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Influence of hemoglobin concentration on the in-hospital outcomes in newly diagnosed heart failure patients with atrial fibrillation

Finding from CCC-AF (improving care for cardiovascular disease in China-atrial fibrillation) project

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Abstract

Atrial fibrillation (AF) and heart failure (HF) coexistence is common of clinical significance. Although anemia is a well-recognized risk factor for adverse outcomes, the prognostic value of hemoglobin is controversial in AF and HF. We aimed to determine whether hemoglobin is associated with in-hospital outcomes in such patients.

On the basis of the data from the CCC-AF (Improving Care for Cardiovascular Diseases in China-Atrial Fibrillation) project, 2367 inpatients with a definitive diagnosis of AF and HF and record of admission hemoglobin concentration were included. Logistic regression analysis was performed to investigate the relationship between hemoglobin and in-hospital outcomes.

All patients were divided into 4 groups according to quartiles of hemoglobin values. Compared with patients with higher hemoglobin, patients with lower hemoglobin had higher proportion of males, heart rate (HR), and diastolic blood pressure (DBP). On the contrary, they had lower age, medical history, left ventricular ejection fraction (LVEF), and brain natriuretic peptide ($P < .05$). Spearman correlation showed that hemoglobin was negatively correlated with age, LVEF, international normalized ratio, and serum creatinine but positively correlated with HR, DBP, and blood urea nitrogen ($P < .05$). Multivariable logistic regression analysis revealed that increasing hemoglobin was an independent protective factor for in-hospital outcomes (odds ratio = 0.989; 95% confidence interval: 0.979–1.000; $P = .046$).

Admission hemoglobin concentration was an independent protective factor for in-hospital outcomes in HF patients with AF. Our study indicated that increasing hemoglobin level and improving anemia degree might improve the prognosis of patients with AF and HF.

Abbreviations: AF = atrial fibrillation, AUC = area under curve, CCC-AF = Improving Care for Cardiovascular Disease in China-Atrial Fibrillation, CI = confidence intervals, DBP = diastolic blood pressure, HF = heart failure, HR = heart rate, LVEF = left ventricular ejection fraction, MACE = major adverse cardiovascular events, OR = odds ratio, ROC = receiver-operating characteristic, SD = standard deviation.

Keywords: atrial fibrillation, heart failure, hemoglobin, prognosis

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There are no linked research data sets for this submission, because the authors do not have permission to share data.

The data that support the findings of this study are available from a third party, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are available from the authors upon reasonable request and with permission of the third party.

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1. Introduction

Atrial fibrillation (AF) is a common cardiac rhythm disturbance. And heart failure (HF) is one of the most common comorbid chronic conditions, which is observed in more than half among patients with AF.[1] AF is a strong independent risk factor for subsequent development of HF.[2,3] Patients with HF are more likely to develop AF as well.[2,4,5] AF and HF can interact to perpetuate and exacerbate each other through many mechanisms, such as rate-dependent worsening of cardiac function and activation of neurohumoral vasoconstrictors.[1] Therefore, additional attention should be paid to patients with AF and HF.

Anemia is one of the most common and widespread disorders in the world, which affects one-quarter of the world's population.[6] Anemia is defined as a decrease in the concentration of circulating red blood cells or in the hemoglobin concentration and a concomitant impaired capacity to trans oxygen.[7] Anemia is not only a risk factor for cardiovascular disease but also an independent predictor for adverse outcome in various disorders including AF and HF.[8] Several studies have investigated the relationship between cardiovascular outcome and anemia in patients with AF.[9–11] Besides, this association has also been reported in HF.[12–15] But some research has suggested that hemoglobin lost its prognostic value in HF, especially in multivariable analysis.[16–18] And in patients with AF and HF, hemoglobin at admission was not found to be predictive of all-cause death or a composite endpoint either.[19] The prognostic role of hemoglobin in patients with AF and HF needs to be further studied.

The present study was performed to determine the relationship between hemoglobin concentration and the in-hospital outcomes in HF patients with AF in China.

