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Original Article

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Association of Higher Hemoglobin Level With Significant Carotid Artery Plaque in the General Population

Seong Soon Kwon,[1] **Seug Yun Yoon**,[2] **Kyoung-Ha Kim**,[2] **Byoung-Won Park**,[1] **Min-Ho Lee**,[1] **Hyoungnae Kim**,[3] **Duk Won Bang**[1]

[1]Division of Cardiology, Department of Internal Medicine, Soonchunhyang University Seoul Hospital, Seoul, Korea
[2]Division of Hematology & Medical Oncology, Department of Internal Medicine, Soonchunhyang University Seoul Hospital, Seoul, Korea
[3]Division of Nephrology, Department of Internal Medicine, Soonchunhyang University Seoul Hospital, Seoul, Korea

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Correspondence to
Duk Won Bang
Division of Cardiology, Department of Internal Medicine, Soonchunhyang University Seoul Hospital, 59 Daesagwan-ro, Yongsan-gu, Seoul 04401, Korea.
Email: ontop04@gmail.com

ORCID iDs
Seong Soon Kwon
https://orcid.org/0000-0001-6516-3220
Seug Yun Yoon
https://orcid.org/0000-0001-8228-0218
Kyoung-Ha Kim
https://orcid.org/0000-0001-8842-4761
Byoung-Won Park
https://orcid.org/0000-0002-7137-9025
Min-Ho Lee
https://orcid.org/0000-0003-0748-7766
Hyoungnae Kim
https://orcid.org/0000-0002-5359-0214
Duk Won Bang
https://orcid.org/0000-0002-6691-7546

ABSTRACT

Objective: Serum hemoglobin (Hb) level affects the viscosity of blood. Several studies have reported that Hb level is associated with adverse cardiovascular outcome. However, there is a paucity of evidence on the association between serum Hb level and the risk of subclinical atherosclerosis. Thus, the objective of this study was to investigate the relationship between Hb level and risk of carotid plaque in a health checkup cohort.
Methods: This retrospective study analyzed a total of 3,805 individuals without history of cardiovascular disease (CVD) who underwent carotid ultrasonography (USG) between January 2016 and June 2018. Participants were divided into 4 groups based on Hb quartiles in each of male and female. Carotid plaque score was calculated based on USG reports. Multivariable logistic regression analysis was performed for each index of quartile groups regarding the risk of carotid plaque.
Results: Of 3,805 individuals (mean age, 52.62±10.25 years; 2,674 [70.28%] males), mean Hb level was 15.11±0.75 g/dL in male and 13.35±0.74 g/dL in female. When the Q1 group was compared to the Q4, increasing quartile of Hb was associated with the presence of significant carotid plaque (plaque score ≥3) in male (adjusted odds ratio [OR], 1.538; 95% confidence interval [CI], 1.182–2.001; p=0.001) and female (adjusted OR, 1.749; 95% CI, 1.058–2.676; p=0.01).
Conclusion: A high Hb level is associated with an increased risk of carotid plaques in individuals without history of CVD. This finding may support the need for early screening of CVD in individuals with high Hb levels.

Keywords: Hemoglobin; Atherosclerosis; Risk factors

INTRODUCTION

Since changes in hemoglobin (Hb) level can affect hemodynamics of the heart, Hb level is closely related to various cardiovascular outcomes. There is some evidence suggesting that high levels of Hb might be associated with an increased risk of developing atherosclerosis, although the exact relationship between the two is not fully understood yet.

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Conflict of Interest

The authors have no conflicts of interest to declare.

Data Availability Statement

The data underlying this article cannot be shared publicly to protect the privacy of individuals that participated in the study. The data will be shared on reasonable request to the corresponding author.
All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Author Contributions

Conceptualization: Yoon SY, Kim KH, Park BW; Data curation: Kwon SS; Formal analysis: Kwon SS, Kim H; Methodology: Kwon SS, Yoon SY; Resources: Kwon SS; Supervision: Bang DW; Visualization: Kwon SS; Writing - original draft: Kwon SS; Writing - review & editing: Yoon SY, Kim KH, Park BW, Lee MH, Kim H, Bang DW.

Potential mechanisms explaining an association of high Hb levels with an increased cardiovascular disease (CVD) risk include increased peripheral platelet activation and increased oxidative stress from increased iron accumulation.[1] On the other side, low Hb levels could potentially lead to increased left ventricular (LV) mass and LV filling pressure ultimately predisposing to development of CVD.[2]

Studies investigating the relationship between Hb level and CVDs have shown inconsistent results. One study has reported that increasing Hb level is associated with a lower severity of atherosclerosis.[3] However, the average Hb in that study was 9.1 g/dL for men and 8.4 g/dL for women, indicating severe anemia. Therefore, it is difficult to apply results of that study to the general population whose Hb levels are within the normal range. Another study has reported that low Hb level is associated with an increased risk of major adverse cardiovascular events.[4] However, since patients were limited to men over 70 years of age, it was difficult to generalize results of that study. Another previous study has suggested that people with high Hb levels might be more likely to have increased arterial stiffness, a risk factor for atherosclerosis.[5] There is also evidence that both lower and higher Hb levels were associated with a higher risk of stroke[6] and all cause mortality.[7] However, there is a paucity of evidence on the association between Hb level and risk of subclinical atherosclerosis, especially in the general population without overt CVD. Carotid ultrasonography (USG) is a fast and non-invasive method to detect subclinical atherosclerotic change of artery. It is a useful tool to assess future risk of CVD.[8] Therefore, the aim of this study was to evaluate the association between Hb level and risk of carotid plaque in a health checkup cohort.

