealed that aminotransferases was the best predictor (due to differences in odd's ratio) than ALP for incident CVDs in the adult population.

Conclusion: Present study verifies that aminotransferases, particularly AST, was significantly associated with the incident CVD and thus, could potentially be measured together with established cardiac biomarkers for the staging and differential diagnosis of CVDs in Nepali adults.

Keywords: Adult population, Alanine aminotransferase, Alkaline phosphatase, Aspartate aminotransferase

INTRODUCTION

The CVDs are the major cause of death globally [1]. However, their prevalence is disproportionately distributed, with the highest rate in low-income countries, moderate in middle-income countries, and the lowest in high-income countries [2]. Of all CVDs deaths, 43% of deaths occur in low-income countries, 41% in middle-income countries, and 23% in high-income countries [3]. The South Asian region including Nepal is considered the hotbed of CVDs in the world [4] and therefore, causing considerable economic loss and draining a large chunk of their national GDPs in their health services. Therefore, measures leading to prevention, early detection, and proper treatment of CVDs save the economy of the country and increase the quality and lifespan of the people [5,6]. The risk factors of CVDs include dietary habits, physical inactivity, tobacco use, diabetes mellitus, hypertension, obesity, and high blood lipids [7,8]. Despite early identification, prevention, and treatment of these risk factors, the overall mortality associated with CVDs is still increasing [9].

The liver plays an important role in the metabolism and homeostasis of multiple biomolecules such as amino acids, proteins, carbohydrates, fatty acids, lipids, and lipoproteins [10]. For this purpose, the liver utilises, myriads of enzyme systems including AST, ALT and ALP. The serum levels of liver enzymes, particularly AST, ALT, and ALP, have been shown to elevate in many types of liver diseases and thus have been used as markers of hepatic dysfunctions in clinical settings. Many studies have shown that the plasma levels of these enzymes are significantly associated with incident CVDs and therefore, could be used as possible risk markers for CVDs [11,12]. However, past studies have shown that there is no proportionate relationship between individual liver enzymes and the risk of CVDs [13,14]. A stratified analysis has shown a positive association between ALT and stroke but a negative association with coronary heart disease [15], while another study has shown that both elevated ALT and AST were associated with CVD mortality [16]. Likewise, a population-based study conducted in Iran showed that ALP was positively associated, and ALT was negatively associated with 10-year CVD risk in both genders [17]. However, there have been no such previous studies conducted in Nepal that validate the findings of these external studies in Nepali adults with incident CVDs. Therefore, the main aim of the present study was to explore the association between liver enzymes and CVDs among the adult from Kaski district, Nepal.

MATERIALS AND METHODS

This was a hospital-based case-control study conducted at Manipal Teaching Hospital, Pokhara, Kaski, Nepal, from January 2018 to December 2021. Before embarking the present study, Ethical Clearance was obtained from the Institutional Review Committee (IRC), (MEMG/IRC/279/GA), of Manipal College of Medical Sciences. A total of 400 subjects were enrolled, out of which 200 were healthy controls and the other 200 were subjects with incident CVDs.

Sample size calculation: In present study the prevalence for sample size calculation i.e. prevalence of 5.7% was taken [4].

$$N=\frac{Z^2\times p\times q}{e^2}$$

Where:

Z=1.96 (for 95% confidence interval)

p=0.057

q=1-p

e=0.05 (allowable error of 5%)

Hence,

$$n=\frac{1.96^2\times 0.057\times(1-0.057)}{0.05^2}$$

=83 in each group

Therefore, minimum sample size=166 but total 400 samples were taken.

Inclusion criteria: The patients who were admitted to emergency department and cardiology unit with the complain of chest pain and history of heart problem were included in the present study. The presence of CVDs in these admitted subjects were diagnosed by the treating cardiologists based on complains and history of disease, serum creatine kinase MB (CK-MB), troponin I (TpI) and electrocardiogram findings.

Exclusion criteria: Patients who had CVDs together with acute or chronic liver disease (liver damage, jaundice, hepatitis, cirrhosis of liver), intestinal disease (inflammatory bowel disease), and musculoskeletal diseases (myopathies, muscular dystrophies, and celiac disease) were excluded from the study.

Written informed consent was obtained from each enrolled study participant for interviews, questionnaires, and sample collection. Data were collected, regarding age, gender and smoking and drinking habits. WHR, BMI, was calculated [18]. The blood pressures of all patients were measured using sphygmomanometer in sitting position.

