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Platelet and white blood cell count are independently associated with sarcopenia: A nationwide population-based study

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ABSTRACT

Introduction: Sarcopenia is attracting increasing attention due to its harmful impacts on health. Chronic inflammation is proposed to be a major cause of sarcopenia. Here, we aimed to identify whether white blood cell (WBC) and platelet count have independent roles in sarcopenia occurrence.

Method and materials: This cross-sectional study analyzed 10,092 adults (4293 men and 5799 women) from the 2008–2011 Korea National Health and Nutrition Survey. Cut-off values for sarcopenia were defined as a skeletal muscle mass index < 0.789 for men and < 0.512 for women. We calculated odds ratios (ORs) and 95% confidence intervals (CIs) using multiple logistic regression analysis after adjusting for confounding variables. ROC curve analysis was used to evaluate the ability of platelet count and white blood cell count to discriminate the presence of sarcopenia.

Results: After adjusting for possible confounders, the OR (95% CI) for sarcopenia occurrence according to platelet counts was 1.62 (1.20–2.19) for the T3 group in men and 1.72 (1.28–2.31) for the T3 group in women, relative to the lowest platelet count tertile. After adjusting for same confounders, the ORs (95% CI) for sarcopenia occurrence according to WBC counts was 1.86 (1.35–2.57) for the T3 group in men, and 2.36 (1.77–3.13) for the T3 group in women, relative to the lowest WBC count tertile. We also found independent significant associations between platelet count, WBC count, and sarcopenia.

Conclusions: Higher platelet and WBC counts within the normal range are each independently associated with sarcopenia in Korean men and women. The inclusion of platelet, WBC, or combined platelet and WBC counts significantly improved the power to discriminate sarcopenia.

1. Introduction

A high white blood cell (WBC) count indicates low-grade inflammation and is a well-known risk factor for cardiovascular disease, diabetes, and metabolic syndrome [1–3]. Platelets, a major component of blood, contribute to hemostasis and thrombosis [4]. Platelet count is also linked to cardiometabolic diseases, subclinical inflammation, and oxidative stress [5–7]. These two components have been used clinical predictor for all-cause mortality and cardiovascular diseases [8–10].

Skeletal muscle mass is approximately 40% of total body mass and is fundamentally important to maintaining health [11]. After age 25, skeletal muscle decreases slightly and then after age 65 decreases rapidly [12]. This aging-related progressive loss of muscle mass and strength was first termed 'sarcopenia' by Rosenberg et al. in 1989 [13]. Sarcopenia leads to functional decline, falls, impaired cardiopulmonary function, and eventually increased mortality [14]. Several factors (i.e. oxidative stress, endocrine abnormality, undernutrition, physical inactivity) are associated with sarcopenia [15]. Considerable evidence

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indicates that systemic inflammation is closely associated with muscle mass loss [16–18].

WBC and platelet counts are widely available and affordable disease indicators that can be used in clinical settings. WBC count is a standardized and stable maker that measures systemic inflammation [19]. Platelet count is also stable marker with low intra-individual variation and also has a role in the inflammation process [20,21]. Therefore, previous studies have explored the use of WBC and platelet counts as possible markers of sarcopenia [22,23]. However, it is not well studied whether WBC count and platelet count are independently associated with sarcopenia. Therefore, we investigated whether WBC and platelet counts within the normal range were each independently associated with sarcopenia based on the hypothesis that these biomarkers are indicative of subclinical inflammation that is linked to muscle mass loss. Additionally, we tested whether WBC and platelet count have the ability in discriminating sarcopenia in the general population.

2. Methods

2.1. Study population

This study is a cross-sectional data analysis from the Korea National Health and Nutrition Survey (KNHANES). Since 1998, KNHANES has been conducted to assess health levels and provide data to predict health problems in the Korean population. The survey includes direct physical examination, clinical and laboratory tests, and personal interviews. The complex sampling plan follows a stratified, multistage, probability cluster design. Detailed information regarding study design, recruitment, and procedures are provided in previous studies [24,25].

KNHANES survey items are partially changed each year. For example, bone density and body fat tests were only available July 2008–May 2011. Therefore, we utilized the 2008–2011 KNHANES dataset to evaluate individual body compositions. During the 2008–2011 KNHANES, 18,550 participants aged 20 and older were evaluated using whole-body dual energy X-ray (DXA) measures. Our study exclusion criteria were as follows: 1) subjects diagnosed with malignancy ($n = 555$) or liver cirrhosis ($n = 35$) were excluded to avoid other confounding determinants affecting muscle loss or platelet function; 2) subjects with leukocyte counts < 3000 cells/μl or > 10000 cells/μl and missing data ($n = 1329$); and 3) subjects with platelet counts < 150 $\times 10^3$/μl or > 450 $\times 10^3$/μl and missing data ($n = 6539$). Our study included a total of 10,092 adults (4293 men and 5799 women). We obtained informed consent from all participants before the survey. This study was approved by Yong-In Severance Hospital Institutional Review Board.

2.2. Measurement of anthropometric and laboratory data

Anthropometric measurement, body composition measurement, and blood samples were taken simultaneously in a predefined mobile examination center on the same day. Anthropometric measurements (body weight, height, and waist circumference) were taken by trained medical staff using a standardized protocol [26]. Body mass index (BMI) was computed as weight divided by height^2 (kg/m^2). Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured twice with a Baumanometer (Baumanometer; Baum, Copiague, NY, USA) using the right arm and in a sitting position. Fasting blood glucose, total cholesterol (TC), triglycerides (TG), and high-density lipoprotein (HDL) cholesterol were measured in blood collected after > 8 h fasting using a Hitachi Automatic Analyzer (Hitachi Co., Tokyo, Japan). WBC counts were measured by Laserflow cytometry (XE-2100D, Sysmex, Japan). Platelet counts were quantified using a DC detection method (XE-2100D, Sysmex, Japan).