MATERIALS AND METHODS

1. Study population

We performed a single-center, retrospective study that a total of 4,306 individuals aged over 20 years old who underwent carotid USG as part of the medical health checkup program in the Health Promotion Center of Soonchunhyang University Seoul Hospital between January 2016 and June 2018. Among them, 129 participants with a history of CVD or stroke were excluded. To confine the analysis to subjects with Hb level in the normal range, polycythemia[9] (Hb greater than 16.5 g/dL in male and 16 g/dL in female) and anemia[10] (Hb less than 13 g/dL in male and 12 g/dL in female) subjects were excluded. Finally, 3,805 subjects were eligible for inclusion in the present study. All participants were stratified into 4 groups based on Hb quartiles in each of male and female (Q1 was the lowest Hb level and Q4 was the highest level) (**Fig. 1**).

This study followed the principles of the Helsinki declaration, and the study protocol was approved by the Institutional Review Board (IRB) of the of Soonchunhyang University Seoul Hospital (IRB No. 2023-01-005). The requirement for informed consent was waived by the IRB owing to its retrospective nature.

2. Variables and definitions

Demographic information were obtained from the medical records. Previous medical history and health behaviors such as smoking status were evaluated using a self-report questionnaire completed during an interview. Body mass index (BMI) was calculated as weight divided by the square of height (kg/m^2). Obesity was defined as BMI ≥25 kg/m^2 according to the World Health Organization standards for Asians. Blood pressure (BP) measurements were

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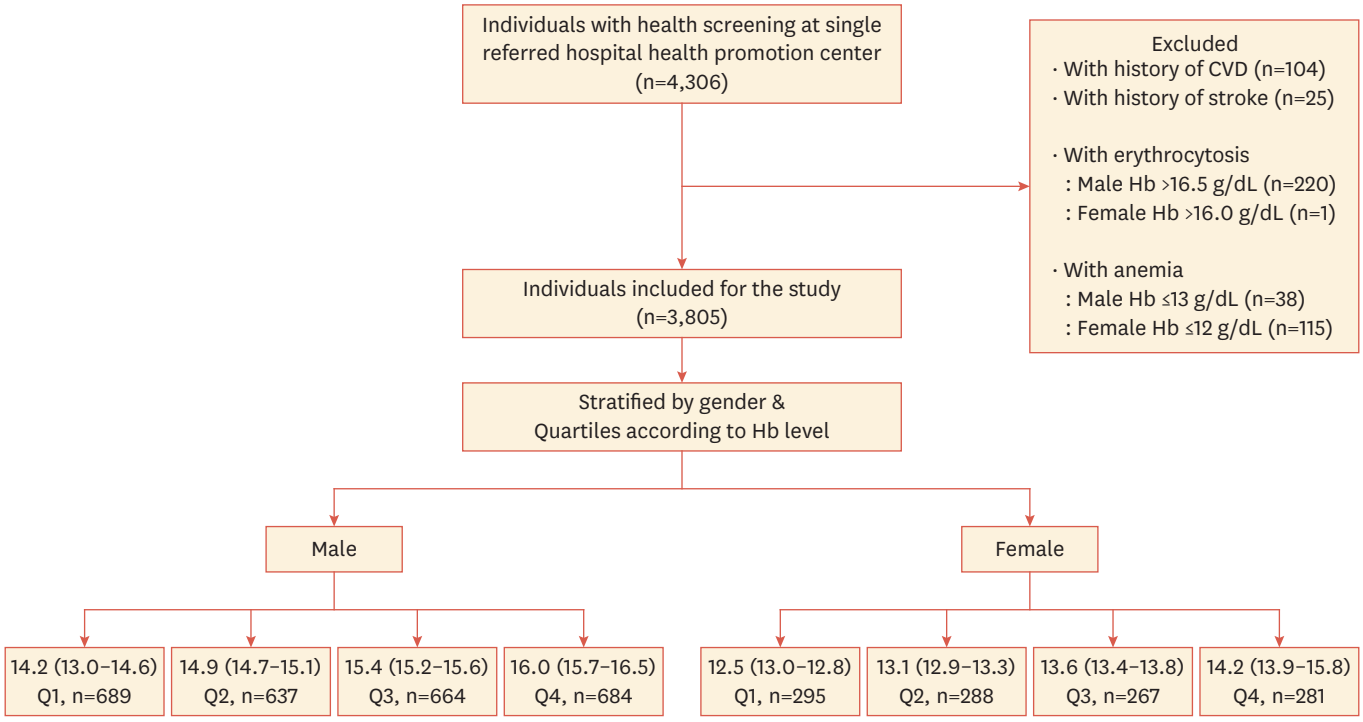

Fig. 1. Patient enrollment flowchart. Hb level is expressed as median (minimum–maximum) value.
Hb, hemoglobin (g/dL); CVD, cardiovascular disease.