Biochemical Analysis

About 5 mL of venous blood samples was collected from each study subject in a plain gel tube with clot activator (micronised silica particles). The collected blood samples were then allowed to clot at room temperature, centrifuged at 4000 rpm for about 10 minutes, and the serum was collected in clean dry serum tubes. The sera obtained were analysed immediately, whenever possible or stored at -20°C in case of delay. The serum levels of AST, ALT, ALP, CK-MB, glucose, TC, TG, and HDL-C were measured using a fully automated dry chemistry-based analyser (VITROS® 350 chemistry system, Ortho-clinical diagnostics, UK) while serum TpI was measured using VITROS EciQ Immunoassay analyzer (Ortho-clinical diagnostics, UK)-according to the protocols provided by the manufacturer. HbA1c was assayed by using a fully automated Biorad D-10 HbA1c analyser. The processed sera were assayed in a single batch after proper standardisation and quality control of the analysers and using the same lots of reagents. Internal Quality Control (QC) was run every day and the observed values were within ±2SD.

Diagnostic Criteria

The CVD was defined based on one or more time findings of elevated cardiac markers, abnormal ECG findings, and Echocardiogram. The serum liver enzymes were classified as high when their reported values were above their suggested reference ranges. The diagnostic reference ranges used were as follows: AST >59 U/L in males and >36 U/L in females, ALT >50 U/L in males and ALT >35 U/L in females, ALP >126 U/L in both males and females [19].

STATISTICAL ANALYSIS

All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) version 21.0 (SPSS, IBM, Chicago, IL). Continuous data were expressed as mean±Standard Deviation (SD and 95% CI, whereas categorical data were presented as numbers and percentages. The statistical differences in mean values of continuous variables between healthy controls and CVD subjects were assessed by the Student's t-test. On the other hand, Chi-square test was used to compare the difference in the frequency of categorical variables between the two study groups. Pearson's correlation analysis was carried out to estimate the level of correlation between liver enzymes and other baseline variables. Association between liver enzymes and CVDs was examined by multinomial logistic regression analysis. The p-value (two-tailed) <0.05 was considered statistically significant.

RESULTS

A total of 400 subjects were enrolled in the present study, out of which 200 were healthy controls and 200 subjects with CVDs. There were 125 males and 75 females in control group and 130 males and 70 females in the patient group. The details of baseline socio-demographic and biochemical variables are presented in [Table/Fig-1].

Variables	Healthy control (n=200)	CVD subjects (n=200)	p-value
Male/Female	125/75	130/70	-
Age (years)	53.0±9.7	61.3±12.7	0.001*
BMI (kg/m^2)	24.8±2.5	25.6±3.1	0.001*
Waist-Hip ratio	0.9447±0.063	0.9964±0.043	0.001*
SBP (mmHg)	118.9±7.5	122.2±15.2	0.006*
DBP (mmHg)	79.14±8.6	78.2±10.2	0.292
CK-MB (U/L)	18.1±6.6	87.7±95.3	0.001*
Troponin-I (µg/L)	0.2±0.2	11.4±23.1	0.001*
AST (U/L)	23.1±5.8	124.6±168.7	0.001*
ALT (U/L)	20.6±6.2	55.5±71.6	0.001*
ALP (U/L)	70.4±18.7	100.3±78.6	0.001*
FBS (mg/dL)	87.0±8.0	112.7±50.9	0.001*
HbA1C (%)	5.1±0.4	6.1±1.6	0.001*
TC (mg/dL)	143.1±21.7	155.4±48.5	0.001*
TG (mg/dL)	102.1±28.2	147.4±86.8	0.001*
HDL-C (mg/dL)	43.4±9.6	35.1±10.0	0.001*
Smoking status$^{\psi}$			
Yes	18 (9)	98 (49)	0.001*
No	182 (91)	102 (51)	
Drinking habits$^{\psi}$			
Yes	95 (47.5)	120 (60)	0.001*
No	105 (52.5)	80 (40)	