2.3. Assessment of body composition and definition of sarcopenia

We assessed body composition using DXA (QDR 4500A; Hologic Inc., Bedford, MA, USA). Bone mineral density (g/m^2) and contents (g), fat and lean mass (g) according to body part were obtained using a whole-body scan. Appendicular skeletal mass (ASM) was calculated as the sum total of skeletal mass from both arms and legs. We calculated skeletal muscle mass index as ASM/BMI. Many study groups, including the European Working Group on Sarcopenia in Older People (EWGSOP) and the Asian Working Group for Sarcopenia (AWGS) have suggested different criteria to assess sarcopenia prevalence [27,28]. In 2014, the FNIH Sarcopenia Project used data from nine large community-based cohorts (total 26,625 subjects) to emphasize the importance of BMI to sarcopenia cut-off points [29]. A recent study conducted in Korea found that the new criteria suggested by FNIH better correlated with increased mortality risk and provided better predictive values [30]. Another study conducted in Korea suggested that ASM/BMI could be more appropriate for diagnosis of sarcopenia, due to different distributions of skeletal muscle mass and height in each age group of Koreans [31]. Thus, in this study, we adopted the ASM/BMI ratio to define sarcopenia. Cut-off values for sarcopenia were defined as skeletal muscle mass index < 0.789 for men and < 0.512 for women, according to FNIH recommendation [29].

2.4. Covariates

Health interviews were a combination of face-to-face interviews and self-administered questionnaires filled out in the mobile examination center. Information on cigarette smoking, alcohol use, and physical activity was obtained by self-administered questionnaire. A current smoker was defined as someone who smoked at the time of the interview and had smoked > 100 cigarettes in their lifetime. High alcohol consumption was defined as more than seven drinks at a time for men or five drinks at a time for women, and more than two or three times a week. The International Physical Activity Questionnaire (IPAQ) was applied to assess physical activity. Physical activity was defined as > 20 min of high intensity activity at least 3 days a week or > 30 min of moderate to light exercise at least 5 days a week. Hypertension was defined as SBP ≥140 or DBP ≥90, or as someone taking antihypertensive medication. Dyslipidemia was defined as TC ≥240 mg/dl, triglycerides (TG) ≥200 mg/dl, or HDL cholesterol < 40 mg/dl, or as someone taking antidyslipidemic medication. We also adjusted for number of chronic diseases that could lead to sarcopenia while taking into account the components of Charlson comorbidity index [32]. Since malignancy and liver cirrhosis were excluded from the study population, we defined five chronic diseases as follows; diabetes mellitus, stroke, myocardial infarction or angina, chronic obstructive pulmonary disease, and chronic kidney disease stages 3 to 5. Number of chronic diseases were classified into three groups as follows; 0, 1, and ≥2.

2.5. Statistical analysis

We conducted all analyses using SPSS version 23.0 statistical software (SPSS version 23.0; IBM Corp., Armonk, NY, USA). To represent the entire Korean population, we took the survey design into account, and used survey sample weight and complex survey design [24]. Data are presented as mean ± standard error (SE) for continuous variables and as percentage (SE) for categorical variables. We compared differences in continuous variables using weighted one-way analysis of variance (ANOVA). The prevalence of current smoking, physical activity, alcohol ingestion, hypertension, dyslipidemia and number of chronic diseases were compared using a weighted chi-square test. Participants were categorized by sex and into tertiles (T) based on platelet counts and WBC counts as follows. Platelet counts for men: T1, 150–220; T2, 221–259; T3, 260–450 (10^3/μl). Platelet counts for women: T1, 150–239; T2, 240–283; T3, 284–450 (10^3/μl). WBC counts for men: T1,

3000–5620; T2, 5630–6900; T3, 6910–10,000 (cells/μl). WBC counts for women: T1, 3000–4980, T2, 4990–6140; T3, 6150–10,000 (cells/μl). We compared the prevalence of sarcopenia in the platelet and WBC count tertile groups using a weighted analysis of covariance (ANCOVA). We adjusted for age and applied the Bonferroni post-hoc test to assess differences among the platelet and WBC count tertile groups. To show the relationship between continuous platelet and WBC counts and prevalence of sarcopenia, we developed a penalized B-spline regression model using the R package, version 3.4.4 (http://www.R-project.org). Multiple logistic regression analysis was used to calculate the odds ratios (ORs) and 95% confidence intervals (CIs) of sarcopenia according to platelet count and WBC count tertiles. These calculations were performed after adjusting for age (model 1); age, smoking, and alcohol intake (model 2); and age, smoking, alcohol intake, hypertension, dyslipidemia, and number of chronic diseases (model 3). All models included platelet count, WBC count, and both platelet and WBC count.

We used receiver operation characteristics (ROC) curve analysis to evaluate the ability of platelet count and white blood cell count to discriminate the presence of sarcopenia by the area under the curve (AUC). AUCs were compared using the DeLong's method. We also compared AUCs to determine whether adding platelet or WBC counts improved the discriminative power over previously known factors, in models 1, 2, and 3. All tests were two-tailed and p-values < 0.05 were regarded as statistically significant.

