

Association of hemoglobin with incidence of in-hospital cardiac arrest in patients with acute coronary syndrome complicated by cardiogenic shock

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Abstract

Objective: This study was performed to investigate the association of the admission hemoglobin level with the incidence of in-hospital cardiac arrest (IHCA) in patients with acute coronary syndrome (ACS) complicated by cardiogenic shock (CS).

Methods: In this retrospective study, we reviewed the medical records of consecutive patients with ACS complicated by CS admitted to the coronary care unit from January 2014 to October 2017. Logistic regression models were carried out to evaluate the association between hemoglobin and the incidence of IHCA. Interaction and subgroup analyses were also performed.

Results: In total, 211 patients were included in the study, and 61 (28.9%) patients developed IHCA. In the multivariable analysis, hemoglobin was a strong independent predictor of IHCA (odds ratio, 0.971; 95% confidence interval, 0.954–0.989). In the fully adjusted model, patients in the higher hemoglobin tertile were less likely to develop IHCA than patients in the lowest hemoglobin tertile (odds ratio, 0.194; 95% confidence interval, 0.071–0.530). The relationship remained stable in most subgroups except patients aged ≥ 70 years.

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Conclusion: In patients with ACS complicated by CS, the incidence of IHCA is related to the hemoglobin concentration, and a high hemoglobin concentration is a protective factor against the development of IHCA.

Keywords

Hemoglobin, in-hospital cardiac arrest, incidence, predictor, acute coronary syndrome, cardiogenic shock

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Abbreviations

IHCA, in-hospital cardiac arrest; ACS, acute coronary syndrome; CS, cardiogenic shock; CCU, coronary care unit; BNP, brain natriuretic peptide; OR, odds ratio; CI, confidence interval.

Introduction

In-hospital cardiac arrest (IHCA) is defined as cessation of cardiac activity as confirmed by the absence of signs of circulation in a hospitalized patient who had a pulse at the time of admission.¹ Because survival to discharge after IHCA remains poor (10%–22%),^{2–6} prevention of this event is crucial. Although systematic research has been performed in an attempt to prevent cardiac arrest by recognizing clinical deterioration in patients, the incidence of IHCA has remained largely unchanged.^{7–10} Additional studies are needed to reduce the incidence rate.

Several studies have shown that patients with hemodynamic instability are more liable to develop cardiac arrest.^{11–13} Cardiogenic shock (CS) is a condition of hemodynamic instability with particularly high mortality.^{14–16} CS is defined as a state of end-organ hypoperfusion due to reduced cardiac output, and it is caused by acute coronary syndrome (ACS).^{14,15,17} Thus, it is necessary to identify patients

with CS who have a high risk of developing cardiac arrest, especially IHCA.

Respiratory problems and deterioration of the mental status are considered predictors of IHCA.^{11–13} However, data on the association between anemia and IHCA are sparse. Previous studies have shown that anemia is closely associated with a high risk of cardiovascular adverse events.^{18–21} Thus, we hypothesized that patients with a low hemoglobin level are more likely to develop IHCA. In this study, we investigated the relationship between the hemoglobin level and the incidence of IHCA in patients admitted with ACS complicated by CS.

Materials and methods

Population

This retrospective study was performed at the First Affiliated Hospital of Wenzhou Medical University. Patients were included if they had been diagnosed with ACS and admitted to the coronary care unit (CCU) from January 2014 to October 2017. To investigate the prognostic role of the hemoglobin level in patients with CS, patients who did not meet the diagnostic criteria for CS were excluded. To identify patients with CS, we used the following three criteria of the Intraaortic Balloon Pump in Cardiogenic Shock II trial¹⁴: systolic blood pressure of

<90 mmHg for ≥ 30 minutes or the need for catecholamines to maintain the systolic blood pressure at >90 mmHg, clinical pulmonary congestion, and impaired end-organ perfusion (altered mental status, cold/clammy skin and extremities, urine output of <30 mL/h, or lactate level of >2.0 mmol/L). Because this was a retrospective study based on medical records, ethics approval and written informed consent were not obtained.