performed by experienced nurses for all subjects on the right arm after a rest ≥5 minutes using automated oscillometric manometers and appropriate cuff sizes. For all subjects, blood tests were performed after at least 8 hours of fasting without intake of caffeine, alcohol, or smoking. Participants who smoked at least one cigarette per day at the time of the health screening were defined as current smokers. Fasting blood samples were collected in an EDTA-2K tube, a heparin sodiumtube and a siliconized tube. Hb was measured using absorption spectrophotometry at Alinity HQ Analyzer® (Abbott). Presence of diabetes mellitus was defined as either fasting blood glucose level ≥126 mg/dL, or Hb A1c level ≥6.5%, or current use of any glucose lowering medications. Hypertension was defined as either current use of antihypertensive medication or having a measured BP ≥140/90 mmHg at health screening examinations. Dyslipidemia was defined based on the information the patient filled out in the self-report questionnaire. Serum creatinine level was measured using a calibration traceable to an isotope dilution mass spectrometry reference. Estimated glomerular filtration rate (eGFR) was calculated with the Chronic Kidney Disease Epidemiology Collaboration equation based on serum creatinine level.[11]

3. Carotid USG examination

A high-resolution B-mode USG (EPIQ 5C or IE 33 USG systems; Philips) equipped with an 11.0 MHz linear array transducer was used for carotid USG. Common carotid artery intima-media thickness (IMT) was measured from the level of the common carotid artery (1 cm proximal to the dilation of the carotid bulb) far wall in a region free of plaque. A new segment was selected if a plaque was found at that location. The leading edge of the lumen-intima interface and the media-adventitia interface of the B-mode frame were measured in order to calculate IMT. Software (Q-lab; Philips Medical Systems) that could automatically assess IMT at 64 places in a 10-mm segment was used. The value given was the arithmetic mean of IMT

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calculated. Mean carotid IMT was determined as the average of all measurements of both left and right arteries. Carotid plaque was defined as local thickening of the IMT of >50% compared to the surrounding vessel wall, an IMT >1.5 mm, or local thickening >0.5 mm.[12] Extracranial carotid arteries were divided into 3 sectors on each side: common carotid artery, carotid bifurcation, and internal carotid artery. To define plaque burden, the carotid plaque score was calculated as a total number of sites with plaques ranging from 0 to 6 (right and left sided common carotid artery, carotid bifurcation, and internal carotid artery).[13] A carotid plaque score of 3 or above was considered significant. All measurements were performed with the same device by the same experienced sonographer (SM Yoon, a registered diagnostic cardiac sonographer with 10 years of experience.). The intra-class correlation coefficient for carotid plaque score was 0.937 (95% confidence interval [CI], 0.890–0.964, $p<0.001$).

4. Data analysis

The expression for continuous variables is mean ± standard deviation (SD). A Student's *t*-test was used to compare them. The expression for categorical variables is numbers and percentages. A χ^2 test was used to compare them. Nonparametric variables are expressed as median and interquartile range using a Mann-Whitney *U* test. We had no missing data except for high-sensitive C-reactive protein (hs-CRP) (10.26%). Thus, we replaced missing data of hs-CRP with values obtained using multiple imputation with missing at random assumption. Multivariable logistic regression model was used to assess relationships between exposures and outcomes in each of male and female. Initially, Hb level was treated as a continuous variable. Thereafter, it was analyzed according to quartiles (Q) (Q1 lowest, Q4 highest). To evaluate the relationship between Hb and significant carotid plaque (plaque score ≥3), we adjusted for the following covariables: age, smoking, history of hypertension, diabetes, dyslipidemia, obesity, fasting blood sugar, low-density lipoprotein (LDL) cholesterol, triglyceride, hs-CRP, and eGFR. In addition to categorical analysis, association between Hb level as a continuous variable and the risk of significant carotid plaque was graphically presented with restricted cubic spline derived with equally distributed 3 knots based on a logistic regression model). In sensitivity analysis, we used various definitions of significant carotid plaque and showed associations with Hb level. Statistical significance was defined at $p<0.05$. All analyses were conducted using the R language version 4.2.2 (R Foundation for Statistical Computing).

RESULTS

1. Baseline characteristics of the study population

Baseline characteristics of participants according to quartiles of Hb level are presented in **Table 1**. The study cohort was divided into the following Hb quartile groups: Q1) 13–14.6 g/dL, Q2) 14.7–15.1 g/dL, Q3) 15.2–15.6 g/dL, and Q4) 15.7–16.5 g/dL. Of 3,805 individuals (mean age, 52.62±10.25 years; 2,674 [70.28%] males), mean Hb level was 15.11±0.75 g/dL in male and 13.35±0.74 g/dL in female. Mean carotid plaque score was 1.74±1.45. Subjects in higher quartiles of Hb group were younger. They had higher prevalence of current smoker and obesity than lower quartiles of Hb group. Blood test results showed that those in higher quartiles of Hb group had higher total cholesterol, LDL cholesterol, and triglyceride level, whereas they had lower levels of high-density lipoprotein cholesterol than those in lower quartiles of Hb group.

