

Serum alkaline phosphatase is associated with arterial stiffness and 10-year cardiovascular disease risk in a Chinese population

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Abstract

Background

Serum alkaline phosphatase (ALP) has been recognized as a biomarker of cardiovascular disease (CVD) risk or mortality, recently. This study aimed to explore the association of ALP with arterial stiffness and 10-year CVD risk.

Methods

A total of 12539 participants without CVD who underwent health examinations including serum ALP level were retrospectively analyzed. Arterial stiffness was measured by brachial ankle pulse wave velocity (baPWV) and 10-year CVD risk was evaluated by Framingham risk score (FRS).

Results

All participants were stratified into four groups according to the quartile of serum ALP. Participants with high ALP quartiles had higher cardiovascular parameters and baPWV, as well as an increase 10-year CVD risk. Logistic regression analysis showed that serum ALP was an independently risk factor for elevated baPWV and 10-year CVD risk after adjustment for traditional CVD risk factors in both women and men. In receiver operating characteristic (ROC) curve analysis, the area under the ROC curve (AUROC) of serum ALP for predicting elevated baPWV was 0.740 (95% CI/0.726–0.754, $P < 0.001$) in women, larger than that in men.

Conclusions

Serum ALP is independently associated with arterial stiffness and 10-year CVD risk in the general Chinese population. Our results also imply the better performance of serum ALP in women than men for predicting subclinical atherosclerosis.

Background

With rapid economic growth and the aging of the population, the prevalence of cardiovascular disease (CVD) has rapidly and substantially increased in China. There were an estimated 93.8 million prevalent cases of CVD overall during 2016 in China, more than twice that of 1990 (40.6million) [1]. CVD is a leading cause of death in China, being the cause of 40% of deaths in the Chinese population [2], representing a major public health concern and severe economic burden. Despite improved understanding and treatment of its risk factors (e.g. diabetes and dyslipidemia), the prevalence of CVD has rapidly increased. Hence, investigation of additional modifiable risk factors is urgently needed.

Alkaline phosphatase (ALP) is an orthophosphate monoester phosphohydrolase and commonly measured in clinical practice as a marker of hepatic or bony disease. Recently, a growing body of evidences have demonstrated that high ALP level, even within the normal range, is significantly correlated with risk of CVD [3, 4]. Furthermore, population-based studies have suggested that elevated ALP level is a risk factor for all-cause and cardiovascular mortality in people with or without kidney disease [5, 6]. The China National Stroke Registry has indicated that ALP may be an independent predictor of all-cause mortality, stroke recurrence, composite end point, and poor functional outcome after stroke [7]. Extensive evidence has indicated that brachial-ankle pulse wave velocity (baPWV) is a reliable marker of subclinical atherosclerosis and may be a predictor of cardiovascular events [8, 9]. The Framingham risk score (FRS) is the most applicable method to evaluate CVD risk and to predict the cumulative 10-year CVD risk [10]. Although the association between ALP levels and CVD risk has been widely investigated, there is limited data on the association of ALP levels with baPWV and FRS. Therefore, the aim of the current study is to explore the association of ALP levels with baPWV and FRS in a general Chinese population.

Methods

Study Participants

This study represented a retrospective analysis of 12539 participants who underwent a health examination at the Health Promotion Center of the First Affiliated Hospital of Nanjing Medical University, between September 2017 and December 2019. We excluded participants with known hepatic, biliary or bone disease, the previous history of cardiovascular events, cerebrovascular accident, malignancy, systemic acute or chronic inflammatory diseases, and reduced renal function with a serum creatinine > 133umol/l. The study was approved by the Human Research Ethics Committee of the First Affiliated Hospital of Nanjing Medical University and was conducted in accordance with the Declaration of Helsinki.

Data collection

Each participant completed a standard questionnaire to self-report their smoking habit, history of acute and chronic illnesses and drug use. Weight, height, and blood pressure were measured in accordance with international standards. The body mass index (BMI)=weight (kg)/height (m)². All blood samples were obtained from the antecubital vein after 10-hour overnight fast. Routine biochemical analyses including lipid profile, fasting blood glucose, renal function and serum ALP level were measured by enzymatic methods (Chemistry Analyzer Hitachi 7020, Japan). Glycated hemoglobin A1c (HbA1c) values were measured by high-performance liquid chromatography.

BaPWV Measurement

VP-1000 automated PWV/ABI analyzer was used to measure baPWV. Briefly, the participants were examined in the supine position after resting for 10-15 minutes. BaPWV was measured as previously

described [11]. We collected data including ΔT_{ba} and La-Lb, and calculated baPWV. ΔT_{ba} was expressed in the time interval between the brachial and ankle waveforms. La-Lb was expressed in the distance between the brachium and the ankle estimated automatically according to the subject's height. baPWV was calculated as $(La-Lb)/\Delta T_{ba}$. The average value of left and right baPWV was used for analysis.

Framingham 10-year risk estimation

Framingham risk score (FRS) is a simplified and common tool for the assessment of risk level of CVD over 10 years. FRS were calculated based on the six coronary risk factors including age, sex, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), systolic blood pressure (SBP) (treated or untreated), smoking habits in men and women, separately [12]. Absolute CVD risk percentage over 10 years was classified as low risk (< 10%), intermediate risk (10–20%), and high risk (> 20%).