2. Methods

2.1. Study design

The CCC-AF (Improving Care for Cardiovascular Disease in China-AF) project is a nationwide registry and quality improvement study with an ongoing database focusing on quality of AF care. This study was launched in 2015 as a collaborative initiative of the American Heart Association and Chinese Society of Cardiology. Details of the design and methodology of the CCC-AF project have been published.[20] Briefly, a certain number of inpatients with AF are monthly enrolled in 150 hospitals across 30 provinces in China. A web-based data collection platform is used to collect clinical information for patients with AF. The quality improvement initiative, including monthly benchmarked reports on hospital quality, training sessions, regular webinars, and recognitions of hospital quality achievement, ensures data quality.

2.2. Study population

On the basis of principal discharge diagnosis, 31,486 patients with AF from 150 hospitals were registered. Of those, 2543 patients were newly diagnosed HF during this hospitalization. Patients without hemoglobin at admission were excluded. Finally, 2367 with AF and HF combined from February 2015 to June 2017 were included in our study. The flowchart of the analysis is presented in Figure 1. Institutional review board approval was granted for this research by the ethics committee of Beijing Anzhen Hospital, Capital Medical University (IRB number: 2014018). No informed consent was required.

2.3. Information collection

Data collected included patients' demographics, medical history, and results of laboratory testing at admission. Current smokers were defined as people who smoked within 1 year. Harmful use of alcohol was defined as excessive use to the point that it caused damage to health. Family history of AF was defined as patients' first or second-degree relative having AF. Diabetes mellitus was defined as having a history of diabetes or receiving glucose-lowering treatment. Hypertension was defined as having a history of hypertension or taking anti-hypertension medications. Coronary artery disease was defined as having a history of coronary artery disease or receiving revascularization procedure. Body mass index was calculated as dividing weight in kilograms by the square of height in meters. CHADS2 score was calculated by age, congestive HF, hypertension, diabetes, and stroke or transient ischemic attacks.

2.4. In-hospital cardiovascular outcomes

Composite end points, including total mortality, cardiac death, cardiogenic shock, and sudden cardiac arrest, were defined as major adverse cardiovascular events (MACE).

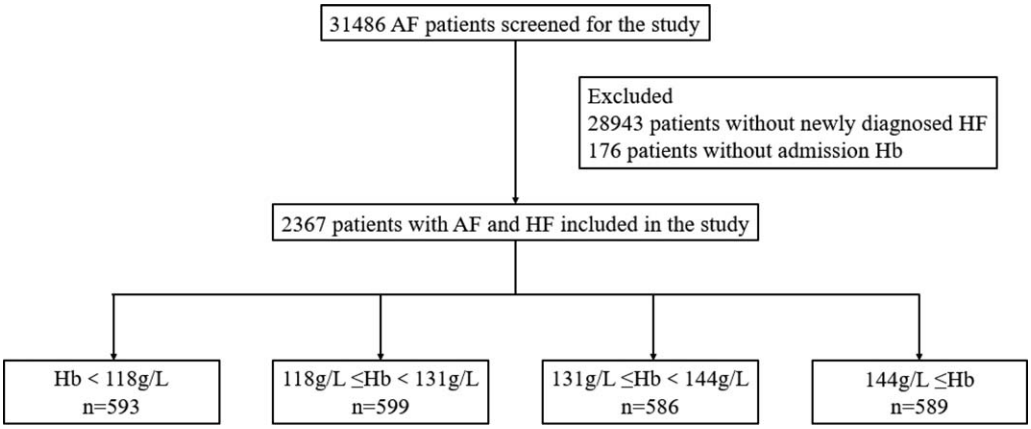

Figure 1. The flowchart of the analysis. AF = atrial fibrillation, Hb = hemoglobin, HF = heart failure.

2.5. Statistical analysis

All patients were divided into 4 groups according to quartiles of hemoglobin. All statistical description was based on quartiles. Continuous variables were presented as mean ± standard deviation (SD). Kolmogorov–Smirnov test was used to test the normality of continuous variables distribution. One-way analysis of variance (ANOVA) and Kruskal–Wallis test were used for the comparisons of continuous variables as appropriate. Categorical variables were shown as frequencies and percentages. χ^2 test was used to analyze the differences between categorical variables. Spearman correlation was conducted to investigate the relationship between hemoglobin and other laboratory tests. Logistic univariate and multivariate regression analysis were performed to determine the relationship between hemoglobin and risk of in-hospital MACE in patients with AF and HF. Sex, smoking, alcohol, family history of AF, diabetes mellitus, hypertension, coronary artery disease, left ventricular hypertrophy, HF, cardiomyopathy, rheumatic heart disease, sinus sick syndrome, cerebrovascular disease, ischemic stroke, hemorrhagic stroke, peripheral arterial disease, deep vein thrombosis, upper gastrointestinal bleeding, pacemaker, heart rate, K were adjusted in the multivariate regression model. The area under curve (AUC) value, optimal cutoff value, specificity, and sensitivity were determined using receiver-operating characteristic (ROC) curve. Odds ratio (OR) and 95% confidence interval (95% CI) were reported. All computations were performed with SPSS software v20.0 (SPSS Inc., Chicago, IL). A statistically significant difference was defined at $P < .05$ using a 2-tailed test.

