Medicine®

The association between serum albumin levels and related metabolic factors and atrial fibrillation
A retrospective study

Dongsheng Zhao, MMa, Huachen Jiao, MDb,*, Xia Zhong, MDa, Wei Wang, MMc, Lianlian Li, MMa

Abstract

The association between serum albumin (ALB) and cardiovascular events has been well established, but the relationship with atrial fibrillation (AF) remains controversial. This study aims to evaluate the association between ALB and AF in a Chinese population. We reviewed the medical records of 2000 hospitalized patients, 1000 patients with AF were included in the AF group, and 1000 age- and sex-matched patients with sinus rhythm and no history of AF were included in the control group. The T test or chi-square test were conducted to analyze clinical baseline data. Logistic regression analysis was conducted to assess the relationship between AF and ALB. The interrelationships of ALB were analyzed by Pearson correlation analyses. The appropriate cutoff value of ALB for AF was analyzed by receiver operating characteristic curves. ALB levels were lower in the AF group than in the control group ($P < .05$). After multivariable adjustment, ALB was independently negatively associated with AF (odds ratio = 0.935, 95% confidence interval: 0.905–0.965, $P < .05$). ALB levels were positively correlated with serum globulin, total cholesterol, triglyceride, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, serum apolipoprotein A1, and serum apolipoprotein B levels ($P < .05$), but negatively correlated with serum creatinine levels ($P < .05$). The optimal cutoff value of ALB for predicting AF was 37.25 g/L, the sensitivity was 78.0%, and the specificity was 4.6%. Low ALB level is independently associated with AF. Since the current study design cannot establish causalities, further prospective cohort studies are needed to determine this finding.

Abbreviations: AF = atrial fibrillation, ALB = serum albumin, APOA1 = serum apolipoprotein A1, APOB = serum apolipoprotein B, CHD = coronary heart disease, GLB = serum globulin, Hcy = homocysteine, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, ROC = receiver operating characteristic, SCr = serum creatinine, TC = total cholesterol, TG = triglyceride.

Keywords: atrial fibrillation, homocysteine, risk, serum albumin

1. Introduction

Atrial fibrillation (AF), the most common arrhythmia in the clinic, significantly affects morbidity and mortality as a risk factor for worsening stroke, heart failure, and cardiovascular disease.[1,2] As of 2010, AF affects more than 33.5 million people worldwide, including 20.9 million men and 12.6 million women. The incidence of AF is expected to increase further as the population ages and change people's lifestyle. From 1990 to 2010, the incidence of AF in men increased by 77.5% and 59.5% in women. Meanwhile, the mortality rate of AF in men increased by 2 times and 1.9 times in women.[3] Furthermore, previous studies estimate that the population with AF in the United States

will be more than double by 2050.[4] As noted above, unfortunately, AF brings huge health and economic burden to human beings, so it is important to attach the early screening and prevention of AF.

Mechanisms underlying AF, the most common and challenging arrhythmia, are not fully elucidated. However, the role of inflammatory response and oxidative stress has been recognized for many years. Serum albumin (ALB), which has many biological functions such as anti-inflammatory, antioxidant, anticoagulant, anti-platelet aggregation, colloid osmotic pressure maintenance, and transport of various endogenous and exogenous substances,[5–8] is the most important protein in the human serum. Moreover, recent studies have reported that ALB

* Correspondence: Huachen Jiao, Affiliated Hospital of Shandong University of Traditional Chinese Medicine, Room 101, Unit 3, Building 1, No. 125, Huanshan Road, Lixia District, Jinan, Shandong 250014, PR China (e-mail: liyixuan0531@163.com).

levels are affected by inflammation and malnutrition, both of which can lower ALB levels by reducing the rate of albumin synthesis, and inflammation can lower ALB levels by accelerating the catabolism of albumin.[5,9] Of note, current evidence demonstrated that low levels of ALB were associated with inducing cardiac structural remodeling,[10] and hypoalbuminemia is associated with coronary heart disease (CHD), myocardial infarction, heart failure, arrhythmia, and stroke.[11–16] In brief, experimental and clinical data indicate that ALB affects the pathophysiology of AF via activation of inflammation, and oxidative stress.[17–22] However, ALB as a biomarker is routinely measured in clinical practice, which performs an important role in the pathogenesis of AF, has not been attached well in clinical practice, and it is still controversial whether the association between ALB levels and AF is affected by complications, different subtypes of AF, and other clinical factors.

