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The effect of albumin-globulin score and albumin/globulin ratio on survival in patients with heart failure

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Abstracts

OBJECTIVES: To investigate the combined effect of albumin (ALB) and globulin (GLB) on the overall survival of patients with heart failure (HF).

DESIGN: Retrospective cohort study.

SETTING: A Hospital.

PARTICIPANTS: 404 firstly diagnosed with heart failure patients.

MEASUREMENTS: Serum ALB and GLB were measured within three days after admission. The albumin/globulin ratio (AGR) was calculated as the ALB divided by the GLB. The receiver operating characteristic (ROC) curve was used to calculate the cut-off point of ALB, GLB, and AGR. Patients with low ALB levels (⩽35.3g/L) and high GLB levels (>27.0 g/L) were assigned an albumin-globulin score AGS of 2, those with only one of the two abnormalities were assigned an AGS of 1, and those with neither of the two abnormalities were assigned an AGS of 0.

RESULTS: The mean age of the 404 patients was 62.69±15.62, and 54.5% were male. During follow-up, 14 patients lost to follow up. 120 patients died from HF and 211 patients were hospital readmitted for worsening HF. Univariate cox regression analysis showed that higher AGR was significantly associated with favorable overall survival (OS) (HR, 0.61; 95% CI, 0.38-0.98; *P*= 0.040) but not AGS.

CONCLUSION: Serum levels of ALB and GLB are objective and easily measurable biomarkers, which can be used in combination to predict the survival of patients with HF.

Key words: albumin; globulin; survival; heart failure

Strengths and limitations of this study

- This is the first study investigating the prognostic value of AGS and AGR in patients with HF.
- The cohort study design.
- To avoid bias, only patients firstly diagnosed with heart failure were selected.
- The information bias could not be avoided owing to the retrospective cohort study design.

Introduction

Heart failure (HF) is a global public health problem, with a prevalence of more than 23 million worldwide[1 2]. In China, there are 4.2 million people living with HF, with 500, 000 new cases diagnosed each year, and this number is expected to increase still further[3], causing enormous social and economic burden. Over the last 30 years, although great improvements have been made in drug and device therapy, the survival and the hospitalization rate in HF patients often remains unsatisfactory[4 5]. Hence, identification of promising prognostic factors contributing to the risk classification and clinical management of such patients could improve their long-term survival.

Numerous prognostic markers of death and/or HF hospitalization have been identified in patients with HF. In recent decades, several multivariable prognostic risk scores have been developed for different populations of patients with HF[6-8]. However, their clinical applicability is limited and precise risk stratification in HF remains challenging. Simple but effective prognostic biomarkers model are needed to improve the management of the HF epidemic.

The correlation between serum albumin (ALB) and globulin (GLB) with HF has recently been emphasized. Albumin and globulin, the two major components of serum proteins, have been confirmed to be involved in the systemic inflammatory process. Serum albumin, one of the

biochemical tests, not only indicates nutritional status but also relates to chronic inflammation in HF[9 10]. Moreover, increased levels of GLB could serve as markers of chronic inflammation response and reflect a cumulative exposure of various proinflammatory cytokines[11]. Previous studies have demonstrated that hypoalbuminemia was associated with impaired survival in HF patients[12]. However, no studies investigated the cumulative effect of both ALB and GLB on HF patients. Therefore, the purpose of this present study was to access the effect of the albumin-globulin score (AGS) and albumin/globulin ratio (AGR) on long-term survival among HF patients.

Methods and material

Participants

Between January 2010 and September 2015, 404 consecutive patients who were firstly diagnosed as HF at the First Affiliated Hospital of Zhengzhou University were included. The diagnosis of HF was based on a history of dyspnea with symptomatic exercise intolerance, and signs of documentation of left ventricular enlargement or peripheral edema or pulmonary congestion or radionuclide ventriculography or dysfunction by chest X-ray and/or echocardiography.[13] Informed consent was obtained from all patients prior to participation, and the study was approved by Zhengzhou University Committee. All methods were performed in

accordance with the relevant guidelines and regulations.

The exclusion criteria for patients were as follows: (1) Acute coronary syndromes; (2) no echocardiographic structural or functional abnormalities; (3) without HF; and (4) dead before discharge

Patient and Public Involvement

All participants were given written informed consent before they joined the study for authorizing to use the data generated from the medical information system. The research question and outcome measures were handed out by hardcopy to each patient. Patients were not involved in the recruitment and conduct of the study. The results will be mailed to each participant.

Clinical and laboratory parameters

Patients' baseline characteristics including demographic parameters, comorbidities, medications, and laboratory variables were retrospectively reviewed and collected from the electronic medical records by two researchers. Fasting venous blood samples were collected from all patients within three days after admission, and were immediately sent for analysis. The serum levels of ALB, GLB and other variables were assayed by using an automatic biochemical analyzer (Hitachi 7600, Japan). The receiver operating characteristic (ROC) curve was used to

calculate the cut-off point of ALB, GLB, and AGR. Patients with low ALB levels (⩽35.3g/L) and high GLB levels (>27.0 g/L) were assigned an AGS of 2, those with only one of the two abnormalities were assigned an AGS of 1, and those with neither of the two abnormalities were assigned an AGS of 0. AGS=1-2 was defined as high, AGS=0 was defined as low, AGR> 1.48 was defined as high, and AGR⩽1.48 was defined as low.

Follow-up

All patients were followed-up every 3 months for the first 2 years, every 6 months in the third, every 1 year afterwards. The primary endpoint was death due to a cardiovascular event (myocardial infarction, progressive HF, stroke, other vascular causes, or sudden cardiac death), the second endpoint was progressive HF requiring re-hospitalization. Follow-up evaluations were performed every 3 months for the first 2 years, every 6 months for the second year, and yearly thereafter. Follow-up was performed until patient death, or until July 2016, which was the cut-off date for this study.

Statistical Analysis

The analysis of variance (ANOVA) was used to examine the differences of continuous variable (age, Albumin, BNP, IVST, PWT,

LVDv, LVSv, LVEF, and LAD), and the chi-square test was used to assess the difference of categorical variables (including gender, Hypertension, Diabetes mellitus, CKD, Prior history of HF, DCM, HCM, HHD, AF, and Medications). The Kaplan-Meier method with Log-rank test was used to estimate survival curves. Univariable cox regression analysis was used to identify variables associated with overall survival time. Variables with a $P<0.05$ on univariable analysis were further assessed with a multivariable Cox regression model. SPSS 21 software (IBM Corp, Armonk, NY) was used for the statistical analysis. The level of significance was established as a two-sided *P* value 0.05.

