PEER REVIEW HISTORY

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ARTICLE DETAILS

Title (Provisional)

Longitudinal assessment of serum albumin levels with the risk of coronary artery calcification progression in an asymptomatic population of Korean adults: An observational cohort study

Authors

Won, Ki-Bum; Choi, Su-Yeon; Chun, Eun Ju; Park, Sung Hak; Sung, Jidong; Jung, Hae Ok; Chang, Hyuk Jae

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VERSION 1 - REVIEW

Reviewer	**1**
Name	**Kanda , Daisuke**
Affiliation	**Kagoshima University, Cardiovascular Medicine and Hypertension, Graduate School of Medical and Dental Sciences**
Date	**16-May-2024**
COI	**no competing interests**

Comments to the Author

I have read with interest the article written by Won et al. entitled “Longitudinal assessment of serum albumin levels with the risk of coronary artery calcification progression in an asymptomatic population of Korean adults: An observational cohort study”.

The result of this study that serum albumin levels were associated with coronary artery calcification (CAC) progression in asymptomatic adults without hypoalbuminemia at baseline is clinically relevant in terms of comprehensive management. Although this article might contribute to the literature, there are some concerns.

Major;

1)The authors evaluated the association of individual clinical factors with CAC changes in Table 3. Although lipid and blood glucose parameters were listed in Table 1, why were these parameters excluded in Table 3? Similarly, interscan period was listed as one of the adjustment factors in Model 2 of Table 4, but was not evaluated in Tables 1 and 2. This information should be made clear.

2)The authors evaluated coronary artery calcium score (CACS) using the Agatston score.

European Society of Cardiology (ESC) guidelines on the management of stable CAD and the Japanese Circulation Society (JCS) guidelines on the diagnosis of chronic coronary heart disease describes a CACS cut-off value 400 as a criterion for the recommendation of myocardial perfusion imaging in asymptomatic patients.

On the other hand, the Society of Cardiovascular CT and Society of Thoracic Radiology guidelines in 2016 classified CACS ≥300 as moderate to severely increased risk.

Therefore, as the author states in the Discussion, it would be an overstatement to describe CACS > 100 as heavy CAC.

How many subjects actually had CACS ≥300, which is considered a moderate to severe risk?

3)Th authors defined the progression of CAC as a difference ≥2.5 between the square roots (√) of the baseline and follow-up CACS (ΔVtransformed CACS. Please explain this definition a little more.

4)The author discusses the relationship between the antioxidant and anti-inflammatory effects of albumin and the risk of CAC progression. However, in the no CAC group and CACS > 100 group, it was difficult to show the effect of albumin.

Table 3 shows the risk factors for CAC progression in univariate analysis, but what is the effect of multivariate analysis that includes lipids, blood sugar, and scan period?

Minor;

1） In Table 2, were there any items that were expressed in terms of standard deviation?

2） Many of the references are outdated. We recommend updating the reference data in addition to the necessary previous data.

Reviewer	**2**
Name	**Huang, Hui**
Affiliation	**Sun Yat-Sen University**
Date	**19-Jun-2024**
COI	**None**

Dear editors,

Thank you for inviting me to review this work. Current work reported the association between serum albumin levels and CAC progression. It is analyzed from a well-designed retrospective population-based cohort in Korea with a huge number of participants. The authors managed to proof the inverse association between serum albumin and CAC

progression, and tried to demonstrate the essential relationship in population with lower group of baseline CAC scores. However, the current results cause some confusions and great concerns, that should be solved before accepted.

Major concerns:

1. Serum albumin is a major content in blood, which was reported to influence both variable physiological and pathological process. It is already demonstrated that serum albumin can influence the calcium metabolism, inflammation and urinary albumin is correlate to serum albumin (PMID: 25641887; 34445853; 30910777). All the related factors play important role in vascular calcification progression. Current work used the huge population cohort, and demonstrated the inverse relationship, which obtains related novelty. However, it remained to be further explained. Thus, could have an inspiratory conclusion. For example, it is hypothesis in the discussion that metabolic disorder can explain the mechanism. Then further analyses are suggested to verify the hypothesis, such as mediation analyses of metabolic tests results in serum albumin effect in CAC progression.