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Table 1. The baseline characteristics of study population according to the Hb level

Characteristics	Total (n=3,805)	Q1 (Hb 13–14.6) (n=984)	Q2 (Hb 14.7–15.1) (n=925)	Q3 (Hb 15.2–15.6) (n=931)	Q4 (Hb 15.7–16.5) (n=965)	*p*-value
Age (yr)	52.62±10.25	54.46±10.49	52.15±10.16	51.69±10.33	52.08±9.76	<0.001
Sex (male)	2,674 (70.28)	689 (70.02)	637 (68.86)	664 (71.32)	684 (70.88)	0.667
Current smoker	784 (20.6)	180 (18.29)	171 (18.49)	206 (22.13)	227 (23.52)	0.007
Hypertension	1,050 (27.6)	264 (26.83)	257 (27.78)	256 (27.5)	273 (28.29)	0.909
Diabetes mellitus	410 (10.78)	118 (11.99)	93 (10.05)	98 (10.53)	101 (10.47)	0.538
Dyslipidemia	413 (10.85)	130 (13.21)	96 (10.38)	95 (10.2)	92 (9.53)	0.046
BMI (kg/m^2)	24.56±3.17	24.02±3.08	24.44±3.09	24.76±3.18	25.01±3.26	<0.001
Obesity	1,591 (41.81)	349 (35.47)	370 (40)	408 (43.82)	464 (48.08)	<0.001
SBP (mmHg)	123 (112–132)	120 (110–130)	122 (112–131)	123 (112–132.5)	125 (115–133)	<0.001
DBP (mmHg)	75 (68–82)	72 (66–80)	74 (68–82)	76 (69–82)	77 (70–84)	<0.001
hs-CRP (mg/L)	0.13±0.35	0.14±0.53	0.12±0.29	0.11±0.19	0.13±0.28	0.129
Hb (g/dL)	14.59±1.10	13.63±0.84	14.34±0.85	14.87±0.83	15.53±0.83	<0.001
eGFR (mL/min/1.73 m^2)	93.49±13.07	93.47±13.83	93.66±13.09	93.91±12.61	92.95±12.67	0.396
FBS (mg/dL)	96.21±19.45	96.33±20.05	96.07±18.23	96.12±19.69	96.32±19.75	0.987
HbA1c (%)	5.63±0.73	5.67±0.71	5.62±0.68	5.60±0.75	5.61±0.76	0.177
Total cholesterol (mg/dL)	193 (169–217)	187 (162–211)	193 (168–215)	194 (171.5–218)	199 (175–222)	<0.001
LDL cholesterol (mg/dL)	127 (105–150)	121 (97–144)	126 (105–148)	128 (107–152)	133 (109–156)	<0.001
HDL cholesterol (mg/dL)	55 (46–66)	57 (48–68)	55 (47–67)	55 (47–65)	53 (44–63)	<0.001
Triglyceride (mg/dL)	114 (81–165)	103 (75–149)	111 (80–155)	116 (82–168.5)	128 (91–182)	<0.001
Carotid IMT (mm)	0.57±0.10	0.58±0.10	0.57±0.10	0.57±0.10	0.58±0.10	0.049
Carotid plaque score	1.74±1.45	1.41±1.32	1.84±1.51	1.83±1.46	1.89±1.47	<0.001

Values are presented as number (%), median (range), or mean ± standard deviation.
Hb, hemoglobin; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; hs-CRP, high-sensitive C-reactive protein; eGFR, estimated glomerular filtration rate; FBS, fasting blood sugar; HbA1c, glycated hemoglobin; LDL, low-density lipoprotein; HDL, high-density lipoprotein; IMT, intima-media thickness.

2. Risk of significant carotid artery plaque according to Hb level

Supplementary Fig. 1. shows differences in carotid plaque score among subjects from quartiles 1 to 4. When we classified carotid plaque score into 0, 1, 2, and ≥3, the number of subjects with significant carotid plaque (score ≥3) was the lowest in the Q1 group, with the number being constantly higher in higher quartiles of Hb in both with male and female. Carotid plaque was most frequently found at the bifurcation site on both sides regardless of Hb quartiles (**Supplementary Table 1**).

In a logistic regression model adjusted for confounding factors, when the Q1 group was set as a reference, it was observed that in male, as the quartile of Hb level increased, the risk of significant carotid plaque increased in a stepwise fashion. In female, the risk of significant carotid plaque was not robust in the Q2 and Q3 group, but significantly associated with Q4 group. Compared to Q1 group, Q4 group showed 1.54 times higher risk of significant carotid plaque (adjusted odds ratio [OR], 1.538; 95% CI, 1.182–2.001; *p*=0.001) in male and 1.75 times higher risk of significant carotid plaque (adjusted OR, 1.749; 95% CI, 1.144–2.676; *p*=0.01) in female. When Hb level was analyzed as a continuous variable, 1-SD increment in Hb level was associated with a 23% higher risk of significant carotid plaque (adjusted OR, 1.230; 95% CI, 1.085–1.394, *p*=0.001) in male and 29% higher risk of significant carotid plaque (adjusted OR, 1.288; 95% CI, 1.058–1.569; *p*=0.012) in female (**Table 2**). Restricted cubic spline analysis showed similar results. In male, the risk of significant carotid plaque increased progressively with increasing Hb level, while in female, there was no significant change in risk at lower percentiles of Hb, but an increased risk was observed as the percentiles increased (**Figs. 2** and **3**).