Data collection

Each patient's clinical data (demographic data, medical history, and vital signs) were collected upon admission to the CCU. Patients were considered to have hypertension or diabetes mellitus based on a previous diagnosis in their medical records or a history of use of related drugs. Blood samples were also collected upon admission. Laboratory data were obtained from the electronic medical record system. Echocardiography and electrocardiography were performed within the first 72 hours, and the left ventricular ejection fraction was recorded. All of the main treatments and surgeries performed before IHCA were recorded.

Definition of IHCA

According to the guidelines (the Utstein Style for in-hospital resuscitation research) that were established to assure a uniform standard for management of IHCA, we diagnosed IHCA in patients who had a pulse at the time of admission but subsequently had no detectable pulse, were unresponsive, and exhibited apnea or agonal respirations.¹

Statistical methods

The tertiles of the whole population were categorized separately as follows: T1, hemoglobin of ≤ 112 g/L; T2, hemoglobin of 113 to 133 g/L; and T3, hemoglobin of ≥ 134 g/L. We established multiple logistic regression models to evaluate the associations between

the hemoglobin level and the incidence of IHCA. Both unadjusted and multivariate adjusted models were applied. Model 1 was a univariate analysis for hemoglobin. Model 2 was used to estimate the odds for hemoglobin after adjusting for sex and age. Model 3 was adjusted for sex, age, coronary revascularization, hypertension, diabetes mellitus, ventricular arrhythmias at admission, brain natriuretic peptide (BNP), creatinine, and lactate. We selected these confounders on the basis of their associations with outcomes or a change in the effect estimate of >10%. The odds ratios (ORs) with 95% confidence intervals (CIs) and P values for IHCA were reported after adjusting for confounding variables across each tertile of the hemoglobin concentration.

Interaction and subgroup analyses were performed in different groups: age (<70 and ≥ 70 years), sex (male and female), smoking status (never-smokers and smokers), ventricular arrhythmias at admission, hypertension, diabetes mellitus, and other factors. All confounding variables were adjusted in each stratification (sex, age, coronary revascularization, hypertension, diabetes mellitus, ventricular arrhythmias, BNP, creatinine, and lactate) except the stratification factor itself.

Continuous variables are presented as mean \pm standard deviation or median (interquartile range) for variables with a skewed distribution. Categorical variables are presented as number and percentage. The characteristics of the study population according to hemoglobin trisectors were compared using one-way analysis of variance or the Kruskal-Wallis test for continuous variables and the X^2 test for categorical variables. All tests were two-sided, and a P value of <0.05 was considered significant. Analyses were performed using the statistical software packages R (<http://www.R-project.org>) and EmpowerStats (X&Y Solutions, Inc., Boston, MA, USA; <http://www.empowerstats.com>).

Results

Baseline characteristics of study population

In total, 1900 patients admitted to the CCU for ACS in the First Affiliated Hospital of Wenzhou Medical University were initially enrolled in the study. After exclusion of patients who did not satisfy the CS criteria, 211 patients with CS were considered eligible for the main analyses of the association between the hemoglobin level and the incidence of IHCA. The distribution of the baseline hemoglobin level is shown in Figure 1. The patients were classified into three groups by hemoglobin level: T1 (≤ 112 g/L), T2 (113–133 g/L), and T3 (≥ 134 g/L). Table 1 shows the characteristics of the overall study population and the characteristics of patients according to their tertile measurements of hemoglobin. A total of 61 (28.9%) patients developed IHCA among all 211 patients. In the T1 group (≤ 112 g/L), 28 (40.6%) of 69

patients developed IHCA, while in the T3 group (≥ 134 g/L), only 13 (17.6%) of 74 patients developed IHCA. Overall, the patients' mean age was 69.6 ± 12.3 years, and 138 (65.4%) were men. More than half of the patients had hypertension (61.1%). The patients' medical history also included a smoking history in 69 (32.7%) patients, a drinking history in 31 (14.7%), diabetes mellitus in 73 (34.6%), and ventricular arrhythmia at admission in 46 (21.8%). Compared with patients in the T1 group, those in T3 were younger, had a male preponderance, and had a lower incidence of hypertension. Vital signs at admission, laboratory test results, echocardiography indices, and surgery-related data during the hospital stay are shown in Table 1.

