Anemia as an Independent Predictor of Adverse Cardiac Outcomes in Patients with Atrial Fibrillation

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Abstract

**Background:** Anemia and echocardiographic systolic and diastolic parameters are useful predictors of cardiovascular outcomes in patients with atrial fibrillation (AF). However, no studies have evaluated the use of anemia for predicting cardiovascular outcome in AF patients when the important echocardiographic parameters are known. Therefore, this study was designed to evaluate whether low hemoglobin is a useful parameter for predicting poor cardiac outcome after adjustment for important echocardiographic parameters in AF patients.

**Methods:** Index beat method was used to measure echocardiographic parameters in 166 patients with persistent AF. Cardiac events were defined as death and hospitalization for heart failure. The association of hemoglobin with adverse cardiac events was assessed by Cox proportional hazards model.

**Results:** The 49 cardiac events identified in this population included 21 deaths and 28 hospitalizations for heart failure during an average follow-up of 20 months (25th-75th percentile: 14-32 months). Multivariable analysis showed that increased left ventricular mass index (LVMI) and decreased body mass index, estimated glomerular filtration rate, and hemoglobin (hazard ratio 0.827; P = 0.015) were independently associated with increased cardiac events. Additionally, tests of a Cox model that included important clinic variables, LVMI, left ventricular ejection fraction, and the ratio of transmitral E-wave velocity to early diastolic mitral annulus velocity showed that including hemoglobin significantly increased value in predicting adverse cardiac events (P = 0.010).

**Conclusions:** Hemoglobin is a useful parameter for predicting adverse cardiac events, and including hemoglobin may improve the prognostic prediction of conventional clinical and echocardiographic parameters in patients with AF.

Key words: Hemoglobin, anemia, atrial fibrillation, cardiac outcomes.

Introduction

Atrial fibrillation (AF) is the most common form of cardiac arrhythmia in adults. Its prevalence increases with age and reportedly reaches 9% in those older than 80 years [1]. Patients with AF often have other cardiovascular comorbidities, including chronic heart failure, stroke, valvular heart disease, hypertension, and diabetes mellitus [2]. AF is independently associated with increased risks of ischemic stroke,
hospitalization for heart failure, and mortality [3-5]. Cardiovascular comorbidities and thromboembolic events significantly increase the mortality rate and treatment cost of AF [6].

Anemia, which is defined as a reduced hemoglobin concentration or hematocrit, is among the most common disorders in the world and is a major public health concern in both industrialized and non-industrialized countries. Globally, anemia affects about 1.62 billion people, which corresponds to 24.8% of the overall population [7]. Anemia, which is a risk factor for cardiovascular disease, is independently associated with an increased mortality rate in patients with chronic heart failure, left ventricular hypertrophy, chronic kidney disease, diabetes mellitus, and acute coronary syndrome [8-12]. Several studies have investigated the relationship between cardiovascular outcome and anemia in patients with AF. For example, an analysis of 3378 Japanese AF patients enrolled in the Fushimi AF Registry indicated that, compared to patients who had AF alone, patients who had both AF and anemia had more clinical comorbidities, including old age, heart failure, coronary artery disease, peripheral artery disease, chronic kidney disease, and stroke [13]. Sharma et al. reported that anemia was an independent predictor of mortality and hospitalizations in 13067 elderly patients with AF in the United States [14]. In elderly AF patients, low hematocrit is also associated with an increased mortality rate. Additionally, echocardiographic parameters, including left ventricular hypertrophy and left ventricular diastolic and systolic dysfunction, are well-established predictors of cardiovascular outcomes in patients irrespective of the presence of AF [15, 16,17-23]. However, no study has investigated the incremental value of anemia for predicting cardiovascular outcome in AF patients when important clinical and echocardiographic parameters are known. Therefore, this study investigated whether low hemoglobin is a useful parameter for predicting poor cardiac outcome and whether including anemia with the clinical and echocardiographic parameters conventionally used to predict adverse cardiac events in AF patients further improves predictive value.