[Table/Fig-1]: Baseline characteristics of study subjects (N=400).
The continuous variables were expressed in mean ± SD while categorical variables were expressed in n (%). Student's t-test for continuous variables and Chi-square test for categorical variables. CVDs: Cardiovascular diseases; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; CK-MB: Creatine kinase-MB; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; FBS: Fasting blood sugar; CK-MB: Creatine kinase-MB; CI: Confidence interval; TC: Total cholesterol; TG: Triglycerides; *p<0.05, statistically significant; ψ categorical variables

The mean ages of healthy controls and CVDs subjects were 53.0±9.7 and 61.3±12.7 years, respectively. The frequency of smoking and drinking habits (p<0.001) and mean values of BMI, SBP, WHR, serum AST, ALT, ALP, glucose, HbA1c, CK-MB, troponin-I, TC and TG were significantly higher in CVD patients while HDL-C (p<0.001) was significantly lower in them. The frequency of elevated liver enzymes was higher in males than females in CVDs, although the difference was not statistically significant [Table/Fig-2].

The results of Pearson's correlation analysis are presented in [Table/Fig-3]. Among the three liver enzymes analysed, it was only AST that showed a significant (p<0.001), and moderate correlation with CK-MB (r=0.448) and troponin-I (r=0.397). The correlations with other baseline variables were weak and not statistically significant (p>0.05).

Variables		Male	Female	Total	p-value
AST	Elevated	75 (37.5)	32 (16)	107 (53.5)	0.143
	Normal	55 (27.5)	38 (19)	93 (46.5)	
ALT	Elevated	45 (22.5)	19 (9.5)	64 (32)	0.105
	Normal	85 (42.5)	51 (25.5)	136 (68)	
ALP	Elevated	13 (6.5)	11 (5.5)	24 (12)	0.280
	Normal	117 (58.5)	59 (29.5)	176 (88)	

[Table/Fig-2]: Prevalence of elevated liver enzyme in CVDs subjects by gender.
Data were represented as n (%), AST (Aspartate aminotransferase), ALT (Alanine aminotransferase), ALP (Alkaline phosphatase)

Variables	AST		ALT		ALP	
	r-value	p-value	r-value	p-value	r-value	p-value
Age	0.086	0.228	0.048	0.501	-0.070	0.324
BMI	0.007	0.916	0.002	0.975	-0.021	0.763
WHR	-0.100	0.161	-0.009	0.902	-0.017	0.809
SBP	-0.051	0.475	-0.074	0.301	0.047	0.506
DBP	-0.100	0.990	-0.081	0.252	0.023	0.746
CK-MB	0.448	0.001**	0.122	0.086	-0.066	0.356
Troponin-I	0.397	0.001**	0.096	0.176	0.013	0.858
FBS	0.019	0.791	0.047	0.509	0.127	0.072
HbA1C	0.036	0.610	-0.015	0.835	0.035	0.624
TC	-0.005	0.947	-0.074	0.296	-0.078	0.273
TG	-0.016	0.831	-0.070	0.326	-0.025	0.073
HDL-C	0.116	0.102	-0.012	0.864	-0.009	0.901

[Table/Fig-3]: Correlation of liver enzyme activity with baseline characteristics of the CVD subjects.
**Correlation is significant at the 0.01 level (2-tailed); BMI: Body mass index; WHR: Waist-to-hip ratio; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; FBS: Fasting blood sugar; TC: Total Cholesterol; TG: Triglycerides; HDL-C: High-density lipoprotein-cholesterol

The different models of adjusted multinomial logistic regression analysis were generated to identify the best predictors of incident CVDs. Present study results showed that liver aminotransferases (AST and ALT) and ALP were statistically significant (p=0.001) in all the models with slightly differences in adjusted odd ratio. Based on the differences in odd ratio, liver aminotransferases (AST and ALT) predict the CVDs better than ALP [Table/Fig-4].

Model	AST		ALT		ALP	
	Adjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Model 1	1.19 (1.14-1.25)	0.001*	1.18 (1.13-1.23)	0.001*	1.04 (1.03-1.06)	0.001*
Model 2	1.20 (1.13-1.27)	0.001*	1.16 (1.11-1.22)	0.001*	1.04 (1.03-1.06)	0.001*
Model 3	1.21 (1.12-1.31)	0.001*	1.18 (1.11-1.25)	0.001*	1.05 (1.03-1.07)	0.001*
Model 4	1.21 (1.11-1.32)	0.001*	1.19 (1.11-1.26)	0.001*	1.05 (1.03-1.07)	0.001*