Statistical analysis

Continuous variables were expressed as mean \pm SD and categorical variables were expressed as percentages (numbers). One-way ANOVA was used to compare means and the Pearson chi-square test was used to compare proportions. Age-adjusted baPWV means and standard errors were calculated using analysis of covariance (ANCOVA) according to serum ALP quartiles. Pearson's correlation was used to analysis the bivariate correlation between baPWV, Framingham risk score and clinical variables. The binary logistic regression analysis was performed to investigate the independent association of serum ALP level with high baPWV (0=normal baPWV, 1=high baPWV) and the 10-year CVD risk (0=low risk, 1=intermediate or high risk). Receiver operator characteristic (ROC) analyses were performed to calculate area under the ROC curve (AUROC) of serum ALP level for incident high baPWV. Dose-response association of serum ALP level with baPWV and elevated baPWV were conducted using generalized additive model (GAM) and a fitted smoothing curve (penalized spline method). All data analyzed were using SPSS18.0 statistical software and Empower (R). The tests were considered significant when the P-value was <0.05.

Results

Baseline characteristics of the study population

The study included 12539 participants (6915men and 5624 women) with a mean age of 49.31 ± 9.91 years. Demographic and clinical characteristics of the study population are listed in Table 1. Participants were stratified into four groups based on their ALP levels. Participants in the upper quartiles of ALP levels were more likely to older and male than those in the lower quartiles of ALP levels. The proportion of smoking, BMI, SPB, DBP, WBCC, neutrophil count, FBG, HbA1c, TC, TG, LDL-C, ALT, AST and GGT were higher, while HDL-C was lower in the upper quartiles of ALP levels than those in the lower quartiles of ALP levels.

BaPWV and the 10-year CVD risk compared across the quartiles of ALP levels

Age-adjusted mean baPWV significantly increased with increasing quartiles of ALP levels in the overall population (1233.99 ± 207.23 vs 1311.92 ± 216.44 vs 1344.09 ± 227.62 vs 1420.91 ± 258.95 cm/s, $P < 0.001$). This phenomenon was also observed in men (1333.39 ± 194.39 vs 1352.06 ± 200.78 vs 1362.04 ± 221.86 vs 1413.57 ± 256.29 cm/s, $P < 0.001$) and women (1140.60 ± 171.11 vs 1236.83 ± 220.92 vs 1316.32 ± 238.51 vs 1434.23 ± 264.27 cm/s, $P < 0.001$) (Figure 1). Figure 2 showed the association between serum ALP level and FRS categories among participants. As shown in this figure, the prevalence of the high CVD risk was significantly higher in the high serum ALP level group than in the low level group, while the prevalence of the low CVD risk was significantly higher in the low serum ALP level group than in the high level group.

Association between baPWV, Framingham risk score and clinical variables

Pearson's correlation analysis showed that baPWV was positively correlated with age, BMI, SPB, DBP, WBCC, neutrophil count, FBG, HbA1c, TC, TG, LDL-C, uric acid, creatinine, ALT, AST, GGT and ALP, while negatively correlated with HDL-C. The relationships between Framingham risk score and clinical variables, including ALP were similar as the associations between baPWV and clinical variables (Table 2)

Serum ALP level and the risk of elevated baPWV

Elevated baPWV was defined as a value greater than the cut-off level between the third and fourth quartiles (> 75 th percentile) of baPWV, which was 1457 cm/s for all participants, 1481 cm/s for men and 1420 cm/s for women. After adjusting for age, smoking status, BMI, SPB, DBP, WBCC, neutrophil count, FBG, HbA1c, TC, TG, LDL-C, HDL-C and uric acid, serum ALP level was independently associated with elevated baPWV in all participants ($OR = 1.012$, 95% CI 1.009-1.015, $P < 0.001$), in men ($OR = 1.011$, 95% CI 1.008-1.015, $P < 0.001$) and in women ($OR = 1.013$, 95% CI 1.008- 1.017, $P < 0.001$), respectively.

Overall, there were significant positive associations of serum ALP level with baPWV and elevated baPWV (Fig. 3 a, b). Per 1 unit increment in serum ALP level, baPWV is changed in 0.998 m/s (95% CI 0.821-1.138, $P < 0.001$) according to the estimation from regression coefficients indication, and the odds ratios (OR) of the risk of elevated baPWV was 1.134 (95% CI 1.103-1.165, $P < 0.001$).

Binary logistic regression analysis showing the independent contribution of serum ALP level to the 10-year CVD risk

As Framingham risk score was calculated by age, sex, smoking status, SBP, TC and HDL-C, we only adjusted for BMI, DBP, WBCC, neutrophil count, HbA1c, FBG, TG, LDL-C and uric acid in the binary logistic regression. Serum ALP level was independently associated with the 10-year CVD risk in all participants ($OR = 1.004$, 95% CI 1.002-1.006, $P < 0.001$), in men ($OR = 1.007$, 95% CI 1.004-1.009, $P < 0.001$) and in women ($OR = 1.021$, 95% CI 1.013-1.029), $P < 0.001$), respectively, after adjusted for confounding variables.

Performance of serum ALP level for diagnosing subjects with elevated baPWV

We further conducted a ROC curve analysis to assess the diagnostic value of serum ALP level (Figure 4 and Figure 5). The area under the ROC (AUROC) curve to analyze the ability of serum ALP level to predict

elevated baPWV was 0.740 (95% CI 0.726-0.754, $P < 0.001$) in women and the optimal cut-off point for serum ALP level was 84U/L (sensitivity: 71.2 %, specificity: 63.4%). The AUROC value of serum ALP level [0.575 (95% CI 0.559-0.590), $P < 0.001$] for predicting elevated baPWV in men was relatively smaller than that in women, which indicated that serum ALP level was an acceptable predictor of elevated baPWV only in women.

Discussion

Here for the first time, we demonstrated the association of serum ALP level with arterial stiffness and 10-year CVD risk in a larger Chinese population. A major finding of our study was that serum ALP level was positively associated with baPWV as a marker of arterial stiffness and 10-year CVD risk evaluated by FRS, independent of classical cardiovascular risk factors in both women and men. Furthermore, gender differences in the effect of serum ALP level on predicting elevated baPWV was reported in the current study.

