Relationship Between Anemia and the Risk of Sudden Cardiac Arrest : A Nationwide Cohort Study in South Korea

In Jung Kim

Department of Medicine

The Graduate School, Yonsei University

Relationship Between Anemia and the Risk of Sudden Cardiac Arrest : A Nationwide Cohort Study in South Korea

In Jung Kim

Department of Medicine

The Graduate School, Yonsei University

Relationship Between Anemia and the Risk of Sudden Cardiac Arrest : A Nationwide Cohort Study in South Korea

Directed by Professor Boyoung Joung

The Master's Thesis
submitted to the Department of Medicine,
the Graduate School of Yonsei University
in partial fulfillment of the requirements for the degree
of Master of Medical Science

In Jung Kim

December 2019

This certifies that the Master's Thesis of
In Jung Kim is approved.

Thesis Supervisor : Chang Soo Kim

Thesis Committee Member#1 : Boyoung Joung

Thesis Committee Member#2 : Hui Nam Pak

The Graduate School
Yonsei University

December 2019

ACKNOWLEDGEMENTS

I would like to thank my master's thesis advisor Dr. Boyoung Joung, who has taught me as a teacher and mentor. He has taught me more than I could ever give him credit for here. He has shown me, by his example, what a good doctor (and person) should be. He has provided me extensive personal and professional guidance and taught me a great deal about both scientific research and life in general. His enduring encouragement and practical advice have been an inestimable source of support for me during this process. I would especially like to thank Dr. Pil Sung Yang who have been supportive of my thesis and who worked actively to provide me with academic feedback to pursue those goals.

Nobody has been more than important to me in the pursuit of this project than the members of my family. I would like to thank my parents, whose love and guidance are with me in whatever I pursue. They are the ultimate role models. Most importantly, I wish to thank my loving and supportive wife, Myoung Jin.

<TABLE OF CONTENTS>

LIST OF FIGURES

LIST OF TABLES

ABSTRACT

Relationship Between Anemia and the Risk of Sudden Cardiac Arrest : A Nationwide Cohort Study in South Korea

In Jung Kim

Department of Medicine
The Graduate School, Yonsei University

(Directed by Professor Boyoung Joung)

Background: The relationship between anemia and sudden cardiac arrest (SCA) is unclear in the general population, so we assessed it in a nationwide cohort.

Methods and Results: We studied 494,948 subjects (mean age, 47.8 years; 245,333 men [49.6%]) with national health check-up data from the Korean National Health Insurance Database Cohort. During a mean follow-up period of 5.4 years, SCA occurred in 616 participants (396 men, 220 women). The incidence rates of SCA increased across the four anemia groups in both men (0.3, 1.5, 5.3, and 4.5 per 1,000 person-years) and women (0.2, 0.5, 0.5, and 1.2 per 1,000 person-years). The SCA risk per 1-unit decrease in hemoglobin (Hb) increased by 21% and 24%, respectively, in multivariable models adjusted for cardiovascular factors, in men (95% confidence interval [CI], 13–29%; $P<0.001$) and women (95% CI, 13–37%; $P<0.001$). A negative correlation between QTc interval and Hb level was observed in men, and a trend was observed in women.

Conclusions: Anemia was associated with an increased risk of SCA even after accounting for concomitant conditions in a South Korean nationwide cohort. The correlation between anemia and SCA might be explained by an increase of arrhythmic risks, such as QTc prolongation.

Key words: anemia; sudden cardiac arrest; general population

Relationship Between Anemia and the Risk of Sudden Cardiac Arrest : A Nationwide Cohort Study in South Korea

In Jung Kim

Department of Medicine
The Graduate School, Yonsei University

(Directed by Professor Boyoung Joung)

I. INTRODUCTION

Anemia is common in patients with cardiovascular disease and is a multifactorial problem, especially in the elderly population.[1] The risks of mortality, morbidity and hospitalization in patients with anemia were similar to those of four other common cardiovascular risk factors: smoking, diabetes mellitus, arterial hypertension, and hypercholesterolemia.[2] Consequently, anemia has lately been characterized as "the fifth cardiovascular risk factor."[1] Anemia is presented in one-third of patients with acute coronary syndrome (ACS); in particular, in 12.8% of patients with acute myocardial infarction (MI), in 43% of the elderly patients with ST-elevation MI and in 5–10% of non-ST elevation ACS patients.[3] Recently, it was reported that anemia is associated with increased mortality and sudden death in patients with diastolic heart failure (HF).[4,5] There are approximately 300,000–350,000 cases of out-of-hospital sudden cardiac arrest (SCA) or sudden cardiac death in the USA yearly, imparting a substantial public health burden.[6-8] Factors that have been most

commonly associated with the occurrence of SCA in the overall population include coronary artery disease and associated markers such as diabetes mellitus, left ventricular hypertrophy (LVH), hyperlipidemia, and cardiomyopathies.[6,9-11]

However, little is known about the association between anemia and the development of SCA in the general population. QT prolongation and LVH are risk factors of ventricular fibrillation.[12] However, it is not known whether the severity of anemia is related to QT prolongation and LVH. The aim of this study was to assess the effect of anemia on SCA in the general population by using a national cohort. Moreover, we analyzed ECG changes according to the severity of anemia by using a hospital cohort.

II. MATERIALS AND METHODS

1. Source of Study Data

A national health insurance system in Korea was established in 1963 according to the National Health Insurance Act, and it is compulsory for all citizens in South Korea to participate. The National Health Insurance Service (NHIS) released the National Sample Cohort (2002–2013) database (NHIS-NSC [2002–2013]) in 2015. It consists of 1,025,340 Koreans as an initial 2002 cohort and followed up the subjects through 2013. The national cohort represents approximately 2.2% of the source population in 2002 (46,605,433). This is a semi-dynamic cohort database; namely, the cohort was

followed up to either the time of the participant's disqualification from health services because of death or emigration, or the end of the study period. The national cohort contains eligibility and demographic information about health insurance and medical aid beneficiaries, medical bill details, medical treatment, disease histories, and prescriptions; such data are constructed after converting insurance claim information to the first day of medical treatment.

In the cohort, the subjects' disease information was classified according to the 10th revision of the International Classification of Diseases (ICD-10) codes, and the subjects' mortality data, as well as the cause of death, were obtained from the Korean National Statistical Office. As this study was based on data from the NHIS, informed consent was not specifically obtained individually. Data were fully anonymized and de-identified for the analysis. This study was approved by the Institutional Review Board of Severance Hospital.