[Table/Fig-4]: Association of liver enzyme with CVDs.
Variables included in the models
Model 1: adjusted for age and sex
Model 2: Model 1plus BMI, WHR, FBS, HbA1C, SBP, and DBP
Model 3: Model 2 plus TC, TG and HDL-C
Model 4: Model 3 plus smoking habits and drinking habits
AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; OR: Odd ratio; CI: Cumulative interval; BMI: Body mass index; WHR: Waist-to-hip ratio; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; FBS: Fasting blood sugar; TC: Total cholesterol; TG: Triglycerides; HDL-C: High-density lipoprotein-cholesterol; *p<0.01 indicates highly statistically significant

DISCUSSION

The present study revealed that liver enzymes were positively associated with CVDs among Nepali adults. The present study was the first study from Nepal that provides information on the association between liver enzymes and CVDs. All socio-demographic variables and biochemical parameters were statistically significant (p<0.05) in CVDs compared to healthy controls, except DBP. The levels of liver enzymes were found to be higher in CVDs. Present findings were supported by previous studies [13,17].

In the present study, elevated liver enzymes were statistically higher (p<0.05) in patients with CVDs. The serum levels of AST, ALT, and ALP were about five, two and a half, and one and a half time higher in patients with CVDs than in the healthy control, respectively. Higher levels of liver enzymes (AST, ALT, and ALP) were found in male than female patients with CVDs. Present study findings showed AST were significantly associated with CVDs and showed a positive correlation with age, BMI, CK-MB, troponin-I, FBS, and HbA1C. Present findings were supported by a number of cohort and population-based studies. A cohort study conducted in Korea showed a strong association between AST activity and all causes of mortality [20]. Arndt V et al., showed an association between liver enzymes and all-cause mortality in southern Germany [21]. A population-based, nationwide cohort study in Korean adults investigated a significant association between AST and Myocadial Infarction (MI) and ischaemic stroke risk [13]. A study conducted by Rehman H et al., showed a positive association between AST and CVDs was more common in the Asian population [22]. The basic mechanism for AST and CVDs association is mainly hypothetical. The AST elevation is commonly due to liver diseases and Non Alcoholic Fatty Liver Disease (NAFLD) is predominantly associated with CVDs [23]. The elevated AST is also associated with cardiovascular risk factors, like obesity, metabolic syndrome, and diabetes mellitus [24].

In present study, ALT showed a significant association with CVDs after adjustment for age, sex, BMI, WHR, FBS, HbA1C, SBP, DBP, TC, TG, smoking habits, and drinking habits. Similarly, ALT showed a positive correlation with age, BMI, CK-MB, troponin-I and FBS. The agreements were found in several studies [21,25]. Choi KM et al., also reported a significant (p<0.001) association between ALT and ischaemic stroke, MI, and total mortality after adjustment for age, sex, alcohol, BMI, exercise, dyslipidemia, hypertension, and diabetes mellitus [13]. Ndrepepa G and Kastrati A found, the association between elevated ALT and CVD or mortality was stronger in the Asian population than US or European populations [12]. According to a study by Goessling W et al., after adjustment for age, sex, alcohol-intake, smoking, physical activity, waist circumference, triglycerides, SBP, fasting glucose and HDL-C, the association with all-cause mortality and CVD events was attenuated, whereas the association with IHD remained significant [26]. Similarly, according to the Framingham offspring heart study, there was an increased risk of CVD in age-sex adjusted models HR=1.23 (1.12–1.34); p<0.01 which was attenuated after multivariable adjustment [27]. The underlying mechanism for elevated ALT and CVDs mainly due to clinical or subclinical liver diseases [12].

In the present study, ALP also showed a positive significant association with CVDs after adjustment for age, sex, BMI, WHR, FBS, HbA1C, SBP, DBP, TC, TG, smoking habits, and drinking habits. ALP showed a positive correlation with SBP, DBP, troponin-I, and FBS. Kunutsor SK et al., reported that ALP was correlated with several risk factors of CVDs but strongly with age [28]. Several studies have shown an association between elevated ALP and CVDs in different populations [15,29,30]. Many underlying mechanisms are explained for the elevated ALP and CVD association. Inflammation is a common connection between elevated ALP and CVDs. The elevated ALP level may be associated with liver disease (NAFLD) [31]. Another possible mechanism, ALP catalyses the hydrolysis of inorganic pyrophosphate, an inhibitor of vascular calcification, causes vascular hardening and enhances the process of atherosclerosis [30,32].