3. Results

3.1. Clinical characteristics

The hemoglobin was 130.49 ± 23.41 g/L and quartiles were 118.00, 131.00, and 144.00 g/L across study population. Kolmogorov–Smirnov test showed that hemoglobin values were not normal distribution ($P < .001$) (Fig. 2).

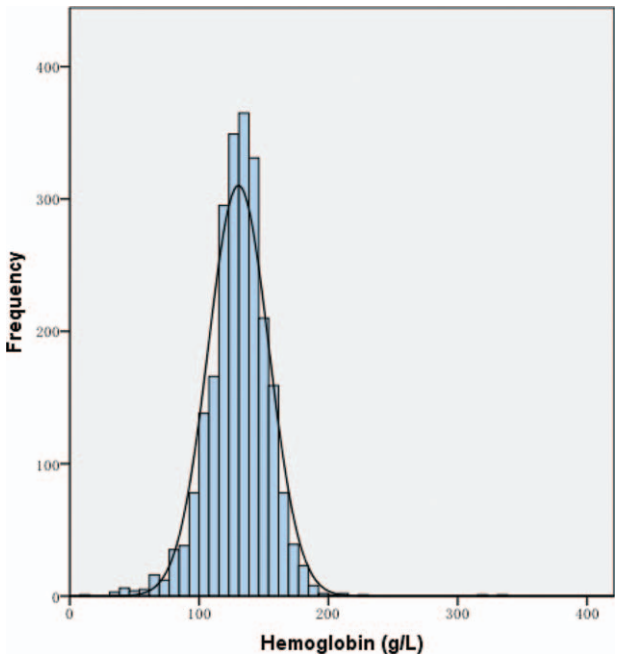

Figure 2. Distribution of hemoglobin values across study population.

Two thousand three hundred sixty-seven patients were divided into 4 groups according to quartiles of hemoglobin values at admission. The main clinical characteristics are summarized in Table 1. 52.0% were males and the proportion of males was higher in the higher quartile group ($P < .001$). The mean age was 70.38 ± 12.06 years and patients were younger with the increasing of hemoglobin ($P < .001$). In the higher quartile group, patients had less rheumatic heart disease, cerebrovascular disease, and upper gastrointestinal hemorrhage history ($P < .05$). Besides, patients with higher hemoglobin had significantly higher body mass index, heart rate, diastolic blood pressure, but lower left ventricular ejection fraction and brain natriuretic peptide ($P < .05$). However, intergroup comparison revealed no significant differences with respect to family history of AF, history of diabetes mellitus, hypertension, coronary artery disease, left ventricular hypertrophy, HF, cardiomyopathy, sinus sick syndrome, ischemia stroke, hemorrhagic stroke, peripheral arterial disease, deep vein thrombosis, pacemaker, systolic blood pressure, blood urea nitrogen, international normalized ratio, Mg, pro-brain natriuretic peptide, and CHADS2 score among patients with different hemoglobin levels.

3.2. Correlation between variables

Next, Spearman correlation was conducted to investigate the relationship between hemoglobin and other laboratory tests at admission and results are summarized in Table 2. Admission hemoglobin was significantly negatively correlated with age ($R^2 = 0.067$; 95% CI -0.154 to 0.114; $P < .001$), left ventricular ejection fraction ($R^2 = 0.028$; 95% CI -0.113–0.066; $P < .001$), international normalized ratio ($R^2 = 0.003$; 95% CI -0.003 to 0.001; $P = .010$), and serum creatinine ($R^2 = 0.016$; 95% CI -0.468 to 0.245; $P < .001$). In addition, hemoglobin was significantly positively correlated with body mass index ($R^2 = 0.040$; 95% CI 0.026–0.045; $P < .001$), heart rate ($R^2 = 0.006$; 95% CI 0.045–0.139; $P < .001$), diastolic blood pressure ($R^2 = 0.026$; 95% CI 0.080–0.131; $P < .001$), and blood urea nitrogen ($R^2 = 0.006$; 95% CI 2.290–20.142; $P = .014$). However, no significant relations were found between hemoglobin and systolic blood pressure, K, Mg, brain natriuretic peptide, or pro-brain natriuretic peptide ($P < .05$).