Therefore, this study aimed to investigate the association between ALB and AF, and determine whether ALB is a valid biomarker of AF.

2. Material and methods

2.1. Study design and data sources

In this study, we reviewed the medical records of 2000 patients aged 16 to 85 who were hospitalized in The Affiliated Hospital of Shandong University of Traditional Chinese Medicine from January 2019 to September 2021. The AF group included 1000 patients with AF (male/female: 506/494, age: 70.45 ± 10.46 years); the control group included 1000 age- and sex-matched patients with sinus rhythm and no history of AF (male/female: 496/504, age: 69.80 ± 9.84 years).

The exclusion criteria were a history of prior cardiac surgery, heart failure, valvular heart disease, rheumatic heart disease, as well patients with current hyperthyroidism, deranged liver or kidney, malignant tumors, and those taking current albumin products, and pregnant women, patients younger than 16 years and older than 85 years.

We retrospectively collected basic clinical data and related laboratory test results of the patients from the electronic medical record system. The baseline clinical data included age, sex, atrial fibrillation subtype and complications, as well as laboratory test data including ALB, GLB (serum globulin), alanine aminotransferase, SCr (serum creatinine), serum uric acid, fasting blood glucose, lipoprotein (α), TG (triglyceride), TC (total cholesterol), HDL-C (high-density lipoprotein cholesterol), LDL-C (low-density lipoprotein cholesterol), APOA1 (serum apolipoprotein A1), Hcy (homocysteine), APOB (serum apolipoprotein B), and carcinoembryonic antigen. Furthermore, all patients were divided into a control group and an AF group according to whether they had AF or not, and all AF patients were also divided by AF subtype for our further study. This retrospective study was approved by the Ethics Committee of The Affiliated Hospital of Shandong University of Traditional Chinese Medicine (no. 20200512FA62) and performed according to the principles of the Declaration of Helsinki. No informed consent was required because the data are anonymized.

2.2. Definition of atrial fibrillation

Paroxysmal AF was defined as AF that could be terminated spontaneously or after treatment within 7 days after onset, and permanent AF was defined as AF with a history of more than 1 year and no desire to return to sinus rhythm.[23]

2.3. Measurement of ALB levels

ALB was measured by the bromocresol green method using an automatic biochemical analyzer (Roche Diagnostics, Mannheim, Germany). In addition, ALB values were measured in g/L after initial admission, and the reference ranges in 35 to 50 g/L, with anything below 35 g/L considered hypoproteinemia.

2.4. Statistical analysis

Statistical analysis was performed using SPSS software (version 24.0). The measurement data were expressed as mean ± standard deviation, and the independent sample T test were used for comparison between groups. Counting data were expressed in percentage, and the chi-square test was used for comparison between groups. Pearson correlation analysis is used to analyze the correlation. Data with a P value less than .05 were analyzed with binary logistic regression analysis, to screen risk factors associated with AF. The appropriate cutoff value of ALB for AF was analyzed by receiver operating characteristic (ROC) curves. A statistically significant difference was defined as $P < .05$.

3. Results

3.1. Baseline characteristics of the study population

Compared with controls, AF patients had lower ALB, GLB, TC, TG, LDL-C, HDL-C, APOA1, and APOB ($P < .05$), and higher SCr and serum uric acid ($P < .05$); moreover, AF patients had more history of hypertension, diabetes, and CHD ($P < .05$) (Table 1).

