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Original Research Article

ASSOCIATION OF ALBUMIN–GLOBULIN RATIO WITH NT-PROBNP LEVELS AND ECHOCARDIOGRAPHIC INDICES IN PATIENTS WITH CHRONIC HEART FAILURE: A CROSS-SECTIONAL OBSERVATIONAL STUDY

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ABSTRACT

Background: Chronic heart failure (HF) is characterized by neurohormonal activation and systemic inflammation, both of which influence serum protein fractions. The albumin–globulin ratio (AGR) has been proposed as an inexpensive marker of inflammatory and nutritional status, but its relationship with established markers of HF severity remains incompletely defined. The objective is to evaluate the association of AGR with NT-proBNP levels and echocardiographic indices in patients with chronic HF.

Materials and Methods: This cross-sectional observational study was conducted at a tertiary care teaching hospital in South India. It enrolled 148 adults with clinically stable chronic HF (New York Heart Association [NYHA] class I-IV) attending the cardiology outpatient department. Serum AGR, calculated as serum albumin divided by serum globulin (total protein minus albumin). The primary outcomes were serum NT-proBNP level and echocardiographic parameters, including left ventricular ejection fraction (LVEF), left atrial volume index, and the ratio of early mitral inflow velocity to early diastolic mitral annular velocity (E/e′). Associations were assessed using Pearson or Spearman correlation and multivariable linear regression adjusted for age, sex, NYHA class, estimated glomerular filtration rate, and diabetes status.

Results: Among 148 participants (mean [SD] age, 61.4 [10.8] years; 91 [61.5%] men), the mean (SD) AGR was 1.12 (0.24). AGR was significantly and inversely correlated with NT-proBNP ($r = -0.42$; $P < .001$) and E/e′ ($r = -0.31$; $P < .001$) and positively correlated with LVEF ($r = 0.38$; $P < .001$). In multivariable analysis, each 0.1-unit decrease in AGR was associated with a 14.6% higher NT-proBNP level (95% CI, 8.2%-21.3%; $P < .001$) and a 1.1-percentage-point lower LVEF (95% CI, 0.4-1.8; $P = .002$). Patients with AGR below the median (<1.10) had higher NT-proBNP levels and lower LVEF than

those with AGR at or above the median (median NT-proBNP, 2450 vs 1180 pg/mL; P < .001).
Conclusion: In this cross-sectional study, lower AGR was independently associated with higher NT-proBNP levels and worse echocardiographic indices of systolic and diastolic function in patients with chronic HF. AGR may serve as a simple, low-cost adjunctive biomarker of HF severity; prospective studies are needed to determine its prognostic value.
Keywords: Chronic heart failure, Albumin–globulin ratio, NT-proBNP, Echocardiography, Cardiac function, Cross-sectional study.

INTRODUCTION

Chronic heart failure (HF) remains a major cause of morbidity and mortality worldwide, and accurate, low-cost biomarkers of disease severity are of substantial clinical interest.[1] Current international guidelines, including the 2022 American College of Cardiology/American Heart Association/Heart Failure Society of America (ACC/AHA/HFSA) guideline and the 2023 focused update of the European Society of Cardiology (ESC) guidelines, emphasize natriuretic peptide-based diagnosis and staging alongside structured phenotyping into HF with reduced, mildly reduced, and preserved ejection fraction (HFrEF, HFmrEF, and HFpEF, respectively).[2,3] N-terminal pro-B-type natriuretic peptide (NT-proBNP) is the most widely used biomarker for the diagnosis and prognostication of HF, reflecting myocardial wall stress and neurohormonal activation.[4] Cross-sectional studies applying multivariable regression have demonstrated independent associations between NT-proBNP and echocardiographic indices of diastolic function, including the E/e′ ratio and left atrial volume index, across a range of cardiac populations.[5,6]

Beyond natriuretic peptides, systemic inflammation and malnutrition are increasingly recognized as important contributors to HF progression. Serum albumin, a negative acute-phase reactant, declines with inflammation, malnutrition, and hepatic or renal dysfunction, all of which are common in chronic HF. [7] Several studies have shown that hypoalbuminemia is independently associated with adverse outcomes in HF and adds incremental prognostic information to NT-proBNP. [8,9]

The albumin–globulin ratio (AGR), which incorporates both a decline in albumin and a rise in globulin fractions (reflecting chronic inflammation and immune activation), has been proposed as a more comprehensive marker of the inflammatory-nutritional milieu than albumin alone. A retrospective cohort study of 404 patients with HF in China found that a higher AGR was an independent predictor of more favorable overall survival.[10] More recently, composite indices combining NT-proBNP and albumin, such as the NT-proBNP-to-albumin ratio, have shown strong discriminative performance for in-hospital mortality in chronic HF. [11]

Despite this evidence linking AGR to HF outcomes, few studies have directly examined its cross-sectional association with contemporaneous NT-proBNP levels and echocardiographic indices of cardiac structure and function. Establishing this relationship would support the biological plausibility of AGR as a marker of disease severity and inform its potential use as an adjunctive, low-cost tool in resource-limited settings. We therefore conducted a cross-sectional observational study to evaluate the association of AGR with NT-proBNP levels and echocardiographic indices among patients with chronic HF.