2. In method section, authors mentioned different CT scan machine and different machine parameters. Strictly controlling of CT scan is important for calcification evaluation. Any efforts to make sure the consistency of the evaluation should be mentioned. And further explain for the flow of collection of CT scan materials should be presented.

3. The author used annualized CAC progression to present a longitude follow-up of CAC evaluation. The motive observation of CAC change is appreciated. However, they used logistic regression to evaluate the associations, which is inappropriate. As the time dependent results, it is suggested to use COX regression instead to keep most information of the raw data. And the cumulative curve is suggested to compare the risk between different serum albumin levels. Otherwise, the annualized CAC progression risk should be presented as a landmarked analysis. So that, avoiding the imbalance of different follow-up time in this retrospective designed cohort. Especially, the insignificant risk in high baseline CAC score group could be examined by insufficient follow-up.

4. Is there any information about CAD or PVD history in patients? As an analyses about vascular calcification, a history of CAD or PVD is very important for risk factors predicting. It affects calcification by not only genetic predisposition to disease but also drug treatment. The author should explain how did they handle this confounders and weather there any effort is done for avoiding this bias.

5. In table 4, the authors presented a lot of analysis of different CAC baseline score groups. In fact, it is another subgroup analysis, and can be integrated in figure 1. And results should be explained by interaction effect if serum albumin makes sense in the high baseline CAC score subgroups. Instead, it is suggested to perform additional RCS analysis to examine the different trend in different serum albumin levels.

6. It is mentioned the baseline data were presented as albumin tertials. But the numbers of patients are quite different. Authors should explain the reasons.

7. In the most results sections, authors described risk effects by the change of “per-1”. It caused great confusions. If the authors means that every decrease of 1 unit or not? But it is mismatch with the conclusions. So, it should be modified to present results accurately.

Minor concerns:

1. In the multiple variables models, the test results of serum glucose and lipid should be added.

2. References should be added in page 11, line 241-245.

3. The author should state that if there are any follow-up serum test results? The follow-up albumin or renal function change is essential in the CAC progression. It should be added as one of the major limitations if there is not additional data can be supplied.

4. In the discussion, author mentioned healthy population. However, current population accompanied with multiple diseases and vascular calcification is a clinical disease by itself. So, similar descriptions should be avoided.

VERSION 1 - AUTHOR RESPONSE

Response to reviewers’ comments

Reviewer: 1

Dr. Daisuke Kanda,
Kagoshima University

Comments to the Author:

I have read with interest the article written by Won et al. entitled “Longitudinal assessment of serum albumin levels with the risk of coronary artery calcification progression in an asymptomatic population of Korean adults: An observational cohort study”. The result of this study that serum albumin levels were associated with coronary artery calcification (CAC) progression in asymptomatic adults without hypoalbuminemia at baseline is clinically relevant in terms of comprehensive management. Although this article might contribute to the literature, there are some concerns.

Major;

1) The authors evaluated the association of individual clinical factors with CAC changes in Table 3. Although lipid and blood glucose parameters were listed in Table 1, why were these parameters

excluded in Table 3? Similarly, interscan period was listed as one of the adjustment factors in Model 2 of Table 4, but was not evaluated in Tables 1 and 2. This information should be made clear.

RE:

Thank you for valuable comments.

a) Because of the observational design, the use of pharmacological agents was not controlled in the present study during the follow-up period. Generally, for observational studies in which the medications are not controlled, the statistical analysis for the effect of specific medications is usually avoided due to substantial selection bias. The levels of lipid and glucose (continuous variables) do not reflect the presence and control status of underlying diseases (i.e. the normal range of blood glucose is not able to distinguish the absence of diabetes and well-controlled glycemic status in cases of established diabetes under anti-diabetic medication). In contrast, the definition of traditional risk factors (binary variables) broadly includes the disease status and medication use (i.e. Diabetes was defined as a fasting glucose level of ≥126 mg/dL, HbA1C level of ≥6.5%, a referral diagnosis of diabetes, or receiving anti-diabetic treatment). Based on these issues which we described above, we initially assessed the association of individual traditional risk factor with the risk of CAC progression in the univariable regression analysis (Table 3). After then, we adjusted these risk factors in the multiple regression models for evaluating the independent association between serum albumin levels and CAC progression (Table 4).