3.3. In-hospital MACE

The mean hospital stay was 11 days (interquartile range: 7–13 days). During this hospitalization, 77 (3.3%) patients had MACE, including 38 (1.6%) total mortality, 30 (1.3%) cardiac death, 56 (2.4%) cardiogenic shock, and 27 (1.1%) sudden cardiac arrest. Details of every endpoint in patients with different admission hemoglobin levels are summarized in Table 3.

Logistic regression analysis was performed to determine the relationship between admission hemoglobin value and the risk of in-hospital MACE in patients with AF and HF. In univariate analysis, hemoglobin was significantly associated with a decreased risk of MACE (OR = 0.985; 95% CI: 0.976–0.994; $P = .001$). After adjustment for other variates we collected, admission hemoglobin value was still an independent protective factor for in-hospital MACE in patients with AF and HF (OR = 0.989; 95% CI: 0.979–1.000; $P = .046$). Other variables, which were independently related with the risk of MACE, are listed in Table 4.

Table 1

Clinical characteristics by hemoglobin level.

Variable	All patients N = 2367	Quartile 1 n = 593 -118g/L	Quartile 2 n = 599 118–131 g/L	Quartile 3 n = 586 131–144 g/L	Quartile 4 n = 589 144 g/L	*P*
Hemoglobin, g/L	130.49 ± 23.41	101.27 ± 16.17	125.29 ± 3.63	127.92 ± 3.83	157.79 ± 14.96	<.001
Males	1230 (52.0)	219 (36.9)	249 (41.6)	323 (55.1)	439 (74.5)	<.001
Age, years	70.38 ± 12.06	74.07 ± 11.35	72.61 ± 11.03	69.37 ± 11.42	65.40 ± 12.53	<.001
Smoking	502 (21.2)	78 (13.2)	97 (16.2)	130 (22.2)	197 (33.4)	<.001
Alcohol	273 (11.5)	37 (6.2)	46 (7.7)	71 (12.1)	119 (20.2)	<.001
Family history of atrial fibrillation	14 (0.6)	4 (0.7)	3 (0.5)	1 (0.2)	6 (1.0)	.290
Past medical history						
Diabetes mellitus	383 (16.2)	88 (14.8)	101 (16.9)	103 (17.6)	91 (15.4)	.559
Hypertension	1150 (48.6)	305 (51.4)	292 (48.7)	265 (45.2)	288 (48.9)	.203
Coronary artery disease	681 (28.8)	162 (27.3)	176 (29.4)	183 (31.2)	160 (27.2)	.363
Left ventricular hypertrophy	5 (0.2)	2 (0.3)	1 (0.2)	1 (0.2)	1 (0.2)	.897
Heart failure	637 (26.9)	162 (27.3)	160 (26.7)	163 (27.8)	152 (25.8)	.880
Cardiomyopathy	129 (5.4)	26 (4.4)	28 (4.7)	32 (5.5)	43 (7.3)	.116
Rheumatic heart disease	244 (10.3)	87 (14.7)	62 (10.4)	56 (9.6)	39 (6.6)	<.001
Sinus sick syndrome	12 (0.5)	1 (0.2)	3 (0.5)	4 (0.7)	4 (0.7)	.562
Cerebrovascular disease	332 (14.0)	98 (16.5)	93 (15.5)	70 (11.9)	71 (12.1)	.042
Ischemia stroke	267 (11.3)	79 (13.3)	74 (12.4)	57 (9.7)	57 (9.7)	.218
Hemorrhagic stroke	32 (1.4)	8 (1.3)	12 (2.0)	5 (0.9)	7 (1.2)	.118
Peripheral arterial disease	38 (1.6)	10 (1.7)	12 (2.0)	9 (1.5)	7 (1.2)	.731
Deep vein thrombosis	19 (0.8)	5 (0.8)	6 (1.0)	4 (0.7)	4 (0.7)	.912
Upper gastrointestinal bleeding	29 (1.2)	15 (2.5)	4 (0.7)	6 (1.0)	4 (0.7)	.009
Pacemaker	73 (3.1)	21 (3.5)	20 (3.3)	21 (3.6)	11 (1.9)	.267
Laboratory test						
Body mass index, kg/m^2	24.07 ± 4.17	22.49 ± 3.68	23.94 ± 4.13	24.70 ± 4.03	25.08 ± 4.33	<.001
Heart rate, bpm	94.81 ± 27.22	91.79 ± 26.69	95.23 ± 28.37	95.26 ± 27.09	96.95 ± 26.47	.015
Systolic blood pressure, mm Hg	130.49 ± 22.08	130.76 ± 22.62	131.08 ± 23.08	129.06 ± 21.29	131.02 ± 21.23	.320
Diastolic blood pressure, mm Hg	79.97 ± 15.13	76.79 ± 15.21	79.42 ± 15.67	80.64 ± 14.12	83.06 ± 14.82	<.001
Left ventricular ejection fraction, %	50.80 ± 12.68	53.76 ± 11.54	52.01 ± 12.05	50.15 ± 12.86	47.37 ± 13.30	<.001
Serum creatinine, μmol/L	96.71 ± 64.59	112.92 ± 102.32	90.08 ± 47.08	89.92 ± 38.10	93.64 ± 45.67	<.001
Blood urea nitrogen, μmol/L	5020.58 ± 2929.52	4541.24 ± 3205.96	5195.33 ± 2830.54	5098.39 ± 2030.02	5179.21 ± 2848.53	.185
International normalized ratio	1.31 ± 0.63	1.37 ± 0.82	1.32 ± 0.64	1.29 ± 0.50	1.26 ± 0.52	.112
K, mmol/L	4.13 ± 0.80	4.15 ± 0.70	4.05 ± 0.57	4.11 ± 0.74	4.20 ± 1.10	.010
Mg, mmol/L	0.89 ± 0.55	0.92 ± 0.90	0.88 ± 0.19	0.92 ± 0.59	0.85 ± 0.13	.689
Brain natriuretic peptide, pg/mL	1590.42 ± 3999.91	1989.52 ± 5945.61	2105.88 ± 4412.19	1202.51 ± 2119.14	1049.18 ± 1558.15	.037
Pro- brain natriuretic peptide, pg/mL	4543.86 ± 5973.71	5508.08 ± 7551.76	4176.69 ± 5294.01	3858.66 ± 4840.36	4726.71 ± 5902.76	.093
CHADS2 score	2.51 ± 1.30	2.52 ± 1.34	2.73 ± 1.24	2.51 ± 1.29	2.28 ± 1.31	.134