Methods

Study patients

This prospective observational cohort study included patients with persistent AF referred for echocardiographic examinations at Kaohsiung Municipal Hsiao-Kang Hospital from April, 2010 to June, 2012. Persistent AF was defined as AF lasting for at least 7 days according to 12-lead electrocardiography (ECG), 24-hour Holter ECG, or ECG during echocardiographic examination. Patients were excluded if they had inadequate echocardiographic visualization and a major valvular heart disease (i.e., moderate/severe mitral stenosis, moderate/severe aortic stenosis or regurgitation, or severe mitral regurgitation). Patients were also excluded if they had acute or chronic bleeding and deficiency of vitamin B12, folate, or iron. The final population included 166 AF patients. The study protocol was approved by the Institutional Review Board of Kaohsiung Municipal Hsiao-Kang Hospital, and all enrolled patients gave written, informed consent to participate in the study.

Echocardiographic evaluation

Echocardiographic examinations were performed with a VIVID 7 (General Electric Medical Systems, Horten, Norway) with the participant resiping quietly in the left decubitus position. All examinations were performed by one experienced cardiologist who was blinded to all clinical data, including history of hypertension, diabetes mellitus, coronary artery disease, etc. Two-dimensional and anatomic M-mode images were recorded in standardized views. The Doppler sample volume was placed at the tips of the mitral leaflets to obtain the left ventricular inflow waveforms in apical 4-chamber view. Pulsed tissue Doppler imaging was obtained with the sample volume placed at the lateral and septal corners of the mitral annulus in apical 4-chamber view. Early diastolic mitral annulus velocity (Ea) was obtained by averaging septal and lateral velocities. The wall filter settings were adjusted to exclude high-frequency signals, and the gain was minimized. Left ventricular ejection fraction (LVEF) was measured using the modified Simpson method. Left ventricular mass was calculated using Devereux-modified method [24]. Left ventricular mass index (LVMI) was calculated by dividing left ventricular mass by body surface area. Left atrial volume was measured using the biplane area-length method [25]. Left atrial volume index (LAVI) was calculated by dividing left atrial volume by body surface area.

The LVEF, LAVI, and LVMI were measured from the index beat [26-28]. Since the early mitral inflow velocity (E), E-wave deceleration time, and Ea could be obtained quickly and easily, they were obtained from five beats and then averaged for later analysis [29]. If the cardiac cycle length was too short to complete the diastolic process, this beat was skipped. Thus, the selection of E, E-wave deceleration time and Ea was not always consecutive. Heart rate was obtained from five consecutive beats. The raw ultrasonic data, including 15 consecutive beats from apical 4-chamber and 2-chamber views, were recorded and analyzed offline using EchoPAC software.
(EchoPAC version 08; GE-Vingmed Ultrasound AS GE Medical Systems).

**Index beat selection**

The index beat was taken after two approximately equal preceding and pre-preceding intervals selected from 15 stored cardiac cycles. The index beat was defined as if both preceding and pre-preceding intervals of the index beat were >500 ms [30] and if the difference between the two intervals was less than 60 ms [31]. The criterion for the cardiac cycle of the index beat was also >500 ms [30]. The patient was excluded if no beat in the 15 stored cardiac cycles met the required index beat. If several beats in the 15 stored cardiac cycles met the criteria for the index beat, the first index beat was used to calculate the echocardiographic data.

**Collection of demographic, medical, and laboratory data**

Demographic and medical data were obtained from medical records or from interviews with patients and included age, gender, and any history of diabetes mellitus, hypertension, coronary artery disease, stroke or chronic heart failure. The body mass index was calculated as the ratio of weight in kilograms divided by the square of height in meters. The systolic and diastolic blood pressures were measured by mercury sphygmomanometer before echocardiographic examination. Diabetes mellitus was defined as a fasting blood glucose level higher than 126 mg/dL or prescription for hypoglycemic agents to control blood glucose levels. Similarly, hypertension was defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg or prescription for anti-hypertensive drugs. Stroke was defined as any history of cerebrovascular accident, including cerebral bleeding and infarction. Coronary artery disease was defined as any history of typical angina with positive stress test, angiographically documented coronary artery disease, myocardial infarction, coronary artery bypass surgery, or angioplasty. Heart failure was defined according to Framingham criteria. Laboratory data collection included total cholesterol and triglyceride. Medical records were reviewed for history of medications during the study period, including use of angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, β-blockers, calcium channel blockers, diuretics, antiplatelet drugs, and anticoagulant drugs. According to the World Health Organization definition, anemic patients were defined as hemoglobin level less than 12 g/dL for women and less than 13 g/dL for men [32].