Association between hemoglobin and prevalence of IHCA

As illustrated in Table 2, the univariate analysis suggested that the hemoglobin

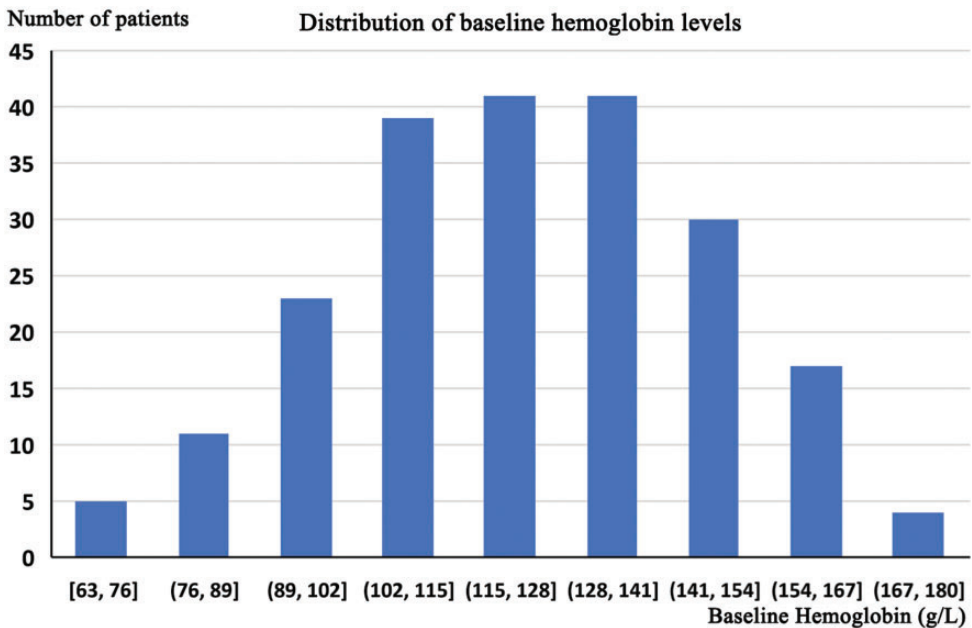


Figure 1. Distribution of baseline hemoglobin levels.

Table 1. Characteristics of study patients.