3.2. Associations between AF and ALB levels

Data with a P value less than .05 were analyzed with binary logistic regression analysis, to screen risk factors associated with AF. After adjusting for hypertension, diabetes, CHD, GLB, and SCr, ALB was negatively related to AF (OR = 0.929, 95% CI: 0.904–0.954, $P < .05$). And after adjusting TC, TG, LDL-C, HDL-C, APOA1, and APOB, ALB still was a negatively related factor of AF (OR = 0.920, 95% CI: 0.896–0.944, $P < .05$). Eventually, after further adjustment for all the above factors, ALB was still negatively correlated with AF (OR = 0.935, 95% CI: 0.905–0.965, $P < .05$) (Table 2).

3.3. Associations of ALB among different AF subtypes and complications

We divided AF patients into groups according to different subtypes of AF and different comorbidities to analyze the difference in ALB levels. The results showed that compared with patients with paroxysmal AF, ALB levels were lower in patients with permanent AF ($P < .05$). And compared with patients with AF without a history of diabetes, ALB levels were lower in patients with AF with a history of diabetes ($P < .05$). Meanwhile, there was no significant difference in ALB levels between AF patients complicated with hypertension and those without hypertension ($P > .05$), as well as AF patients with CHD and without CHD ($P > .05$) (Table 3).

3.4. Associations between ALB and metabolic factors AF-related

We used Pearson correlation analysis to determine the correlations between ALB and metabolic factors in AF patients. ALB levels were positively related to GLB, TC, TG, LDL-C, HDL-C, APOA1, and APOB levels ($P < .05$), and negatively related to SCr levels ($P < .05$) (Table 4).

Table 1

Baseline characteristics of patient information in the atrial fibrillation and control groups.

Variables	Control group (n = 1000)	AF group (n = 1000)	t/χ^2	P value
Age, yr	69.80 ± 9.84	70.45 ± 10.46	−1.446	.148
Male, n (%)	496 (49.6)	506 (50.6)	0.200	.665
Female, n (%)	504 (50.4)	494 (49.4)		
ALB, g/L	40.11 ± 4.30	37.96 ± 4.70	10.720	<.001*
GLB, g/L	28.50 ± 4.33	28.04 ± 4.43	2.324	.020*
ALT, U/L	20.51 ± 14.74	22.39 ± 27.52	1.908	.057
SCr, μmol/L	65.16 ± 26.88	79.87 ± 52.21	−7.920	<.001*
SUA, μmol/L	311.39 ± 118.42	345.91 ± 118.88	−7.282	<.001*
FBG, mmol/L	6.19 ± 1.92	6.20 ± 2.13	−0.215	.830
LPα, mg/dL	22.49 ± 24.30	23.76 ± 26.80	−1.105	.269
TG, mmol/L	1.36 ± 1.23	1.25 ± .88	2.335	.019*
TC, mmol/L	4.99 ± 1.10	4.19 ± 1.10	16.235	<.001*
HDL-C, mmol/L	1.21 ± 0.32	1.07 ± 0.30	9.823	<.001*
LDL-C, mmol/L	2.94 ± 0.86	2.50 ± 0.90	11.101	<.001*
APOA1, g/L	1.23 ± 0.25	1.13 ± 0.26	8.684	<.001*
APOB, g/L	0.98 ± 0.25	0.80 ± 0.37	12.791	<.001*
Hcy, μmol/L	14.62 ± 9.82	15.48 ± 8.85	−1.561	.119
CEA, ng/ml	2.69 ± 2.25	6.32 ± 36.09	1.302	.193
Hypertension, n (%)	329 (32.9)	674 (67.4)	238.052	<.001*
Diabetes, n (%)	160 (16)	306 (30.6)	59.638	<.001*
CHD, n (%)	244 (24.4)	884 (88.4)	832.845	<.001*

AF = atrial fibrillation, ALB = serum albumin, ALT = alanine aminotransferase, APOA1 = serum apolipoprotein A1, APOB = serum apolipoprotein B, CEA = carcinoembryonic antigen, CHD = coronary heart disease, FBG = fasting blood glucose, GLB = serum globulin, Hcy = homocysteine, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, Lp (a) = lipoprotein (a), SCr = serum creatinine, SUA = serum uric acid, TC = total cholesterol, TG = triglyceride.
*Statistically significant value ($P < .05$).