**Definition of cardiac events**

Cardiac events were defined as all-cause mortality and hospitalization for heart failure. Hospitalization for heart failure was defined as admission due to dyspnea with chest radiographic evidence of pulmonary congestion and treatment with intravenous diuretics. Cardiac events were ascertained and adjudicated by two cardiologists based on the course of hospital treatment indicated in the medical record. In the case of a disagreement, a third cardiologist defined the cardiac event. If a patient had multiple cardiac events, only the first event was coded. However, the death of a patient after a heart failure episode during the same admission was coded as a death. Patients who reached the study endpoints were followed up until the first adverse event. All other patients were followed up until May, 2013.

**Statistical analysis**

The SPSS 18.0 software (SPSS, Chicago, IL, USA) was used for statistical analysis. Continuous and categorical variables were compared between groups by independent sample t-test and by Chi-square test, respectively. The significant variables in the univariable analysis were selected for multivariable analysis. Time to adverse events and covariates of risk factors were modeled using a Cox proportional hazards model. Incremental model performance was assessed by a change in the Chi-square value. Kaplan-Meier survival plots were calculated from baseline to the time of an adverse event and compared by Log-rank test. All tests were 2-sided, and a P value less than 0.05 was considered statistically significant.

**Results**

For the 166 patients in this study, the mean age and the mean serum hemoglobin value were 71.0 ± 10.0 years and 13.4 ± 2.2 g/dL, respectively. Table 1 compares the clinical and echocardiographic characteristics between anemic and non-anemic patients. The two groups significantly differed in age, history of coronary artery disease, history of congestive heart failure, diastolic blood pressure, total cholesterol, estimated glomerular filtration rate, hemoglobin, use of β-blockers, LAVI, LVMI, E, Ea, and E/Ea.

For all patients, the follow-up period to cardiac events was 20 months (25th-75th percentile: 14-32 months). Forty-nine cardiac events were documented during the follow-up period, including 21 deaths and 28 hospitalizations for heart failure. Table 2 shows the results of a Cox proportional hazards regression analysis of cardiac events. Univariable analysis of adverse cardiac events revealed significant associations with old age, presence of chronic heart failure, diuretic use, decreased body mass index, estimated glomerular filtration rate, hemoglobin (hazard ratio [HR] 0.789; 95% confidence interval [CI] 0.700 to 0.890;
P <0.001), LVEF, and Ea, and increased LVMI, E, E-wave deceleration time, and E/Ea were significantly related to adverse cardiac events. In the multivariable analysis, increased cardiac events had significant independent associations with increased LVMI, decreased body mass index, estimated glomerular filtration rate, and hemoglobin (HR 0.827; 95% CI 0.709 to 0.964; P = 0.015).

Table 1. Comparison of clinical and echocardiographic characteristics between anemic and non-anemic patients

| Characteristics | Anemic patients (n = 54) | Non-anemic patients (n = 112) | P value | All patients (n = 166) |
|-----------------|-------------------------|-----------------------------|--------|----------------------|
| Age (years)     | 74.4 ± 8.0              | 69.4 ± 10.4                 | 0.003  | 71.0 ± 10.0          |
| Male (%)        | 68.5                    | 67.9                        | 0.932  | 68.1                 |
| Diabetes mellitus (%) | 34.0                    | 25.9                        | 0.284  | 28.5                 |
| Hypertension (%) | 63.0                    | 66.1                        | 0.694  | 65.1                 |
| CAD (%)         | 18.9                    | 8.0                         | 0.042  | 11.5                 |
| Stroke (%)      | 15.1                    | 19.6                        | 0.479  | 18.2                 |
| CHF (%)         | 45.3                    | 24.1                        | 0.006  | 30.9                 |
| SBP (mmHg)      | 129.5 ± 21.1            | 133.0 ± 20.3                | 0.355  | 131.9 ± 20.5         |
| DBP (mmHg)      | 71.6 ± 12.5             | 78.4 ± 12.5                 | 0.004  | 76.1 ± 12.8          |
| Heart rate (min⁻¹) | 83.1 ± 21.2             | 83.8 ± 18.9                 | 0.833  | 83.6 ± 19.6          |
| Body mass index (kg/m²) | 25.4 ± 4.4              | 26.3 ± 3.9                  | 0.171  | 26.0 ± 4.1           |
| Triglyceride (mg/dL) | 125.4 ± 84.2           | 118.0 ± 74.4                | 0.615  | 120.2 ± 77.3         |
| Total cholesterol (mg/dL) | 154.9 ± 33.3           | 180.8 ± 35.1                | <0.001 | 172.9 ± 36.5         |
| eGFR (mL/min/1.73 m²) | 45.6 ± 21.0            | 56.2 ± 15.8                 | 0.001  | 53.0 ± 18.1          |
| Hemoglobin (g/dL) | 11.0 ± 1.4              | 14.6 ± 1.2                  | <0.001 | 13.4 ± 2.2           |