3. Results

We included 4293 men and 5799 women in this study. Table 1 shows the baseline characteristics of participants according to platelet and WBC counts. In both men and women, the appendicular skeletal muscle mass (ASM)/BMI ratio was significantly lower in the increasing platelet counts tertile ($p = 0.008$ and $p < 0.001$). Similarly, ASM/BMI was also significantly lower in the increasing WBC tertile ($p < 0.001$ in both men and women). In women, body fat percentages significantly positively correlated with platelet counts tertiles ($p < 0.001$), and with WBC tertiles in both men and women (both $p < 0.001$). Body fat percentage positively correlated with platelet counts in men, but the difference was no significant ($p = 0.088$).

Table 2 shows clinical characteristics of participants categorized by sarcopenia occurrence in both men and women. We found a sex-difference in subject characteristics. In total, 472 men and 574 women had sarcopenia. Participants with sarcopenia were significantly older than those without sarcopenia ($p < 0.001$ in both men and women). Both men and women with sarcopenia had higher SBP, fasting glucose, and TG, but lower HDL cholesterol (all p-value < 0.001). Additionally, the proportions of hypertension, dyslipidemia, number of chronic diseases were higher in the sarcopenia group in both men and women (all p-value < 0.001).

Mean WBC count and platelet count were also significantly higher in women with sarcopenia than those without ($p < 0.001$ and $p = 0.002$). In men, mean WBC count was significantly higher in those with sarcopenia ($p < 0.001$). Although the mean platelet count was higher in men with sarcopenia, the difference was not significant ($p = 0.115$). In both men and women, body fat percentages were significantly higher in those with sarcopenia (both p-value < 0.001).

Fig. 1 shows the prevalence of sarcopenia in men and women according to platelet count tertiles and WBC count tertiles after adjusting for age. We found that sarcopenia prevalence was highest in the highest tertile of platelet counts, and this finding was significant for both men and women (6.8% for T1 and 10.1% for T3 in men [p-value < 0.05]; 6.8% for T1 and 10.9% for T3 in women [p-value < 0.01]). Similarly, sarcopenia prevalence was also highest in the highest tertile of WBC counts, and this finding was significant for both men and women (5.2% for T1 and 9.9% for T3 in men [p-value < 0.01]; 5.4% for T1 and 12.6% for T3 in women [p-value < 0.01]).

A penalized-spline curve shows linear relationships between platelet counts, WBC counts, and increased sarcopenia prevalence after adjusting for age (Fig. 2).

Odds ratios (ORs) and 95% confidence intervals (CIs) are shown in Table 3. After adjusting for age, smoking, alcohol intake, hypertension, dyslipidemia, the number of chronic diseases, and ORs (95% CI) for sarcopenia occurrence according to platelet counts in men were 1.03 (0.74–1.42) for T2 and 1.62 (1.20–2.19) for T3, and in women were 1.19 (0.87–1.62) for T2 and 1.72 (1.28–2.31) for T3, relative to the lowest tertile. After adjusting for the same confounders, the ORs (95% CI) for sarcopenia occurrence according to WBC counts in men were 1.66 (1.20–2.29) for T2 and 1.86 (1.35–2.57) for T3, and in women were 1.31 (0.98–1.76) for T2 and 2.36 (1.77–3.13) for T3, relative to the lowest tertile. After considering tertiles for both platelet count and WBC count in all models, there were still significant independent associations between platelet count, WBC count, and sarcopenia.

We also conducted age group-specific analyses after classifying the age groups as follows; young (20–49 yrs), middle aged (50–64 yrs), and elderly adults (over 65 yrs) (Appendix Table). Independent and significant associations were notable in middle aged adults in men, and in elderly adults in women.

The ROC curve analysis for sarcopenia prediction in Table 4 shows the AUC of platelet counts, WBC counts, and combined platelet and WBC counts. We found that platelet counts, WBC counts, and combined platelet and WBC counts had discriminative power in an unadjusted model. Despite the relatively low AUC, we found that predictive powers were significantly higher for the combined platelet and WBC counts than for platelet counts alone ($p = 0.008$ in men and $p < 0.001$ in women). Interestingly, the discriminative powers of WBC counts alone were significantly higher than those of platelet counts alone in both men and women ($p = 0.026$ and $p < 0.001$, respectively). Notably, although the discriminative power of combined WBC and platelet counts was higher than that of WBC count, the difference was not statistically significant ($p = 0.820$ in men and $p = 0.312$ in women).

We also found that the discriminative power of previously known factors in models 1, 2, and 3 could be improved by adding platelet, WBC, or combined platelet and WBC counts. In women, adding platelet, WBC, or combined platelet and WBC counts significantly improved the discriminative power of all models. In men, adding WBC, or combined platelet and WBC counts significantly improved the discriminative powers of in all models. Adding platelet counts significantly improved the discriminative powers only in model 3.

4. Discussion

Our results show that platelet count and WBC count are each independently associated with sarcopenia, after controlling for many possible confounders. In men and women, the power of combined platelet and WBC counts to discriminative sarcopenia was significantly higher than that of platelet counts alone. Additionally, the sarcopenia discrimination power of lifestyle and chronic disease covariates significantly improved upon adding platelet, WBC or combined platelet and WBC counts. This study concerns subjects who fall within normal ranges for platelet and WBC count variability. Our observations suggest that sarcopenia is significantly related to platelet and WBC counts that may indicate chronic low-grade inflammation.