Table 2

Correlation between serum albumin and atrial fibrillation.

	B	SE	Wald χ^2	P	OR	95% CI
Model 1	−0.110	0.011	102.220	<.001*	0.896	0.877–0.915
Model 2	−0.042	0.015	8.004	.005*	0.929	0.904–0.954
Model 3	−0.083	0.013	40.180	<.001*	0.920	0.896–0.944
Model 4	−0.048	0.016	8.796	.003*	0.935	0.905–0.965

Model 1: crude, no adjustment. Model 2: adjusting for hypertension, diabetes, CHD, GLB, SCr, SUA. Model 3: adjusting for TG, TC, HDL-C, LDL-C, APO-A1, APO-B. Model 4: adjusting for all these factors.
APOA1 = serum apolipoprotein A1, APOB = serum apolipoprotein B, CHD = coronary heart disease, GLB = serum globulin, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, SCr = serum creatinine, SUA = serum uric acid, TC = total cholesterol, TG = triglyceride.
*Statistically significant value ($P < .05$).

Table 3

Differences in serum albumin levels in patients with atrial fibrillation of different subtypes and complications.

Variables	n	ALB g/L	P value
1-Paroxysmal AF	354	37.49 ± 4.93	.023*
2-Permanent AF	646	38.21 ± 4.54	
1-AF + hypertension	674	38.09 ± 4.56	.202
2-AF + non-hypertension	326	37.67 ± 4.97	
1-AF + CHD	884	37.86 ± 4.67	.087
2-AF + non-CHD	118	38.66 ± 4.87	
1-AF + diabetes	307	37.41 ± 5.02	.014*
2-AF + non-diabetes	693	38.2 ± 4.53	

AF = atrial fibrillation, ALB = serum albumin, CHD = coronary heart disease.
*Statistically significant value ($P < .05$).

3.5. ROC curve of serum albumin in predicting AF

We used ROC curve analysis to determine the ALB diagnostic cutoff values for AF. The diagnostic cutoff value of ALB levels for AF was 37.25 g/L. The AUC was 0.632 (95% CI: 0.608–0.656), sensitivity 0.78, and specificity 0.406 (Table 5; Fig. 1).

4. Discussion

The current results revealed that ALB has an independent negative association with AF. The diagnostic cutoff value of ALB levels for AF was 37.25 g/L. The AUC was 0.632 (95% CI: 0.608–0.656), sensitivity 0.78, and specificity 0.406. Furthermore, we found that ALB levels were influenced by many metabolic factors AF-related. ALB was positively related to GLB, TC, TG, LDL-C, HDL-C, APO-A1, and APO-B, but negatively related to SCr. In addition, compared with patients with paroxysmal AF, ALB levels were lower in patients with permanent AF; compared with patients with AF without a history of diabetes, ALB levels were lower in patients with AF with a history of diabetes.

At present, despite the pathological mechanism of AF still being unclear, the important role of vascular endothelial dysfunction, inflammation and oxidative stress in AF has been clinically confirmed for many years.[18,24] ALB is the most important protein in the human serum, its physiological functions include anti-inflammatory, antioxidant, anticoagulant, anti-platelet aggregation, maintenance of colloid osmotic pressure, and transport of various endogenous and exogenous substances.[5–8,25,26] Moreover, previous studies suggest that ALB is rich in mercaptan groups, accounting for about 80% of the total mercaptan of plasma scavenging reactive oxygen species and nitrogen, and can carry NO, so it has strong antioxidant stress activity.[8,26]

Of note, the increase of reactive oxygen species may enhance ryanodine receptor activity, increase sarcoplasmic reticulum calcium ion release, and shorten atrial action potential time to increase the possibility of AF.[24,27] Furthermore, under physiological conditions, ALB can selectively inhibit TNF-α -induced upregulation of vascular cell adhesion molecule-1 expression and monocyte adhesion, so it has a strong anti-inflammatory function.[8,28,29] Accordingly, we postulate that the decrease in ALB levels may be related to the decrease in anti-inflammatory and antioxidant capacity of the body, which could further result in atrial structural and electrical remodeling, and thus participate in the pathological process of AF.