Medications

| ACEI and/or ARB (%) | 50.9 | 58.0 | 0.392 | 55.8 |
| β-blocker (%)       | 30.2 | 48.2 | 0.029 | 42.4 |
| CCB (%)             | 30.2 | 35.7 | 0.484 | 35.9 |
| Diuretics (%)       | 52.8 | 38.4 | 0.080 | 43.0 |
| Antiplatelet (%)    | 51.9 | 62.5 | 0.191 | 59.0 |
| Anticoagulant (%)   | 25.9 | 33.9 | 0.298 | 31.3 |

Echocardiographic data

| LAVI (ml/m²) | 52.5 ± 21.1 | 45.7 ± 18.9 | 0.047 | 47.9 ± 19.8 |
| LVMi (g/m²) | 149.7 ± 37.7 | 135.6 ± 41.5 | 0.041 | 140.2 ± 40.7 |
| LVEF (%)    | 53.7 ± 15.5 | 54.5 ± 14.1 | 0.724 | 54.3 ± 14.5 |
| E (cm/s)    | 106.5 ± 23.8 | 92.3 ± 21.1 | <0.001 | 96.8 ± 22.9 |
| EDT (ms)    | 156.5 ± 48.3 | 147.8 ± 45.3 | 0.270 | 150.6 ± 46.3 |
| Ea (cm/s)   | 8.0 ± 2.0    | 9.0 ± 2.5   | 0.009 | 8.7 ± 2.4   |
| E/Ea        | 14.1 ± 5.4   | 11.0 ± 4.0  | <0.001 | 12.0 ± 4.7  |

ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin II receptor blocker; CAD: coronary artery disease; CCB: calcium channel blocker; CHF: chronic heart failure; DBP: diastolic blood pressure; E: early mitral inflow velocity; eGFR: estimated glomerular filtration rate; Ea: early diastolic mitral annulus velocity; EDT: E wave deceleration time; LAVI: left atrial volume index; LVEF: left ventricular ejection fraction; LVMi: left ventricular mass index; SBP: systolic blood pressure.

Table 2. Predictors of cardiac events (all-cause mortality and hospitalization for heart failure) using Cox proportional hazards model

| Parameter             | Univariable          | P value | Multivariable          | P value |
|-----------------------|----------------------|---------|------------------------|---------|
| Age (years)           | 1.042 (1.010, 1.074) | 0.009   | 1.019 (0.975, 1.064)   | 0.406   |
| Male versus female    | 0.858 (0.477, 1.546) | 0.611   | -                      | -       |
| Diabetes mellitus     | 1.259 (0.685, 2.315) | 0.458   | -                      | -       |
| Hypertension          | 1.419 (0.806, 2.499) | 0.226   | -                      | -       |
| CAD (%)               | 0.892 (0.400, 1.989) | 0.780   | -                      | -       |
| Stroke (%)            | 1.121 (0.503, 2.501) | 0.780   | -                      | -       |
| CHF (%)               | 3.475 (1.976, 6.111) | <0.001  | 1.429 (0.656, 3.112)   | 0.368   |
| SBP (mmHg)            | 1.004 (0.988, 1.020) | 0.658   | -                      | -       |
| DBP (mmHg)            | 1.005 (0.980, 1.031) | 0.676   | -                      | -       |
| Heart rate (min⁻¹)    | 1.006 (0.992, 1.021) | 0.377   | -                      | -       |
| Body mass index (kg/m²) | 0.904 (0.835, 0.978) | 0.012   | 0.911 (0.833, 0.998)   | 0.045   |
| Triglyceride (mg/dL)  | 1.000 (0.995, 1.004) | 0.855   | -                      | -       |
| Total cholesterol (mg/dL) | 0.999 (0.990, 1.008) | 0.842   | -                      | -       |
| eGFR (mL/min/1.73 m²) | 0.974 (0.958, 0.990) | 0.002   | 0.986 (0.969, 1.002)   | 0.092   |
| Hemoglobin (g/dL)     | 0.789 (0.700, 0.890) | <0.001  | 0.827 (0.709, 0.964)   | 0.015   |