2. Study Population

A total of 506,805 subjects had a nationwide health examination after 2009. However, 11,857 were excluded because of missing data in variables of the health examination. Finally, this study included 494,948 subjects older than 18 years, who had had a physical examination in 2009 and had follow-up data until December 2013 **(Figure 1)**. To ensure diagnostic accuracy, we defined patients with comorbidities, including hypertension, diabetes mellitus, and HF,

only when the condition was a discharge diagnosis or confirmed more than twice in the outpatient department.[13,14] Furthermore, the laboratory and survey questionnaire data of general and life-transition health examinations for all cohort members were merged.

Anemia was analyzed as both a continuous and a categorical variable. According to the World Health Organization criteria, anemia is defined as a hemoglobin (Hb) concentration of <13 g/dL in men and <12 g/dL in women. We also defined mild anemia as an Hb concentration of 11 to <13 for men and 11 to <12 for women, moderate anemia as Hb 8 to <11 g/dL, and severe anemia as Hb <8 g/dL.[15] At the time of Hb measurement, systolic and diastolic pressures were also measured; serum samples for fasting glucose, Hb, and total cholesterol levels were also obtained after an overnight fast at each examination site. Detailed histories of smoking status, alcohol consumption, and physical activity (including amount and frequency) were obtained through questionnaires.

To evaluate the relationships between anemia and ECG parameters, including QT, QTc intervals (corrected QT interval), T-wave abnormality, and LVH, additional analyses were performed using the MUSE system in 11,782 individuals who were admitted to Severance Hospital from 2004 to 2009. QTc prolongation was defined as >450 ms in men and >470 ms in women. The study protocol was approval by the Institutional Review Board of Severance Hospital and complied with the Declaration of Helsinki.

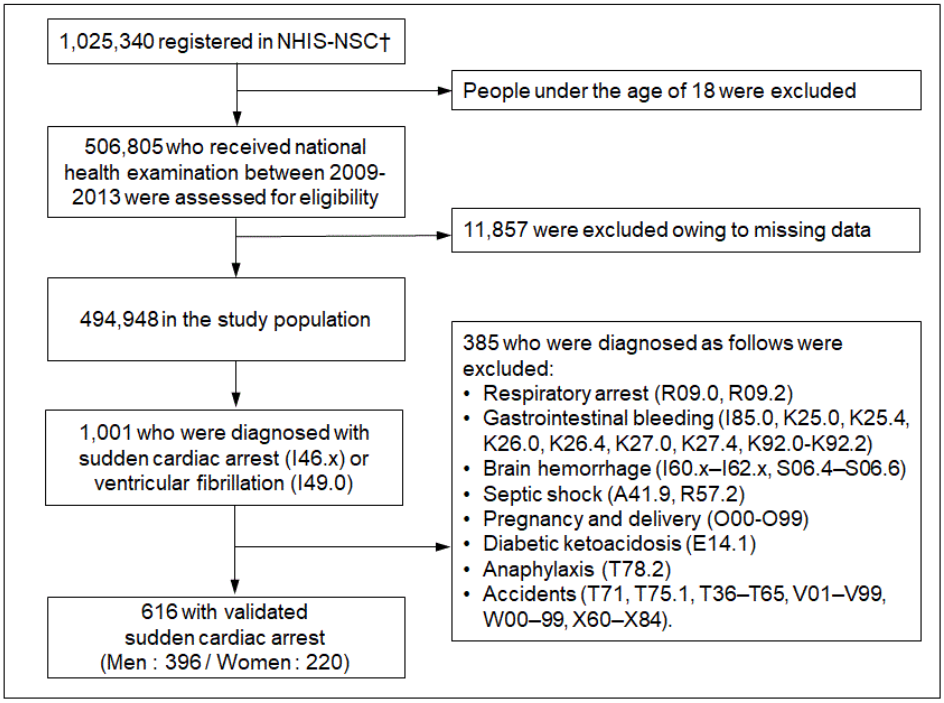


Figure 1. Study Cohort. †National Health Insurance Service-National Sample Cohort.

3. Definition and Validation of SCA

In the NHIS-NSC, the cause of deaths was coded using the ICD-10 codes. We identified 1,001 patients (men 651, women 350) with SCA and ICD-10 codes I46.x (cardiac arrest) and I49.0 (ventricular fibrillation). To exclude patients with non-cardiac arrest, we excluded 385 patients (men 255, women 130) with a diagnosis of sudden cardiac arrest accompanied by respiratory arrest (R09.0, R09.2), gastrointestinal bleeding (I85.0, K25.0, K25.4, K26.0, K26.4, K27.0, K27.4, K92.0-K92.2), brain hemorrhage (I60.x–I62.x, S06.4–S06.6), septic shock (A41.9, R57.2), pregnancy and delivery (O00-O99),

diabetic ketoacidosis (E14.1), anaphylaxis (T78.2), and accidents including asphyxiation, drowning, poisoning, traffic accident, fall, and suicide (T71, T75.1, T36–T65, V01–V99, W00–99, X60–X84) **(Figure 1)**.

To evaluate the accuracy of our definition of SCA, we conducted a validation study with medical records of two independent tertiary hospitals from 2009 to 2013. We found 731 patients with code I46.x or I49.0 after excluding those with diagnosis codes for non-cardiac causes, as mentioned before. Their medical records were then reviewed by five physicians, and we ascertained the patients with true SCA. The positive predictive value was 80.2% (586 of 731) using our criteria of SCA, suggesting good diagnostic accuracy of our definition. False-positive cases were respiratory arrest (7.0%), history of SCA (4.2%), arrest due to cancer progression (1.9%), accidents (1.8%), bleeding (1.8%), metabolic acidosis (1.0%), septic shock (0.8%), stroke (0.5%), and others (0.9%).

4. Statistical Analysis

The baseline characteristics of the two groups were compared by Student's *t*-test for continuous variables, and by the chi-square test or Fisher's exact test for categorical variables. The matched patient groups were compared by paired *t*-test for continuous variables and McNemar's test for categorical variables. We used a sex-specific Kaplan-Meier plot for the presentation of survival curves in the anemia group and a log-rank test to assess whether the

survival curves were statistically significantly different. To investigate the association between anemia or anemia category and the risk of SCA, we used a sex-specific Cox's proportional hazard regression model with adjustment for clinical variables including age, body mass index, chronic kidney disease or end-stage renal disease, chronic obstructive pulmonary disease, diabetes mellitus, dyslipidemia, hypertension, HF, interim MI and HF, malignancy, previous MI, previous ischemic stroke, smoking pack-years. The four anemia categories were modeled with three predictor variables (for mild, moderate, and severe anemia). We also estimated other models with an ordinal predictor variable for the anemia category to test for a linear trend across anemia categories. We studied whether anemia predisposed patients to SCA through an interim MI or HF event. We used a linear-by-linear association trend test for the calculation of the rates of QTc prolongation and LVH, as well as T-wave abnormality according to the severity of anemia. All statistical analyses were performed using SPSS software version 20.0 (IBM Corp., Chicago, IL, USA). Statistical significance was established at a *P* value of <0.05.