Emerging evidence indicates a relationship between chronic low-grade inflammation and muscle mass loss [17,33]. Progressive muscle mass loss is an inevitable age-related physiologic change [12]. Aging itself is closely associated with chronic low-grade inflammation [34]. Notably, inflammation is thought to play an important role in sarcopenia development [17,33]. White blood cells are core components in the inflammation process, and are also linked to various pathologic conditions such as non-communicable diseases [1,2,35]. Leng and colleagues showed a significant association between WBC counts within the normal range and frailty in elderly women, independent of IL-6 [36]. In addition to this direct association between WBC count and

Table 1
General characteristics of study population according to platelet counts and white blood cell counts[a].

	Men				Women			
	Platelet count quartiles (*10^3/μl)				Platelet count quartiles (*10^3/μl)			
	T1 (150–220)	T2 (221–259)	T3 (260–450)	P-value	T1 (150–239)	T2 (240–283)	T3 (284–450)	P-value
N	1407	1447	1439		1912	1938	1949	
Age	45.7 (0.6)	42.6 (0.5)	42.4 (0.5)	< 0.001	45.9 (0.5)	46.1 (0.4)	44.8 (0.5)	0.092
SBP (mmHg)	116.6 (0.5)	116.5 (0.5)	117.4 (0.5)	0.426	113.7 (0.5)	114.5 (0.5)	115.9 (0.5)	0.003
DBP (mmHg)	76.6 (0.4)	76.5 (0.4)	76.8 (0.4)	0.860	72.8 (0.3)	73.2 (0.3)	74.1 (0.3)	0.001
FBG (mg/dl)	99.1 (0.8)	98.3 (0.9)	97.7 (0.6)	0.380	93.9 (0.5)	94.3 (0.4)	95.3 (0.5)	0.098
TC (mg/dl)	181.4 (1.1)	187.5 (1.2)	190.7 (1.1)	< 0.001	182.8 (1.0)	186.2 (1.1)	192.9 (1.0)	< 0.001
TG (mg/dl)	145.2 (4.0)	157.8 (5.1)	161.4 (3.8)	0.008	103.2 (2.4)	111.4 (2.0)	119.6 (2.1)	< 0.001
HDL-C (mg/dl)	46.0 (0.4)	46.0 (0.3)	46.0 (0.4)	0.995	51.2 (0.3)	50.9 (0.3)	50.6 (0.3)	0.375
Current smoker (%)	41.7 (1.5)	46.0 (1.7)	52.6 (1.6)	< 0.001	5.0 (0.6)	6.7 (0.8)	8.0 (0.8)	0.012
Physical activity (%)	53.9 (1.7)	55.9 (1.6)	55.1 (1.6)	0.670	48.9 (1.4)	50.9 (1.5)	46.9 (1.6)	0.155
Alcohol intake (%)	35.2 (1.7)	37.3 (1.6)	39.0 (1.8)	0.271	9.5 (0.9)	8.7 (0.8)	10.8 (1.0)	0.231
Hypertension (%)	29.8 (1.5)	26.9 (1.4)	29.9 (1.4)	0.203	20.4 (1.0)	22.8 (1.1)	23.0 (1.1)	0.139
Dyslipidemia (%)	41.0 (1.4)	41.3 (1.7)	44.4 (1.6)	0.214	25.5 (1.2)	26.3 (1.1)	30.0 (1.4)	0.023
Number of chronic diseases, (%)				0.309				0.672
0	88.2 (0.9)	90.5 (0.9)	89.6 (1.0)		90.8 (0.8)	92.2 (0.6)	91.8 (0.7)	
1	10.6 (0.9)	8.9 (0.9)	9.7 (1.0)		8.5 (0.8)	7.1 (0.6)	7.6 (0.7)	
≥2	1.2 (0.3)	0.7 (0.2)	0.6 (0.2)		0.7 (0.2)	0.7 (0.2)	0.6 (0.2)	
ASM (kg)	22.9 (0.1)	22.8 (0.1)	22.5 (0.1)	0.061	14.4 (0.1)	14.4 (0.1)	14.5 (0.1)	0.448
ASM/BMI	0.957 (0.0)	0.953 (0.0)	0.942 (0.0)	0.008	0.643 (0.0)	0.634 (0.0)	0.621(0.0)	< 0.001
Body fat mass (kg)	15.6 (0.2)	15.7 (0.2)	15.9 (0.2)	0.448	185.1 (0.2)	188.6 (0.2)	199.5 (0.2)	< 0.001
Body fat percentage (%)	21.8 (0.2)	22.1 (0.2)	22.4 (0.2)	0.088	32.4 (0.2)	32.9 (0.2)	33.9 (0.2)	< 0.001