Results

The baseline characteristics of patients are presented in table 1. A total of 404 patients with HF whose mean age was 62.70±15.62 years old entered the analysis. Among them, 260 patients (64.25%) were classified as high AGS, 189 patients (46.78%) were classified as higher AGR. Patients with lower AGS were more often among individuals without chronic kidney disease (CKD), with idiopathic dilated cardiomyopathy (DCM), using beta-blocker and angiotensin converting enzyme inhibitor (ACE-I), they also had lower B-type natriuretic peptide (BNP), higher left ventricular end-systolic volume (LVSv), higher left ventricular ejection fraction (LVEF), and lower left atrial dimension

(LAD). Patients with higher AGR were more often among individuals without diabetes mellitus, without coronary heart disease (CHD), with DCM, using beta-blocker ACE-I, they also had lower B-type natriuretic peptide (BNP).

By July 2016, 404 patients had been followed up. 120 patients died, 211 patients were hospital readmitted, and 14 patients lost to follow up. The follow-up rate was 96.5%. The mean and median survival times were 47.23 months and 62.00 months, respectively. Figures 1 and 2 showed the Kaplan-Meier curves of overall survival and hospital free survival according to AGR (>1.48 vs. ≤ 1.48) and AGS (0 vs. 1-2).

As shown in table 2, univariate analysis showed that higher AGR and lower AGS were significantly associated with favorable overall survival 0.54 (0.37-0.80) and 0.56 (0.37-0.84), respectively. Moreover, age (per year), CKD (yes vs. no), BNP (per 100 pg/mL), LVDv (per ml), LVSv (per ml), and LAD (per mm) were other significant prognostic variables identified by univariate analysis. On multivariate analysis, AGR remained to be an independent predictor for overall survival (HR, 0.61; 95% CI, 0.38-0.98), but not AGS (HR, 0.81; 95% CI, 0.41-1.57).

The univariate and multivariate analysis of rehospitalization are presented in Table 3. Univariate analysis showed that AGR and AGS had no significant effect on rehospitalization 0.92 (0.70-1.22) and 0.99 (0.75-1.32), respectively. However, age (per year), CKD (yes vs. no),

Prior history of HF (yes vs. no), BNP (per 100 pg/mL), IVST (per mm), and LAD (per mm) were significant prognostic variables for rehospitalization. On multivariate analysis, age (per year), CKD (yes vs. no), IVST (per mm), and LAD (per mm) were independent prognostic indicator for rehospitalization.

Discussion

This study showed that the combination of ALB and GLB have potential predictive effect in predicting survival in patients with HF, higher AGR was significantly associated with favorable overall survival among patients with HF. To the best of our knowledge, this is the first study investigating the prognostic value of AGS and AGR in patients with HF.

The prediction of HF prognosis is a cornerstone of HF management. Accurately predicting prognosis can be of benefit for patients with heart failure. Patients with a poorer prognosis might benefit more from aggressive treatment and a closer follow-up[14]. There exist previous risk models for patients with HF[15 16], which adopted a systems biology approach, by incorporating information from demographic, biomarker, genomic, proteomic, and the initial response to therapy might create a more effective prediction model and hopefully aid in understanding HF prognosis. However, these models are complex in clinical application and

just provide moderate accuracy prediction in survival and rehospitalization in patients with HF[17]. Hence, designing a simple survival model based on routine blood biochemical indexes for clinician is helpful for better identification high risk HF patients.

The role of serum albumin is complex. Serum albumin is synthesized in the liver and plays multiple physiological roles, including maintenance of pH and normal microvascular permeability and mediation of coagulation, and has antioxidant properties[18]. The decrease in plasma albumin concentration may be due to malnutrition and cachexia (decreased albumin intake)[19], diffuse inflammation (increased albumin consumption)[20], renal impairment (increased urinary albumin loss)[21], plasma volume expansion (dilutional hypoalbuminemia) and hepatic dysfunction (decreased albumin synthesis)[22 23].Serum albumin is used in assessment of protein malnutrition without calorie malnutrition in which serum albumin becomes low without affection of anthropometric measurements[24].Malnutrition was found to be associated with worsening of symptoms and poor prognosis. Multiple European studies showed malnourished heart failure patients are weaker and fatigue earlier[25 26]. Heart failure with hypoalbuminemia, as indicator of malnutrition, was found to be associated with higher New York heart association (NYHA) functional class, elevated serum blood urea nitrogen and C-reactive protein[24]. It should be noted that although hypoalbuminemia might reflect

poor nutritional status, albumin reduction in chronic inflammation is frequent[11].

Similar to the low albumin, high non-albumin protein was a predictor of mortality in HF patients. We postulate that the high serum non-albumin proteins status is a marker of inflammation in HF patients. Chronic inflammation is known to increase acute-phase proteins (eg, C-reactive protein [CRP], serum amyloid A, complement C3, fibrinogen, ceruloplasmin), which constitute part of the calculated globulins[11].And the increased level of globulin serves as a marker of chronic inflammation and reflects cumulative exposure to various pro-inflammatory cytokines such as interleukins (IL), particularly IL-6 and IL-1b, and tumor necrosis factor-a, which stimulates the production of acute-phase proteins[11].Chronic inflammation is a critical contributor to HF occurrence, development, survival, and is also related to the risk of recurrence among HF patients[27].Hence,we propose that low AGR and high AGS measure the extent of such activities related to chronic inflammation, which influence mortality.

What's more, we found that LAD was a significant independent predictor for the long-term survival and rehospitalization in HF patients. The result is consistent with previous research findings[28]. As a predictor reflecting left atrium (LA) structural remodeling, LAD relates to all key risk factors for AF, such as advancing age, male sex, and greater blood

pressure[29]. LA enlargement, as characterized by echocardiographic LAD, is related to incident AF, heart failure, stroke, and mortality[28 30-33]. Moreover, LA enlargement can reflect atrial volume or pressure overload in valvular or ischemic heart disease, or as a consequence of AF[34-36].

Prior studies have demonstrated that low serum albumin is an independent predictor of HF long-term mortality. Liu et.al showed that patients with hypoalbuminemia had a significantly lower survival rate (53% vs. 84%, log-rank $\chi(2) = 53.3$, $P < 0.001$) and a higher rate of cardiovascular death (21.8% vs. 8.9% , $P< 0.001$)[37]. Su et.al. reported that the patients with higher NT-pro BNP and lower albumin than median had the highest risk for cardiac events (HR, 2.89, CI 1.90-4.40,)[38]. The finding of our study that AGR is independent predictor of long-term mortality in HF patients was consistent with previous studies.

Conclusions

In conclusion, the present study suggests that the AGR is convenient and effective tool to predict the overall survival time in HF patients. Further larger prospective studies are required to validate this finding and to investigate other prognostic indicators in HF patients.

Conflict of interests

The authors declare that they have no conflict of interests.