b) Because CAC progression was not a clinical event such as death, myocardial infarction, or stroke, the interscan period could not reflect the exact time of CAC progression. Therefore, after receiving the opinion of a medical statistician, we used multivariable logistic regression analysis with adjustment of interscan period alike previous papers of KOICA registry. After receiving your comment, we adjusted interscan period in model 1 of Table 4.

c) In table 2, we compared the annualized Δ √transformed CACS, which defined as Δ√transformed CACS divided by interscan period, among albumin tertile groups. This parameter shows the changes of CAC during interscan period. We also evaluated the association of each traditional risk factor with Δ √transformed CACS in Table 3.

d) We analyzed the association of serum albumin levels (per-1 g/dL increase) and the annualized Δ√transformed CAC with consecutive adjustment of clinical variables of age, sex, SBP, fasting glucose, triglyceride, LDL-C, BMI, current smoking, and alcohol consumption, serum creatinine levels, and baseline CACS. The results were described in the Supplementary table 1 following as:

Supplementary table 2 Multiple regression models for the association between serum albumin levels (per-1 g/dL increase) and the annualized Δ√transformed CAC

	Annualized Δ√transformed CAC		
	β	SE	p
Model 1	-0.186	0.076	0.014
Model 2	-0.196	0.076	0.010

BMI, body mass index; CAC, coronary artery calcification; LDL-C, low-density lipoprotein cholesterol; SBP,

systolic blood pressure.

Models:1 = adjusted for age, sex, SBP, fasting glucose, triglyceride, LDL-C, BMI, current smoking, and alcohol consumption; 2 = adjusted for age, sex, SBP, fasting glucose, triglyceride, LDL-C, BMI, current smoking, and alcohol consumption, serum creatinine levels, and baseline CACS.

2) The authors evaluated coronary artery calcium score (CACS) using the Agatston score. European Society of Cardiology (ESC) guidelines on the management of stable CAD and the Japanese Circulation Society (JCS) guidelines on the diagnosis of chronic coronary heart disease describes a CACS cut-off value 400 as a criterion for the recommendation of myocardial perfusion imaging in asymptomatic patients. On the other hand, the Society of Cardiovascular CT and Society of Thoracic Radiology guidelines in 2016 classified CACS ≥300 as moderate to severely increased risk. Therefore, as the author states in the Discussion, it would be an overstatement to describe CACS >100 as heavy CAC. How many subjects actually had CACS ≥300, which is considered a moderate to severe risk?

RE:

Thank you for comments.

a) The proportion of CACS >300 and CACS >400 is 3.7% and 2.6%, respectively. According to the HNR (Heinz Nixdorf Recall) study, repeat CT scans after 5 years provided the readjustment of risk attributable to the increased risk in baseline CACS <400. However, although a high CV risk was present in baseline CACS more than 400, additional CACS evaluation could not add the prognostic value in this condition. In addition, the PARADIGM (Progression of AtheRosclerotic PlAque DetermIned by Computed TomoGraphic Angiography Imaging) registry, baseline coronary plaque burden was the most important factor, when compared with clinical and laboratory factors, in identifying patients at the risk of rapid plaque progression. These findings emphasize the significance of early detecting both the presence of subclinical coronary atherosclerosis and its progression. The strength of present study is that the risk of CAC progression is assessed in asymptomatic adult population without heavy CAC at baseline. We added these contents in the discussion section.

b) I apologize for using an ambiguous expression such as ‘heavy CAC’ in this manuscript. Nasir et al. previously reported that the frequency of a CACS >100 in the Asian population is significantly lower than that in Western populations (J Am Coll Cardiol. 2007;50:953-960). Also, previous KOICA registry data have suggested that it is hard to predict the progression of CAC using specific biomarkers in condition with CACS of >100 at baseline (Reference 32 and 33). During this revision process, we avoided the expression of ‘heavy CAC’ and instead endeavored to use specific cut-off of CACS.