In recent years, the relationship between AF and ALB has been reported. A prospective community arteriosclerosis study involving 15,792 participants suggested that ALB was negatively correlated with AF.[18] In addition, in a study of new-onset AF in ICU patients, they demonstrated that low ALB levels were significantly associated with the incidence of new-onset AF, as well as with a 14% reduction in the risk of new-onset AF for each additional 1g/L of ALB before ICU admission.[19] Similarly, a study of new-onset AF after coronary artery bypass grafting reached similar conclusions.[20] What's more, two other studies concluded that reduced ALB was a significant risk factor for paroxysmal AF.[30,31] Herein, our current data reported that ALB was independently associated with AF, which was consistent with previous reports. These findings implied that it may be reasonable to interpret the way that patients with reduced ALB levels as candidates for more intensive rhythm monitoring and it may be useful to realize the early screening and prevention of AF.

Hcy is a recognized risk factor for cardiovascular disease,[32] clinical studies on Hcy and cardiovascular diseases mainly focus on CHD, hypertension, and myocardial infarction,[33,34] but only a few clinical studies tried to research the associations between Hcy and AF. Surprisingly, contrary to common clinical conclusions, the results of our study showed that the relationship between Hcy and AF was not statistically significant. Despite

this fact, this discrepancy may be attributed to a variety of complex factors, such as the patient's usual drug treatment and other factors. Certainly, these speculations need to be determined by more studies.

In addition, we also observed differences in the distribution of ALB levels between different AF subtypes and complications. To date, few studies of ALB levels between different AF subtypes have been reported. Our data indicated that compared with patients with paroxysmal AF, ALB levels were lower in patients with permanent AF. We speculate that this result may indicate higher levels of inflammatory response and oxidative stress in patients with permanent AF than paroxysmal AF. In addition, the consequences of this study showed that patients with AF combined with diabetes have lower ALB levels than those without diabetes. And there is no relevant study that has reached a similar conclusion at present. Indeed, previous studies suggest that patients with diabetes have high levels of inflammatory response and oxidative stress.[35] Therefore, we suppose it may be associated with low ALB levels in AF combined diabetes.

Moreover, our study found that ALB was associated with metabolic factors in AF patients. Our results show that ALB levels were positively related to GLB, TG, TC, HDL-C, LDL-C, APOA1, and APOB, and negatively related to SCr. Previous studies have shown that higher TC, TG, and LDL-C are risk factors for cardiovascular disease, and high levels of HDL-C are protective factors for cardiovascular disease.[36–42] Also, APOA1 is the main apolipoprotein of HDL-C, mediating the anti-atherosclerosis and cardiac protective function of HDL-C,[43] and APOB is a key structural component of LDL-C, which plays an important role in lipid metabolism and is a risk factor for cardiovascular disease.[44] Interestingly, the results of our study show a lipid paradox, in which lipid-related cardiovascular risk factors and protective factors are both reduced in patients with AF. Although previous studies have found similar findings,[45] however, the mechanism of this phenomenon remains to be further studied.

In this study, we excluded risk factors related to the occurrence of AF, such as rheumatic heart disease, cardiac valvular disease, and hyperthyroidism, as well factors that may affect ALB levels, such as heart failure, malignant tumors, and the use of albumin products, to reduce the influence of interfering factors on this study as much as possible. However, there are still some potential limitations to this study. Firstly, persistent AF was not recorded, so the results cannot be fully applicable to all patients with AF. Secondly, this study was a single-center retrospective study, which could only study the association between ALB and AF rather than the causal relationship. Thirdly, no markers of inflammation and oxidative stress were recorded. Fourthly, this study is a retrospective study, and the results are inevitably affected by some confounding factors, and it was subject to inherent limitations associated with the retrospective study. Therefore, further prospective studies need to verify our results.

Table 4

Associations between serum albumin and metabolic factors AF-related.