The strength of the present study included an adjustment for well-defined cardiovascular risk factors including age, BMI, lipids, drinking habits, and smoking habits to investigate the relationships. However, some limitations should be considered in the present study.

Limitation(s)

The limitations of the present study were a small sample size and that the study was conducted at single centre. Therefore, prospective large-scale studies in the general population are needed to investigate the possible mechanisms between liver enzymes and the incident of CVDs.

CONCLUSION(S)

Elevated serum aminotransferease, in particular AST, was found to be the strongest predictor of incident CVDs in Nepali adults. Therefore, their measurement together with the established cardiac biomarkers could potentially help in the differential diagnosis of CVDs and ascertain the liver damage which may appear at the last stage of the disease.

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REFERENCES

[1] Mc Namara K, Alzubaidi H, Jackson JK. Cardiovascular disease as a leading cause of death: How are pharmacists getting involved? Integr Pharm Res Pract. 2019;8:1.
[2] World Health Organization. Cardiovascular Disease Programme, World Health Organization & World Health Organization. Noncommunicable Disease and Mental Health Cluster, Integrated Management of Cardiovascular Risk. (World Health Organization, 2002). 9-12 July 2002. https://www.who.int/cardiovascular_diseases/ media/en/635.pdf.
[3] Dagenais GR, Leong DP, Rangarajan S, Lanas F, Lopez-Jaramillo P, Gupta R, et al. Variations in common diseases, hospital admissions, and deaths in middle-aged adults in 21 countries from five continents (PURE): A prospective cohort study. The Lancet. 2020;395(10226):785-94.
[4] Vaidya A, Pokharel PK, Nagesh S, Karki P, Kumar S, Majhi S. Prevalence of coronary heart disease in the urban adult males of eastern Nepal: A population-based analytical cross-sectional study. Indian Heart J. 2009;61(4):341-47.
[5] Hu X, Sun X, Li Y, Gu Y, Huang M, Wei J, et al. Potential gains in health-adjusted life expectancy from reducing four main non-communicable diseases among Chinese elderly. BMC Geriatrics. 2019;19(1):01-07.
[6] Klenk J, Rapp K, Büchele G, Keil U, Weiland SK. Increasing life expectancy in Germany: Quantitative contributions from changes in age-and disease-specific mortality. Eur J Public Health. 2007;17(6):587-92.
[7] Buttar HS, Li T, Ravi N. Prevention of cardiovascular diseases: Role of exercise, dietary interventions, obesity and smoking cessation. Exp Clin Cardiol. 2005;10(4):229.
[8] Mensah GA, Wei GS, Sorlie PD, Fine LJ, Rosenberg Y, Kaufmann PG, et al. Decline in cardiovascular mortality: Possible causes and implications. Circulation Res. 2017;120(2):366-80.
[9] Hajar R. Risk factors for coronary artery disease: Historical perspectives. Heart Views: The Official Journal of the Gulf Heart Association. 2017;18(3):109.
[10] Cox M, Nelson DL. Lehninger Principles of Biochemistry, 4th ed; New York, NY, USA: W.H. Freeman; 2005. ISBN 0716743396.
[11] Henrion J. Hypoxic hepatitis. Liver International. 2012;32(7):1039-52.
[12] Ndrepepa G, Kastrati A. Alanine aminotransferase- A marker of cardiovascular risk at high and low activity levels. J Lab Precis Med. 2019;4(4):29.
[13] Choi KM, Han K, Park S, Chung HS, Kim NH, Yoo HJ, et al. Implication of liver enzymes on incident cardiovascular diseases and mortality: A nationwide population-based cohort study. Sci Rep. 2018;8(1):01-09.
[14] Park EO, Bae EJ, Park BH, Chae SW. The associations between liver enzymes and cardiovascular risk factors in adults with mild dyslipidemia. J Clin Med. 2020;9(4):1147.
[15] Kunutsor SK, Apekey TA, Khan H. Liver enzymes and risk of cardiovascular disease in the general population: A meta-analysis of prospective cohort studies. Atherosclerosis. 2014;236(1):07-17.