Authors' contributions

Kuan Li and Yongjian Zhu designed the study and provided critical review of the manuscript. Yongjian Zhu, Yacong Bo and Wanrong Fu reviewed the literature. Yongjian Zhu and Kuan Li analyzed the data and wrote the first draft of the manuscript. Yacong Bo, Wanrong Fu, and Yongjian Zhu revised the manuscript.

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Tables

Table 1 Correlation between AGS, AGR, and clinicopathologic parameters in 404 chronic heart failure patients

Variables	AGS (High=260, Low=144)			AGR (High=189, Low=215)		
	High (1-2)	Low (0)	*P*	High (>1.48)	Low (≤1.48)	*P*
Age (years)	63.82±15.63	60.67±15.45	0.051	59.46±15.34	65.41±15.34	<0.001
Gender						
Male	133(51.2%)	87 (60.4%)	0.073	111(58.7%)	109(51.2%)	0.129
Albumin(g/dl)	37.39±6.15	36.49±9.24	0.242	36.56±8.49	37.50±6.28	0.203
Hypertension	107(41.2%)	59(41.0%)	0.972	78(41.3%)	88(41.3%)	0.993
Diabetes mellitus	80(30.8%)	32(22.2%)	0.066	42(22.2%)	70(32.9%)	0.018
CKD	32(12.3%)	7(4.9%)	0.015	16(8.5%)	23(10.8%)	0.430
Prior history of HF	185(71.2%)	110(76.4%)	0.256	145(76.7%)	148(69.5%)	0.103
VHD	35(13.5%)	18(12.5%)	0.784	24(12.7%)	29(13.6%)	0.786
CHD	118(45.4%)	68(47.2%)	0.723	75(39.7%)	110(51.6%)	0.016
DCM	39(15.0%)	33(22.9%)	0.046	47(24.9%)	25(11.7%)	0.001
HCM	7(2.7%)	2(1.4%)	0.395	5(2.6%)	4(1.9%)	0.604
HHD	5(1.9%)	5(3.5%)	0.337	5(2.6%)	5(2.3%)	0.848
AF	81(31.2%)	40(27.8%)	0.478	60(31.7%)	60(28.2%)	0.434
BNP (pg/mL)	7262.94±7634.99	4201.68±5032.32	<0.001	5175.84±6486.63	7122.99±7318.87	0.007
Echocardiography findings						
IVST (mm)	10.03±1.86	9.67±1.63	0.082	9.87±1.74	9.94±1.83	0.748
PWT (mm)	9.59±1.67	9.38±1.50	0.247	9.45±1.51	9.59±1.71	0.447
LVDv (ml)	172.86±123.37	187.86±85.67	0.245	183.94±86.00	172.71±131.69	0.367
LVSv (ml)	94.21±73.03	112.68±70.78	0.027	108.78±70.76	93.12±70.07	0.367
LVEF (%)	48.25±12.97	45.08±13.07	0.031	45.84±13.48	48.43±12.63	0.068
LAD(mm)	41.47±9.10	43.92±11.83	0.035	43.30±10.66	41.47±9.72	0.105
Medications, n (%)						
Beta-blocker	152(58.5%)	99(68.8%)	0.041	130(68.8%)	120(56.3%)	0.010
CCB	57(21.9%)	31(21.5%)	0.927	43(22.8%)	45(21.1%)	0.694
Statins	120(46.2%)	70(48.6%)	0.636	92(48.7%)	97(45.5%)	0.529
ARB	83(31.9%)	41(28.5%)	0.471	63(33.3%)	61(28.6%)	0.309
ACE-I	74(28.5%)	69(47.9%)	<0.001	83(43.9%)	59(27.7%)	0.001

CKD, chronic kidney disease; DCM, idiopathic dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; HHD, hypertensive heart disease; AF, atrial fibrillation; VHD, valvular heart disease; CHD, coronary heart disease; BNP, B-type natriuretic peptide; IVST, interventricular septum thickness; PWT, posterior wall thickness; LVDv, left ventricular end-diastolic volume; LVSv, left ventricular

end-systolic volume; LVEF, left ventricular ejection fraction; LAD, left atrial dimension; ARB, angiotensin receptor blocker; CCB, calcium-channel blocker; ACE-I, angiotensin converting enzyme inhibitor; AGS, albumin-globulin score; AGR, albumin/globulin ratio.

Table 2. Univariate and multivariate analysis of overall survival

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI of HR	P Value	HR	95% CI of HR	P Value
Age (per year)	1.02 (1.01-1.03)		0.011	1.03 (1.01-1.05)		0.006
Gender (female vs. male)	0.94 (0.78-1.13)		0.501			
Hypertension (yes vs. no)	0.95 (0.66-1.37)		0.774			
Diabetes mellitus (yes vs. no)	1.27 (0.87-1.87)		0.221			
CKD (yes vs. no)	2.37 (1.43-3.94)		0.001	2.13 (1.11-4.09)		0.023
Prior history of HF (yes vs. no)	1.27 (0.85-1.90)		0.244			
VHD (yes vs. no)	1.50 (0.95-2.37)		0.079			
CHD (yes vs. no)	0.96 (0.67-1.37)		0.808			
DCM (yes vs. no)	0.63 (0.37-1.11)		0.114			
HCM (yes vs. no)	0.70 (0.17-2.81)		0.610			
HHD (yes vs. no)	0.64 (0.16-2.60)		0.536			
AF (yes vs. no)	1.26 (0.87-1.84)		0.221			
BNP (per 100 pg/mL)	1.01 (1.00-1.02)		<0.001	1.01 (1.00-1.02)		0.034
LVEF (per 1%)	1.00 (0.98-1.01)		0.623			
IVST (per mm)	1.10 (0.99-1.21)		0.066			
PWT (per mm)	1.09 (0.99-1.19)		0.076			
LVDv (per ml)	1.01 (1.00-1.02)		0.028	1.00 (0.99-1.01)		0.393
LVSv (per ml)	1.01 (1.00-1.02)		0.033	1.01 (1.00-1.02)		0.006
LAD (per mm)	1.02 (1.01-1.04)		0.001	1.03 (1.01-1.05)		0.001
AGR (>1.48 vs. ≤1.48)	0.54 (0.37-0.80)		0.001	0.61 (0.38-0.98)		0.040
AGS (0 vs. 1-2)	0.56 (0.37-0.84)		0.005	0.81 (0.41-1.57)		0.525

CKD, chronic kidney disease; DCM, idiopathic dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; HHD, hypertensive heart disease; AF, atrial fibrillation; VHD, valvular heart disease; CHD, coronary heart disease; BNP, B-type natriuretic peptide; IVST, interventricular septum thickness; PWT, posterior wall thickness; LVDv, left ventricular end-diastolic volume; LVSv, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction; LAD, left atrial dimension; AGS, albumin-globulin score; AGR, albumin/globulin ratio