Characteristics	Overall	Tertiles of hemoglobin (g/L) among all 211 patients			P value
		T1 (≤112)	T2 (113–133)	T3 (≥134)	
Patients, n	211	69	68	74	
IHCA	61 (28.9)	28 (40.6)	20 (29.4)	13 (17.6)	0.010
Demographics					
Age, years	69.6 ± 12.3	73.5 ± 11.5	71.3 ± 10.5	64.4 ± 13.0	<0.001
Male	138 (65.4)	33 (47.8)	39 (57.4)	66 (89.2)	<0.001
Medical history					
Hypertension	129 (61.1)	49 (71.0)	41 (60.3)	39 (52.7)	0.079
Diabetes mellitus	73 (34.6)	21 (30.4)	26 (38.2)	26 (35.1)	0.626
Smoking	69 (32.7)	11 (15.9)	17 (25.0)	41 (55.4)	<0.001
Drinking	31 (14.7)	7 (10.1)	7 (10.3)	17 (23.0)	0.044
Ventricular arrhythmia	46 (21.8)	11 (15.9)	13 (19.1)	22 (29.7)	0.111
Surgery					
Coronary revascularization	153 (72.5)	45 (65.2)	50 (73.5)	58 (78.4)	0.206
Stent	135 (64.0)	38 (55.1)	44 (64.7)	53 (71.6)	0.118
PTCA	91 (43.1)	31 (44.9)	29 (42.6)	31 (41.9)	0.931
Thrombus aspiration	44 (20.9)	10 (14.5)	15 (22.1)	19 (25.7)	0.247
IABP	40 (19.0)	12 (17.4)	13 (19.1)	15 (20.3)	0.907
Laboratory tests					
BNP, ng/L	490.0 (122.5–1970.0)	1287.0 (266.0–3176.0)	535.0 (129.2–1927.5)	223.5 (70.5–920.5)	<0.001
Creatinine, μmol/L	113.0 (78.0–168.0)	135.0 (84.0–228.0)	109.5 (71.0–136.2)	114.0 (79.0–159.5)	<0.001
CRP, mg/L	42.3 (13.7–76.8)	46.6 (21.6–77.8)	26.9 (10.9–65.2)	43.1 (13.6–84.8)	0.187
Lactate, mmol/L	3.9 (2.5–6.8)	2.9 (1.8–6.8)	4.0 (2.5–5.7)	4.5 (3.2–7.3)	0.275
Uric acid, μmol/L	441.0 (363.2–592.5)	475.0 (340.0–590.5)	428.5 (381.5–562.8)	438.5 (366.2–620.0)	0.825
D-dimers, mg/L	2.0 (1.2–4.9)	1.9 (1.4–5.5)	1.7 (1.1–3.5)	2.1 (1.3–6.3)	0.231
Procalcitonin, ng/L	0.2 ± 0.1	0.2 ± 0.1	0.2 ± 0.1	0.2 ± 0.1	0.105
Potassium, mmol/L	4.1 ± 0.7	4.1 ± 0.8	4.1 ± 0.6	4.0 ± 0.7	0.785
INR	1.3 ± 0.4	1.4 ± 0.5	1.3 ± 0.2	1.3 ± 0.4	0.660

(continued)

Table 1. Continued.

Characteristics	Tertiles of hemoglobin (g/L) among all 211 patients			P value
	T1 (≤ 112)	T2 (113–133)	T3 (≥ 134)	
Overall				
Echocardiography				
LVEF, %	41.1 \pm 9.2	42.3 \pm 9.2	40.4 \pm 8.9	0.474
LVEDD, mm	50.9 \pm 6.5	49.6 \pm 6.6	50.6 \pm 5.8	0.038
Vital signs at admission				
Temperature, °C	37.0 \pm 0.7	36.8 \pm 0.7	37.0 \pm 0.6	0.063
Heart rate, beats/min	98.6 \pm 23.1	97.6 \pm 26.4	103.7 \pm 22.1	0.039
SBP, mmHg	110.1 \pm 24.5	107.8 \pm 23.6	111.8 \pm 25.8	0.618
DBP, mmHg	68.0 \pm 16.2	67.2 \pm 15.2	71.0 \pm 17.8	0.119
Respiratory rate, breaths/min	21.7 \pm 6.2	20.7 \pm 5.8	22.2 \pm 6.6	0.296

Data are presented as n (%), mean \pm standard deviation, or median (interquartile range). Abbreviations: IHCA, in-hospital cardiac arrest; PTCA, percutaneous transluminal coronary angioplasty; IABP, intra-aortic balloon pump; BNP, brain natriuretic peptide; CRP, C-reactive protein; INR, international normalized ratio; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic dimension; SBP, systolic blood pressure; DBP, diastolic blood pressure.

concentration was a strong independent predictor of IHCA (OR, 0.979; 95% CI, 0.966–0.992; $P=0.002$) when hemoglobin was analyzed as a continuous variable. After adjusting for sex and age, the multivariate analysis revealed that the hemoglobin concentration was still closely associated with the incidence of IHCA (OR, 0.976; 95% CI, 0.962–0.990; $P=0.001$). Furthermore, the OR of model 3 (adjusted for sex, age, coronary revascularization, hypertension, diabetes mellitus, ventricular arrhythmias, BNP, creatinine, and lactate) was 0.971 (95% CI, 0.954–0.989; $P=0.001$).