	White blood cell counts (cells/μl)				White blood cell counts (cells/μl)			
	T1 (3000–5620)	T2 (5630–6900)	T3 (6910–10,000)	P-value	T1 (3000–4980)	T2 (4990–6140)	T3 (6150–10,000)	P-value
N	1429	1430	1434		1939	1916	1944	
Age	44.0 (0.5)	43.6 (0.5)	42.9 (0.5)	0.185	45.2 (0.4)	45.0 (0.5)	46.6 (0.6)	0.028
SBP (mmHg)	118.6 (0.5)	119.3 (0.5)	120.6 (0.5)	0.007	113.3 (0.5)	113.9 (0.5)	116.9 (0.6)	< 0.001
DBP (mmHg)	78.0 (0.3)	79.0 (0.4)	80.2 (0.4)	< 0.001	72.9 (0.3)	73.1 (0.3)	74.1 (0.3)	0.002
FBG (mg/dl)	97.0 (0.8)	98.6 (0.7)	99.3 (0.7)	0.136	91.8 (0.4)	94.5 (0.5)	97.2 (0.6)	< 0.001
TC (mg/dl)	182.6 (1.2)	188.3 (1.0)	189.4 (1.2)	< 0.001	184.1 (1.0)	187.2 (0.9)	190.8 (1.0)	< 0.001
TG (mg/dl)	135.6 (4.1)	155.8 (4.7)	174.1 (4.1)	< 0.001	92.9 (1.6)	111.2 (2.2)	130.1 (2.2)	< 0.001
HDL-C (mg/dl)	47.5 (0.4)	46.0 (0.3)	44.5 (0.3)	< 0.001	52.8 (0.3)	50.8 (0.3)	49.2 (0.3)	< 0.001
Current smoker (%)	35.3 (1.7)	45.8 (1.5)	59.8 (1.5)	< 0.001	3.8 (0.6)	5.5 (0.7)	10.5 (1.0)	< 0.001
Physical activity (%)	55.3 (1.5)	54.9 (1.6)	54.8 (1.6)	0.965	51.8 (1.5)	50.6 (1.4)	44.4 (1.5)	< 0.001
Alcohol intake (%)	35.6 (1.7)	37.1 (1.6)	39.0 (1.5)	0.298	9.1 (1.0)	8.8 (0.9)	11.0 (0.9)	0.189
Hypertension (%)	25.9 (1.4)	27.9 (1.4)	32.7 (1.6)	< 0.001	17.8 (1.0)	21.6 (1.1)	26.7 (1.3)	< 0.001
Dyslipidemia (%)	36.9 (1.7)	41.4(1.6)	48.6 (1.6)	< 0.001	22.2 (1.1)	26.1 (1.3)	33.6 (1.3)	< 0.001
Number of chronic diseases, (%)				0.009				< 0.001
0	91.6 (0.8)	89.7 (1.0)	87.1 (1.0)		94.6 (0.6)	92.1 (0.8)	88.1 (0.8)	
1	7.8 (0.8)	9.4 (1.0)	11.9 (0.9)		4.9 (0.6)	7.3 (0.8)	10.9 (0.8)	
≥2	0.6 (0.2)	0.9 (0.2)	0.9 (0.3)		0.5 (0.2)	0.6 (0.2)	1.0 (0.3)	
ASM (kg)	22.6 (0.1)	22.7 (0.1)	22.8 (1.1)	0.473	14.4 (0.1)	14.5 (0.1)	14.5 (0.1)	0.040
ASM/BMI	0.970 (0.0)	0.948 (0.0)	0.932 (0.0)	< 0.001	0.646 (0.0)	0.637 (0.0)	0.614 (0.0)	< 0.001
Body fat mass (kg)	14.7 (0.2)	15.9 (0.2)	16.7 (0.2)	< 0.001	18.0 (0.2)	19.0 (0.2)	20.3 (0.2)	< 0.001
Body fat percentage (%)	21.1 (0.2)	22.3 (0.2)	23.0 (0.2)	< 0.001	32.1 (0.2)	33.0 (0.2)	34.2 (0.2)	< 0.001

T, tertile; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; ASM, appendicular skeletal muscle mass; BMI, body mass index.
P-values are calculated by weighted one-way analysis of variance (ANOVA) for continuous variables and weighted chi-test for categorical variables.
[a] Data are presented as the mean ± standard error (SE) for continuous variables or percentage (%) ± SE.

frailty, WBC are also known to induce secretion of pro-inflammatory cytokines, such as IL-6 [37]. Chronic IL-6 exposure in skeletal muscle induces protein degradation pathways that lead to muscle loss [38]. A Health ABC study of 3075 elderly persons showed that higher IL-6 and TNF-α levels are associated with lower muscle mass [39].

Platelets also facilitate the rolling and adhesion of leukocytes, and these platelet and leukocyte interactions induce the release of pro-inflammatory cytokines [40,41] Interrelatedly, inflammation can activate platelets via complex interactions between platelets, endothelial cells, and leukocytes [42].

Our study also found an independent and significant association between platelet count and sarcopenia, even after adjusting for WBC counts. Although the potential mechanism by which platelet counts contribute to sarcopenia is not fully investigated, it is known that platelets interact with leukocytes as well as if self, secrete inflammatory cytokines [43]. Second, a higher platelet count reflects both prothrombotic and inflammation status [44]. Interaction between coagulation and inflammation over the course of aging facilitate sarcopenia development [44]. Third, platelets could regulate to bone reabsorption and remodeling through vitamin D receptor [45]. Aging-related bone and muscle loss closely share common pathophysiology [46].

In age-specific analyses, there were some discrepancies across the age groups. The independent associations between platelet count, WBC counts, and sarcopenia were only significant in middle aged group

Table 2
Characteristics of study population according to presence of sarcopenia[a].