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Table 2. Multivariable logistic regression analysis for the association of hemoglobin to the risk of significant carotid plaque

Exposures	Male		Female	
	Adjusted OR* (95% CI)	*p*-value	Adjusted OR* (95% CI)	*p*-value
Quartiles of hemoglobin				
Q1	Ref.	-	Ref.	-
Q2	1.448 (1.113–1.884)	0.006	1.442 (0.929–2.238)	0.103
Q3	1.461 (1.121–1.902)	0.005	1.547 (0.996–2.403)	0.052
Q4	1.538 (1.182–2.001)	0.001	1.749 (1.144–2.676)	0.010
Hemoglobin as continuous variable (Per 1 SD increment)	1.230 (1.085–1.394)	0.001	1.288 (1.058–1.569)	0.012

Significant carotid plaque was defined as carotid plaque score ≥3.
OR, odds ratio; CI, confidence interval; SD, standard deviation; eGFR, estimated glomerular filtration rate; FBS, fasting blood sugar; LDL, low-density lipoprotein; hs-CRP, high-sensitive C-reactive protein.
*Adjusted for age, smoking, history of hypertension, diabetes, dyslipidemia, obesity, eGFR, FBS, LDL cholesterol, triglyceride, and hs-CRP.

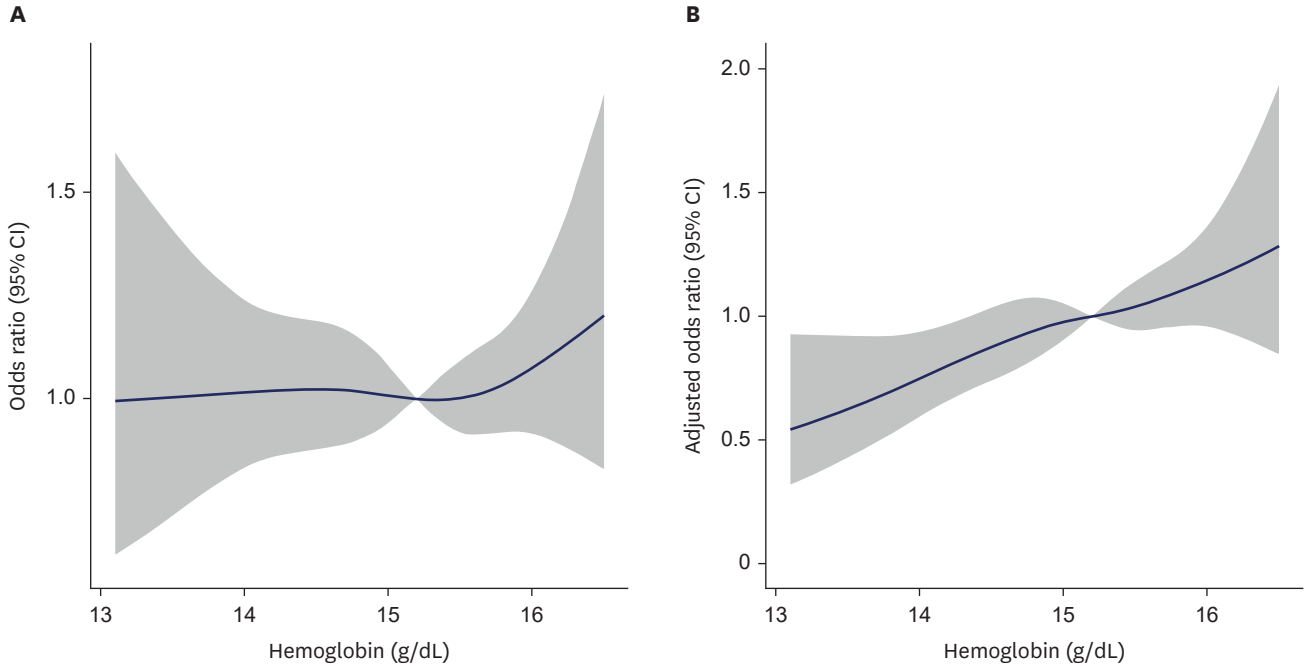

Fig. 2. Restrictive cubic spline curve for the relationship between hemoglobin and significant carotid plaque in male. (A) Unadjusted; (B) Adjusted. Adjusted curve is derived from multivariable logistic regression model with adjusting for age, smoking, history of hypertension, diabetes, dyslipidemia, obesity, estimated glomerular filtration rate, fasting blood sugar, low-density lipoprotein cholesterol, triglyceride, and high-sensitive C-reactive protein.
CI, confidence interval.

3. Sensitivity analysis

We performed a sensitivity analysis to determine the association of Hb with differently defined significant carotid plaque. When using the carotid plaque score from 1 to 4 as a definition of significant carotid plaque, consistent results were observed regardless of the score in male, whereas in female there was no significant correlation at scores 1 and 2. However, when defined as scores 3 and 4 or higher, significant results were found (**Table 3**).