Different incidence of IHCA between patients with higher and lower hemoglobin concentrations

As presented in Table 2 and Figure 2, the multivariate analysis suggested that the risk of IHCA in the T3 group was lower (OR, 0.312; 95% CI, 0.145–0.672; $P=0.003$) with T1 as a reference in the unadjusted model. When sex and age were adjusted, however, the prevalence of IHCA became higher (OR, 0.257; 95% CI, 0.111–0.597; $P=0.002$) with T1 as a reference. Furthermore, in model 3 (adjusted for sex, age, coronary revascularization, hypertension, diabetes mellitus, ventricular arrhythmias, BNP, creatinine, and lactate), patients in the T3 group were less likely to develop IHCA (OR, 0.194; 95% CI, 0.071–0.530; $P=0.001$) with T1 as a reference. Although the OR for T2 compared with T1 was not statistically significant, the overall trend was that patients with a higher hemoglobin level were less likely to develop IHCA (all P for trend <0.01).

Subgroup analyses

The results of the interaction and stratified analyses are shown in Figure 3. The relationship between hemoglobin and IHCA

Table 2. Association between hemoglobin concentration and incidence of in-hospital cardiac arrest

	Events/incidence	Model 1		Model 2		Model 3	
		OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
All patients (N = 211)							
Continuous	61/28.9%	0.979 (0.966–0.992)	0.002	0.976 (0.962–0.990)	0.001	0.971 (0.954–0.989)	0.001
T1 (n = 69)	28/40.6%	Ref		Ref		Ref	
T2 (n = 68)	20/29.4%	0.610 (0.300–1.240)	0.172	0.576 (0.279–1.192)	0.137	0.572 (0.252–1.300)	0.182
T3 (n = 74)	13/17.6%	0.312 (0.145–0.672)	0.003	0.257 (0.111–0.597)	0.002	0.194 (0.071–0.530)	0.001

Model 1: unadjusted.

Model 2: adjusted for sex and age.

Model 3: adjusted for sex, age, coronary revascularization, hypertension, diabetes mellitus, ventricular arrhythmias, brain natriuretic peptide, creatinine, and lactate.

Tertiles of hemoglobin: T1 (≤ 112 g/L), T2 (113–133 g/L), T3 (≥ 134 g/L).

Abbreviations: OR, odds ratio; CI, confidence interval; Ref, reference.

remained stable in most subgroups except patients aged ≥ 70 years. There was a significant association between hemoglobin and IHCA in patients aged < 70 years ($P = 0.001$), but not in patients aged ≥ 70 years (Figure 3). The interaction between an age of < 70 and ≥ 70 years was significant (P for interaction = 0.021). The interactions in the other groups were not statistically significant, indicating that the relationship between hemoglobin and IHCA remained stable in the other groups.

Discussion

In this retrospective observational study, we investigated whether the serum hemoglobin level was independently associated with an increased risk of IHCA in patients with ACS complicated by CS. We found that the incidence of IHCA was related to the hemoglobin concentration. In addition, the results suggested that a higher hemoglobin concentration was associated with a lower prevalence of IHCA. Indeed, a 1-g/L increase in the hemoglobin level was associated with a 2.9% lower risk of IHCA, further confirming the relationship between hemoglobin and IHCA. Moreover, patients with a higher hemoglobin level had a 0.194-fold lower risk of developing IHCA compared with patients with a lower hemoglobin level. Interestingly, a prior study showed that older patients had a higher risk of IHCA during hospitalization.²² In the subgroup analysis of our study, however, no such association was observed in patients aged > 70 years. The following explanation seems plausible. As previously reported, a low hemoglobin level is more common in patients of advanced age^{23,24} and may be a sign of frailty in younger patients.²⁵ Younger patients with frailty are more likely to have many comorbidities, which may play a role in the occurrence of IHCA. From this viewpoint, a low hemoglobin level is more closely associated with