Alkaline phosphatase (ALP) is mainly expressed in bone, liver, and kidney. Besides the role in increasing ALP level for hepatic or bony disease, elevated ALP is also significantly associated with other diseases including metabolic syndrome, diabetes and non-alcoholic fatty liver disease [13-15], all of which are risk factors for CVD [16, 17]. In this regard, there is a growing interest in the relationship of ALP level with CVD. A meta-analysis of prospective cohort studies showed that each standard deviation increment in the baseline ALP was associated with 8% greater risk of CVD [18]. A prospective population-based study found that ALP level >179 IU/L was associated with over 30% higher risk of CVD, independent of several established traditional CVD risk factors [19]. Two prospective cohort study conducted in a German and Iranian population, respectively, have demonstrated that elevated ALP is independently associated with the risk of all-cause mortality in patients with coronary heart disease [19, 20]. Moreover, medicine such as extra-terminal (BET) protein inhibitor apabetalone lowering serum ALP level is paralleled by a reduction of risk of cardiovascular events [21]. In view of the robust evidence presented in the review, Haarhaus M et al, proposed that ALP was an evolving treatment target for CVD and metabolic syndrome [22]. Thus, ALP is not only a marker of cardiovascular risk but also a novel treatment target for CVD. BaPWV is a simple, noninvasive method which correlates well with arterial stiffness, and it is also a useful tool for identifying a subgroup in the population that are at increased risk for cardiovascular events [23]. However, there are limit date about the association between serum ALP and baPWV, especially in a large Chinese population. To the best of our knowledge, there is only one study about the correlation between serum ALP and baPWV in Korean adults [24], but the sample of this study was relatively small and did not calculate the cut-off value of serum ALP for high baPWV. In the present study, which was conducted in a relatively large number of Chinese adults, we found that serum ALP level was positively correlated with baPWV, which was consistent with the study conducted in Korean adults [24]. In addition, we also found that elevated ALP level was an independent risk factor for high baPWV for both men and women even adjustment for traditional CVD risk factors, demonstrating that serum ALP level can be an important biomarker of subclinical atherosclerosis. Furthermore, we observed significant gender differences in the predict value of serum ALP level for high baPWV. By ROC curve analysis, the AUROC of serum ALP level

to predict high baPWV was 0.740 (95% CI 0.726-0.754) in women, larger than that in men (0.575, 95% CI 0.559-0.590). This result implied that serum ALP level predictability of high baPWV could be better in women than in men. Consistent with our findings, there have been several previous studies indicating the gender difference of cardiovascular risk-predictive value of screening tools. Nakagomi A et al. found that all insulin surrogate markers including triglyceride glucose (TyG) index were also associated with increased baPWV and the associations were stronger in women than in men [25]. Rhee TM et al. showed that baPWV was positively correlation with four cardiovascular different risk scores and the correlation was stronger in women than in men [26]. A systematic review and meta-analysis also found that serum uric acid was positively association with baPWV in women, but not in men [27]. Along with these findings, our result highlights the evidence to support more powerful predicted value of serum ALP level for high baPWV in women than in men. The pathophysiology of the gender difference in high baPWV prediction by serum ALP has not yet been clearly understood and needs further study. Although underlying mechanisms of the association of ALP with baPWV are not properly known, some causes were suggested including endothelial dysfunction, vascular calcification, inflammation, Vitamin D deficiency [22, 28, 29]. On the other hand, elevated ALP levels could be caused by non-alcoholic fatty liver disease (NAFLD). It is well established that NAFLD is closely associated baPWV [30]. Further studies on precise mechanism of ALP responsible for subclinical atherosclerosis are warranted.

The Framingham risk score (FRS) is a simplified and has been widely used in different populations to estimate the 10-year risk of CVD [31, 32]. A limited number of studies have assessed the association between serum ALP level and FRS. In the present study, we found that the prevalence of the high CVD risk was increased along with the increased level of serum ALP. Meanwhile, the prevalence of the low CVD risk was decreased along with the increased level of serum ALP. Of note, we also found that serum ALP level was an independent risk factor of intermediate or high 10-year CVD risk after adjusting for confound factors.

This study has several limitations. Firstly, it is difficult to determine whether serum ALP causative effect on arterial stiffness because of the cross-sectional design. Thus, further prospective study is warranted to explore whether participants with high ALP will develop arterial stiffness in future. Secondly, we did not detect inflammatory factors such as C-reactive protein (CRP) and TNF, so the potential role of ALP in arterial stiffness via inflammation could not be studied. Thirdly, the participants in the current study were enrolled in a single hospital for health examination, thus the generalizability of the results may be difficult.

Conclusion

Serum ALP level was positively associated with arterial stiffness measured by baPWV and 10-year CVD risk evaluated by Framingham risk score in the general Chinese population. Serum ALP could perform better in predicting subclinical atherosclerosis of healthy population, especially for women. Prospective and multi-center studies are needed to confirm our results.

Declarations

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Authors' contributions

Wen Guo, and Qun Zhang participated in the study design. Wen Guo, Xiaona Li, Juan Wu, Wenfang Zhu, Jing Lu, Qin Pei, Qingqing Diao and Nianzhen Xu were involved in the conduct of the study and data collection. Wen Guo and Xiaona Li made contributions to the data analysis and interpretation of the results. Wen Guo and Qun Zhang wrote and modified the manuscript and prepared the tables and figures. All authors read and approved the final manuscript.

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Data availability

The datasets used to support this study are not freely available due to participants' privacy protection.

Ethics approval and consent to participate

The study was approved by the Human Research Ethics Committee of the First Affiliated Hospital of Nanjing Medical University. Written informed consents were obtained from all participants before data collection.

Consent for publication

Not applicable.

Conflict of Interest

The authors declare that they have no competing interest.