3) The authors defined the progression of CAC as a difference ≥2.5 between the square roots (√) of the baseline and follow-up CACS (Δ√transformed CACS. Please explain this definition a little more.

RE:

Thank you. There are several methods for identifying CAC progression such as absolute difference of

CACS, precent change of CACS, and the SQRT method which you mentioned above. As you know, percent change of CACS is impossible to use in the CACS of 0 at baseline. Budoff et al. reported that the best CAC progression model to predict mortality was the SQRT method beyond age, sex, and baseline CACS (Reference 5). In the present study, participants with baseline CACS of 0 were 56.2% and the CAC progression defined using SQRT method in this population was observed in 13.0%. Considering that a) the large proportion of KOICA participants has baseline CACS of 0 and 2) the KOICA registry focuses on the changes of CAC in asymptomatic adults without heavy CAC at baseline, the SQRT method has been used to define CAC progression in the previous KOICA studies.

4) The author discusses the relationship between the antioxidant and anti-inflammatory effects of albumin and the risk of CAC progression. However, in the no CAC group and CACS >100 group, it was difficult to show the effect of albumin. Table 3 shows the risk factors for CAC progression in univariate analysis, but what is the effect of multivariate analysis that includes lipids, blood sugar, and scan period?

RE:

Thank you for comments. As we answered above, we identified the association of traditional risk factors, baseline CACS, and serum albumin levels with the risk of CAC progression. After then, we evaluated the association between serum albumin levels and CAC progression with adjustment of traditional risk factors, baseline CACS, and interscan periods in overall participants as well as participants of each categorical CACS at baseline. Alike previous KOICA studies which identified the limited availability of biomarkers to predict CAC progression in condition with CACS >100 at baseline (reference 32 and 33), the present study found that serum albumin levels did not have an independent association with the risk of CAC progression in baseline CACS >100.

Minor;

1) In Table 2, were there any items that were expressed in terms of standard deviation?

RE:

Thank you. There is no item for the expression of standard deviation. We corrected Table 2.

2) Many of the references are outdated. We recommend updating the reference data in addition to the necessary previous data.

RE:

Thank you for valuable comment. As you know, the CACS is a traditional imaging modality for assessing coronary atherosclerosis among asymptomatic adult population. In the present study, we endeavored to use representative papers for the usefulness of CACS regarding its prognostic value, and both variability and reproducibility of CACS as references, even if the papers are outdated.

Reviewer: 2

Prof. Hui Huang,

Sun Yat-Sen University

Comments to the Author:

Dear editors,

Thank you for inviting me to review this work. Current work reported the association between serum albumin levels and CAC progression. It is analyzed from a well-designed retrospective population-based cohort in Korea with a huge number of participants. The authors managed to proof the inverse association between serum albumin and CAC progression, and tried to demonstrate the essential relationship in population with lower group of baseline CAC scores. However, the current results cause some confusions and great concerns, that should be solved before accepted.

Major concerns:

1. Serum albumin is a major content in blood, which was reported to influence both variable physiological and pathological process. It is already demonstrated that serum albumin can influence the calcium metabolism, inflammation and urinary albumin is correlate to serum albumin (PMID: 25641887; 34445853; 30910777). All the related factors play important role in vascular calcification progression. Current work used the huge population cohort, and demonstrated the inverse relationship, which obtains related novelty. However, it remained to be further explained. Thus, could have an inspiratory conclusion. For example, it is hypothesis in the discussion that metabolic disorder can explain the mechanism. Then further analyses are suggested to verify the hypothesis, such as mediation analyses of metabolic tests results in serum albumin effect in CAC progression.