III. RESULTS

1. Study Subjects

The baseline characteristics of the study are presented in **Table 1**. The mean age was 47.8 (range, 18–98) years in men and 47.8 (range, 18–98) years

in women. Of the 494,948 participants, 59,565 (12.0%) were anemic, including 42,185, 16,323, and 1,057 with mild, moderate, and severe anemia, respectively. 12,932 (5.3%) men and 46,633 (18.8%) women had anemia. Anemia was more common in women than in men (P<0.001). Participants with anemia were older, and more frequently had comorbidities than those without anemia.

2. Incidence of SCA

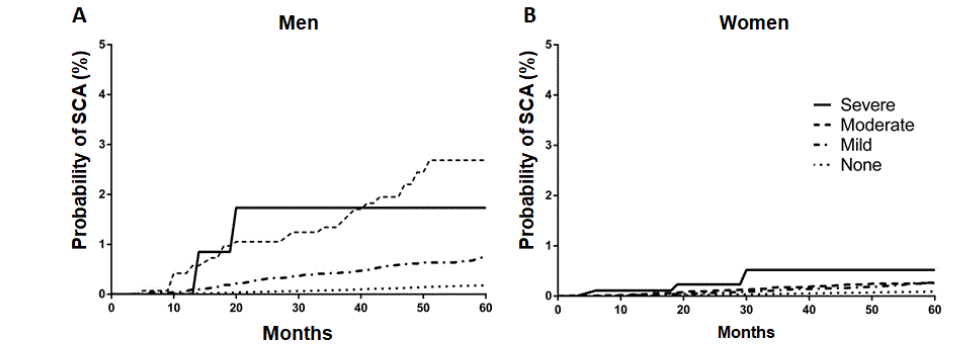
During a mean follow-up of 5.4 years, 616 participants (men 396, women 220) had a SCA. Demographics of participants with SCA are presented in **Supplementary Table 1**. Of the 616 participants, 181 (29.7%) were anemic. A total of 92 (23.2%) men and 89 (40.5%) women had anemia. Before developing SCA, 930 men and 364 women had experienced MI, and 1,513 men and 1,384 women had experienced HF. During the follow-up period, 6,219 participants (4,003 men, 2,216 women) died.

The age-adjusted incidence rates of SCA are presented in **Table 1**. The incidence rates of SCA increased across the categories of anemia in men (0.3, 1.5, 5.3, and 4.5 per 1,000 person-years) and women (0.2, 0.5, 0.5, and 1.2 per 1,000 person-years), respectively. **Figure 2** shows the Kaplan-Meier curves for SCA in patients with different categories of anemia. The probability of developing SCA over time increased across the categories of anemia.

Table 1. Baseline Characteristics of Participants and Incidence of Sudden Cardiac Arrest by Severity of Anemia Among South Koreans

	Men				Women			
	None (n=232,401)	**Mild anemia (n=11,337)**	**Moderate anemia (n=1,451)**	**Severe anemia (n=144)**	**None (n=202,982)**	**Mild anemia (n=30,848)**	**Moderate anemia (n=14,872)**	**Severe anemia (n=913)**
Age, years	46.0±13.7	59.8±14.3	63.3±13.8	59.6±14.6	48.6±14.5	50.1±15.4	48.9±15.1	47.1±11.6
BMI	24.3±3.1	23.0±3.1	22.3±3.2	22.4±3.2	23.3±3.5	22.8±3.2	22.7±3.3	22.9±3.3
Systolic BP, mmHg	124.8±14.2	125.2±15.9	125.9±17.6	124.2±18.0	119.9±15.8	118.6±15.8	118.6±15.5	117.4±13.9
Diastolic BP, mmHg	78.1±9.9	76.3±10.3	75.6±10.7	73.9±10.7	74.4±10.1	73.0±10.0	72.9±10.1	71.4±9.3
Hypertension	46,283 (19.9)	4,995 (44.1)	805 (55.5)	55 (38.2)	46,108 (22.7)	7,518 (24.4)	3,264 (21.9)	111 (12.2)
Diabetes mellitus	28,326 (12.2)	3,429 (30.2)	599 (41.3)	38 (26.4)	25,625 (12.6)	4,366 (14.2)	2,113 (14.2)	80 (8.8)
HF	4,001 (1.7)	719 (6.3)	154 (10.6)	12 (8.3)	5,603 (2.8)	1,148 (3.7)	649 (4.4)	20 (2.2)
Dyslipidemia	40,321 (17.3)	3,596 (31.7)	547 (37.7)	37 (25.7)	43,023 (21.2)	6,661 (21.6)	2,723 (18.3)	90 (9.9)
CKD	11,269 (4.8)	1,755 (15.5)	459 (31.6)	28 (19.4)	11,636 (5.7)	2,618 (8.5)	1,589 (10.7)	57 (6.2)
ESRD	65 (0.1)	93 (0.8)	68 (4.7)	3 (2.1)	76 (0.1)	41 (0.1)	59 (0.4)	1 (0.1)
COPD	12,559 (5.4)	9,719 (14.3)	256 (17.6)	11 (7.6)	13,709 (6.8)	2,426 (7.9)	1,054 (7.1)	32 (3.5)
Previous MI	2,579 (1.1)	378 (3.3)	76 (5.2)	3 (2.1)	1,486 (0.7)	325 (1.1)	182 (1.2)	4 (0.4)
Previous ischemic stroke	5,279 (2.3)	939 (8.7)	177 (12.2)	12 (8.3)	5,306 (2.6)	1,096 (3.6)	558 (3.8)	23 (2.5)
Malignancy	14,114 (6.1)	1,924 (17.0)	387 (26.7)	22 (15.3)	13,856 (6.8)	2,316 (7.5)	1,075 (7.2)	44 (4.8)
Smoking, pack-years	11.6±14.2	14.1±17.9	13.4±17.8	13.3±18.8	0.4±2.6	0.3±2.1	0.2±1.8	0.2±1.9
Creatinine, mg/dL	1.2±1.3	1.2±1.4	1.7±2.2	1.6±2.3	1.0±0.9	1.0±0.9	1.1±1.2	1.0±0.7
eGFR, mL/min/1.73 m^2	89.3±20.3	80.6±22.3	69.6±29.2	78.1±27.3	90.0±20.7	89.0±21.8	89.0±24.0	94.0±22.0
Total cholesterol, mg/dL	194.5±36.3	181.4±38.6	166.7±36.7	146.8±33.8	197.1±37.7	191.1±36.8	185.4±35.4	164.1±30.2
No. of events/person-years	304/909,660	64/43,095	26/4,892	2/448	131/768,343	55/118,119	30/55,106	4/3,245
SCA incidence per 1000 person-years	0.3	1.5	5.3	4.5	0.2	0.5	0.5	1.2