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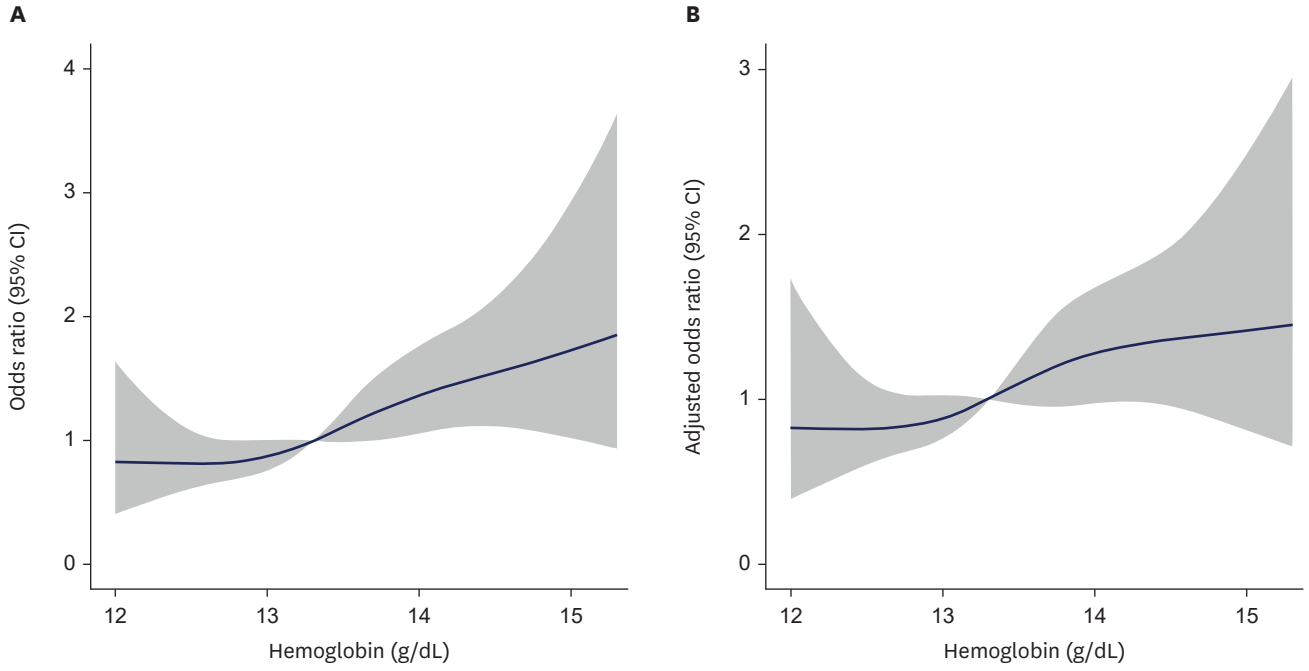

Fig. 3. Restrictive cubic spline curve for the relationship between hemoglobin and significant carotid plaque in female. (A) Unadjusted; (B) Adjusted. Adjusted curve is derived from multivariable logistic regression model with adjusting for age, smoking, history of hypertension, diabetes, dyslipidemia, obesity, estimated glomerular filtration rate, fasting blood sugar, low-density lipoprotein cholesterol, triglyceride, and high-sensitive C-reactive protein.
CI, confidence interval.

Table 3. Sensitivity analysis of the association between the hemoglobin (as continuous variable) and various definition of significant carotid plaque

Carotid plaque score	Male		Female	
	Adjusted OR (95% CI)*	*p*-value	Adjusted OR (95% CI)*	*p*-value
≥1	1.008 (1.003–1.012)	0.002	1.168 (0.956–1.428)	0.129
≥2	1.221 (1.060–1.407)	0.006	1.188 (0.968–1.456)	0.099
≥3	1.230 (1.085–1.394)	<0.001	1.288 (1.058–1.569)	0.012
≥4	1.111 (1.094–1.129)	<0.001	1.215 (1.036–1.425)	0.017

OR, odds ratio; CI, confidence interval.
*Adjusted for age, smoking, history of hypertension, diabetes, dyslipidemia, obesity, estimated glomerular filtration rate, fasting blood sugar, low-density lipoprotein cholesterol, triglyceride, and high-sensitive C-reactive protein.

DISCUSSION

In the present study, we examined the relationship between Hb and significant carotid plaque in individuals who had undergone a general health checkup. As a result, we found that increased Hb level was related to significant carotid artery plaque. This finding was consistent in sensitivity analyses.

Because the diagnostic criteria and prevalence of anemia and erythrocytosis are very different in men and women, we analyzed each gender separately. Many studies that evaluated the relationship between Hb and cardiovascular outcome analyzed men and women separately.[5,6,14] Our result was consistent regardless of gender.

Blood viscosity is important for flow. When its viscosity increases, the force applied to the vessel wall also increases, causing vessel damage.[15] The most important contributor to an increased viscosity is a high haematocrit.[16] There is an evidence that erythrocytosis is associated with cardiovascular morbidity/mortality, and all-cause mortality in large

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population-based cross-sectional study.[17] Higher level of hematocrit is also associated with increased short-term mortality compared to a normal hematocrit in ST-segment elevation myocardial infarction.[18]

Results of this study indicate that Hb can potentially affect the development and progression of atherosclerosis. Multiple mechanisms could explain how Hb is directly involved in and contributes to the progression of atherosclerosis. When red blood cells collide with the arterial wall, they can cause local hemolysis and membrane lipid retention, releasing heme-Fe++ that is toxic to the endothelial wall. This damage to the endothelium is associated with development and progression of atherosclerosis.[19] Furthermore, Hb can induce the secretion of pro-inflammatory transcription factors such as NF-κB.[20] It is well known that atherosclerosis is an inflammatory process.[21] In our study, hs-CRP level was higher in higher quartiles of the Hb group, suggesting the involvement of an inflammatory process in the development of atherosclerosis.