	ALB	
Variables	r	P
GLB	0.084	.008*
SCr	−0.118	<.001*
SUA	0.029	.364
TG	0.187	<.001*
TC	0.292	<.001*
HDL-C	0.311	<.001*
LDL-C	0.204	<.001*
APOA1	0.464	<.001*
APOB	0.127	<.001*

APOA1 = serum apolipoprotein A1, APOB = serum apolipoprotein B, GLB = serum globulin, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, SCr = serum creatinine, SUA = serum uric acid, TC = total cholesterol, TG = triglyceride.
*Statistically significant value ($P < .05$).

5. Conclusion

In conclusion, the current findings implied that low ALB was significantly related to AF, ALB may be a valuable serum

Table 5

Significance of serum albumin in predicting atrial fibrillation.

	AUC (95% CI)	Cutoff values (g/L)	Sensitivity (%)	Specificity (%)	Youden index
ALB	0.632 (0.608–0.656)	37.25	78.0	40.6	0.186

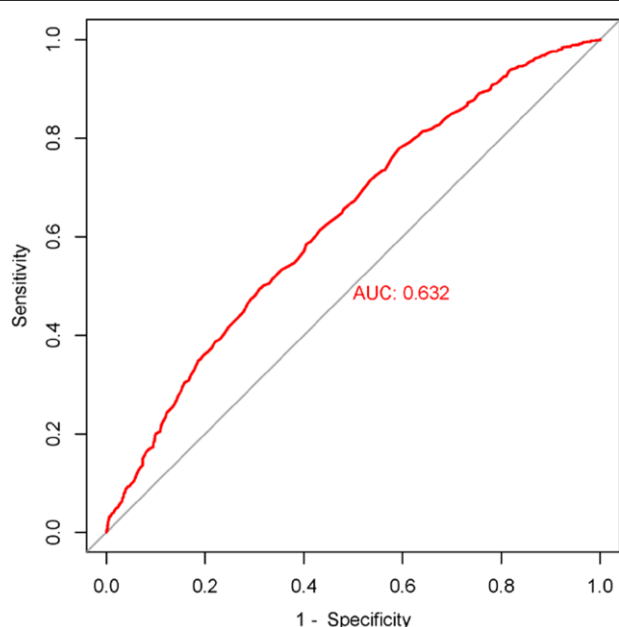ALB = serum albumin, AUC = area under the curve.

Figure 1. ROC curve of serum albumin in predicting AF. The diagnostic cut-off value of ALB levels for AF was 37.25 g/L. The AUC was 0.632 (95% CI: 0.608–0.656), sensitivity 0.78, and specificity 0.406. AF = atrial fibrillation, ALB = serum albumin, AUC = area under the curve, ROC = receiver operating characteristic.

biomarker for predicting AF. Focusing on monitoring albumin levels may provide a meaningful perspective for predicting AF. Furthermore, prospective cohort studies with larger sample sizes are needed in the future to validate the current findings.

Acknowledgements

Author contributions

All authors read and approved the final articles.
Conceptualization: Huachen Jiao, Dongsheng Zhao.
Data curation: Dongsheng Zhao, Xia Zhong.
Formal analysis: Dongsheng Zhao, Xia Zhong, Huachen Jiao.
Funding acquisition: Huachen Jiao.
Investigation: Dongsheng Zhao, Lianlian Li, Wei Wang.
Methodology: Dongsheng Zhao, Huachen Jiao, Xia Zhong, Wei Wang.
Project administration: Dongsheng Zhao, Xia Zhong, Lianlian Li, Wei Wang.
Resources: Dongsheng Zhao, Lianlian Li.
Software: Dongsheng Zhao, Xia Zhong, Huachen Jiao, Wei Wang.
Supervision: Huachen Jiao, Dongsheng Zhao, Lianlian Li, Xia Zhong, Wei Wang.
Validation: Dongsheng Zhao, Huachen Jiao, Xia Zhong, Wei Wang.
Visualization: Dongsheng Zhao, Xia Zhong, Wei Wang.
Writing – original draft: Dongsheng Zhao.
Writing – review & editing: Huachen Jiao, Dongsheng Zhao, Lianlian Li, Xia Zhong, Wei Wang.