Continuous variables are expressed as mean ± standard deviation. Numbers in parenthesis are percentage value. The Hb categories are as follows: normal, ≥13 g/dL for men and ≥12 g/dL for women; mild anemia, 11 to <13 g/dL for men and 11 to <12 g/dL for women; moderate anemia, 8 to <11 g/dL; and severe anemia, <8 g/dL. BMI, body mass index; BP, blood pressure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; Hb, hemoglobin; HF, heart failure; MI, myocardial infarction; SCA, sudden cardiac arrest.



No. at risk														
Severe	144	142	112	84	68	67	42	913	907	813	694	545	542	285
Moderate	1,451	1,430	1,225	1,023	804	405	389	14,872	14,841	13,498	11,828	9,665	5,283	5,254
Mild	11,339	11,280	10,379	9,199	7,767	4,491	4,419	30,848	30,827	28,693	25,549	21,201	11,871	11,826
None	232,404	232,265	215,970	193,618	163,370	104,625	104,236	202,985	202,920	187,458	165,669	136,461	75,944	75,777

Figure 2. Cumulative incidence of sudden cardiac arrest (SCA) according to anemia group in men (**A**) and women (**B**).

3. The Risk of SCA according to Anemia

The results of the multivariable Cox's proportional hazard regression are shown in **Table 2**. After adjustment for age alone, each 1-unit decrease in Hb was associated with an increase of 26% for men (P<0.001) and 32% for women (P<0.001), respectively. These relations remained significant in the multivariable-adjusted models, with an increase in the risk of SCA per 1-unit decrease in Hb of 32% for men (P<0.001) and 25% for women (P<0.001). Similarly, the age-adjusted and fully adjusted hazard ratios (HRs) for SCA increased across Hb categories in both men and women **(Table 2)**. The multivariable-adjusted HRs for SCA were 1.50 (95% confidence interval [CI], 1.13–1.99) for mild anemic men and 1.88 (95% CI, 1.36–2.59) for mild anemic women. These findings were not attenuated in models adjusting for interim MI

or HF in addition to baseline covariates. Each 1-unit decrease in Hb was associated with an increase of 21% for men (P<0.001) and 24% for women (P<0.001).

The association between Hb and the risk of SCA did not vary by age, sex, or systolic blood pressure (P>0.10 for all interaction terms). To assess the influence of different degrees of anemia, we estimated regressions with four Hb categories (normal, mild, moderate, and severe anemia). The age-adjusted HRs for SCA increased progressively across the four Hb categories in men (1.00, 1.72 [95% CI, 1.30–2.28], 5.33 [95% CI, 3.53–8.03], 5.82 [95% CI, 1.45–23.41]; P=0.001 for trend) and women (1.00, 2.04 [95% CI, 1.48–2.80], 2.35 [95% CI, 1.57–3.52], 10.10 [95% CI, 3.73–27.34]; P=0.001 for trend). After adjustment for clinical variables and interim MI or HF, these findings remained significant in men (1.00, 1.50 [95% CI, 1.13–1.99], 4.01 [95% CI, 2.64–6.08], 6.19 [95% CI, 1.53–25.01]; P=0.001 for trend) and women (1.00, 1.88 [95% CI, 1.37–2.59], 1.86 [95% CI, 1.23–2.81], 8.77 [95% CI, 3.22–23.86]; P=0.001 for trend).

In a secondary analysis restricted to mild-moderate anemia, the association between anemia and the risk of SCA remained significant (sex-pooled multivariable-adjusted HR per 1-unit increase in Hb, 1.50 [95% CI, 1.34–1.67]; P<0.001). Additionally, the relationship between anemia and the risk of SCA in female population is presented in **Figure 3**. Adjusted HRs significantly increased in premenopausal women (3.83 [95% CI, 1.34–10.93,

P=0.012]). Adjusted HRs for SCA also significantly increased in patients without hypertension (2.05 [95% CI, 1.24–3.34, *P*=0.005]), diabetes mellitus (1.96 [95% CI, 1.37–2.81, *P*<0.001]), HF (1.82 [95% CI, 1.32–2.51, *P*<0.001]), chronic kidney disease or end-stage renal disease (2.26 [95% CI, 1.60–3.19, *P*<0.001]), malignancy (1.98 [95% CI, 1.46–2.69, *P*<0.001]) and severe anemia (1.88 [95% CI, 1.42–2.50, *P*<0.001]), respectively.

Female population (n=249,618)	Anemia (n=46,633)	No anemia (n=202,985)	Hazard Ratio (95% CI)	P value
	Sudden cardiac arrest/total at risk (%)			
Subgroups				
≤ 50 years	7/28,286	7/113,423	3.83(1.34-10.93)	0.012
> 50 years	82/18,347	124/89,562	1.92(1.43-2.58)	<0.001
Hypertension (-)	24/35,740	44/156,876	2.05(1.24-3.34)	0.005
Hypertension (+)	65/10,893	87/46,109	1.93(1.38-2.70)	<0.001
Diabetes mellitus (-)	48/40,074	84/177,359	1.96(1.37-2.81)	<0.001
Diabetes mellitus (+)	41/6,559	47/25,626	2.03(1.31-3.15)	0.001
Heart failure (-)	60/44.816	108/197,382	1.82(1.32-2.51)	<0.001
Heart failure (+)	29/1,817	23/5,603	2.75(1.56-4.86)	0.001
CKD or ESRD (-)	52/42,358	89/191,324	2.26(1.60-3.19)	<0.001
CKD or ESRD (+)	37/4,275	42/11,661	1.67(1.06-2.62)	0.28
Malignancy (-)	77/43,198	110/189,129	1.98(1.46-2.69)	<0.001
Malignancy (+)	12/3,435	21/13,856	1.64(0.79-3.41)	0.188
Severe anemia (-)	85/45,720	131/202,895	1.88(1.42-2.50)	<0.001
Severe anemia (+)	4/913	-	-	-

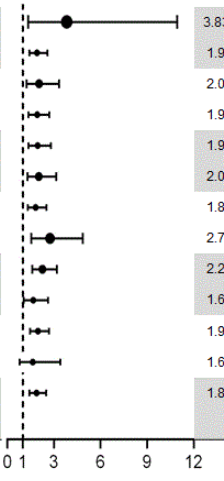


Figure 3. Forest plot of the anemia effect on sudden cardiac arrest (SCA) in subgroups. CI, confidence interval; CKD, chronic kidney disease; ESRD, end-stage renal disease.