RE:

Thank you for valuable comments.

a) The KOICA registry is designed to identify the effectiveness of coronary artery calcium score (CACS) for primary prevention of cardiovascular disease in asymptomatic Korean adults who participated in general health examination. In clinical practice, serum albumin is widely used to identify the nutritional status of patients. And, hypernutritional status could increase the risk of obesity and other metabolic diseases such as hypertension, diabetes and hyperlipidemia. The present study found that 1) the prevalence of hypertension, diabetes, hyperlipidemia, and obesity significantly increased with increasing serum albumin tertile groups and 2) these metabolic disease had a positive association with the risk of CAC progression. In overall participants, serum albumin levels were inversely associated with the risk of CAC progression, and this association was consistently observed irrespective of the presence of metabolic disease. Considering that this study is a retrospective and observational cohort study, it might be unreasonable to evaluate the mechanism in relation to metabolic disorder. This study

is meaningful in identifying that serum albumin levels have an inverse association with the risk of CAC progression even after considering these metabolic diseases. Further prospective investigation for the mechanism regarding the protective effect of serum albumin for CAC progression should be necessary.
b) Previous KOICA study reported the limited availability of biomarkers such as atherogenic index of plasma or triglyceride glucose index to predict CAC progression in condition with CACS >100 at baseline (reference 32 and 33). Therefore, we evaluated the association of serum albumin levels with the risk of CAC progression according to baseline CACS. Alike the results of previous KOICA studies, this study found that serum albumin levels did not have a significant association with the risk of CAC progression in participants with baseline CACS >100.

2. In method section, authors mentioned different CT scan machine and different machine parameters. Strictly controlling of CT scan is important for calcification evaluation. Any efforts to make sure the consistency of the evaluation should be mentioned. And further explain for the flow of collection of CT scan materials should be presented.

RE:

Thank you for valuable comments. When it comes to CT methodology, it is well-established that the difference between retrospective and prospective ECG-triggering method does not significantly affect CACS measured by the scoring system described by Agatston et al. In cases of retrospective ECG gating, the radiation dose might be increased; however, since the image which was reconstructed at a certain time was analysed, retrospective or prospective ECG-triggering would not significantly affect scoring. In addition, all participants were examined using the same CT scanner with identical ECG-triggering method during the initial and follow-up image acquisitions in the present study. Because early validation studies were described in the 2008 CAC screening recommendations, we have added this to the references. In addition, to avoid misunderstanding of the method for CAC measurement, we have amended the manuscript as follows:

Sixth, different CT scanners were used among the participating centers; however, all participants were examined using the same CT scanner with identical ECG-triggering method during the initial and follow-up image acquisitions. Also, CAC progression was defined with the SQRT method, considering interscan variability in the present study.[5,21] Seventh, the present study did not perform the variability analysis based on the strong evidence regarding variability and reproducibility of CACS measurement.

3. The author used annualized CAC progression to present a longitude follow-up of CAC evaluation. The motive observation of CAC change is appreciated. However, they used logistic regression to evaluate the associations, which is inappropriate. As the time dependent results, it is suggested to use COX regression instead to keep most information of the raw data. And the cumulative curve is suggested to compare the risk between different serum albumin levels. Otherwise, the annualized CAC progression risk should be presented as a landmarked analysis. So that, avoiding the imbalance of

different follow-up time in this retrospective designed cohort. Especially, the insignificant risk in high baseline CAC score group could be examined by insufficient follow-up.

RE:

Thank you for valuable comments.

a) Because CAC progression was not a clinical event such as death, myocardial infarction, or stroke, the interscan period could not reflect the exact time of CAC progression. Therefore, after receiving the opinion of a medical statistician, we used multivariable logistic regression analysis with adjustment of interscan period instead of COX regression analysis or cumulative curve alike previous papers of KOICA registry. In the abstract, we described the method of statistical analysis following as:

Association of serum albumin with the risk of CAC progression was analyzed using multivariate logistic regression models with adjustment of interscan period.