Abbreviations

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; WBCC, white blood cell count ; FBG, fasting blood glucose ; TC, total cholesterol; TG, triacylglyceride; LDL-C, high-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol ; ALT, alanine aminotransferase; AST, aspartate transaminase; GGT, gamma-glutamyl transpeptidase; ALP, alkaline phosphatase; baPWV, brachial ankle pulse wave ; CVD, cardiovascular disease CVD; FRS, Framingham risk score

References

1. Liu S, Li Y, Zeng X, Wang H, Yin P, Wang L, et al. Burden of Cardiovascular Diseases in China, 1990-2016: Findings From the 2016 Global Burden of Disease Study. *JAMA Cardiol.* 2019; 4: 342-352.
2. Zhao D, Liu J, Wang M, Zhang X, Zhou M. Epidemiology of cardiovascular disease in China: current features and implications. *Nat Rev Cardiol.* 2019; 16: 203-212.
3. Panh L, Ruidavets JB, Rousseau H, Petermann A, Bongard V, Bérard E, et al. Association between serum alkaline phosphatase and coronary artery calcification in a sample of primary cardiovascular prevention patients. *Atherosclerosis.* 2017; 260: 81-86.
4. 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: 1070-1076.
5. Fan Y, Jin X, Jiang M, Fang N. Elevated serum alkaline phosphatase and cardiovascular or all-cause mortality risk in dialysis patients: A meta-analysis. *Sci Rep.* 2017; 7: 13224.
6. 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: 1784-1792.
7. Zong L, Wang X, Li Z, Zhao X, Liu L, Li H, et al. Alkaline Phosphatase and Outcomes in Patients With Preserved Renal Function: Results From China National Stroke Registry. *Stroke.* 2018; 49: 1176-1182.
8. Ueki Y, Miura T, Minamisawa M, Abe N, Nishimura H, Hashizume N, et al. The usefulness of brachial-ankle pulse wave velocity in predicting long-term cardiovascular events in younger patients. *Heart Vessels.* 2017; 32: 660-667.
9. Ohkuma T, Ninomiya T, Tomiyama H, Kario K, Hoshide S, Kita Y, et al. Collaborative Group for J-BAVEL (Japan Brachial-Ankle Pulse Wave Velocity Individual Participant Data Meta-Analysis of Prospective Studies). Brachial-Ankle Pulse Wave Velocity and the Risk Prediction of Cardiovascular Disease: An Individual Participant Data Meta-Analysis. *Hypertension.* 2017; 69: 1045-1052.
10. Artigao-Rodenas LM, Carbayo-Herencia JA, División-Garrote JA, Gil-Guillén VF, Massó-Orozco J, Simarro-Rueda M, et al. Framingham risk score for prediction of cardiovascular diseases: a population-based study from southern Europe. *PLoS One.* 2013; 8: e73529.
11. Yamashina A, Tomiyama H, Takeda K, Tsuda H, Arai T, Hirose K, et al. Validity, reproducibility, and clinical significance of noninvasive brachial-ankle pulse wave velocity measurement. *Hypertens Res.* 2002; 25: 359-364.
12. Park B, Lee YJ. Borderline high serum calcium levels are associated with arterial stiffness and 10-year cardiovascular disease risk determined by Framingham risk score. *J Clin Hypertens (Greenwich).* 2019; 21: 668-673.
13. Kim JH, Lee HS, Park HM, Lee YJ. Serum alkaline phosphatase level is positively associated with metabolic syndrome: A nationwide population-based study. *Clin Chim Acta.* 2020; 500: 189-194.

14. Chen SC, Tsai SP, Jhao JY, Jiang WK, Tsao CK, Chang LY. Liver Fat, Hepatic Enzymes, Alkaline Phosphatase and the Risk of Incident Type 2 Diabetes: A Prospective Study of 132,377 Adults. *Sci Rep.* 2017; 7: 4649.
15. Zhou YJ, Zou H, Zheng JN, Zou TT, Vitale A, Miele L, et al. Serum alkaline phosphatase, a risk factor for non-alcoholic fatty liver, but only for women in their 30s and 40s: evidence from a large cohort study. *Expert Rev Gastroenterol Hepatol.* 2017; 11: 269-276
16. 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: 1138-1153.
17. Wilson PW, D'Agostino RB, Parise H, Sullivan L, Meigs JB. Metabolic syndrome as a precursor of cardiovascular disease and type 2 diabetes mellitus. *Circulation.* 2005; 112: 3066-3072.
18. 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: 7-17.
19. Kabootari M, Raei MR, Akbarpour S, Asgari S, Azizi F, Hadaegh F. Serum alkaline phosphatase and the risk of coronary heart disease, stroke and all-cause mortality: Tehran Lipid and Glucose Study. *BMJ Open.* 2018; 8: e023735.
20. Ndrepepa G, Xhepa E, Braun S, Cassese S, Fusaro M, Schunkert H, et al. Alkaline phosphatase and prognosis in patients with coronary artery disease. *Eur J Clin Invest.* 2017; 47: 378-387.
21. Haarhaus M, Ray KK, Nicholls SJ, Schwartz GG, Kulikowski E, Johansson JO, et al. Apabetalone lowers serum alkaline phosphatase and improves cardiovascular risk in patients with cardiovascular disease. *Atherosclerosis.* 2019; 290: 59-65.
22. Haarhaus M, Brandenburg V, Kalantar-Zadeh K, Stenvinkel P, Magnusson P. Alkaline phosphatase: a novel treatment target for cardiovascular disease in CKD. *Nat Rev Nephrol.* 2017; 13: 429-442.
23. Kubozono T, Miyata M, Kawasoe S, Ojima S, Yoshifuku S, Miyahara H, et al. High Pulse Wave Velocity Has a Strong Impact on Early Carotid Atherosclerosis in a Japanese General Male Population. *Circ J.* 2017; 81: 310-315.
24. Lee JH, Lee JW, Lee YJ. The Relationship between Serum Alkaline Phosphatase and Arterial Stiffness in Korean Adults. *J Atheroscler Thromb.* 2019; 26: 1084-1091.
25. Nakagomi A, Sunami Y, Kawasaki Y, Fujisawa T, Kobayashi Y. Sex difference in the association between surrogate markers of insulin resistance and arterial stiffness. *J Diabetes Complications.* 2019 : 107442.
26. Rhee TM, Kim HL, Oh S, Lim WH, Seo JB, Chung WY, et al. Gender difference in the association between brachial-ankle pulse wave velocity and cardiovascular risk scores. *Korean J Intern Med.* 2019; 34: 539-548.
27. Reborá P, Andreano A, Triglione N, Piccinelli E, Palazzini M, Occhi L, et al. Association between uric acid and pulse wave velocity in hypertensive patients and in the general population: a systematic review and meta-analysis. *Blood Press.* 2020 : 1-12.
28. Savinov AY, Salehi M, Yadav MC, Radichev I, Millán JL, Savinova OV. Transgenic Overexpression of Tissue-Nonspecific Alkaline Phosphatase (TNAP) in Vascular Endothelium Results in Generalized