Medications

| ACEI and/or ARB (%) | 1.119 (0.632, 1.978) | 0.700   | -                      | -       |
| β-blocker (%)       | 0.915 (0.519, 1.614) | 0.760   | -                      | -       |
| CCB (%)             | 0.844 (0.468, 1.521) | 0.572   | -                      | -       |
| Diuretics (%)       | 2.767 (1.536, 4.984) | 0.001   | 1.844 (0.916, 3.713)   | 0.086   |
| Antiplatelet (%)    | 1.143 (0.651, 2.008) | 0.641   | -                      | -       |
Anticoagulant (%) 0.935 (0.502, 1.738) 0.831 -

Echocardiographic data

| Parameter | Value (95% CI)  | P-value | Value (95% CI)  | P-value |
|-----------|-----------------|---------|-----------------|---------|
| LAVI (ml/m²) | 1.009 (0.996, 1.022) | 0.156 | 1.009 (1.001, 1.018) | 0.028 |
| LVMI (g/m²) | 1.013 (1.006, 1.020) | <0.001 | 0.991 (0.961, 1.023) | 0.590 |
| LVEF (%) | 0.962 (0.944, 0.981) | <0.001 | 0.961 (0.961, 1.023) | 0.992 |
| E (cm/s) | 1.014 (1.003, 1.026) | 0.017 | 1.023 (0.996, 1.051) | 0.092 |
| EDT (ms) | 1.006 (1.000, 1.011) | 0.036 | 0.999 (0.992, 1.006) | 0.815 |
| Ea (cm/s) | 0.727 (0.637, 0.830) | <0.001 | 0.762 (0.524, 1.107) | 0.154 |
| E/Ea | 1.116 (1.072, 1.162) | <0.001 | 0.959 (0.813, 1.132) | 0.622 |

HR: hazard ratio; CI: confidence interval; other abbreviations as in Table 1.

Figure 1 compares Kaplan-Meier curves for cardiac event-free survival between anemic and non-anemic patients (Log-rank P < 0.001). The incremental value of hemoglobin level in outcome prediction is shown in Figure 2. The basic clinical model consisted of the potential variables which were related to the adverse cardiac outcomes in the univariable analysis. These variables included age, body mass index, estimated glomerular filtration rate, chronic heart failure, and use of diuretics. The basic clinical model could significantly predict the adverse cardiac events (Chi-square = 44.149, P< 0.001). The addition of LVEF, LVMI, and E/Ea to the basic clinical model could significantly improve the prediction of adverse cardiac events (P <0.001). When hemoglobin was added to the final prediction model including basic clinical model, LVEF, LVMI, and E/Ea, it could significantly improve the prediction of adverse cardiac events (P = 0.010).

Discussion

This study evaluated hemoglobin for associations with cardiac outcomes in AF patients. Statistical analyses revealed that decreased hemoglobin was independently associated with increased cardiac events in the AF patients in this study. Inclusion of serum hemoglobin value significantly increased prognostic value compared to the combination of conventional clinical parameters and echocardiographic parameters.