Table 3. Univariate and multivariate analysis of rehospitalization

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P Value	HR (95% CI)	P Value
Age (per year)	1.01 (1.00-1.02)	0.009	1.01 (1.00-1.02)	0.028
Gender (female vs. male)	1.01 (1.00-1.02)	0.882		
Hypertension (yes vs. no)	1.00 (0.76-1.32)	0.998		
Diabetes mellitus (yes vs. no)	1.25 (0.94-1.68)	0.130		
CKD (yes vs. no)	1.68 (1.07-2.62)	0.023	1.80 (1.07-3.03)	0.027
Prior history of HF (yes vs. no)	1.42 (1.04-1.94)	0.028	1.30 (0.87-1.95)	0.202
VHD (yes vs. no)	1.14 (0.78-1.68)	0.490		
CHD (yes vs. no)	1.26 (0.96-1.65)	0.096		
DCM (yes vs. no)	0.61 (0.33-1.12)	0.108		
HCM (yes vs. no)	1.28 (0.60-2.73)	0.523		
HHD (yes vs. no)	0.77 (0.29-2.08)	0.609		
AF (yes vs. no)	1.11 (0.83-1.47)	0.487		
BNP (per 100 pg/mL)	1.01 (1.00-1.02)	0.050	1.00 (0.99-1.01)	0.967
LVEF (per 1%)	1.01 (0.99-1.02)	0.187		
IVST (per mm)	1.09 (1.01-1.17)	0.023	1.10 (1.00-1.20)	0.050
PWT (per mm)	1.04 (0.97-1.13)	0.296		
LVDv (per ml)	1.00 (0.99-1.01)	0.967		
LVSv (per ml)	1.00 (0.99-1.01)	0.839		
LAD (per mm)	1.01 (1.00-1.03)	0.041	1.02 (1.00-1.03)	0.011
AGR (>1.48 vs.≤1.48)	0.92 (0.70-1.22)	0.573		
AGS (0 vs. 1-2)	0.99 (0.75-1.32)	0.959		

CKD, chronic kidney disease; DCM, idiopathic dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; HHD, hypertensive heart disease; AF, atrial fibrillation; VHD, valvular heart disease; CHD, coronary heart disease; BNP, B-type natriuretic peptide; IVST, interventricular septum thickness; PWT, posterior wall thickness; LVDv, left ventricular end-diastolic volume; LVDs, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction; LAD, left atrial dimension; AGS, albumin-globulin score; AGR, albumin/globulin ratio

Figure legends

Figure 1. Kaplan–Meier survival curves according to AGR (A) and AGS (B).

Figure 2. Kaplan–Meier hospital free curves according to AGR (A) and AGS (B).

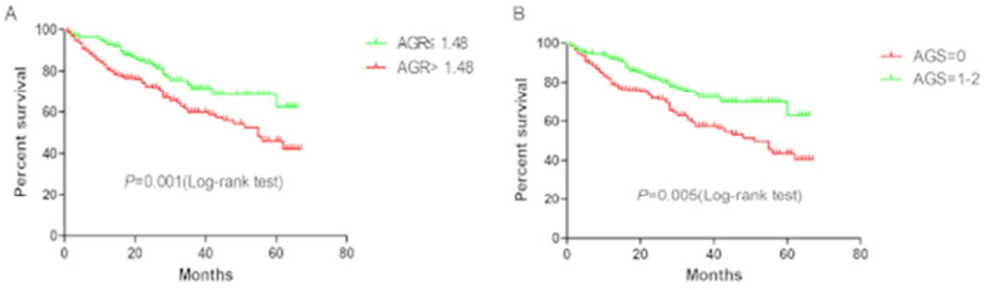

Figure 1. Kaplan–Meier survival curves according to AGR (A) and AGS (B).

62x19mm (300 x 300 DPI)

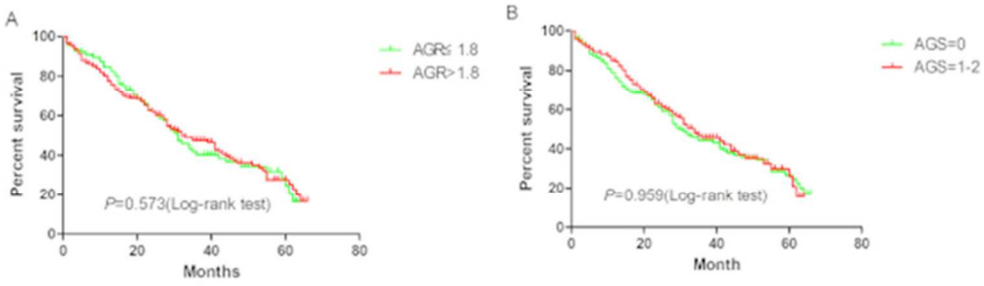

Figure 2. Kaplan–Meier hospital free curves according to AGR (A) and AGS (B).

61x18mm (300 x 300 DPI)

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The effect of albumin-globulin score and albumin/globulin ratio on survival in patients with heart failure: A retrospective cohort study in China

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The effect of albumin-globulin score and albumin/globulin ratio on survival in patients with heart failure: A retrospective cohort study in China

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Abstracts

OBJECTIVES: To investigate the combined effect of albumin (ALB) and globulin (GLB) on the overall survival of patients with heart failure (HF).

DESIGN: Retrospective cohort study.

SETTING: A Hospital.

PARTICIPANTS: 404 firstly diagnosed with heart failure patients.

MEASUREMENTS: Serum ALB and GLB were measured within three days after admission. The albumin/globulin ratio (AGR) was calculated as the ALB divided by the GLB. The receiver operating characteristic (ROC) curve was used to calculate the cut-off point of ALB, GLB, and AGR. Patients with low ALB levels (≤35.3g/L) and high GLB levels (>27.0 g/L) were assigned an albumin-globulin score AGS of 2, those with only one of the two abnormalities were assigned an AGS of 1, and those with neither of the two abnormalities were assigned an AGS of 0.

RESULTS: The mean age of the 404 patients was 62.69±15.62, and 54.5% were male. During follow-up, 14 patients lost to follow up. 120 patients died from HF and 211 patients were hospital readmitted for worsening HF. Univariate cox regression analysis showed that higher AGR was significantly associated with favorable overall survival (OS) (HR, 0.61; 95% CI, 0.38-0.98; *P*= 0.040) but not AGS.

CONCLUSION: Serum levels of ALB and GLB are objective and easily measurable biomarkers, which can be used in combination to predict the survival of patients with HF.