b) In table 2, we compared the annualized Δ √transformed CACS, which defined as Δ√transformed CACS divided by interscan period, among albumin tertile groups. This parameter shows the changes of CAC considering interscan period. We evaluated the association of each traditional risk factor with Δ √transformed CACS in Table 3. In addition, we analyzed the association of serum albumin levels (per-1 g/dL increase) and the annualized Δ√transformed CAC with consecutive adjustment of clinical variables of age, sex, SBP, fasting glucose, triglyceride, LDL-C, BMI, current smoking, and alcohol consumption, serum creatinine levels, and baseline CACS. These results are present in the Supplementary table 1 following as:

Supplementary table 2 Multiple regression models for the association between serum albumin levels (per-1 g/dL increase) and the annualized Δ√transformed CAC

	Annualized Δ√transformed CAC		
	β	SE	p
Model 1	-0.186	0.076	0.014
Model 2	-0.196	0.076	0.010

BMI, body mass index; CAC, coronary artery calcification; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.

Models:1 = adjusted for age, sex, SBP, fasting glucose, triglyceride, LDL-C, BMI, current smoking, and alcohol consumption; 2 = adjusted for age, sex, SBP, fasting glucose, triglyceride, LDL-C, BMI, current smoking, and alcohol consumption, serum creatinine levels, and baseline CACS.

c) According to the HNR (Heinz Nixdorf Recall) study, repeat CT scans after 5 years provided the readjustment of risk attributable to the increased risk in baseline CACS <400. However, although a high CV risk was present in baseline CACS more than 400, additional CACS evaluation could not add the prognostic value in this condition. In addition, the PARADIGM (Progression of AtheRosclerotic PlAque DetermIned by Computed TomoGraphic Angiography Imaging) registry, baseline coronary plaque burden was the most important factor, when compared with clinical and laboratory factors, in identifying patients at the risk of rapid plaque progression. These findings emphasize the significance

of early detecting both the presence of subclinical coronary atherosclerosis and its progression. In the present study, the proportion of CACS >400 is only 2.6%. The strength of our study is that the risk of CAC progression is assessed in asymptomatic adult population without heavy CAC at baseline.

4. Is there any information about CAD or PVD history in patients? As an analyses about vascular calcification, a history of CAD or PVD is very important for risk factors predicting. It affects calcification by not only genetic predisposition to disease but also drug treatment. The author should explain how did they handle this confounders and weather there any effort is done for avoiding this bias.

RE:

Thank you for comments.

a) The KOICA registry was performed in asymptomatic Korean adults to evaluate the effectiveness of CACS for the primary prevention of CV disease; Therefore, subjects with previous history of percutaneous coronary intervention using metal stents, those who were treated with percutaneous peripheral intervention, or those with previous history of major adverse cardiovascular events were not included in the present study.

b) Because of the observational design, the use of pharmacological agents was not controlled in the present study during the follow-up period. Generally, for observational studies in which the medications are not controlled, the statistical analysis for the effect of specific medications is usually avoided due to substantial selection bias. The levels of lipid and glucose (continuous variables) do not reflect the presence and control status of underlying diseases (i.e. the normal range of blood glucose is not able to distinguish the absence of diabetes and well-controlled glycemic status in cases of established diabetes under anti-diabetic medication). In contrast, the definition of traditional risk factors (binary variables) broadly includes the disease status and medication use (i.e. Diabetes was defined as a fasting glucose level of ≥126 mg/dL, HbA1C level of ≥6.5%, a referral diagnosis of diabetes, or receiving anti-diabetic treatment). Based on these issues which we described above, we initially assessed the association of individual traditional risk factor with the risk of CAC progression in the univariable regression analysis (Table 3). After then, we adjusted these risk factors in the multiple regression models for evaluating the independent association between serum albumin levels and CAC progression with consideration of baseline CACS (Table 4).

5. In table 4, the authors presented a lot of analysis of different CAC baseline score groups. In fact, it is another subgroup analysis, and can be integrated in figure 1. And results should be explained by interaction effect if serum albumin makes sense in the high baseline CAC score subgroups. Instead, it is suggested to perform additional RCS analysis to examine the different trend in different serum albumin levels.

RE:

Thank you for valuable comments.