	Men (N = 4293)			Women (N = 5799)		
	Without sarcopenia	With sarcopenia	P-value	Without sarcopenia	With sarcopenia	P-value
N	3821	472		5225	574	
Age	42.4 (0.4)	55.1 (0.8)	< 0.001	44.1 (0.3)	60.4 (0.8)	< 0.001
Systolic blood pressure (mmHg)	116.2 (0.3)	123.7 (1.0)	< 0.001	112.4 (0.4)	126.1 (1.1)	< 0.001
Diastolic blood pressure (mmHg)	76.6 (0.3)	77.5 (0.7)	0.208	72.0 (0.2)	76.0 (0.6)	< 0.001
Fasting glucose (mg/dl)	97.5 (0.4)	107.1 (1.5)	< 0.001	93.8 (0.3)	101.0 (1.2)	< 0.001
Total cholesterol (mg/dl)	186.5 (0.7)	189.5 (2.3)	0.213	185.7 (0.6)	203.8 (1.8)	< 0.001
Triglyceride (mg/dl)	152.7 (2.7)	186.7 (8.6)	< 0.001	108.6 (1.3)	138.9 (3.6)	< 0.001
HDL cholesterol (mg/dl)	46.2 (0.2)	43.8 (0.6)	< 0.001	51.1 (0.2)	48.8 (0.5)	< 0.001
Current smoker, (%)	48.0 (0.9)	37.2 (2.8)	< 0.001	6.8 (0.5)	4.3 (1.1)	0.067
Physical activity, (%)	55.4 (1.0)	49.9 (3.1)	0.082	49.4 (0.9)	42.8 (2.7)	0.017
Alcohol intake, (%)	37.2 (1.0)	40.0 (3.1)	0.379	9.9 (0.6)	6.7 (1.3)	0.052
Hypertension, (%)	26.9 (0.9)	50.3 (2.8)	< 0.001	19.1 (0.7)	52.0 (2.3)	< 0.001
Dyslipidemia, (%)	40.8 (1.0)	59.9 (2.8)	< 0.001	25.4 (0.8)	46.7 (2.5)	< 0.001
Number of chronic diseases, (%)			< 0.001			< 0.001
0	93.6 (0.5)	71.9 (2.6)		92.7 (0.4)	79.8 (1.8)	
1	8.4 (0.6)	24.5 (0.6)		6.8 (0.4)	17.8 (1.7)	
≥2	0.6 (0.1)	3.5 (1.0)		0.5 (0.1)	2.4 (0.7)	
White blood cell counts	6340 (29)	6660 (82)	< 0.001	5640 (24)	6250 (67)	< 0.001
Platelet counts	246 (1.0)	251 (2.9)	0.115	265 (0.9)	274 (2.7)	0.002
Appendicular skeletal mass (kg)	23.0 (0.1)	19.1 (0.2)	< 0.001	14.7 (0.0)	12.5 (0.1)	< 0.001
Appendicular skeletal mass/BMI	0.968 (0.0)	0.742 (0.0)	< 0.001	0.647 (0.0)	0.478 (0.0)	< 0.001
Body fat mass (kg)	15.4 (0.1)	19.5 (0.4)	< 0.001	18.7 (0.1)	23.1 (0.3)	< 0.001
Body fat percentage (%)	21.6 (0.2)	28.3 (0.3)	< 0.001	32.5 (0.1)	39.6 (0.2)	< 0.001

P-values are calculated by weighted one-way analysis of variance (ANOVA) for continuous variables and weighted chi-test for categorical variables.
[a] Data are presented as the mean ± standard error (SE) for continuous variables or percentage (%) ± SE.