Key words: albumin; globulin; survival; heart failure

Strengths and limitations of this study

- This is the first study investigating the prognostic value of AGS and AGR in patients with HF.
- The cohort study design.
- To avoid bias, only patients firstly diagnosed with heart failure were selected.
- The information bias could not be avoided owing to the retrospective cohort study design.

Introduction

Heart failure (HF), with a prevalence of more than 23 million worldwide[1 2], is a global public health problem. In China, there are 4.2 million people living with HF, with 500, 000 new cases diagnosed each year, and this number is expected to increase still further[3], causing enormous social and economic burden. Over the last 30 years, although great improvements have been made in drug and device therapy, the survival and the rehospitalization rate in HF patients often remains unsatisfactory[4 5]. Hence, identification of promising prognostic factors contributing to the risk classification and clinical management of such patients could improve their long-term survival.

Numerous prognostic markers of death and/or HF hospitalization have been identified in patients with HF. In recent decades, several multivariable prognostic risk scores have been developed for different populations of patients with HF[6-8]. However, their clinical applicability is limited and precise risk stratification in HF remains challenging. Simple but effective prognostic biomarkers model are needed to improve the management of the HF epidemic.

The correlation between serum albumin (ALB) and globulin (GLB) with HF has recently been emphasized. Albumin and globulin, the two major components of serum proteins, have been confirmed to be involved in the systemic inflammatory process. Serum albumin, one of the

biochemical tests, not only indicates nutritional status but also relates to chronic inflammation in HF[9 10]. Moreover, increased levels of GLB could serve as markers of chronic inflammation response and reflect a cumulative exposure of various proinflammatory cytokines[11]. Previous studies have demonstrated that hypoalbuminemia was associated with impaired survival in HF patients[12]. However, no study investigated the cumulative effect of ALB and GLB on HF patients. Therefore, the purpose of this present study was to access the effect of the albumin-globulin score (AGS) and albumin/globulin ratio (AGR) on long-term survival among HF patients.

Methods and material

Participants

Between January 2010 and September 2015, 404 consecutive patients who were firstly diagnosed as HF at the First Affiliated Hospital of Zhengzhou University were included. The diagnosis of HF was based on a history of dyspnea with symptomatic exercise intolerance, and signs of documentation of left ventricular enlargement or peripheral edema or pulmonary congestion or radionuclide ventriculography or dysfunction by chest X-ray and/or echocardiography.[13] Informed consent was obtained from all patients prior to participation, and the study was approved by Zhengzhou University Committee. All methods were performed in

accordance with the relevant guidelines and regulations.

The exclusion criteria for patients were as follows: (1) Acute coronary syndromes; (2) no echocardiographic structural or functional abnormalities; (3) without HF; and (4) dead before discharge

Patient and Public Involvement

All participants were given written informed consent before they joined the study for authorizing to use the data generated from the medical information system. The research question and outcome measures were handed out by hardcopy to each patient. Patients were not involved in the recruitment and conduct of the study. The results will be mailed to each participant.

Clinical and laboratory parameters

Patients' baseline characteristics including demographic parameters, comorbidities, medications, and laboratory variables were retrospectively reviewed and collected from the electronic medical records by two researchers. Fasting venous blood samples were collected from all patients within three days after admission, and were immediately sent for analysis. The serum levels of ALB, GLB and other variables were assayed by using an automatic biochemical analyzer (Hitachi 7600, Japan). The receiver operating characteristic (ROC) curve was used to

calculate the cut-off point of ALB, GLB, and AGR. Patients with low ALB levels (⩽35.3g/L) and high GLB levels (>27.0 g/L) were assigned an AGS of 2, those with only one of the two abnormalities were assigned an AGS of 1, and those with neither of the two abnormalities were assigned an AGS of 0. AGS=1-2 was defined as high, AGS=0 was defined as low, AGR> 1.48 was defined as high, and AGR⩽1.48 was defined as low. Moreover, AGR was divided into three equal tertiles.

Follow-up

All patients were followed-up every 3 months for the first 2 years, every 6 months in the third, every 1 year afterwards. The primary endpoint was death due to a cardiovascular event (myocardial infarction, progressive HF, stroke, other vascular causes, or sudden cardiac death), the second endpoint was progressive HF requiring re-hospitalization. Follow-up was performed until patient death, or until July 2016, which was the cut-off date for this study.

Statistical Analysis

The analysis of t-test was used to examine the differences of age, rank-sum test was used to measure the difference of non-normally continuous variable [Albumin, B-type natriuretic peptide (BNP), interventricular septum thickness (IVST), posterior wall thickness (PWT),

left ventricular end-diastolic volume (LVDv), left ventricular end-systolic volume (LVSv), left ventricular ejection fraction (LVEF), and left atrial dimension (LAD)], and the chi-square test was used to assess the difference of categorical variables [including gender, Hypertension, Diabetes mellitus, chronic kidney disease (CKD), Prior history of HF, idiopathic dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), hypertensive heart disease (HHD), atrial fibrillation (AF), and Medications]. The Kaplan-Meier method with Log-rank test was used to estimate survival curves. Univariable cox regression analysis was used to identify variables associated with overall survival. Variables with a $P<0.05$ on univariable analysis were further assessed with a multivariable Cox regression model. SPSS 21 software (IBM Corp, Armonk, NY) was used for the statistical analysis. The level of significance was established as a two-sided P value 0.05.

Results

The baseline characteristics of patients are presented in table 1. A total of 404 patients with HF whose mean age was 62.70±15.62 years old entered the analysis. Among them, 260 patients (64.25%) were classified as high AGS, 189 patients (46.78%) were classified as higher AGR. Patients with lower AGS were more often among individuals without chronic kidney disease (CKD), with idiopathic dilated

cardiomyopathy (DCM), using beta-blocker and angiotensin converting enzyme inhibitor (ACE-I), they also had lower B-type natriuretic peptide (BNP), higher left ventricular end-systolic volume (LVSv), higher left ventricular ejection fraction (LVEF), and lower left atrial dimension (LAD). Patients with higher AGR were more often among individuals without diabetes mellitus, without coronary heart disease (CHD), with DCM, using beta-blocker ACE-I, they also had lower B-type natriuretic peptide (BNP).

By July 2016, 404 patients had been followed up. 120 patients died, 211 patients were hospital readmitted, and 14 patients lost to follow up. The follow-up rate was 96.5%. The mean and median survival times were 47.23 months and 62.00 months, respectively. Figures 1 and 2 showed the Kaplan-Meier curves of overall survival and hospital free survival according to AGR (>1.48 vs. ≤ 1.48) and AGS (0 vs. 1-2), Figure 3 showed the Kaplan-Meier curves of overall survival and hospital free survival according to AGR tertiles.