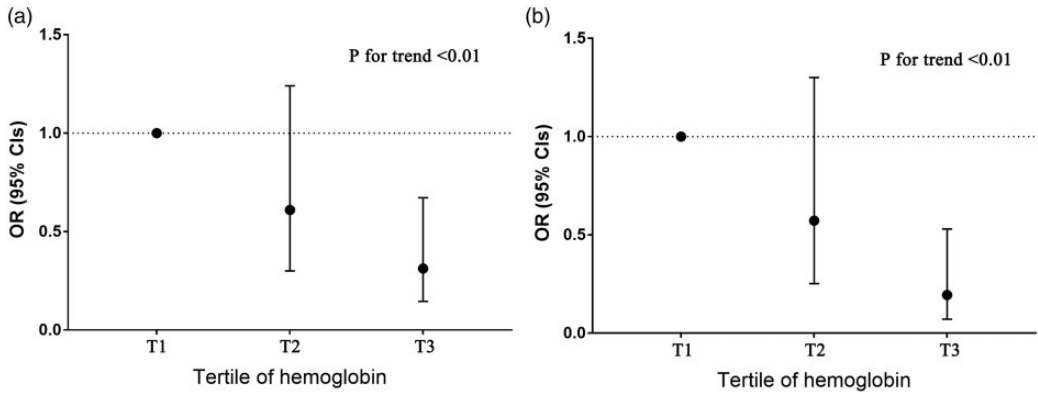


Figure 2. ORs of hemoglobin for IHCA. (a) Unadjusted. (b) Adjusted for sex, age, coronary revascularization, hypertension, diabetes mellitus, ventricular arrhythmias, brain natriuretic peptide, creatinine, and lactate. OR, odds ratio; CI, confidence interval; IHCA, in-hospital cardiac arrest.

Subgroup	No. of Patients	IHCA(%)	Odds Ratio(95% CI)	P Value	P Value for Interaction
Overall	211	61(28.9)	0.971 (0.954, 0.989)	0.001	
Age					0.021
≥70yr	119	38(31.9)	0.988 (0.966, 1.010)	0.277	
<70yr	92	23(25.0)	0.952 (0.926, 0.978)	0.001	
Sex					0.597
Male	138	42(30.4)	0.968 (0.948, 0.989)	0.003	
Female	73	19(26.0)	0.978 (0.948, 1.009)	0.166	
Hypertension					0.878
Yes	129	40(31.0)	0.972 (0.952, 0.993)	0.009	
No	82	21(25.6)	0.969 (0.943, 0.997)	0.031	
Diabetes mellitus					0.166
Yes	73	23(31.5)	0.955 (0.927, 0.985)	0.004	
No	138	38(27.5)	0.978 (0.958, 0.998)	0.035	
Ventricular arrhythmias at admission					0.960
Yes	46	22(47.8)	0.970 (0.940, 1.002)	0.064	
No	165	39(23.6)	0.971 (0.952, 0.991)	0.005	
Smoking					0.612
Yes	69	17(24.6)	0.966 (0.937, 0.996)	0.025	
No	142	44(31.0)	0.975 (0.955, 0.995)	0.017	

Each stratification adjusted for all the factors(Sex; Age; Coronary Revascularization; Hypertension; Diabetes mellitus; Ventricular arrhythmias; Brain natriuretic peptide; Creatinine and Lactate) except the stratification factor itself.

Figure 3. Association between hemoglobin and IHCA according to baseline characteristics. Each stratification was adjusted for all factors (sex, age, coronary revascularization, hypertension, diabetes mellitus, ventricular arrhythmias, brain natriuretic peptide, creatinine, and lactate) except the stratification factor itself. OR, odds ratio; CI, confidence interval; IHCA, in-hospital cardiac arrest.

IHCA in younger than older patients. There are several other possibilities for how our study population differs from those of previous studies, and the number of patients in the present study may not have been large enough. Further research is needed to more fully investigate the association.