- Arterial Calcification. *J Am Heart Assoc.* 2015; 4: e002499.
29. Kerner A, Avizohar O, Sella R, Bartha P, Zinder O, Markiewicz W, et al. Association between elevated liver enzymes and C-reactive protein: possible hepatic contribution to systemic inflammation in the metabolic syndrome. *Arterioscler Thromb Vasc Biol.* 2005; 25: 193-197.
30. Li N, Zhang GW, Zhang JR, Jin D, Li Y, Liu T, et al. Non-alcoholic fatty liver disease is associated with progression of arterial stiffness. *Nutr Metab Cardiovasc Dis.* 2015; 25: 218-223.
31. Gurka MJ, Filipp SL, Pearson TA, DeBoer MD. Assessing Baseline and Temporal Changes in Cardiometabolic Risk Using Metabolic Syndrome Severity and Common Risk Scores. *J Am Heart Assoc.* 2018; 7: e009754.
32. Fujihara K, Suzuki H, Sato A, Ishizu T, Kodama S, Heianza Y, et al. Comparison of the Framingham risk score, UK Prospective Diabetes Study (UKPDS) Risk Engine, Japanese Atherosclerosis Longitudinal Study-Existing Cohorts Combine (JALS-ECC) and maximum carotid intima-media thickness for predicting coronary artery stenosis in patients with asymptomatic type 2 diabetes. *J Atheroscler Thromb.* 2014; 21: 799-815.

Tables

Table 1 Characteristics of the study population according to ALP

	Q1 (lowest) 3294	Q2 3103	Q3 3014	Q4 (highest) 3128	P value
(years)	46.00±9.02	48.88±9.70	50.11±9.73	52.45±10.07	<0.01
(male/Female)	1481/1813	1835/1268	1843/1171	1756/1372	<0.01
Smoking (n, %)	418(12.69)	559(18.01)	650(21.57)	689(22.02)	<0.01
Weight (kg/m ²)	23.86±3.25	24.71±3.14	24.82±3.13	24.95±3.16	<0.01
Systolic (mmHg)	121.14±15.83	125.77±16.47	127.71±16.51	132.08±17.75	<0.01
Diastolic (mmHg)	74.74±11.39	77.39±11.06	78.32±11.06	80.02±11.12	<0.01
WBC (10 ⁹ /L)	5.54±1.36	5.70±1.42	5.79±1.51	6.03±1.58	<0.01
Eosinophil count(10 ⁹ /L)	3.21±1.06	3.31±1.09	3.37±1.17	3.54±1.22	<0.01
Urea (mmol/L)	5.29±0.82	5.43±1.04	5.56±1.22	5.74±1.64	<0.01
HbA1c (%)	5.48±0.52	5.59±0.62	5.64±0.70	5.80±0.95	<0.01
Glucose (mmol/L)	5.26±1.01	5.33±1.02	5.41±1.05	5.46±1.10	<0.01
Triglyceride (mmol/L)	1.47±1.05	1.71±1.21	1.86±1.49	2.00±1.53	<0.01
LDL-C(mmol/L)	3.23±0.75	3.31±0.76	3.38±0.76	3.41±0.78	<0.01
HDL-C(mmol/L)	1.40±0.32	1.33±0.30	1.31±0.30	1.30±0.30	<0.01
Uric acid (umol/l)	315.81±88.31	338.68±87.13	341.80±85.21	336.19±82.47	<0.01
Alanine aminotransferase (U/L)	65.19±13.92	68.64±14.57	68.68±14.13	67.44±14.17	<0.01
Aspartate transaminase (U/L)	19.76±12.70	23.43±14.92	25.45±15.49	27.46±17.93	<0.01
Gamma-glutamyl transpeptidase (U/L)	21.33±7.23	23.02±8.13	23.95±8.09	25.35±9.55	<0.01
Alkaline phosphatase (U/L)	26.10±20.91	30.69±23.28	33.53±25.33	37.12±28.84	<0.01
Alkaline phosphatase (U/L)	57.72±7.45	74.15±3.71	87.54±4.22	111.48±14.73	<0.01

Values are presented as mean ± standard deviation.