As shown in table 2, univariate analysis showed that higher AGR and lower AGS were significantly associated with favorable overall survival 0.54 (0.37-0.80) and 0.56 (0.37-0.84), respectively. Moreover, age (per year), CKD (yes vs. no), BNP (per 100 pg/mL), LVDv (per ml), LVSv (per ml), and LAD (per mm) were other significant prognostic variables identified by univariate analysis. On multivariate analysis, AGR

remained to be an independent predictor for overall survival (HR, 0.61; 95% CI, 0.38-0.98), but not AGS (HR, 0.81; 95% CI, 0.41-1.57).

The univariate and multivariate analysis of rehospitalization are presented in Table 3. Univariate analysis showed that AGR and AGS had no significant effect on rehospitalization 0.92 (0.70-1.22) and 0.99 (0.75-1.32), respectively. However, age (per year), CKD (yes vs. no), Prior history of HF (yes vs. no), BNP (per 100 pg/mL), IVST (per mm), and LAD (per mm) were significant prognostic variables for rehospitalization. On multivariate analysis, age (per year), CKD (yes vs. no), IVST (per mm), and LAD (per mm) were independent prognostic indicator for rehospitalization.

Discussion

This study demonstrated that the combination of ALB and GLB have potential predictive effect on predicting survival in patients with HF, higher AGR was significantly associated with favorable overall survival among patients with HF. To the best of our knowledge, this is the first study investigating the prognostic value of AGS and AGR in patients with HF.

The prediction of HF prognosis is a cornerstone of HF management. Accurately predicting prognosis can be of benefit for patients with heart failure. Patients with a poor prognosis might benefit more from

aggressive treatment and a closer follow-up[14]. There exist previous risk models for patients with HF[15 16], which adopted a systems biology approach, by incorporating information from demographic, biomarker, genomic, proteomic, and the initial response to therapy might create a more effective prediction model and hopefully aid in understanding HF prognosis. However, these models are complex in clinical application and just provide moderate accuracy prediction in survival and rehospitalization in patients with HF[17]. Hence, designing a simple survival model based on routine blood biochemical indexes for clinician is helpful for better identification high risk HF patients.

The role of serum albumin is complex. Serum albumin is synthesized in the liver and plays multiple physiological roles, including maintenance of pH and normal microvascular permeability and mediation of coagulation, and has antioxidant properties[18]. The decrease in plasma albumin concentration may be due to malnutrition and cachexia (decreased albumin intake)[19], diffuse inflammation (increased albumin consumption)[20], renal impairment (increased urinary albumin loss)[21], plasma volume expansion (dilutional hypoalbuminemia), and hepatic dysfunction (decreased albumin synthesis)[22 23].Serum albumin is used in assessing protein malnutrition without calorie malnutrition in which serum albumin becomes low without affection of anthropometric measurements[24].Malnutrition was found to be associated with worsening

of symptoms and poor prognosis. Multiple European studies showed malnourished heart failure patients are weaker and fatigue earlier[25 26]. Heart failure with hypoalbuminemia, the indicator of malnutrition, was found to be associated with higher New York heart association (NYHA) functional class, elevated serum blood urea nitrogen and C-reactive protein[24]. It should be noted that although hypoalbuminemia might reflect poor nutritional status, albumin reduction in chronic inflammation is frequent[11].

Similar to the low albumin, high non-albumin protein was a predictor of mortality in HF patients. We postulate that the high serum non-albumin proteins status is a marker of inflammation in HF patients. Chronic inflammation is known to increase acute-phase proteins [eg, C-reactive protein (CRP), serum amyloid A, complement C3, fibrinogen, ceruloplasmin], which constitute part of the calculated globulins[11].And the increased level of globulin serves as a marker of chronic inflammation and reflects cumulative exposure to various pro-inflammatory cytokines such as interleukins (IL), particularly IL-6 and IL-1b, and tumor necrosis factor-a, which stimulates the production of acute-phase proteins[11].Chronic inflammation is a critical contributor to HF occurrence, development, survival, and is also related to the risk of recurrence among HF patients[27].Hence,we propose that low AGR and high AGS measure the extent of such activities related to chronic

inflammation, which influence mortality.

What's more, we found that LAD was a significant independent predictor for the long-term survival and rehospitalization in HF patients. The result is consistent with previous research findings[28]. As a predictor reflecting left atrium (LA) structural remodeling, LAD relates to all key risk factors for AF, such as advancing age, male sex, and greater blood pressure[29]. LA enlargement, as characterized by echocardiographic LAD, is related to incident AF, heart failure, stroke, and mortality[28 30-33]. Moreover, LA enlargement can reflect atrial volume or pressure overload in valvular or ischemic heart disease, or as a consequence of AF[34-36].

Prior studies have demonstrated that low serum albumin is an independent predictor of HF long-term mortality. Liu et.al showed that patients with hypoalbuminemia had a significantly lower survival rate (53% vs. 84%, log-rank $\chi(2) = 53.3$, $P < 0.001$) and a higher rate of cardiovascular death (21.8% vs. 8.9% , $P< 0.001$)[37]. Su et.al. reported that the patients with higher NT-pro BNP and lower albumin than median had the highest risk for cardiac events (HR, 2.89, CI 1.90-4.40,)[38]. The finding of our study that AGR is independent predictor of long-term mortality in HF patients was consistent with previous studies.

Conclusions

In conclusion, the present study suggests that the AGR is convenient

and effective tool to predict the overall survival time in HF patients. Further larger prospective studies are required to validate this finding and to investigate other prognostic indicators in HF patients.

Authors' contributions

Kuan Li and Yongjian Zhu designed the study and provided critical review of the manuscript. Yongjian Zhu, Yacong Bo and Wanrong Fu reviewed the literature. Yongjian Zhu and Kuan Li analyzed the data and wrote the first draft of the manuscript. Yacong Bo, Wanrong Fu, and Yongjian Zhu revised the manuscript.

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None

Competing interests

The authors declare that they have no conflict of interests.

Data sharing statement

Additional data are available from Yongjian Zhu for reasonable requesting.

Ethics approval

The study was approved by Ethics Research Committee in Zhengzhou University.