In one large cohort study, Hb levels showed a U-shaped relationship with all-cause mortality.[22] In our study, all subjects are within normal range Hb level. Thus, it was not a U-shaped relationship. A gradually increasing risk of significant carotid plaque was found when Hb increased. However, this relationship was not well-established. More studies are needed to confirm the link between Hb level and atherosclerosis.

It is well known that individuals with obese and poor metabolic profiles have high Hb level.[23,24] In our study, BMI, BP and cholesterol profiles also tended to be worse in the high Hb group. However, even after adjusting the variables included in the metabolic syndrome, Hb level was confirmed to be a significant factor in carotid plaque. Additionally, increasing Hb level can be caused by a variety of underlying conditions such as lung disease[25] which can increase the risk for atherosclerotic CVD.[26] Despite this limitation, since Hb is an easily measurable parameter, it is convenient to evaluate patients' cardiovascular risk indirectly in clinical practice.

In our study, we did not present a clear cut-off value of Hb to predict increased carotid plaque and only confirmed tendency according to quartile of Hb. We performed ROC analysis to suggest the optimal Hb level, but there are limitations due to the low area under the curve value. Even in a large-scale study related to Hb level, analysis was only performed by stratifying into quantile of Hb, and a clear cutoff value was not presented.[7,27] Perhaps this is because Hb level can be very different depending on the study population. Additional research is needed to confirm the cutoff value in the future.

Our study had some limitations. First, since this was a retrospective cross-sectional study, causal inferences could not be drawn. To clarify the relationship between Hb and progression of atherosclerosis, a prospective longitudinal study is needed to confirm the occurrence of major adverse cardiovascular events according to the degree of Hb level. Second, because our data had no information about specific medication, we could not examine the effect of medication such as statin that could modify carotid plaque and lipid profiles. This study also lacked information on other exposures, including alcohol intake, physical activity. Therefore, we cannot rule out the possibility of residual confounding variables for some measured and unmeasured factors. Finally, in our study, only the carotid plaque score could be counted. It has been reported that assessment of plaque burden by volume measurement is a better parameter of atherosclerosis than a simple assessment of the presence or

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absence of plaques.[28] However, the presence of carotid plaques has been reported to be an independent marker of CVD events in asymptomatic individuals.[29] In the future study, a new 3-dimensional volumetric USG method for accurate quantification of atherosclerotic plaque volume[30] is needed.

In conclusion, our study suggests that a high Hb level is associated with an increased risk of carotid plaques in individuals without history of CVD. This finding may support the need for early screening for CVD in individuals with high Hb levels. It can be used as a basis for recommending preemptive medical treatment and lifestyle modifications to these patients.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Distribution of carotid artery plaque according to hemoglobin quartiles

Supplementary Fig. 1

Carotid plaque score according to quartile of the hemoglobin level. Carotid plaque score was classified into 0,1,2, and ≥3. Quartiles were described as Q1 to Q4 (Q1 as the lowest).

REFERENCES

1. Praticó D, Pasin M, Barry OP, Ghiselli A, Sabatino G, Iuliano L, et al. Iron-dependent human platelet activation and hydroxyl radical formation: involvement of protein kinase C. Circulation 1999;99:3118-3124. PUBMED | CROSSREF
2. Cho IJ, Mun YC, Kwon KH, Shin GJ. Effect of anemia correction on left ventricular structure and filling pressure in anemic patients without overt heart disease. Korean J Intern Med 2014;29:445-453. PUBMED | CROSSREF
3. Dijk JM, Wangge G, Graaf Y, Bots ML, Grobbee DE, Algra A, et al. Hemoglobin and atherosclerosis in patients with manifest arterial disease. The SMART-study. Atherosclerosis 2006;188:444-449. PUBMED | CROSSREF
4. Gnanenthiran SR, Ng AC, Cumming RG, Brieger DB, le Couteur DG, Waite LM, et al. Hemoglobin, frailty, and long-term cardiovascular events in community-dwelling older men aged ≥ 70 years. Can J Cardiol 2022;38:745-753. PUBMED | CROSSREF
5. Shimizu Y, Nakazato M, Sekita T, Kadota K, Yamasaki H, Takamura N, et al. Association between hemoglobin levels and arterial stiffness for general Japanese population in relation to body mass index status: the Nagasaki Islands study. Geriatr Gerontol Int 2014;14:811-818. PUBMED | CROSSREF
6. Panwar B, Judd SE, Warnock DG, McClellan WM, Booth JN 3rd, Muntner P, et al. Hemoglobin concentration and risk of incident stroke in community-living adults. Stroke 2016;47:2017-2024. PUBMED | CROSSREF
7. Kabat GC, Kim MY, Verma AK, Manson JE, Lessin LS, Kamensky V, et al. Association of hemoglobin concentration with total and cause-specific mortality in a cohort of postmenopausal women. Am J Epidemiol 2016;183:911-919. PUBMED | CROSSREF
8. Polak JF, Szklo M, Kronmal RA, Burke GL, Shea S, Zavodni AE, et al. The value of carotid artery plaque and intima-media thickness for incident cardiovascular disease: the multi-ethnic study of atherosclerosis. J Am Heart Assoc 2013;2:e000087. PUBMED | CROSSREF
9. Barbui T, Thiele J, Gisslinger H, Kvasnicka HM, Vannucchi AM, Guglielmelli P, et al. The 2016 WHO classification and diagnostic criteria for myeloproliferative neoplasms: document summary and in-depth discussion. Blood Cancer J 2018;8:15. PUBMED | CROSSREF
10. Nutritional anaemias. Report of a WHO scientific group. World Health Organ Tech Rep Ser 1968;405:5-37. PUBMED
11. Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med 2012;367:20-29. PUBMED | CROSSREF