Recent data have shown that baseline coronary plaque burden is the most important factor when compared with clinical and laboratory factors for predicting both rapid progression of coronary atherosclerosis and adverse clinical outcomes (Reference 6 and 19). Similarly, previous KOICA studies reported the limited availability of biomarkers to predict CAC progression in condition with CACS >100 at baseline (reference 32 and 33). Figure 1 shows the risk of CAC progression related to serum albumin levels (per-1 g/dL increase) according to the presence of traditional risk factor without adjustment of confounding factors. As we answered preciously, we initially assessed the association of traditional risk factors and baseline CACS with the risk of CAC progression in the univariable regression analysis (Table 3). After then, we adjusted these factors and interscan periods in the multiple regression models to identify an independent association between serum albumin levels and CAC progression according to baseline CACS (Table 4). In the present study, all participants had a normal range of serum albumin levels. We focused on a different association of serum albumin levels with the risk of CAC progression according to baseline CACS rather than different trend of CAC progression in different serum albumin levels.

6. It is mentioned the baseline data were presented as albumin tertials. But the numbers of patients are quite different. Authors should explain the reasons.

RE:

Thank you. As you mentioned above, we described baseline characteristics according to serum albumin tertiles. This makes it easy to identify the differences in clinical characteristics according to serum albumin levels. There are many participants with the same cut-offs for dividing serum albumin tertiles, so the numbers in the three groups are not the same. Considering this finding, we evaluated the risk of CAC progression related to serum albumin levels on the basis of a 1 g/dL increase of serum albumin in the univariable and multivariable regression models.

7. In the most results sections, authors described risk effects by the change of “per-1”. It caused great confusions. If the authors means that every decrease of 1 unit or not? But it is mismatch with the conclusions. So, it should be modified to present results accurately.

RE:

Thank you. As we mentioned above, we evaluated the risk of CAC progression related to serum albumin levels on the basis of a 1 g/dL increase of serum albumin. After receiving your comment, we have clearly described this content in the tables and figures.

Minor concerns:

1. In the multiple variables models, the test results of serum glucose and lipid should be added.

RE:

Thank you. We previously answered why we assessed the risk of CAC progression related to the traditional risk factors (binary variables). We added Supplementary table 1 for the association of serum glucose and lipid levels with the risk of CAC progression following as:

Supplementary table 1 Univariable linear regression analysis for the risk of CAC progression related to the levels of glucose, triglyceride, HDL-C, and LDL-C

	CAC progression		
Variables	OR	95% CI	P
Glucose, per 1-mg/dL increase	1.013	1.011−1.015	<0.001
Triglyceride, per 1-mg/dL increase	1.002	1.002−1.003	<0.001
HDL-C, per 1-mg/dL increase	0.994	0.992−0.997	<0.001
LDL-C, per 1-mg/dL increase	1.005	1.003−1.006	<0.001

CAC, coronary artery calcification; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; OR, odds ratio.

2. References should be added in page 11, line 241-245.

RE:

Thank you. We described the reference number in the sentences which you mentioned above.

3. The author should state that if there are any follow-up serum test results? The follow-up albumin or renal function change is essential in the CAC progression. It should be added as one of the major limitations if there is not additional data can be supplied.

RE:

Thank you for comment. We added the content which you mentioned above in the limitation section following as:

Eighth, we only evaluated the association of the baseline serum albumin levels with CAC progression; any consecutive serum albumin changes during follow-up were not confirmed.

4. In the discussion, author mentioned healthy population. However, current population accompanied with multiple diseases and vascular calcification is a clinical disease by itself. So, similar descriptions should be avoided.

RE:

Thank you for valuable comment.

A majority of participants had no CAC at baseline (56.2%), and the proportion of baseline CACS >400 was only 2.6%. Therefore, we used the expression of ‘a relatively healthy population’. As you recommended, we avoided the expression you pointed out.

VERSION 2 - REVIEW

Reviewer	**1**
Name	**Kanda , Daisuke**
Affiliation	**Kagoshima University, Cardiovascular Medicine and Hypertension, Graduate School of Medical and Dental Sciences**

Date	**24-Oct-2024**
COI	

The authors made the suggested revisions. I have no additional suggestions.