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Tables

Table 1 Correlation between AGS, AGR, and clinicopathologic parameters in 404 chronic heart failure patients

Variables	AGS (High=260, Low=144)			AGR (High=189, Low=215)		
	High (1-2)	Low (0)	*P*	High (>1.48)	Low (⩽1.48)	*P*
Age (years)	63.82±15.63	60.67±15.45	0.051	59.46±15.34	65.41±15.34	<0.001
Gender						
Male	133(51.2%)	87 (60.4%)	0.073	111(58.7%)	109(51.2%)	0.129
Albumin(g/dl)	37.8(26.8-47.1)	36.0(24.2-45.1)	0.026	36.3(26.1-46.3)	38.2(25.7-47.5)	0.017
Hypertension	107(41.2%)	59(41.0%)	0.972	78(41.3%)	88(41.3%)	0.993
Diabetes mellitus	80(30.8%)	32(22.2%)	0.066	42(22.2%)	70(32.9%)	0.018
CKD	32(12.3%)	7(4.9%)	0.015	16(8.5%)	23(10.8%)	0.430
Prior history of HF	185(71.2%)	110(76.4%)	0.256	145(76.7%)	148(69.5%)	0.103
VHD	35(13.5%)	18(12.5%)	0.784	24(12.7%)	29(13.6%)	0.786
CHD	118(45.4%)	68(47.2%)	0.723	75(39.7%)	110(51.6%)	0.016
DCM	39(15.0%)	33(22.9%)	0.046	47(24.9%)	25(11.7%)	0.001
HCM	7(2.7%)	2(1.4%)	0.395	5(2.6%)	4(1.9%)	0.604
HHD	5(1.9%)	5(3.5%)	0.337	5(2.6%)	5(2.3%)	0.848
AF	81(31.2%)	40(27.8%)	0.478	60(31.7%)	60(28.2%)	0.434
BNP (pg/mL)	3948.5(500.7-18807.6)	2643.0(409.6-12089.1)	<0.001	2881.0(532.4-20725.8)	4155.5(445.2-17685.2)	<0.001
Echocardiography findings						

Variables	AGS (High=260, Low=144)			AGR (High=189, Low=215)		
	High (1-2)	Low (0)	*P*	High (>1.48)	Low (⩽1.48)	*P*
IVST (mm)	10.0(7.8-13.0)	9.7(8.0-13.4)	0.027	10.0(8.0-14.0)	10.0(7.7-13.0)	0.813
PWT (mm)	9.0(8.0-12.0)	9.0(7.2-12.9)	0.172	9.0(2.2-12.8)	9.0(8.0-11.0)	0.423
LVDv (ml)	152.0(71.6-347.6)	170.0(72.6-346.0)	0.014	150.5(72.0-365.7)	170.0(67.8-343.2)	0.023
LVSv (ml)	75.5(27.0-225.6)	98.0(27.0-232.1)	0.007	95.0(26.4-230.0)	74.5(27.0-231.1)	0.019
LVEF (%)	48.0(28.0-67.5)	45.0(27.0-64.0)	0.031	45.0(27.0-65.0)	48.0(28.0-67.0)	0.086
LAD(mm)	40.0(29.0-58.4)	42.0(28.3-63.7)	0.047	42.0(29.4-62.2)	39.0(29.0-60.6)	0.032
Medications, n (%)						
Beta-blocker	152(58.5%)	99(68.8%)	0.041	130(68.8%)	120(56.3%)	0.010
CCB	57(21.9%)	31(21.5%)	0.927	43(22.8%)	45(21.1%)	0.694
Statins	120(46.2%)	70(48.6%)	0.636	92(48.7%)	97(45.5%)	0.529
ARB	83(31.9%)	41(28.5%)	0.471	63(33.3%)	61(28.6%)	0.309
ACE-I	74(28.5%)	69(47.9%)	<0.001	83(43.9%)	59(27.7%)	0.001

CKD, chronic kidney disease; DCM, idiopathic dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; HHD, hypertensive heart disease; AF, atrial fibrillation; VHD, valvular heart disease; CHD, coronary heart disease; BNP, B-type natriuretic peptide; IVST, interventricular septum thickness; PWT, posterior wall thickness; LVDv, left ventricular end-diastolic volume; LVSv, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction; LAD, left atrial dimension; ARB, angiotensin receptor blocker; CCB, calcium-channel blocker; ACE-I, angiotensin converting enzyme inhibitor; AGS, albumin-globulin score; AGR, albumin/globulin ratio.

Table 2. Univariate and multivariate analysis of overall survival

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI of HR	P Value	HR	95% CI of HR	P Value
Age (per year)	1.02 (1.01-1.03)		0.011	1.03 (1.01-1.05)		0.006
Gender (female vs. male)	0.94 (0.78-1.13)		0.501			
Hypertension (yes vs. no)	0.95 (0.66-1.37)		0.774			
Diabetes mellitus (yes vs. no)	1.27 (0.87-1.87)		0.221			
CKD (yes vs. no)	2.37 (1.43-3.94)		0.001	2.13 (1.11-4.09)		0.023
Prior history of HF (yes vs. no)	1.27 (0.85-1.90)		0.244			
VHD (yes vs. no)	1.50 (0.95-2.37)		0.079			
CHD (yes vs. no)	0.96 (0.67-1.37)		0.808			
DCM (yes vs. no)	0.63 (0.37-1.11)		0.114			
HCM (yes vs. no)	0.70 (0.17-2.81)		0.610			
HHD (yes vs. no)	0.64 (0.16-2.60)		0.536			
AF (yes vs. no)	1.26 (0.87-1.84)		0.221			
BNP (per 100 pg/mL)	1.01 (1.00-1.02)		<0.001	1.01 (1.00-1.02)		0.034
LVEF (per 1%)	1.00 (0.98-1.01)		0.623			
IVST (per mm)	1.10 (0.99-1.21)		0.066			
PWT (per mm)	1.09 (0.99-1.19)		0.076			
LVDv (per ml)	1.01 (1.00-1.02)		0.028	1.00 (0.99-1.01)		0.393
LVSv (per ml)	1.01 (1.00-1.02)		0.033	1.01 (1.00-1.02)		0.006
LAD (per mm)	1.02 (1.01-1.04)		0.001	1.03 (1.01-1.05)		0.001
AGR (>1.48 vs. ⩽1.48)	0.54 (0.37-0.80)		0.001	0.61 (0.38-0.98)		0.040
AGR ((ref: 1ST tertile))						
AGR 2nd tertile	0.84 (0.55-1.28)		0.412	0.82 (0.54-1.25)		0.350
AGR 3rd tertile	0.56 (0.36-0.89)		0.014	0.62 (0.39-0.98)		0.040
AGS (0 vs. 1-2)	0.56 (0.37-0.84)		0.005	0.81 (0.41-1.57)		0.525

CKD, chronic kidney disease; DCM, idiopathic dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; HHD, hypertensive heart disease; AF, atrial fibrillation; VHD, valvular heart disease; CHD, coronary heart disease; BNP, B-type natriuretic peptide; IVST, interventricular septum thickness; PWT, posterior wall thickness; LVDv, left ventricular end-diastolic volume; LVSv, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction; LAD, left atrial dimension; AGS, albumin-globulin score; AGR, albumin/globulin ratio