MATERIALS AND METHODS

Study Design and Setting: This cross-sectional observational study was conducted in the Department of Cardiology at Chettinad Hospital and Research Institute, a tertiary care teaching hospital in Kelambakkam, Chengalpattu district, Tamil Nadu, India. The study was approved by the Institutional Human Ethics Committee, Chettinad Academy of Research and Education (Ref No: IHEC-I/017/07/2026), and written informed consent was obtained from all participants. Reporting followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidance.[12]

Participants: Adults aged 18 years or older with a clinical diagnosis of chronic HF (NYHA class I-IV), stable for at least 4 weeks without hospitalization, were consecutively enrolled from the outpatient cardiology clinic. Exclusion criteria were acute decompensated HF requiring hospitalization within the preceding 4 weeks, known chronic liver disease, active infection or malignancy, chronic kidney disease stage 5 or on dialysis, and inability to undergo transthoracic echocardiography.

Sample Size: Sample size was estimated for the principal correlation analysis between AGR and NT-proBNP using established methodology for correlation-based studies.[13] To detect a minimum correlation coefficient of 0.30 with 80% power and a 2-sided type I error of .05, a minimum of 84 participants was required. The final analytic sample of 148 participants exceeded this requirement, providing more than 80% power to detect correlations as small as $r \approx 0.23$.

Variables and Data Collection: Demographic and clinical data, including age, sex, HF etiology,NYHA class, comorbidities, and medication use, were recorded from clinical records and structured interviews. Fasting venous blood samples were collected for measurement of serum albumin, total

protein, and NT-proBNP. Serum albumin was measured by the bromocresol green (BCG) method, and total protein was measured by the biuret method using an automated clinical chemistry analyzer (Siemens Dimension RxL, Siemens Healthineers, Germany). NT-proBNP was measured by electrochemiluminescence immunoassay using a Beckman Coulter immunoassay analyzer (DxI 600, Beckman Coulter, USA). Albumin–globulin ratio (AGR) was calculated as serum albumin/ (total protein − serum albumin). Albumin and total protein were reported in g/dL, and NT-proBNP was reported in pg/mL. Transthoracic echocardiography was performed by a single trained cardiologist blinded to laboratory results, using a Philips Affiniti 50 ultrasound system (Philips Healthcare) and a standardized protocol to measure left ventricular ejection fraction (LVEF, Simpson biplane method), left atrial volume index, and E/e′ ratio, in accordance with American Society of Echocardiography recommendations.[14] To assess measurement reproducibility, a randomly selected 10% subset of studies was re-read blind to the initial reading by the same observer (intra-observer) and by a second trained echocardiographer (inter-observer), with agreement quantified using the intraclass correlation coefficient (ICC).

Statistical Analysis

Continuous variables are presented as mean (SD) or median (IQR) as appropriate, and categorical variables as number (percentage). The association between AGR and NT-proBNP, LVEF, left atrial volume index, and E/e′ was assessed using Pearson or Spearman correlation coefficients, depending on distribution. Multivariable linear regression models were used to evaluate the independent association of AGR with NT-proBNP (log-transformed) and echocardiographic indices, adjusting for age, sex, NYHA class, estimated glomerular filtration rate, and diabetes status. Participants were also dichotomized at the median AGR for descriptive comparison using the Mann-Whitney U test or independent-samples t test. A 2-sided $P < .05$ was considered statistically significant. Analyses were performed using standard statistical software.