Table 2. Hb and the Risk of Sudden Cardiac Arrest (Multivariable Models)

	Men		Women	
Model	Hazard Ratio (95% CI)	*P* value	Hazard Ratio (95% CI)	*P* value
With Hb as a continuous variable (per 1 g/dL decrease)				
Age adjusted	1.26 (1.18–1.35)	<0.001	1.32 (1.20–1.45)	<0.001
Adjusted for clinical variables†	1.32 (1.13–1.29)	<0.001	1.25 (1.13–1.38)	<0.001
Adjusted for clinical variables and interim MI, HF†	1.21 (1.13–1.29)	<0.001	1.24 (1.13–1.37)	<0.001
With anemia as a categorical variable*				
None	1		1	
Mild anemia	1.50 (1.13–1.99)	<0.001	1.88 (1.37–2.59)	<0.001
Moderate anemia	4.01 (2.64–6.08)	<0.001	1.86 (1.23–2.81)	<0.001
Severe anemia	6.19 (1.53–25.01)	<0.001	8.77 (3.22–23.86)	<0.001
Trend across categories	4.25 (1.03–17.65)	0.05	5.77 (2.03–16.36)	<0.001

The Hb categories are as follows: normal, ≥13 g/dL for men and ≥12 g/dL for women; mild anemia, 11 to <13 g/dL for men and 11 to <12 g/dL for women; moderate anemia, 8 to <11 g/dL; and severe anemia, <8 g/dL. *Adjusted for clinical variables including age, BMI, CKD or ESRD, COPD, diabetes mellitus, dyslipidemia, hypertension, HF, interim MI and HF, malignancy, previous MI, previous ischemic stroke, regular use of cigarettes in the prior year. CI, confidence interval; HR, hazard ratio. Other abbreviations as in Table 1.

4. ECG Changes Associated With Anemia

The relationship between anemia and QTc prolongation was evaluated in 11,782 individuals (mean age: 61.2±14.4 years; 6,151 [52.2%] women), who were admitted to Severance Hospital from 2004 to 2009. The characteristics of patients are presented in **Table 3**. The overall rate of QTc prolongation was 28.7%, 33.6%, 31.4% and 36.2% in normal, mild, moderate and severe anemia, respectively (P<0.001 for trend). A significant negative correlation between QTc interval and Hb level was observed in men **(Figure 4)**. The associations between anemia and other ECG characteristics including LVH and T-wave abnormality were not observed.

The prevalence of QTc prolongation, T-wave abnormality and LVH did not differ among microcytic, normocytic and macrocytic anemia in either men or women (**Supplementary Table 2**).

Table 3. Characteristics of the Study Population by Severity of Anemia

\	None (n=7,056)	Mild anemia (n=2,214)	Moderate anemia (n=2,122)	Severe anemia (n=390)	*P* value
Age, years	60.4±14.3	63.6±13.7	62.2±14.9	57.9±17.1	<0.001
Hb, g/dL	14.0±1.3	11.8±0.5	9.8±0.8	6.7±1.1	<0.001
MCV, fL	91.6±4.9	91.8±6.3	90.8±7.7	88.3±11.9	<0.001
Serum Iron, μg/dL	61.6±59.5	60.1±50.1	57.4±52.0	65.1±95.7	0.13
TIBC, μg/dL	228.3±89.2	226.3±81.2	229.9±81.6	259.9±135.5	<0.001
Tranferrin saturation, %	29.0±24.1	29.8±30.0	28.6±25.8	28.0±29.8	0.02
Ferritin, ng/ml	693.5±2209.7	602.9±2091.5	498.3±1429.2	876.3±3429.8	0.01
QTc, ms	443.8±25.1	444.9±25.0	446.4±24.5	447.7±25.9	<0.001
QTc prolongation					
Overall	2,027 (28.7)	744 (33.6)	667 (31.4)	141 (36.2)	<0.001
Men	1,405 (43.0)	567 (44.4)	472 (51.4)	89 (53.3)	<0.001
Women	622 (16.4)	177 (18.9)	195 (16.2)	52 (23.3)	0.13
T wave abnormality					
Overall	2,205 (31.2)	716 (32.3)	729 (34.4)	120 (30.8)	0.04
Men	821 (25.1)	346 (27.1)	286 (31.1)	36 (21.6)	0.01
Women	1,384 (36.5)	370 (39.4)	443 (36.8)	84 (37.7)	0.57
LVH					
Overall	828 (11.7)	277 (12.5)	272 (12.8)	44 (11.3)	0.29
Men	478 (14.6)	180 (14.1)	146 (15.9)	26 (3.1)	0.45
Women	350 (9.2)	97 (10.3)	126 (10.5)	18 (81)	0.41

Continuous variables are expressed as mean ± standard deviation. Numbers in parenthesis are percentage value. MCV defined as follows: microcytic, <80 fL; normocytic, 80 to ≤100 fL; macrocytic, >100 fL. fL indicates femtoliters (10^{-15}). LVH, left ventricular hypertrophy; MCV, mean cell volume; QTc, corrected QT interval; TIBC, total iron binding capacity.

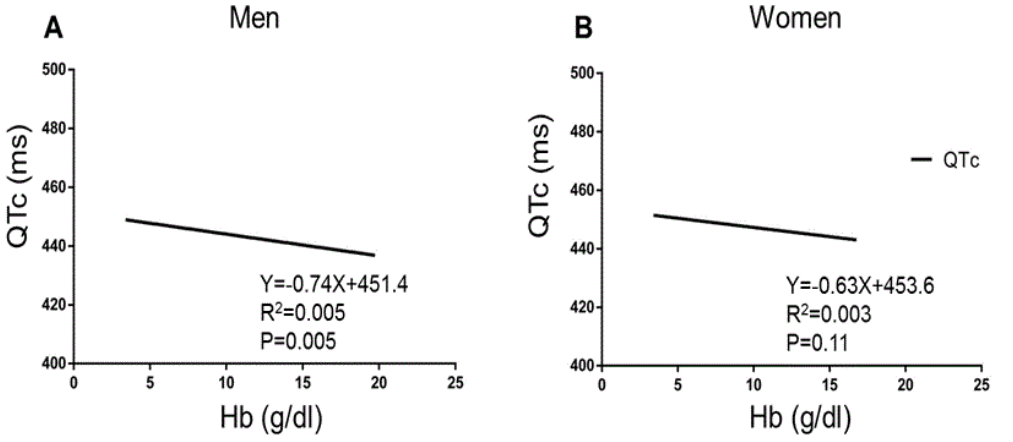


Figure 4. Correlation between QTc interval and hemoglobin (Hb) concentration in men (**A**) and women (**B**).