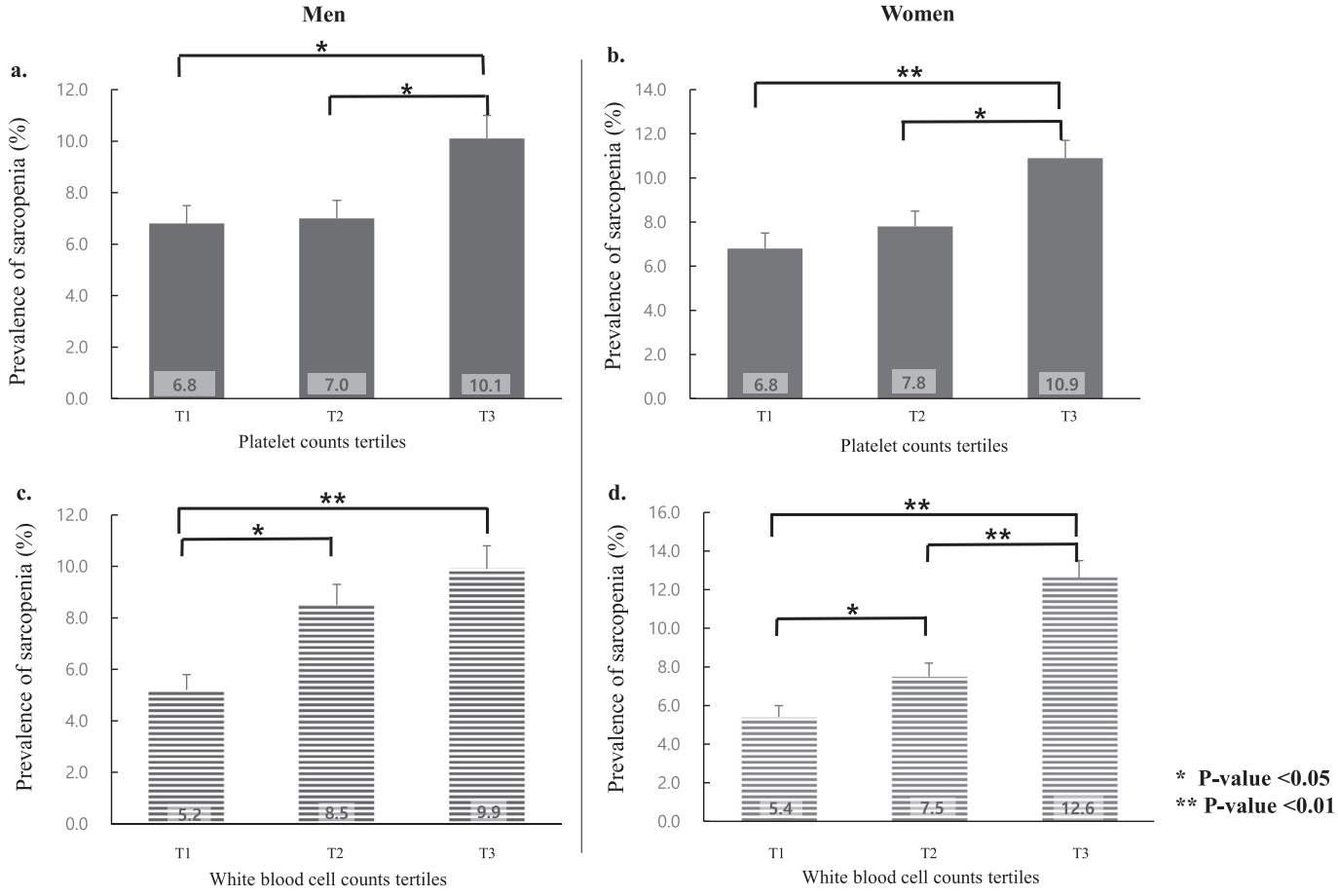

Fig. 1. Prevalence of sarcopenia according to platelet count tertile and white blood cell count tertile after adjusting for age in men and women.
P-values calculated as a weighted analysis of covariance (ANCOVA) and adjusted for age. The Bonferroni post-hoc test was applied.
*P-value < 0.05
**P-value < 0.01.

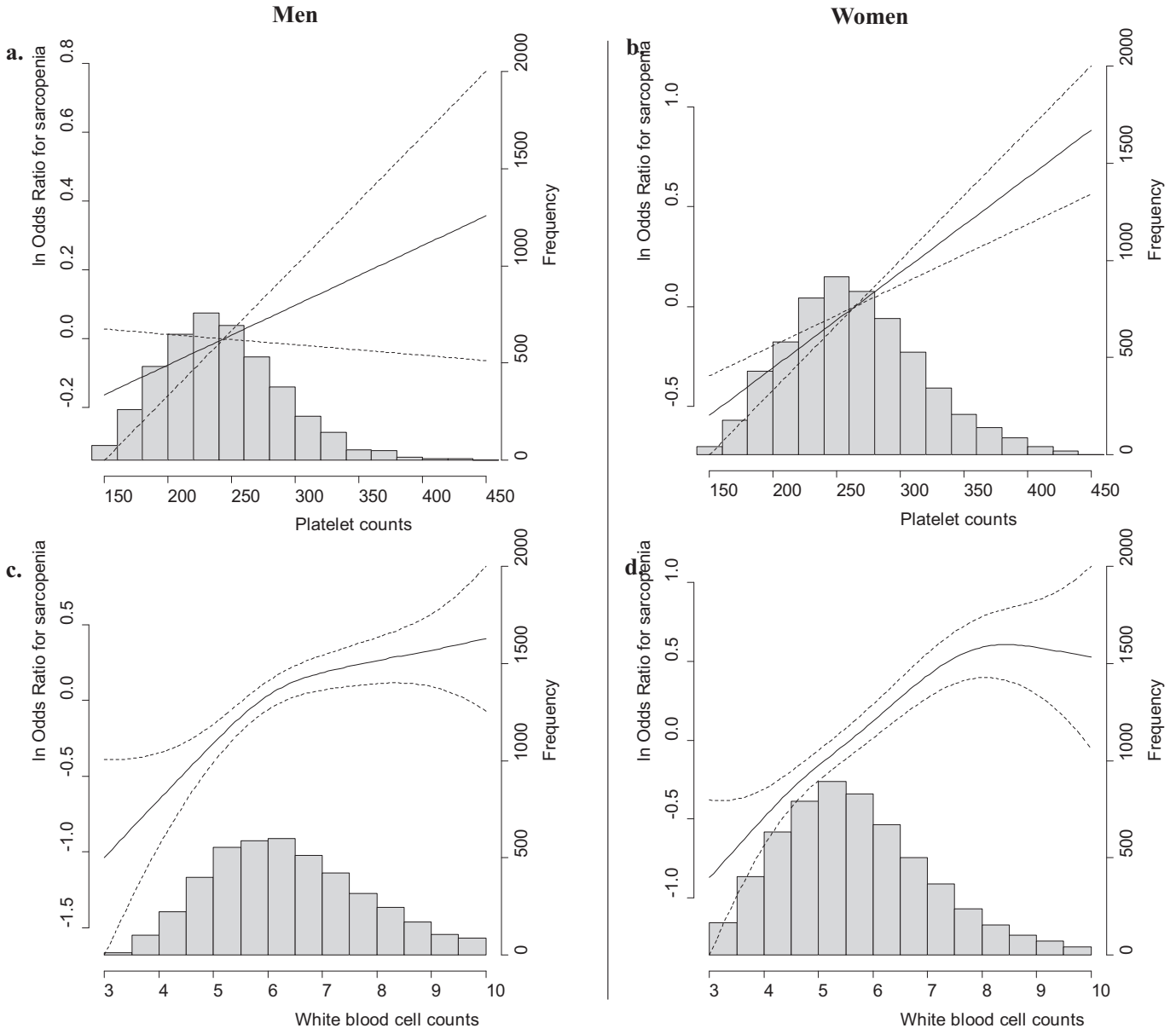

Fig. 2. Relationship between platelet counts, white blood cell counts, and sarcopenia.
The solid line represents the log odds ratio and the dotted lines represent 95% confidence intervals. The odd ratios were adjusted for age. The bar represents the platelet counts or white blood cell (WBC) count distribution.
(a) Relationship between platelet counts and sarcopenia in men
(b) Relationship between platelet counts and sarcopenia in women
(c) Relationship between WBC counts and sarcopenia in men
(d) Relationship between WBC counts and sarcopenia in women.