12. Naqvi TZ, Lee MS. Carotid intima-media thickness and plaque in cardiovascular risk assessment. JACC Cardiovasc Imaging 2014;7:1025-1038. PUBMED | CROSSREF
13. Hollander M, Bots ML, Del Sol AI, Koudstaal PJ, Witteman JC, Grobbee DE, et al. Carotid plaques increase the risk of stroke and subtypes of cerebral infarction in asymptomatic elderly: the Rotterdam study. Circulation 2002;105:2872-2877. PUBMED | CROSSREF
14. 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. PUBMED | CROSSREF
15. Pop GA, Duncker DJ, Gardien M, Vranckx P, Versluis S, Hasan D, et al. The clinical significance of whole blood viscosity in (cardio)vascular medicine. Neth Heart J 2002;10:512-516. PUBMED
16. Nader E, Skinner S, Romana M, Fort R, Lemonne N, Guillot N, et al. Blood rheology: key parameters, impact on blood flow, role in sickle cell disease and effects of exercise. Front Physiol 2019;10:1329. PUBMED | CROSSREF
17. Wouters HJ, Mulder R, van Zeventer IA, Schuringa JJ, van der Klauw MM, van der Harst P, et al. Erythrocytosis in the general population: clinical characteristics and association with clonal hematopoiesis. Blood Adv 2020;4:6353-6363. PUBMED | CROSSREF
18. Greenberg G, Assali A, Vaknin-Assa H, Brosh D, Teplitsky I, Fuchs S, et al. Hematocrit level as a marker of outcome in ST-segment elevation myocardial infarction. Am J Cardiol 2010;105:435-440. PUBMED | CROSSREF
19. Michel JB, Martin-Ventura JL. Red blood cells and hemoglobin in human atherosclerosis and related arterial diseases. Int J Mol Sci 2020;21:6756. PUBMED | CROSSREF
20. Moreno PR, Purushothaman KR, Sirol M, Levy AP, Fuster V. Neovascularization in human atherosclerosis. Circulation 2006;113:2245-2252. PUBMED | CROSSREF
21. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. Circulation 2002;105:1135-1143. PUBMED | CROSSREF
22. Martinsson A, Andersson C, Andell P, Koul S, Engström G, Smith JG. Anemia in the general population: prevalence, clinical correlates and prognostic impact. Eur J Epidemiol 2014;29:489-498. PUBMED | CROSSREF
23. Wu S, Lin H, Zhang C, Zhang Q, Zhang D, Zhang Y, et al. Association between erythrocyte parameters and metabolic syndrome in urban Han Chinese: a longitudinal cohort study. BMC Public Health 2013;13:989. PUBMED | CROSSREF
24. He S, Gu H, Yang J, Su Q, Li X, Qin L. Hemoglobin concentration is associated with the incidence of metabolic syndrome. BMC Endocr Disord 2021;21:53. PUBMED | CROSSREF
25. Zhang J, DeMeo DL, Silverman EK, Make BJ, Wade RC, Wells JM, et al. Secondary polycythemia in chronic obstructive pulmonary disease: prevalence and risk factors. BMC Pulm Med 2021;21:235. PUBMED | CROSSREF
26. Chen W, Thomas J, Sadatsafavi M, FitzGerald JM. Risk of cardiovascular comorbidity in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. Lancet Respir Med 2015;3:631-639. PUBMED | CROSSREF
27. Chang JY, Lee JS, Kim BJ, Kim JT, Lee J, Cha JK, et al. Influence of hemoglobin concentration on stroke recurrence and composite vascular events. Stroke 2020;51:1309-1312. PUBMED | CROSSREF
28. Spence JD. Measurement of carotid plaque burden. Curr Opin Lipidol 2020;31:291-298. PUBMED | CROSSREF
29. Mehta A, Rigdon J, Tattersall MC, German CA, Barringer TA 3rd, Joshi PH, et al. Association of carotid artery plaque with cardiovascular events and incident coronary artery calcium in individuals with absent coronary calcification: the MESA. Circ Cardiovasc Imaging 2021;14:e011701. PUBMED | CROSSREF
30. López-Melgar B, Mass V, Nogales P, Sánchez-González J, Entrekin R, Collet-Billon A, et al. New 3-dimensional volumetric ultrasound method for accurate quantification of atherosclerotic plaque volume. JACC Cardiovasc Imaging 2022;15:1124-1135. PUBMED | CROSSREF