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; WBC, white blood cell count ; FBG, fasting blood glucose ; TC, total cholesterol; TG, triacylglyceride; LDL-C, high-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol ; ALT, alanine aminotransferase; AST, aspartate transaminase; GGT, gamma-glutamyl transpeptidase; ALP, alkaline phosphatase

Table 2 Correlation between baPWV, Framingham risk score and clinical variables

	baPWV		Framingham risk score	
	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>
years)	0.544	<0.001	0.431	<0.001
(kg/m ²)	0.184	<0.001	0.287	<0.001
(mmHg)	0.620	<0.001	0.346	<0.001
(mmHg)	0.492	<0.001	0.332	<0.001
C (10 ⁹ /L)	0.098	<0.001	0.191	<0.001
rophil count(10 ⁹ /L)	0.100	<0.001	0.145	<0.001
(mmol/L)	0.258	<0.001	0.235	<0.001
lc (%)	0.271	<0.001	0.243	<0.001
nmol/L)	0.111	<0.001	0.178	<0.001
nmol/L)	0.170	<0.001	0.291	<0.001
C(mmol/L)	0.199	<0.001	0.212	<0.001
-C(mmol/L)	-0.120	<0.001	-0.305	<0.001
acid (umol/l)	0.167	<0.001	0.333	<0.001
tinine (umol/l)	0.132	<0.001	0.378	<0.001
U/L)	0.111	<0.001	0.156	<0.001
U/L)	0.135	<0.001	0.106	<0.001
(U/L)	0.178	<0.001	0.284	<0.001
U/L)	0.315	<0.001	0.170	<0.001

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; WBCC, white blood cell count ; FBG, fasting blood glucose ; TC, total cholesterol; TG, triacylglyceride; LDL-C, high-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol ; ALT, alanine aminotransferase; AST, aspartate transaminase; GGT, gamma-glutamyl transpeptidase; ALP, alkaline phosphatase; baPWV, brachial ankle pulse wave

Figures

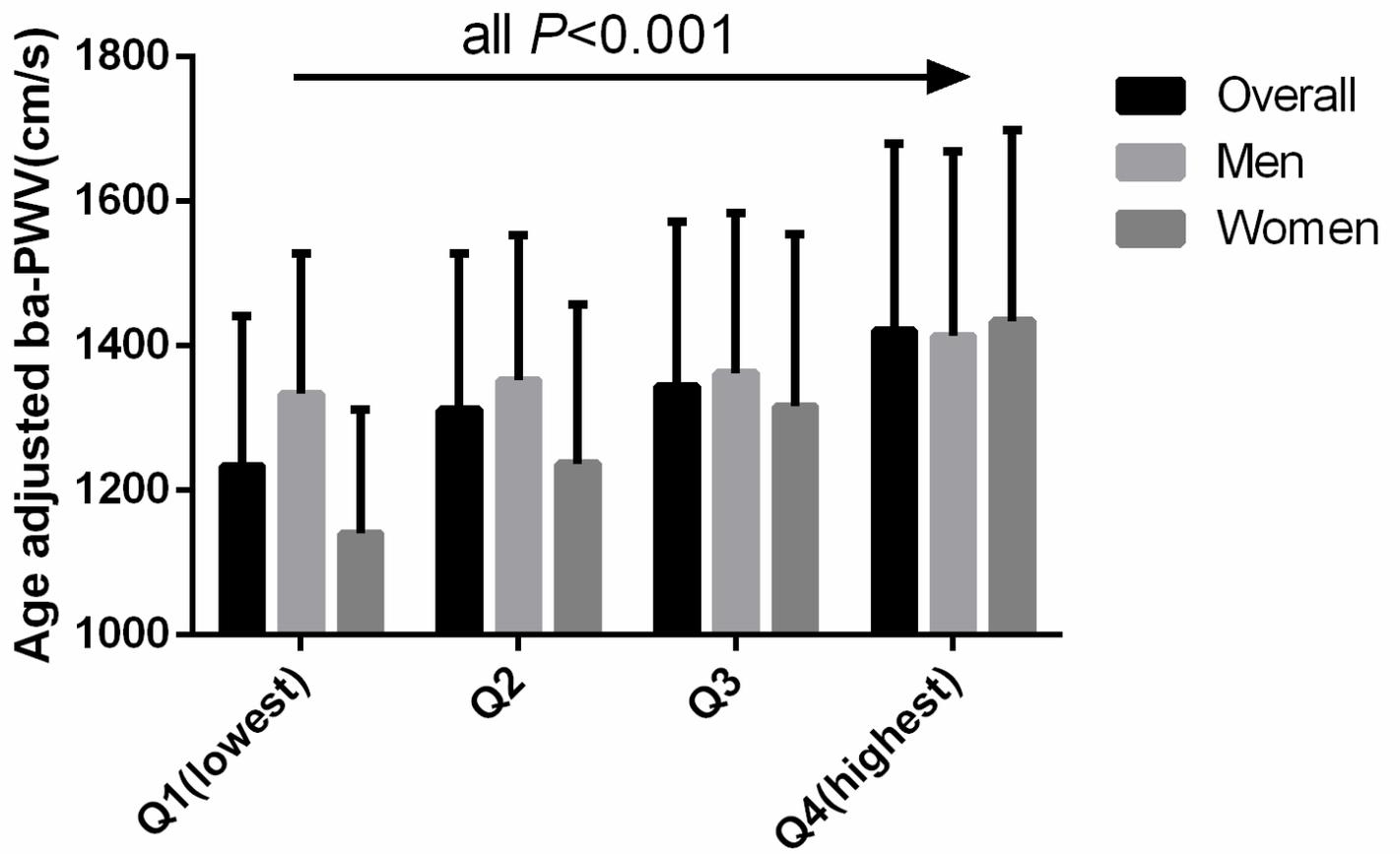


Figure 1

Age adjusted BaPWV compared across the ALP levels quartiles for all participants, men, and women