RESULTS

Baseline Characteristics

Of 162 patients screened, 148 met eligibility criteria and were included in the analysis. [Table 1] The mean (SD) age was 61.4 (10.8) years, and 91 (61.5%) were men. Ischemic heart disease was the predominant HF etiology (63 [42.6%]), followed by hypertensive heart disease (41 [27.7%]) and dilated cardiomyopathy (28 [18.9%]). The mean (SD) AGR was 1.12 (0.24), and the median (IQR) NT-proBNP level was 1620 (890-3140) pg/mL. By echocardiographic phenotype, 58 patients (39.2%) had HF with reduced ejection fraction (HFrEF, LVEF <40%), 46 (31.1%) had HF with mildly reduced ejection fraction (HFmrEF, LVEF 40%-49%), and 44 (29.7%) had HF with preserved ejection fraction (HFpEF, LVEF ≥50%); the proportion with HFrEF was higher among patients with AGR below the median than at or above the median (51.4% vs 27.0%). [Table 1] By NYHA functional class, 24 patients (16.2%) were class I, 72 (48.6%) class II, 40 (27.0%) class III, and 12 (8.1%) class IV, with a higher proportion of NYHA class III-IV among patients with AGR below the median than at or above the median (51.4% vs 18.9%). [Table 1] Regarding baseline guideline-directed medical therapy, beta-blockers were the most frequently used agents (128 [86.5%]), followed by mineralocorticoid receptor antagonists (79 [53.4%]), SGLT2 inhibitors (71 [48.0%]), and angiotensin receptor-neprilysin inhibitors (54 [36.5%]). [Table 1]

Table 1: Baseline Demographic, Clinical, Laboratory, and Echocardiographic Characteristics by AGR Group

Characteristic	Overall (N = 148)	AGR < 1.10 (n = 74)	AGR ≥ 1.10 (n = 74)
Age, mean (SD), y	61.4 (10.8)	62.9 (11.2)	59.9 (10.1)
Men, No. (%)	91 (61.5)	44 (59.5)	47 (63.5)
NYHA class I, No. (%)	24 (16.2)	8 (10.8)	16 (21.6)
NYHA class II, No. (%)	72 (48.6)	28 (37.8)	44 (59.5)
NYHA class III, No. (%)	40 (27.0)	27 (36.5)	13 (17.6)
NYHA class IV, No. (%)	12 (8.1)	11 (14.9)	1 (1.4)
Diabetes, No. (%)	66 (44.6)	35 (47.3)	31 (41.9)
HFrEF (LVEF <40%), No. (%)	58 (39.2)	38 (51.4)	20 (27.0)
HFmrEF (LVEF 40%-49%), No. (%)	46 (31.1)	22 (29.7)	24 (32.4)
HFpEF (LVEF ≥50%), No. (%)	44 (29.7)	14 (18.9)	30 (40.5)
eGFR, mean (SD), mL/min/1.73m²	68.2 (19.4)	62.5 (20.1)	73.9 (17.3)
Serum albumin, mean (SD), g/dL	3.6 (0.5)	3.2 (0.4)	4.0 (0.3)
NT-proBNP, median (IQR), pg/mL	1620 (890-3140)	2450 (1340-4210)	1180 (620-2050)
LVEF, mean (SD), %	42.6 (12.1)	38.4 (12.6)	46.8 (10.4)
E/e′ ratio, mean (SD)	13.8 (4.6)	15.2 (4.9)	12.4 (4.0)
Beta-blocker use, No. (%)	128 (86.5)	62 (83.8)	66 (89.2)
ARNI use, No. (%)	54 (36.5)	31 (41.9)	23 (31.1)
MRA use, No. (%)	79 (53.4)	46 (62.2)	33 (44.6)
SGLT2 inhibitor use, No. (%)	71 (48.0)	34 (45.9)	37 (50.0)

AGR indicates albumin–globulin ratio; ARNI, angiotensin receptor-neprilysin inhibitor; eGFR, estimated glomerular filtration rate; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; SGLT2, sodium-glucose cotransporter-2.

Association of AGR with NT-proBNP and Echocardiographic Indices

AGR was significantly and inversely correlated with NT-proBNP level (r = −0.42; P < .001) and E/e′ ratio (r = −0.31; P < .001) and positively correlated with LVEF (r = 0.38; P < .001) and left atrial volume index (r = −0.27; P = .001). [Table 2] In multivariable linear regression adjusted for age, sex, NYHA class, eGFR, and diabetes status, AGR remained independently associated with log-transformed NT-proBNP (β = −1.42; 95% CI, −1.98 to −0.86; P < .001) and LVEF (β = 10.6; 95% CI, 4.3-16.9; P = .002).

Table 2: Correlation and Adjusted Association of AGR with NT-proBNP and Echocardiographic Indices

Variable	r	P Value	Adjusted β (95% CI) *
NT-proBNP, log pg/mL	−0.42	<.001	−1.42 (−1.98 to −0.86)
LVEF, %	0.38	<.001	10.6 (4.3 to 16.9)
E/e′ ratio	−0.31	<.001	−4.8 (−7.6 to −2.0)
Left atrial volume index, mL/m²	−0.27	.001	−9.1 (−15.4 to −2.8)

*Adjusted for age, sex, NYHA class, estimated glomerular filtration rate, and diabetes status; β represents the change in outcome per 1-unit increase in AGR.