The findings of our study are consistent with those of previous research in that the patients with a lower hemoglobin concentration were more likely to develop an adverse prognosis.²⁶⁻²⁸ Previous reports have described hemoglobin as a predictor of mortality, major bleeding, and cardiovascular events in patients with ACS,²⁶⁻²⁸

but the association between hemoglobin and IHCA has not been reported. Several studies have investigated the risk factors for IHCA. One study showed that a cardiac etiology was the dominant cause of IHCA.²⁹ Both pneumonia and a hypoxic etiology were also related to IHCA.^{30,31} Joundi et al.³² found that aging and diabetes were important predictive factors for IHCA. To the best of our knowledge, the present study is the first to describe the relationship between the hemoglobin concentration and the incidence of IHCA.

Different from previous studies,^{29–32} the population in our study comprised patients with ACS complicated by CS. CS is a state of end-organ hypoperfusion due to reduced cardiac output,^{14–16} which is considered a sign of hemodynamic instability. Patients with hemodynamic instability are more liable to develop cardiac arrest.^{11–13} From this viewpoint, our research is clinically meaningful, and the population in this study represents typical patients with hemodynamic instability who are in danger of developing IHCA. Thus, the incidence rate of IHCA in this study may be much higher than that in other ordinary patients. Identification of patients with CS who have a high risk of developing cardiac arrest should be given more attention in the clinical setting.

Given the observational nature of our cohort, we were limited to describing the association between the hemoglobin concentration and the incidence of IHCA. Therefore, further studies are necessary to elucidate the underlying pathophysiological mechanisms, which may include the following. First, anemia is reportedly related to left ventricular dysfunction.^{33,34} Chronic left ventricular dysfunction often causes ventricular remodeling, including left ventricular hypertrophy and dilatation.³⁵ Left ventricular hypertrophy and left ventricular expansion increase the risk of cardiac arrest and sudden cardiac death in patients with

cardiovascular disease.^{36–38} Second, patients with anemia may be prone to developing ventricular arrhythmia,³⁷ which is the most common pathophysiological mechanism of cardiac arrest. Third, previous studies have demonstrated that anemia induces tissue hypoxia in the most vulnerable regions affected by ischemia.^{39–41} Patients with CS have an increased wedge pressure and thus hampered oxygen and carbon dioxide exchange at the pulmonary level, resulting in even lower oxygenation of the already decreased hemoglobin level on admission.⁴² In a sense, anemia has the same effect on IHCA as do respiratory problems by decreasing oxygen delivery. Fourth, anemia reportedly worsens the outcome of patients with heart failure by enhancing their myocardial workload.⁴³ In patients with cardiac shock with already poor cardiac function, the increased myocardial workload makes cardiac arrest more likely to occur.

Considering that the outcomes of IHCA are very poor,^{32,44–46} prevention of IHCA is extremely important. The present study showed that a low hemoglobin concentration may be related to the incidence of IHCA and could thus serve as a clinical monitoring index and facilitate early decision-making. We believe that more methods with which to effectively predict the occurrence of IHCA, such as a risk score that includes hemoglobin or other indicators, will be developed in future clinical practice. Furthermore, it may be valuable to explore whether we can reduce the risk of IHCA by increasing the patient's hemoglobin concentration. Notably, previous studies have shown that the relationship between the baseline hemoglobin level and an adverse prognosis is curvilinear (reverse J-shaped curve) in patients with ACS.^{47,48} Although the same phenomenon was not observed in our study, it may still exist in other populations. This is an interesting question that should be further

studied in the future and may help to identify the risk threshold of hemoglobin in the development of IHCA.

The present study has some limitations. First, the study was based on a single-center cohort, which limits the generalizability of the results. Physicians should conduct a longitudinal large-scale, multicenter study of a general population to confirm the relationship between the hemoglobin concentration and the incidence of IHCA. Second, the self-reported history of chronic disease in this study may have led to recall bias, affecting the accuracy of disease prevalence estimations. Third, the study may still have some selection bias, including frailty of the patients, despite the fact that we adjusted for possible confounding variables in the multiple logistic regression models.

Conclusion

In patients with ACS complicated by CS, the incidence of IHCA is related to the hemoglobin concentration. Furthermore, a high hemoglobin concentration is a protective factor against the development of IHCA.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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