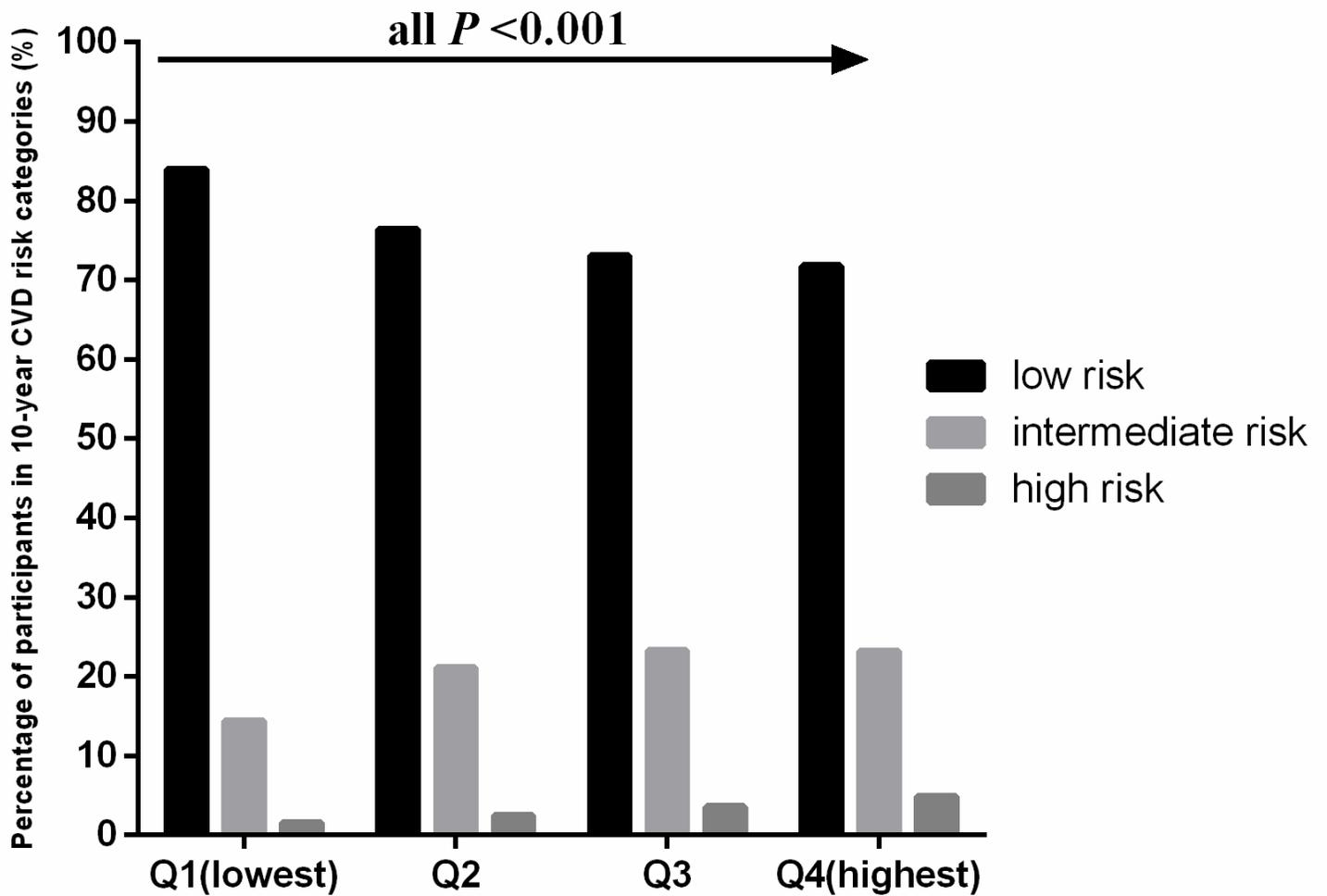


Figure 2

Percentages of 10-CVD risk categorise compared across the quartiles of the ALP levels

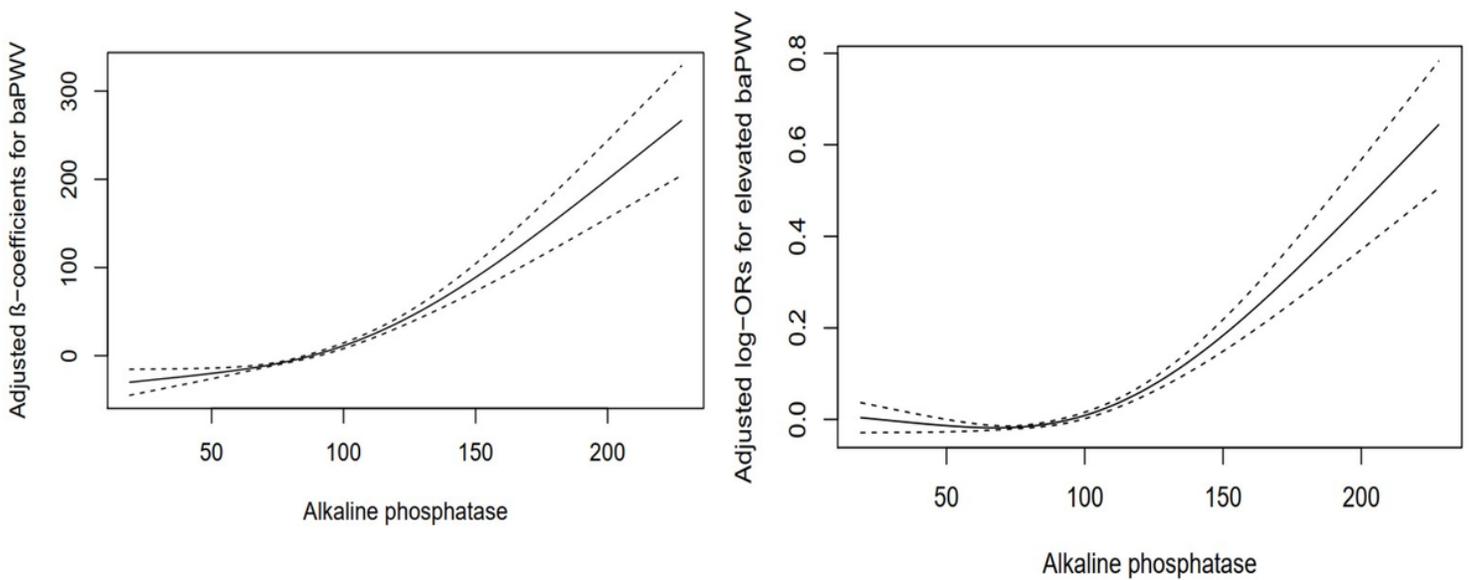


Figure 3

Dose-response relationship between serum ALP level and baPWV. (a) Serum ALP level and baPWV; (b) Serum ALP level and elevated baPWV.