[16] Lee H, Shin DW, Lee TH, Yang HK, Ahn E, Yoon JM, et al. Association between change in serum aminotransferase and mortality: A nationwide cohort study in Korea. Medicine (Baltimore). 2016;95(12):e3158.
[17] Motamed N, Rabiee B, Poustchi H, Dehestani B, Hemasi GR, Khonsari MR, et al. Non-alcoholic Fatty Liver Disease (NAFLD) and 10-year risk of cardiovascular diseases. Clin Res Hepatol Gastroenterol. 2017;41(1):31-38.
[18] Lohman TG, Roche AF, Martorell R. Anthropometric standardization reference manual. Human Kinetics Books. 1988.
[19] Vitros micro slide assay summary. Pub. No. J23323_EN. 2018-07-03. Ortho Clinical Diagnostics, Inc 2018. Rochester, New York 14626. https://www.scribd.com/document/458550250/MSAS-J23323-EN. April 27, 2020.
[20] Kim HC, Nam CM, Jee SH, Han KH, Oh DK, Suh I. Normal serum aminotransferase concentration and risk of mortality from liver diseases: Prospective cohort study. BMJ. 2004;328:983.
[21] Arndt V, Brenner H, Rothenbacher D, Zschenderlein B, Fraisse E, Fliedner TM. Elevated liver enzyme activity in construction workers: Prevalence and impact on early retirement and all-cause mortality. Int Arch Occup Environ Health. 1998;71(6):405-12.
[22] Rehman H, Samad Z, Mishra SR, Merchant AT, Narula JP, Mishra S, et al. Epidemiologic studies targeting primary cardiovascular disease prevention in South Asia. Indian Heart J. 2018;70(5):721-30.
[23] Adams LA, Anstee QM, Tilg H, Targher G. Non-alcoholic fatty liver disease and its relationship with cardiovascular disease and other extrahepatic diseases. Gut. 2017;66(6):1138-53.
[24] Porter SA, Pedley A, Massaro JM, Vasan RS, Hoffmann U, Fox CS. Aminotransferase levels are associated with cardiometabolic risk above and beyond visceral fat and insulin resistance: The Framingham Heart Study. Arterioscler Thromb Vasc Biol. 2013;33(1):139-46.
[25] Kim HC, Kang DR, Nam CM, Hur NW, Shim JS, Jee SH, et al. Elevated serum aminotransferase level as a predictor of intracerebral hemorrhage: Korea medical insurance corporation study. Stroke. 2005;36(8):1642-47.
[26] Goessling W, Massaro JM, Vasan RS, D'Agostino Sr RB, Ellison RC, Fox CS. Aminotransferase levels and 20-year risk of metabolic syndrome, diabetes, and cardiovascular disease. Gastroenterology. 2008;135(6):1935-44.
[27] Schindhelm RK, Dekker JM, Nijpels G, Bouter LM, Stehouwer CD, Heine RJ, et al. Alanine aminotransferase predicts coronary heart disease events: A 10-year follow-up of the Hoorn Study. Atherosclerosis. 2007;191(2):391-96.
[28] Kunutsor SK, Bakker SJ, Kootstra-Ros JE, Gansevoort RT, Gregson J, Dullaart RP. Serum alkaline phosphatase and risk of incident cardiovascular disease: Interrelationship with high sensitivity c-reactive protein. PloS One. 2015;10(7):e0132822.
[29] Tonelli M, Curhan G, Pfeffer M, Sacks F, Thadhani R, Melamed ML, et al. Relation between alkaline phosphatase, serum phosphate, and all-cause or cardiovascular mortality. Circulation. 2009;120(18):1784-92.
[30] Wannamethee SG, Sattar N, Papcosta O, Lennon L, Whincup PH. Alkaline phosphatase, serum phosphate, and incident cardiovascular disease and total mortality in older men. Arterioscler Thromb Vasc Biol. 2013;33(5):1070-76.
[31] Targher G, Bertolini L, Padovani R, Rodella S, Tessari R, Zenari L, et al. Prevalence of nonalcoholic fatty liver disease and its association with cardiovascular disease among type 2 diabetic patients. Diabetes Care. 2007;30(5):1212-18.
[32] Abramowitz M, Muntner P, Coco M, Southern W, Lotwin I, Hostetter TH, et al. Serum alkaline phosphatase and phosphate and risk of mortality and hospitalization. Clin J Am Soc Nephrol. 2010;5(6):1064-71.

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