References

[1] Thrall G, Lane D, Carroll D, et al. Quality of life in patients with atrial fibrillation: a systematic review. Am J Med. 2006;119:448.e1–e19.

[2] Wang TJ, Larson MG, Levy D, et al. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. Circulation. 2003;107:2920–5.

[3] Chugh SS, Havmoeller R, Narayanan K, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. Circulation. 2014;129:837–47.

[4] Go A, Hylek E, Phillips K, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. JAMA. 2001;285:2370–5.

[5] Soeters PB, Wolfe RR, Shenkin A. Hypoalbuminemia: pathogenesis and clinical significance. J Parenter Enteral Nutr. 2019;43:181–93.

[6] Paar M, Rossmann C, Nusshold C, et al. Anticoagulant action of low, physiologic, and high albumin levels in whole blood. PLoS One. 2017;12:e0182997.

[7] Lam FW, Cruz MA, Leung HC, et al. Histone induced platelet aggregation is inhibited by normal albumin. Thromb Res. 2013;132:69–76.

[8] Garcia-Martinez R, Caraceni P, Bernardi M, et al. Albumin: pathophysiologic basis of its role in the treatment of cirrhosis and its complications. Hepatology. 2013;58:1836–46.

[9] Verbruggen SC, Schierbeek H, Coss-Bu J, et al. Albumin synthesis rates in post-surgical infants and septic adolescents; influence of amino acids, energy, and insulin. Clin Nutr. 2011;30:469–77.

[10] Enia G, Mallamaci F, Benedetto F, et al. Long-term CAPD patients are volume expanded and display more severe left ventricular hypertrophy than haemodialysis patients. Nephrol Dial Transplant. 2001;16:1459–64.

[11] Prenner SB, Kumar A, Zhao L, et al. Effect of serum albumin levels in patients with heart failure with preserved ejection fraction (from the TOPCAT Trial). Am J Cardiol. 2020;125:575–82.

[12] Ancion A, Allepaerts S, Oury C, et al. Serum albumin level and hospital mortality in acute non-ischemic heart failure. ESC Heart Fail. 2017;4:138–45.

[13] Ancion A, Allepaerts S, Robinet S, et al. Serum albumin level and long-term outcome in acute heart failure. Acta Cardiol. 2019;74:465–71.

[14] Arques S. Human serum albumin in cardiovascular diseases. Eur J Intern Med. 2018;52:8–12.

[15] Arques S. Serum albumin and cardiovascular disease: state-of-the-art review. Ann Cardiol Angeiol (Paris). 2020;69:192–200.

[16] Arques S. Serum albumin and cardiovascular diseases: a comprehensive review of the literature. Ann Cardiol Angeiol (Paris). 2018;67:82–90.

[17] Che R, Huang X, Zhao W, et al. Low serum albumin level as a predictor of hemorrhage transformation after intravenous thrombolysis in ischemic stroke patients. Sci Rep. 2017;7:7776.

[18] Liao LZ, Zhang SZ, Li WD, et al. Serum albumin and atrial fibrillation: insights from epidemiological and mendelian randomization studies. Eur J Epidemiol. 2020;35:113–22.

[19] van Beek DEC, Kuijpers YAM, Konigs MHH, et al. Low serum albumin levels and new-onset atrial fibrillation in the ICU: a prospective cohort study. J Crit Care. 2020;56:26–30.

[20] Karabacak K, Kubat E, Akyol FB, et al. The C-reactive protein/albumin ratio as a new predictor for postoperative atrial fibrillation after coronary artery bypass graft surgery. J Card Surg. 2020;35:2747–53.

[21] Wang Y, Du P, Xiao Q, et al. Relationship between serum albumin and risk of atrial fibrillation: a dose-response meta-analysis. Front Nutr. 2021;8:728353.

[22] Ronit A, Kirkegaard-Klitbo DM, Dohlmann TL, et al. Plasma albumin and incident cardiovascular disease: results from the CGPS and an updated meta-analysis. Arterioscler Thromb Vasc Biol. 2020;40:473–82.