IV. DISCUSSION

The National Health Insurance Database Cohort-based data indicate that anemia is a risk factor for SCA. The association of anemia with the subsequent development of SCA persists even after accounting for concomitant conditions such as hypertension, diabetes mellitus, and MI. The validity of our results is supported by the large sample size and their consistency in multiple analyses adjusting for known confounders in men and women. Finally, our findings have biological plausibility because QTc prolongation and LVH, which are associated with SCA, increased with the severity of anemia.

1. Anemia, Cardiovascular Disease, and SCA

The association between anemia and cardiovascular disease is well known. Anemia is presented in one-third of patients with ACS, especially in the

12.8% of patients with acute MI and 43% of elderly patients with ST-elevation MI.[3] A clear correlation between anemia and death has been reported in patients with ACS.[3,16-19] Hb levels <11 g/dL is related to a significant risk of cardiovascular death in patients with ACS. However, it is also worth mentioning that an Hb concentration of >17 g/dL confers very serious risks.[20] The frequency of anemia is constantly increasing in HF. It is estimated that anemia is presented in approximately 9.0–15.6% of patients with HF in the USA.[21] Moreover, the prevalence of anemia increases with worsening functional class, from 9% for New York Heart Association (NYHA) class I to 79% for NYHA class IV.[22] Anemia is considered an independent risk factor for LV dysfunction and is associated with increased risks of morbidity and mortality.[23,24] However, the association between SCA and anemia has not been revealed. This study showed that anemia was an independent risk factor of SCA even after accounting for concomitant conditions such MI and HF. However, further studies are needed to verify the associations and proper mechanisms between anemia and SCA.

2. ECG Change by Anemia

In this study, the QTc interval increased with the severity of anemia. Anemia is associated with increased inflammation markers and aggravated oxidative stress condition.[25,26] Notably, oxidative stress in cardiomyocytes has been shown to activate Ca^{2+}/calmodulin-dependent protein kinase II,[27]

sequentially inducing the prolongation of the APD and QT intervals.[28] Moreover, reduced Hb concentration is associated with impaired oxygen delivery, salt and water retention, and chronic volume overload.[29] However, the negative correlation between QTc prolongation and Hb was weak in women. This might be related to a sex difference in the definition of QTc prolongation. Second, compared with men, women had low hematocrit and hypochromic states related to menstruation.[30] These chronic anemic conditions might induce the increased QTc prolongation across Hb categories and decrease the statistical power in women.

3. Study limitations

First, we identified patients with SCA by using ICD-10 codes I46.x (cardiac arrest) and I49.0 (ventricular fibrillation). SCAs were confirmed by emergency medical service personnel or during hospitalization. However, we cannot exclude the possibility that some episodes of SCA were missed or overestimated. To resolve this problem, we excluded patients with SCA diagnosis accompanied by other diseases. With this method, we confirmed that the positive predictive value of our criteria of SCA was 80.2%. Moreover, such misclassification would not be expected to differentially affect persons with and without anemia. Second, we only analyzed anemia at entry in this study, and we did not consider possible changes in Hb levels during the follow-up period. Third, serum iron, ferritin, total iron binding capacity were not available in the

national cohort. Therefore, we analyzed the relationship between the type of anemia and ECG parameters using additional hospital cohort. There was no statistically meaningful association between the type of anemia and ECG parameters. Fourth, we adjusted for multiple confounders but it is possible that residual confounding influenced the results. Finally, inherited arrhythmic disorders such as Long QT syndrome, Brugada syndrome, short QT syndrome are well-known cause of SCA. These channelopathies might be affected by anemia that could impair cardiac autonomic function[31-33] and worsen metabolic condition such metabolic acidosis[34], increased inflammation and aggravated oxidative stress.[25,26] Thus, further studies are necessary to understand the association of anemia and inherited arrhythmic disorder that precedes SCA.

V. CONCLUSION

Anemia was associated with an increased the risk of SCA even after accounting for concomitant conditions in a South Korean nationwide cohort. The correlation between anemia and SCA might be explained by the increase in arrhythmic risks, such as QTc prolongation.

REFERENCES

1. Spence RK. The economic burden of anemia in heart failure. Heart Fail Clin 2010;6:373-83.
2. Kaiafa G, Kanellos I, Savopoulos C, Kakaletsis N, Giannakoulas G, Hatzitolios AI. Is anemia a new cardiovascular risk factor? Int J Cardiol 2015;186:117-24.
3. Meneveau N, Schiele F, Seronde MF, Descotes-Genon V, Oettinger J, Chopard R, et al. Anemia for risk assessment of patients with acute coronary syndromes. Am J Cardiol 2009;103:442-7.
4. O'Meara E, Clayton T, McEntegart MB, McMurray JJ, Lang CC, Roger SD, et al. Clinical correlates and consequences of anemia in a broad spectrum of patients with heart failure: results of the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) Program. Circulation 2006;113:986-94.
5. Tada T, Shiba N, Watanabe J, Matsuki M, Kagaya Y, Shinozaki T, et al. Prognostic value of anemia in predicting sudden death of patients with diastolic heart failure. Int J Cardiol 2008;128:419-21.
6. Chugh SS, Jui J, Gunson K, Stecker EC, John BT, Thompson B, et al. Current burden of sudden cardiac death: multiple source surveillance versus retrospective death certificate-based review in a large U.S. community. J Am Coll Cardiol 2004;44:1268-75.

7. Chugh SS, Reinier K, Teodorescu C, Evanado A, Kehr E, Al Samara M, et al. Epidemiology of sudden cardiac death: clinical and research implications. Prog Cardiovasc Dis 2008;51:213-28.

8. Cobb LA, Fahrenbruch CE, Olsufka M, Copass MK. Changing incidence of out-of-hospital ventricular fibrillation, 1980-2000. JAMA 2002;288:3008-13.