Table 3. Univariate and multivariate analysis of rehospitalization

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P Value	HR (95% CI)	P Value
Age (per year)	1.01 (1.00-1.02)	0.009	1.01 (1.00-1.02)	0.028
Gender (female vs. male)	1.01 (1.00-1.02)	0.882		
Hypertension (yes vs. no)	1.00 (0.76-1.32)	0.998		
Diabetes mellitus (yes vs. no)	1.25 (0.94-1.68)	0.130		
CKD (yes vs. no)	1.68 (1.07-2.62)	0.023	1.80 (1.07-3.03)	0.027
Prior history of HF (yes vs. no)	1.42 (1.04-1.94)	0.028	1.30 (0.87-1.95)	0.202
VHD (yes vs. no)	1.14 (0.78-1.68)	0.490		
CHD (yes vs. no)	1.26 (0.96-1.65)	0.096		
DCM (yes vs. no)	0.61 (0.33-1.12)	0.108		
HCM (yes vs. no)	1.28 (0.60-2.73)	0.523		
HHD (yes vs. no)	0.77 (0.29-2.08)	0.609		
AF (yes vs. no)	1.11 (0.83-1.47)	0.487		
BNP (per 100 pg/mL)	1.01 (1.00-1.02)	0.050	1.00 (0.99-1.01)	0.967
LVEF (per 1%)	1.01 (0.99-1.02)	0.187		
IVST (per mm)	1.09 (1.01-1.17)	0.023	1.10 (1.00-1.20)	0.050
PWT (per mm)	1.04 (0.97-1.13)	0.296		
LVDv (per ml)	1.00 (0.99-1.01)	0.967		
LVSv (per ml)	1.00 (0.99-1.01)	0.839		
LAD (per mm)	1.01 (1.00-1.03)	0.041	1.02 (1.00-1.03)	0.011
AGR (>1.48 vs.⩽1.48)	0.92 (0.70-1.22)	0.573		
AGR ((ref: 1ST tertile))				
AGR 2nd tertile	1.14 (0.82-1.58)	0.448		
AGR 3rd tertile	0.97 (0.69-1.36)	0.850		
AGS (0 vs. 1-2)	0.99 (0.75-1.32)	0.959		

CKD, chronic kidney disease; DCM, idiopathic dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; HHD, hypertensive heart disease; AF, atrial fibrillation; VHD, valvular heart disease; CHD, coronary heart disease; BNP, B-type natriuretic peptide; IVST, interventricular septum thickness; PWT, posterior wall thickness; LVDv, left ventricular end-diastolic volume; LVDs, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction; LAD, left atrial dimension; AGS, albumin-globulin score; AGR, albumin/globulin ratio

Figure legends

Figure 1. Kaplan–Meier survival curves according to AGR (A) and AGS (B).

Figure 2. Kaplan–Meier hospital free curves according to AGR (A) and AGS (B).

Figure 3. Kaplan–Meier survival (A) and hospital free curves (B) according to AGR tertiles.

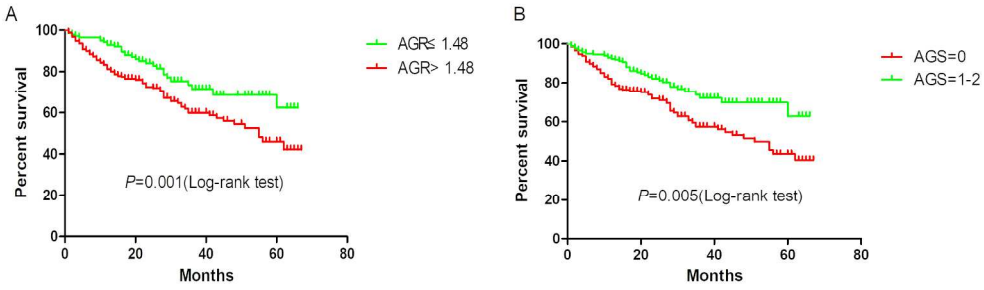

Figure 1. Kaplan–Meier survival curves according to AGR (A) and AGS (B).

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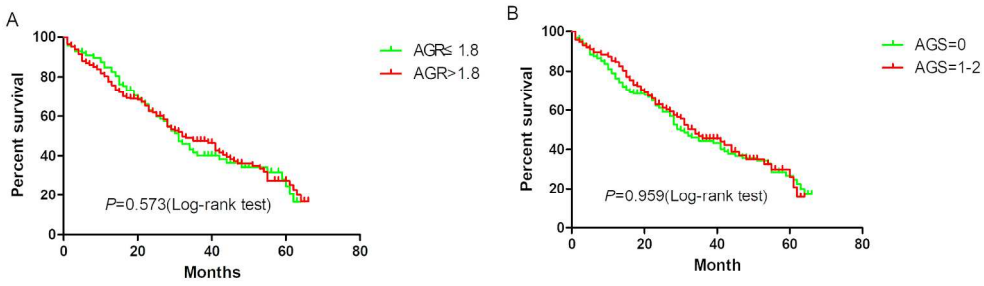

Figure 2. Kaplan–Meier hospital free curves according to AGR (A) and AGS (B).

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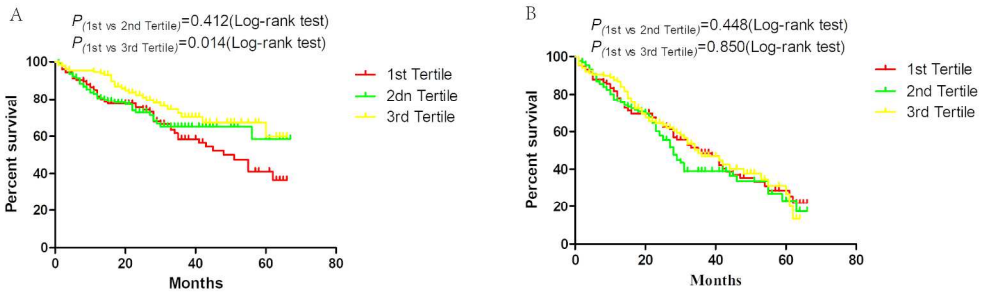

Figure 3. Kaplan–Meier survival (A) and hospital free curves (B) according to AGR tertiles.

293x90mm (300 x 300 DPI)

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page4-5
Objectives	3	State specific objectives, including any pre-specified hypotheses	Page5
Methods			
Study design	4	Present key elements of study design early in the paper	Page5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	Page5-7
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page6-7
Bias	9	Describe any efforts to address potential sources of bias	Page6-7
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page7-8
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	Page7-8
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	Page7-9

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	NA
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Page8-9
		(b) Indicate number of participants with missing data for each variable of interest	Page8-9
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	Page8-9
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	Page8-9
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Page8-9
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Page8-9
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page3
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page10-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 11-13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	NA

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.