Data are presented as mean ± SD or number (%).

Finally, ROC curve was used to assess the prognostic value of hemoglobin for MACE and the result is shown in Figure 3 (AUC = 0.383; 95% CI: 0.317–0.450; *P* = .001). In addition, the optimal cutoff value of hemoglobin for MACE was 117.98 g/L, with a specificity of 83.8% and sensitivity of 44.9%.

Table 2

Correlation of hemoglobin with other laboratory tests.

Variable	Adjusted R square	Coefficient	95% confidence intervals		Standard error of measurement	*P*
Age	0.067	−0.134	−0.154	−0.114	0.010	<.001
Body mass index	0.040	0.036	0.026	0.045	0.005	<.001
Heart rate	0.006	0.092	0.045	0.139	0.024	<.001
Systolic blood pressure	<0.001	0.007	−0.032	0.045	0.019	.738
Diastolic blood pressure	0.026	0.105	0.080	0.131	0.013	<.001
Left ventricular ejection fraction	0.028	−0.089	−0.113	−0.066	0.012	<.001
International normalized ratio	0.003	−0.002	−0.003	<0.001	0.001	.010
Serum creatinine	0.016	−0.357	−0.468	−0.245	0.057	<.001
Blood urea nitrogen	0.006	11.216	2.290	20.142	4.547	.014
K	<0.001	<0.001	−0.001	0.002	0.001	.630
Mg	<0.001	<0.001	−0.002	0.001	0.001	.514
Brain natriuretic peptide	0.003	−9.934	−20.730	0.861	5.499	.071
Pro-brain natriuretic peptide	0.002	−14.858	−32.435	2.720	8.957	.097

Table 3

In-hospital major adverse cardiovascular events of patients with atrial fibrillation and heart failure according to the quartiles of admission hemoglobin values.