9. Havmoeller R, Reinier K, Teodorescu C, Uy-Evanado A, Mariani R, Gunson K, et al. Low rate of secondary prevention ICDs in the general population: multiple-year multiple-source surveillance of sudden cardiac death in the Oregon Sudden Unexpected Death Study. J Cardiovasc Electrophysiol 2013;24:60-5.

10. Jouven X, Desnos M, Guerot C, Ducimetiere P. Predicting sudden death in the population: the Paris Prospective Study I. Circulation 1999;99:1978-83.

11. Albert CM, Chae CU, Grodstein F, Rose LM, Rexrode KM, Ruskin JN, et al. Prospective study of sudden cardiac death among women in the United States. Circulation 2003;107:2096-101.

12. Piva e Mattos B, Torres MA, Freitas VC, Scolari FL, Loreto MS. Ventricular arrhythmias and left ventricular hypertrophy in hypertrophic cardiomyopathy. Arq Bras Cardiol 2013;100:452-9.

13. Chao TF, Huang YC, Liu CJ, Chen SJ, Wang KL, Lin YJ, et al. Acute myocardial infarction in patients with atrial fibrillation with a

CHA2DS2-VASc score of 0 or 1: a nationwide cohort study. Heart Rhythm 2014;11:1941-7.

14. Chao TF, Wang KL, Liu CJ, Lin YJ, Chang SL, Lo LW, et al. Age Threshold for Increased Stroke Risk Among Patients With Atrial Fibrillation: A Nationwide Cohort Study From Taiwan. J Am Coll Cardiol 2015;66:1339-47.

15. Nutritional anaemias. Report of a WHO scientific group. World Health Organ Tech Rep Ser 1968;405:5-37.

16. Sarnak MJ, Tighiouart H, Manjunath G, MacLeod B, Griffith J, Salem D, et al. Anemia as a risk factor for cardiovascular disease in The Atherosclerosis Risk in Communities (ARIC) study. J Am Coll Cardiol 2002;40:27-33.

17. Nikolsky E, Aymong ED, Halkin A, Grines CL, Cox DA, Garcia E, et al. Impact of anemia in patients with acute myocardial infarction undergoing primary percutaneous coronary intervention: analysis from the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) Trial. J Am Coll Cardiol 2004;44:547-53.

18. Ishani A, Weinhandl E, Zhao Z, Gilbertson DT, Collins AJ, Yusuf S, et al. Angiotensin-converting enzyme inhibitor as a risk factor for the development of anemia, and the impact of incident anemia on mortality in patients with left ventricular dysfunction. J Am Coll Cardiol

2005;45:391-9.

19. de Denus S, Tardif JC, White M, Bourassa MG, Racine N, Levesque S, et al. Temporal variations in hematocrit values in patients with left ventricular dysfunction: Relationship with cause-specific mortality and morbidity and optimal monitoring--further insights from SOLVD. Can J Cardiol 2008;24:45-8.

20. Sabatine MS, Morrow DA, Giugliano RP, Burton PB, Murphy SA, McCabe CH, et al. Association of hemoglobin levels with clinical outcomes in acute coronary syndromes. Circulation 2005;111:2042-9.

21. Maggioni AP, Opasich C, Anand I, Barlera S, Carbonieri E, Gonzini L, et al. Anemia in patients with heart failure: prevalence and prognostic role in a controlled trial and in clinical practice. J Card Fail 2005;11:91-8.

22. Silverberg DS, Wexler D, Blum M, Keren G, Sheps D, Leibovitch E, et al. The use of subcutaneous erythropoietin and intravenous iron for the treatment of the anemia of severe, resistant congestive heart failure improves cardiac and renal function and functional cardiac class, and markedly reduces hospitalizations. Journal of the American College of Cardiology 2000;35:1737-44.

23. Anand I, McMurray JJ, Whitmore J, Warren M, Pham A, McCamish MA, et al. Anemia and its relationship to clinical outcome in heart failure. Circulation 2004;110:149-54.

24. Maggioni AP, Opasich C, Anand I, Barlera S, Carbonieri E, Gonzini L, et al. Anemia in Patients With Heart Failure: Prevalence and Prognostic Role in a Controlled Trial and in Clinical Practice. Journal of Cardiac Failure 2005;11:91-8.

25. van der Zee S, Baber U, Elmariah S, Winston J, Fuster V. Cardiovascular risk factors in patients with chronic kidney disease. Nat Rev Cardiol 2009;6:580-9.

26. Kovesdy CP, Kalantar-Zadeh K. Review article: Biomarkers of clinical outcomes in advanced chronic kidney disease. Nephrology (Carlton) 2009;14:408-15.

27. Erickson JR, Joiner ML, Guan X, Kutschke W, Yang J, Oddis CV, et al. A dynamic pathway for calcium-independent activation of CaMKII by methionine oxidation. Cell 2008;133:462-74.

28. Xie LH, Chen F, Karagueuzian HS, Weiss JN. Oxidative-stress-induced afterdepolarizations and calmodulin kinase II signaling. Circ Res 2009;104:79-86.

29. McCullough PA, Lepor NE. The deadly triangle of anemia, renal insufficiency, and cardiovascular disease: implications for prognosis and treatment. Rev Cardiovasc Med 2005;6:1-10.

30. Chaudhry HS, Kasarla MR. Anemia, Microcytic Hypochromic. StatPearls. Treasure Island (FL): StatPearls Publishing

StatPearls Publishing LLC.; 2018.

31. Sozen AB, Demirel S, Akkaya V, Kudat H, Tukek T, Yeneral M, et al. Autonomic dysfunction in vitamin B12 deficiency: a heart rate variability study. J Auton Nerv Syst 1998;71:25-7.

32. Romero Mestre JC, Hernandez A, Agramonte O, Hernandez P. Cardiovascular autonomic dysfunction in sickle cell anemia: a possible risk factor for sudden death? Clin Auton Res 1997;7:121-5.

33. Franzoni F, Galetta F, Di Muro C, Buti G, Pentimone F, Santoro G. Heart rate variability and ventricular late potentials in beta-thalassemia major. Haematologica 2004;89:233-4.

34. Prchal JT, Crist WM, Roper M, Wellner VP. Hemolytic anemia, recurrent metabolic acidosis, and incomplete albinism associated with glutathione synthetase deficiency. Blood 1983;62:754-7.