[23] Calkins H, Hindricks G, Cappato R, et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation: executive summary. Europace. 2018;20:157–208.

[24] Ziolo MT, Mohler PJ. Defining the role of oxidative stress in atrial fibrillation and diabetes. J Cardiovasc Electrophysiol. 2015;26:223–5.

[25] Arques S, Ambrosi P. Human serum albumin in the clinical syndrome of heart failure. J Card Fail. 2011;17:451–8.

[26] Roche M, Rondeau P, Singh NR, et al. The antioxidant properties of serum albumin. FEBS Lett. 2008;582:1783–7.

[27] Sovari AA, Dudley SC Jr. Reactive oxygen species-targeted therapeutic interventions for atrial fibrillation. Front Physiol. 2012;3:311.

[28] Wiedermann CJ. Anti-inflammatory activity of albumin. Crit Care Med. 2007;35:981–2.

[29] Zhang W, Frei B. Albumin selectively inhibits TNF alpha-induced expression of vascular cell adhesion molecule-1 in human aortic endothelial cells. Cardiovasc Res. 2002;55:820–9.

[30] He Y, Yang X, Hui J, et al. Low serum albumin levels in patients with paroxysmal atrial fibrillation: what does it mean? Acta Cardiol. 2006;61:333–7.

[31] Liu Y, Liu H, Dong L, et al. Prevalence of atrial fibrillation in hospitalized patients over 40 years old: ten-year data from the People's Hospital of Peking University. Acta Cardiol. 2010;65:221–4.

[32] Clarke R, Daly L, Robinson K, et al. Hyperhomocysteinemia: an independent risk factor for vascular disease. N Engl J Med. 1991;324:1149–55.

[33] Skovierova H, Vidomanova E, Mahmood S, et al. The molecular and cellular effect of homocysteine metabolism imbalance on human health. Int J Mol Sci. 2016;17:1733.

[34] Kaplan P, Tatarkova Z, Sivonova MK, et al. Homocysteine and mitochondria in cardiovascular and cerebrovascular systems. Int J Mol Sci. 2020;21:7698.

[35] Zhu T, Meng Q, Ji J, et al. TLR4 and Caveolin-1 in monocytes are associated with inflammatory conditions in diabetic neuropathy. Clin Transl Sci. 2017;10:178–84.

[36] The Lipid Research Clinics Coronary Primary Prevention Trial results. I. Reduction in incidence of coronary heart disease. JAMA. 1984;251:351–64.

[37] The Lipid Research Clinics Coronary Primary Prevention Trial results. II. The relationship of reduction in incidence of coronary heart disease to cholesterol lowering. JAMA. 1984;251:365–74.

[38] Pedersen TR, Kjekshus J, Berg K, et al. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet. 1994;344:1383–9.

[39] Shepherd J, Cobbe S, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. N Engl J Med. 1995;333:1301–7.

[40] Byington R, Jukema J, Salonen J, et al. Reduction in cardiovascular events during pravastatin therapy. Pooled analysis of clinical events of the Pravastatin Atherosclerosis Intervention Program. Circulation. 1995;92:2419–25.

[41] Gordon D, Rifkind B. High-density lipoprotein – the clinical implications of recent studies. N Engl J Med. 1989;321:1311–6.

[42] Gordon D, Probstfield J, Garrison R, et al. High-density lipoprotein cholesterol and cardiovascular disease. Four prospective American studies. Circulation. 1989;79:8–15.

[43] Chistiakov DA, Orekhov AN, Bobryshev YV. ApoA1 and ApoA1-specific self-antibodies in cardiovascular disease. Lab Invest. 2016;96:708–18.

[44] Yu Q, Zhang Y, Xu C. Apolipoprotein B, the villain in the drama? Eur J Pharmacol. 2015;748:166–9.

[45] Annoura M, Ogawa M, Kumagai K, et al. Cholesterol paradox in patients with paroxysmal atrial fibrillation. Cardiology. 1999;92:21–7.