DISCUSSION

In this cross-sectional study of 148 patients with chronic HF, a lower AGR was independently associated with higher NT-proBNP levels and worse echocardiographic indices of systolic and diastolic function, including lower LVEF, higher E/e′ ratio, and larger left atrial volume index. These associations persisted after adjustment for age, sex, NYHA class, renal function, and diabetes status.

These findings are consistent with prior observational data linking hypoalbuminemia and low AGR to HF severity and adverse outcomes. Su and colleagues reported that serum albumin added independent prognostic information to NT-proBNP in a Chinese HF cohort, with the combination of high NT-proBNP and low albumin identifying patients at highest risk for cardiac events.[8] Liu and colleagues similarly found that hypoalbuminemia was associated with significantly lower survival in patients with heart failure and preserved ejection fraction.[9] In a retrospective cohort of 404 patients with HF, Li and colleagues found that a higher AGR was an independent predictor of more favorable overall survival, supporting its role as a convenient prognostic tool.[10] More recently, a composite NT-proBNP-to-albumin ratio has shown strong discriminative performance for in-hospital mortality across sexes in chronic HF.[11] A 2024 systematic review and meta-analysis of albumin-based indices, encompassing albumin-globulin ratio among other ratios, found consistent associations between these low-cost inflammatory-nutritional markers and both short- and long-term mortality after HF, reinforcing the broader prognostic relevance of albumin-based ratios across diverse HF populations.[15] A 2025 practical review similarly emphasized hypoalbuminemia, and by extension a reduced AGR, as a marker of adverse fluid and inflammatory status in HF, while noting that routine albumin supplementation itself has not been shown to improve outcomes—underscoring that AGR's clinical value most likely lies in risk stratification rather than as a direct treatment target.[16] Consistent with the cross-sectional associations reported here, prior multivariable regression analyses in other cardiac populations have linked NT-proBNP with echocardiographic markers of diastolic dysfunction such as E/e′, and have shown that natriuretic-peptide-based ratios relate independently to left atrial volume index and ejection fraction.[5,6] Our findings extend this literature by demonstrating a direct, cross-sectional relationship between AGR and echocardiographic indices of cardiac structure and function, supporting the biological plausibility of these previously reported prognostic associations.

The mechanisms linking AGR to HF severity are likely multifactorial. Declining albumin in HF may reflect a combination of chronic systemic inflammation, hepatic congestion, malnutrition, and hemodilution from volume overload, while rising globulin fractions reflect immune activation.[9] Because AGR captures both processes simultaneously, it may provide a more integrated signal of the inflammatory-nutritional state than albumin alone, potentially explaining its correlation with natriuretic peptide levels and measures of ventricular function observed in this study.

From a clinical implementation standpoint, these findings may be particularly relevant to resource-limited settings, where NT-proBNP testing is often constrained by assay cost, cold-chain reagent requirements, and limited laboratory infrastructure, whereas albumin and total protein are part of routine, low-cost biochemistry panels available in most primary and secondary care facilities. Rather than replacing NT-proBNP, AGR may be best positioned as a complementary, first-line triage tool: a low AGR in a patient with symptoms suggestive of HF could

prompt closer clinical evaluation or expedited referral for NT-proBNP testing and echocardiography where these are not immediately available, whereas a normal AGR alone should not be relied on to exclude HF given the only moderate correlation coefficients observed. Because AGR can be derived at no additional cost from albumin and total protein values already collected as part of routine metabolic panels, it could also offer a pragmatic adjunct for longitudinal monitoring of inflammatory-nutritional status in HF clinics with constrained access to natriuretic peptide testing, pending prospective studies confirming its incremental and prognostic value alongside NT-proBNP.

Limitations

This study has several limitations. First, the cross-sectional design precludes causal inference and does not permit assessment of AGR's prognostic value for clinical outcomes. Second, the single-center design may limit generalizability. Third, unmeasured confounders, such as detailed nutritional status or subclinical infection, could not be fully accounted for. Prospective, multicenter studies with longitudinal follow-up are needed to determine whether AGR predicts clinical outcomes independent of NT-proBNP and echocardiographic parameters.

CONCLUSION

In this cross-sectional study, lower AGR was independently associated with higher NT-proBNP levels and worse echocardiographic indices of systolic and diastolic function in patients with chronic HF. AGR is an inexpensive, widely available biomarker that may serve as an adjunctive marker of disease severity in chronic HF, warranting further prospective evaluation.

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