Outcome	All patients	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*P*
MACE	77 (3.3)	28 (4.7)	24 (4.0)	13 (2.2)	12 (2.0)	.019
Total mortality	38 (1.6)	18 (3.0)	11 (1.8)	5 (0.9)	4 (0.7)	.004
Cardiac death	30 (1.3)	13 (2.2)	9 (1.5)	4 (0.7)	4 (0.7)	.056
Cardiogenic shock	56 (2.4)	19 (3.2)	16 (2.7)	11 (1.9)	10 (1.7)	.285
Sudden cardiac arrest	27 (1.1)	10 (1.7)	9 (1.5)	3 (0.5)	5 (0.8)	.190

Data are presented as number (%).
MACE = major adverse cardiovascular events.

Table 4

Multivariate logistic regression analysis of in-hospital major adverse cardiovascular events.

Variable	Odds ratio	95% Confidence interval		*P*
Hemoglobin	0.989	0.979	1.000	.046
Age	1.030	1.007	1.054	.012
Systolic blood pressure	0.980	0.969	0.992	.001
Serum creatinine	1.003	1.001	1.005	.001

Adjusted for sex, smoking, alcohol, family history of atrial fibrillation, diabetes mellitus, hypertension, coronary artery disease, left ventricular hypertrophy, heart failure, cardiomyopathy, rheumatic heart disease, sinus sick syndrome, cerebrovascular disease, ischemic stroke, hemorrhagic stroke, peripheral arterial disease, deep vein thrombosis, upper gastrointestinal bleeding, pacemaker, heart rate, K.

4. Discussion

AF and HF coexistence is common of clinical significance, which produces immense health and economic burdens. Although anemia is a risk factor for adverse outcomes in AF and HF, the prognostic value of hemoglobin in patients with AF and HF is still controversial. Our present study was a nationwide, multicenter study in China and found that hemoglobin at admission was an independent protective factor of in-hospital MACE in patients with AF and HF. To the best of our knowledge, our study is one of the largest analyses on the association between hemoglobin concentration and in-hospital outcomes in patients with AF and HF.

Anemia, which is defined as a decrease in the hemoglobin concentration, is a well-recognized risk factor for cardiovascular outcome in various disorders including AF and HF.[7,8] As a diagnostic criterion of anemia, the prognostic value of hemoglobin

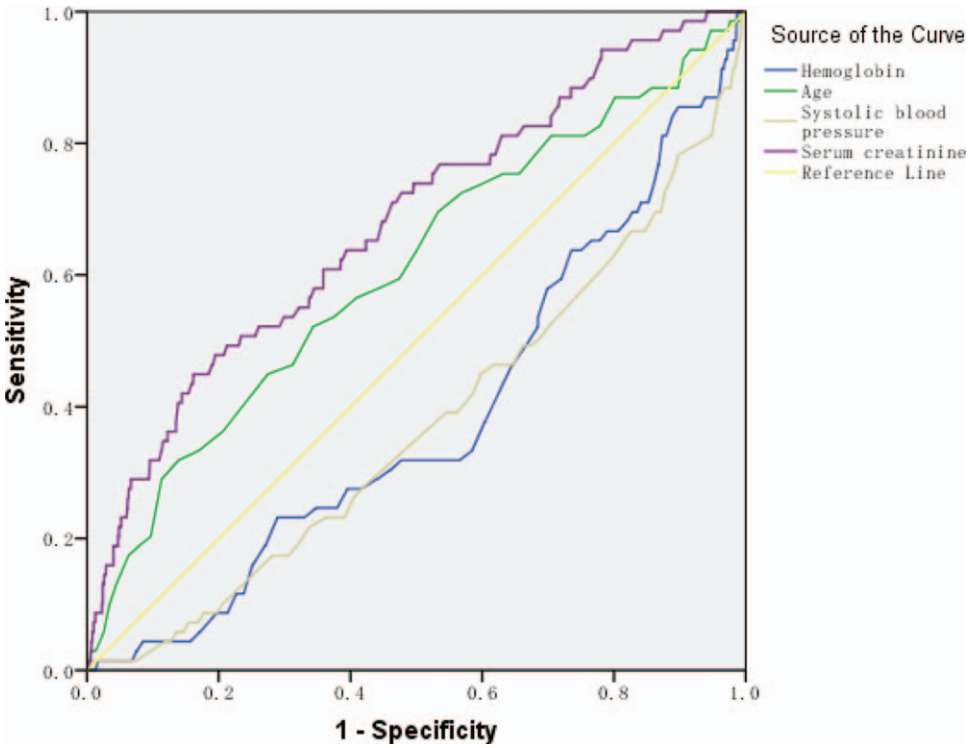

Figure 3. Receiver-operating characteristic curve was used to evaluate the prognostic value of hemoglobin for MACE.