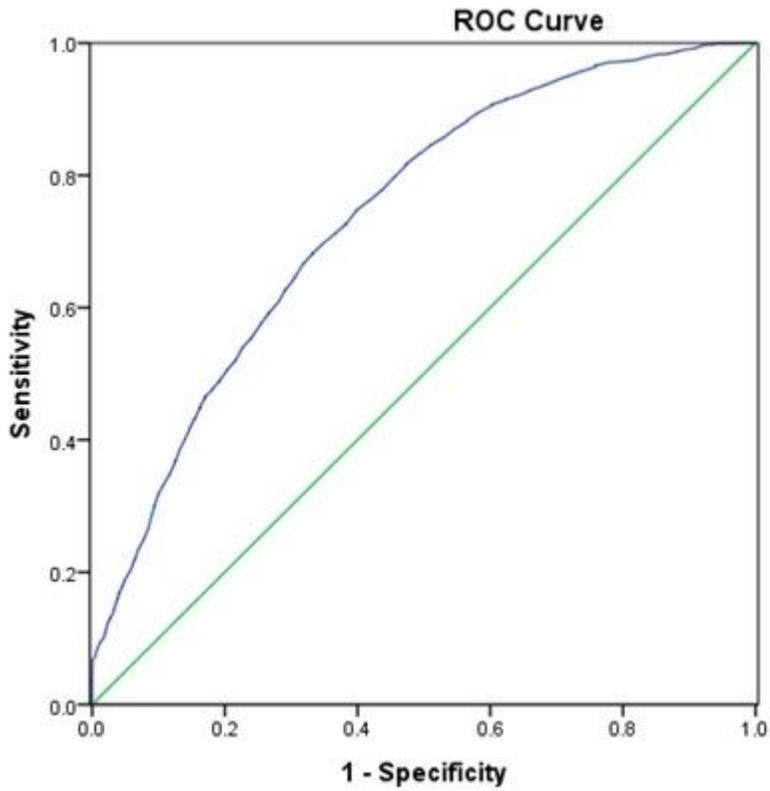


Figure 4

The area under the ROC (AUROC) of the ALP level for predicting high baPWV in women

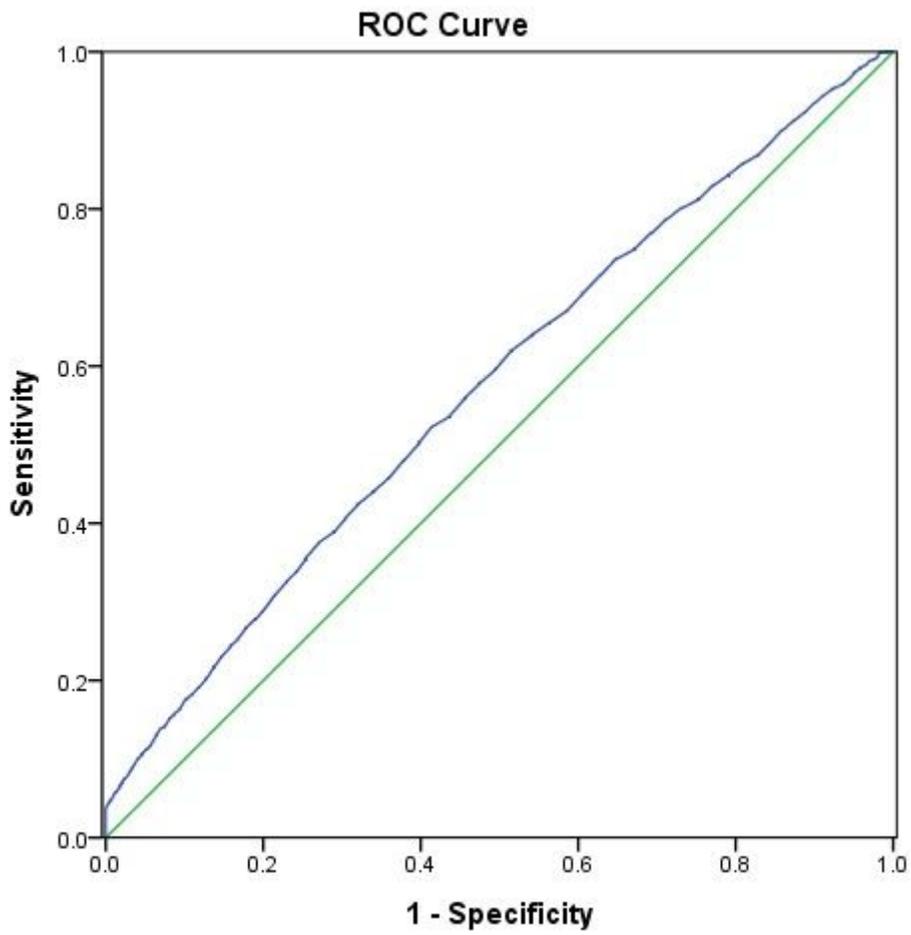


Figure 5

The area under the ROC (AUROC) of the ALP level for predicting high baPWV in men