Anemia is an independent predictor of adverse cardiovascular outcomes in patients with various cardiovascular diseases [8, 9, 33]. In patients with chronic heart failure, anemia is associated with increased severity of symptoms and increased mortality [34]. Treatment with erythropoietin and/or iron supplements can improve exercise tolerance, symptoms, and clinical outcomes in anemic patients with chronic heart failure [34-36]. These managements are associated with improvements in LVEF, New York Heart Association class, plasma B-type natriuretic peptide level, renal function, days of hospitalization, and required dose of diuretics [35-37]. The Atherosclerosis Risk in Communities cohort study of patients with coronary heart disease has also revealed that anemia has an independent association with increased risk (HR 1.41) of poor cardiovascular outcome [8]. However, the effect of blood transfusion in anemic patients
with acute coronary syndrome is complex and controversial [38-40].

Several studies have investigated the relationship between anemia and mortality in patients with AF. In elderly patients with AF, Sharma et al. demonstrated that hematocrit level is an independent predictor of all-cause mortality [14]. An analysis of data in the AFCAS (Atrial Fibrillation undergoing Coronary Artery Stenting) registry by Puurunen et al. revealed that, in AF patients who undergo percutaneous coronary intervention, major adverse cardiac, cerebrovascular, and bleeding events are more likely in those with anemia compared to those without anemias [41]. The 1-year follow-up data in the AFCAS registry further revealed that anemia was an independent predictor of all-cause mortality (HR 1.62).

Our study similarly showed that anemia is a predictor of adverse cardiac events in AF patients. Additionally, left ventricular systolic and diastolic dysfunction [22, 42, 43, 44-46], and left ventricular hypertrophy [47] were significantly associated with high risks of cardiovascular morbidity and mortality in patients with AF. After adjustment for these essential echocardiographic parameters in the present study, serum hemoglobin was still an independent predictor of poor cardiac outcome in AF patients. Furthermore, in a Cox model consisting of the basic clinical model, LVEF, LVMI, and E/Ea, improvement in predicting poor cardiac prognosis in these patients was further increased by including hemoglobin. Hence, even when the conventional clinical and echocardiographic parameters are known, including serum hemoglobin further improves value in predicting cardiac outcome in AF patients.

Anemia is a risk factor in cardiovascular outcome for several reasons. First, chronic anemia is associated with left ventricular hypertrophy and heart failure. Patients with chronic anemia and hemoglobin less than 10 g/dL exhibit several hemodynamic compensatory responses, including high cardiac output, low systemic vascular resistance, sodium and water retention, and reduction of renal blood flow and glomerular filtration rate. These responses may lead to increased cardiac workload and, consequently, left ventricular remodeling [48-50]. An abnormal left ventricular geometry may cause chronic heart failure and increase mortality risk. In the Randomized Etanercept North American Strategy to Study Antagonism of Cytokines (RENAISSANCE) trial, a 1 g/dL increase in hemoglobin was associated with a 4.1 g/m² decrease in left ventricular mass and with a 15.8% reduction in mortality risk over a 24-week period [51]. Second, anemia is also a risk factor for myocardial ischemia in patients with atherosclerosis and a mortality predictor in patients with acute coronary syndrome [8, 12]. In the Atherosclerosis Risk in Communities (ARIC) cohort study, anemia with atherosclerosis was associated with increased risks of cardiovascular disease (HR 1.41) and all-cause mortality (HR 1.65) [8]. In a meta-analysis that included 27 studies, anemia was associated with increased all-cause mortality risk (HR 1.49) in patients with acute coronary syndrome [12]. The present study further found that low hemoglobin is a useful parameter for predicting adverse cardiac events in AF patients after adjusting for important clinical and echocardiographic parameters. Therefore, serum hemoglobin value should be measured in AF patients to improve prognostic value.

**Study limitations**

Most patients in this study received antihypertensive, antiplatelet, and anticoagulant medications for chronic conditions. For ethical reasons, these medications could not be withdrawn. Hence, their effects could not be excluded from this analysis. However, the use of medications was considered in the multivariable analysis. Since the subjects of this study were already being evaluated for heart disease by echocardiography, the generalizability of our conclusions is limited by the potential for selection bias. Other noted limitations are the large number of variables and the small number (49) of outcomes.

**Conclusions**

In patients with AF, hemoglobin is a useful parameter for predicting adverse cardiac events and improves prognostic value when combined with conventional clinical and echocardiographic parameters.

**Competing Interests**

The authors have declared that no competing interest exists.

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