has been investigated in AF and Hufford example, an analysis of 219 older Chinese patients with AF indicated that hemoglobin was significantly associated with all-cause mortality.[21] And Metra et al[22] and Argan et al[23] found that hemoglobin was also an independent protective factor for adverse outcomes in HF. However, several studies showed that hemoglobin lost its prognostic value in HF.[16,17,19,24–27] In addition, Ozierański et al[19] showed that hemoglobin at admission was not a predictor of death at 1 year in HF patients with AF. Discrepant results indicate that the prognostic role of hemoglobin needs to be further determined, especially in patients with AF and HF combined. In our present study, we found that admission hemoglobin was an independent protective factor for in-hospital adverse cardiovascular outcomes in patients with AF and HF.

Hemoglobin is contained in the red blood cells and deliver oxygen from the lung to the far reaches of the body. The biological significance of hemoglobin is well-illustrated by anemia, the most prominent characteristic of which is the decrease of hemoglobin.[28] Reduced oxygen delivery to metabolizing tissues in anemia triggers a host of hemodynamic, neurohormonal, and renal alterations, leading to increased myocardial workload.[29] In our current study, we showed that patients with lower hemoglobin level had lower cardiac output, more severe myocardial injury, and worse renal function. Chronic anemia could cause adverse left ventricular remodeling and hypertrophy, which is undoubtedly of a double blow for HF patients.[29] And treatment of anemia in patients with HF can improve clinical outcomes through lots of aspects, including improvements in cardiac function, renal function, and required dose of diuretics.[30–32] The pros and cons of evidences indicated that improving anemia and increasing hemoglobin levels were of vital importance in patients with HF.

In addition, we also found other variables that were independent risk or protective factors for in-hospital outcomes in patients with AF and HF. One of the most remarkable observation was serum creatinine. Our results showed that serum creatinine was an independent risk factor for in-hospital MACE in HF patients with AF (OR = 1.003; 95% CI: 1.001–1.005; $P = .001$). Creatinine, as a metabolomics biomarker with pathophysiological implication for impaired renal function, is a potent predictor of adverse outcomes in both HF and AF patients.[33–36] And our paper first reported the prognostic role of creatinine in HF patients with AF. Besides, it has been reported that more than half of patients with severe chronic kidney disease had anemia.[37] We also showed that there was a significantly negatively relationship between hemoglobin and creatinine ($R^2 = 0.016$; 95% CI -0.468 to 0.245; $P < .001$), which indicated that treating anemia was necessary for improving prognosis, especially for patients with kidney disease combined.

One of the greatest strengths of our study is the sample, which is large and representative of the China AF population. In addition, the quality of data in the CCC-AF project was high due to a series of quality improvement initiative.

The current study has several limitations. First, hemoglobin was available only at a single point in time (at admission), which limited analysis of the effect of change in hemoglobin on the in-hospital outcomes. Second, although we adjusted for many variables in our multivariable logistic regression analysis, the observed association between hemoglobin and outcomes in part reflects residual confounding. Third, we only investigated the relationship between hemoglobin and the risk of in-hospital outcomes. Longer follow-up is needed to determine the prognostic value of hemoglobin.

In conclusion, hemoglobin at admission was associated with decreased risk of in-hospital outcomes in patients with AF and HF combined. Our results indicated that increasing hemoglobin level and improving anemia degree might improve the prognosis of patients with AF and HF.

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Author contributions

M. Dong, Z. Yuan, and J. Zhou conceived and designed the study; M. Dong and C. Xu collected data; M. Dong analyzed data; M. Dong and J. Zhou wrote the paper. All authors read, critically revised, and approved the final manuscript.
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Data curation: Mengya Dong, Chenbo Xu.
Methodology: Mengya Dong.
Writing – original draft: Mengya Dong.
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