APPENDICES

Supplementary Table 1. Demographics of the Study Population With Sudden Cardiac Arrest According to Severity of Anemia

	Men				Women			
	None (n=304)	**Mild anemia (n=64)**	**Moderate anemia (n=26)**	**Severe anemia (n=2)**	**None (n=131)**	**Mild anemia (n=55)**	**Moderate anemia (n=30)**	**Severe anemia (n=4)**
Age, years	62.5±12.2	69.0±11.7	67.5±12.3	69.0±21.2	69.9±11.3	72.8±10.7	68.2±13.3	76.3±16.1
BMI	23.6±3.1	22.3±3.4	21.9±3.0	20.2±3.0	23.8±3.3	22.7±3.0	22.5±3.5	23.7±0.5
Systolic BP, mmHg	129.5±16.6	123.3±15.6	128.3±15.7	112.5±31.8	129.7±17.3	126.4±15.9	123.6±15.9	112.5±12.6
Diastolic BP, mmHg	79.7±10.4	73.5±11.2	74.5±8.6	70.0±14.1	77.8±10.5	76.8±9.5	76.1±13.3	70.0±8.2
Hypertension	157 (51.6)	41 (64.1)	16 (61.5)	1 (50.0)	87 (66.4)	39 (70.9)	22 (73.3)	4 (100.0)
Diabetes mellitus	89 (29.3)	34 (53.1)	14 (53.8)	1 (50.0)	47 (35.9)	25 (45.5)	15 (50.0)	1 (25.0)
HF	23 (7.6)	6 (9.4)	3 (11.5)	0 (0.0)	23 (17.6)	15 (27.3)	11 (36.7)	3 (75.0)
Dyslipidemia	101 (33.2)	28 (43.8)	10 (38.5)	1 (50.0)	53 (40.5)	24 (43.6)	13 (43.3)	1 (25.0)
CKD	49 (16.1)	21 (32.8)	8 (30.8)	2 (100.0)	42 (32.1)	20 (36.4)	15 (50.0)	1 (25.0)
ESRD	1 (0.3)	2 (3.1)	1 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)	2 (6.7)	0 (0.0)
COPD	46 (15.1)	13 (20.3)	4 (15.4)	0 (0.0)	25 (19.1)	10 (18.2)	7 (23.3)	1 (25.0)
Previous MI	21 (6.9)	9 (14.1)	2 (7.7)	0 (0.0)	5 (3.8)	5 (9.1)	4 (13.3)	0 (0.0)
Previous ischemic stroke	37 (12.2)	8 (12.5)	5 (19.2)	0 (0.0)	21 (16.0)	9 (16.4)	5 (16.7)	3 (75.0)
Malignancy	48 (15.8)	17 (26.6)	7 (26.9)	0 (0.0)	21 (16.0)	7 (12.7)	4 (13.3)	1 (25.0)
Smoking, pack-years	17.1±18.6	13.6±17.1	20.5±31.1	12.0±11.3	0.8±3.5	1.4±5.1	1.0±3.1	0.0±0.0
Creatinine, mg/dL	1.2±1.3	1.4±1.2	2.3±4.2	1.0±0.0	1.2±1.3	1.1±0.6	1.4±1.7	1.3±0.5
eGFR, $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$	79.0±22.8	68.8±25.0	68.1±30.5	73.4±4.6	70.8±20.8	65.6±19.5	59.6±26.8	67.6±28.7
Total cholesterol, mg/dL	193.2±38.6	177.8±43.3	163.9±32.7	113.5±61.5	206.9±46.1	198.0±43.6	187.8±58.0	168.0±36.0

Continuous variables are expressed as mean ± standard deviation and categorical variables as number (%). BP, blood pressure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; heart failure, HF; MI, myocardial infarction.

Supplementary Table 2. Incidence of QTc Prolongation by the Mean Cell Volume Category

	Microcytic anemia (n=78)	Normocytic anemia (n=934)	Macrocytic anemia (n=102)	*P* value
QTc prolongation, n. (%)				
Overall	24 (31)	366 (39)	44 (43)	0.11
Men	13 (50)	253 (59)	35 (59)	0.56
Women	11 (21)	113 (22)	9 (21)	0.98
T-wave abnormality, n. (%)				
Overall	1,203 (33)	332 (36)	30 (29)	0.32
Men	8 (31)	125 (29)	15 (25)	0.54
Women	23 (44)	207 (41)	15 (35)	0.37
LVH, n. (%)				
Overall	8 (10)	143 (15)	11 (11)	0.92
Men	3 (12)	85 (20)	7 (12)	0.55
Women	5 (10)	58 (11)	4 (9)	0.99

Numbers in parenthesis are percentage value. Data analysis was done for patients whose MCV parameters were available. MCV defined as follows: microcytic, <80 fL; normocytic, 80 to ≤100 fL; macrocytic, >100 fL. fL, femtoliters (10^{-15}); LVH, Left ventricular hypertrophy; MCV, mean cell volume; QTc, corrected QT interval.

ABSTRACT(IN KOREAN)

빈혈과 급성 심정지 위험성의 상관관계 : 국민건강보험공단 코호트 분석

<지도교수 정보영>

연세대학교 대학원 의학과

김 인 중

서론 : 일반 인구에서 빈혈과 급성 심정지의 관계는 명확하지 않으며 따라서 우리는 국민건강보험공단 표본 코호트 분석을 통하여 이들의 관계를 알아보고자 한다.

재료 및 방법 : 우리는 국민건강보험공단에서 제공하는 검진을 받은 494,948명을(평균연령, 47.8세; 남성 245,333[49.6%]) 대상으로 연구하였다. 평균 5.4년의 추적조사기간 동안 616명(남성 391, 여성 220)의 대상에서 급성 심정지가 발생하였다. 네 개의 빈혈 군에서 발생한 급성 심정지는 남성(1000인년 당 0.3, 1.5, 5,3, 4,5)과 여성(1000인년 당 0.2, 0.5, 0.5, 1.2)에서 각각 증가하였다. 다변량 모델로 심혈관 위험 인자를 보정하였을 때 급성 심정지의 위험은 헤모글로빈이 1g/dL 감소할 때마다 남성과 여성에서 각각 21%(95% 신뢰구간, 13–29%; $P<0.001$)와 24%(95% 신뢰구간, 13–37%; $P<0.001$)로 증가하였다. 남성에서 QTc 간격과 헤모글로빈은 음의 상관관계를 보였다.

결과 : 국민건강보험공단 표본 코호트 분석을 통하여 빈혈이 급성 심정지의 위험을 증가시켰고 수반되는 위험인자들을 보정한 후에도 급성 심정지의 위험은 증가하였다. 빈혈과 급성 심정지의 연관성은 빈혈에 의한 부정맥 위험률 증가 등으로 연관이 있을 수 있으며 이에 대한 추가적인 연구가 필요하다.

핵심되는 말: 빈혈; 급성 심정지; 일반 인구