(50–64 yrs) for men, and in elderly (over the 65 yrs) for women. Although the reason for these discrepancies in the analyses is unclear, hormonal influence and stem-cell reserve in aging might have led to age and sex-specific results [47]. Previous studies have reported that age and sex are important determinants for platelet counts [48,49]. Platelet counts decreased during aging, and women had significantly higher platelet count than men [48,49]. In the current study, age was significantly higher in lower platelet count tertile groups (T1) compared to highest platelet count tertile group (T3) (45.7 yrs. vs 42.4 yrs., $p < 0.001$). Furthermore, many researchers have demonstrated that sarcopenia is a multifactorial syndrome related to various risk factors [50]. Endocrine abnormalities, such as insulin resistance and dysregulated lipids, are also important causes of decline in muscle mass [15]. Platelets can be affected by changes in insulin sensitivity [51]. Taniguchi et al. suggested that platelet counts are an independent predictor of insulin resistance [52]. In our study, fasting glucose and TG were significantly higher in sarcopenia group in both men and women. HDL-C was significantly lower in sarcopenia group in both men and women. Further study will be required to uncover the biological mechanism of these age and sex-differences.

There are several limitations that should be considered when interpreting our results. First, because this study had a cross-sectional design, we could not determine causality between WBC or platelet counts and sarcopenia. Second, we defined sarcopenia to include only skeletal muscle mass. Because we used secondary data collected by KNHNES, we could only obtain muscle mass information using DXA, and were unable to evaluate skeletal muscle function or strength. Third, the 2008–2011 KNHANES database did not include information about

Table 3
Odds ratios (ORs) and 95% Confidence intervals (CIs) for sarcopenia according to platelet counts and white blood cell counts.

	Men			Women		
	Model 1[a]	Model 2[b]	Model 3[c]	Model 1[a]	Model 2[b]	Model 3[c]
Platelet counts	OR (95% CIs)			OR (95% CIs)		
T1	1	1	1	1	1	1
T2	1.02 (0.75-1.38)	1.04 (0.77-1.42)	1.03 (0.74-1.42)	1.20 (0.88-1.63)	1.20 (0.88-1.63)	1.19 (0.87-1.62)
T3	1.58 (1.19-2.11)	1.65 (1.24-2.20)	1.62 (1.20-2.19)	1.75 (1.32-2.33)	1.73 (1.29-2.31)	1.72 (1.28-2.31)
White blood cell counts						
T1	1	1	1	1	1	1
T2	1.59 (1.16-5.17)	1.70 (1.23-2.33)	1.66 (1.20-2.29)	1.38 (1.03-1.85)	1.40 (1.05-1.87)	1.31 (0.98-1.76)
T3	1.92 (1.40-2.63)	2.13 (1.55-2.92)	1.86 (1.35-2.57)	2.42 (1.85-3.18)	2.48 (1.88-3.27)	2.36 (1.77-3.13)
Platelet counts						
T1	1	1	1	1	1	1
T2	0.96 (0.71-1.30)	0.98 (0.72-1.33)	0.97 (0.70-1.35)	1.06 (0.78-1.45)	1.07 (0.78-1.45)	1.07 (0.78-1.47)
T3	1.42 (1.06-1.91)	1.46 (1.09-1.97)	1.48 (1.09-2.01)	1.45 (1.09-1.93)	1.43 (1.07-1.91)	1.44 (1.07-1.93)
White blood cell counts						
T1	1	1	1	1	1	1
T2	1.56 (1.14-2.12)	1.66 (1.21-2.28)	1.62 (1.18-223)	1.32 (0.99-1.77)	1.34 (1.00-1.79)	1.26 (0.95-1.68)
T3	1.77 (1.28-2.45)	1.97 (1.42-2.72)	1.72(1.24-2.39)	2.22 (1.68-2.94)	2.29 (1.72-3.04)	2.17 (1.62-2.90)

T, tertile
[a] Model 1: adjusted for age.
[b] Model 2: adjusted for age, smoking, and alcohol intake.
[c] Model 3: adjusted for age, smoking, alcohol intake, hypertension, dyslipidemia, number of chronic diseases.

possible inflammatory markers, such as IL-6 and C-reactive protein (CRP), or indices of platelet function. Despite these weaknesses, platelet and WBC count have not been previously compared with relation to sarcopenia to our knowledge. Here, we show that both platelet and WBC count can be independently used to discriminate sarcopenia. Additional studies are necessary to determine whether intervention to decrease low-grade inflammation could prevent muscle mass loss.

5. Conclusion

In conclusion, platelet and WBC counts in the high end of the normal range were each independently and positively associated with sarcopenia in both Korean men and women. By measuring AUC, we observed improved discrimination power between those with and without sarcopenia when using both platelet and WBC counts. Furthermore, the ability to discriminate increased when platelet and WBC counts were combined with previously known variables including age, smoking, alcohol intake, and medical history. This combinatorial effect was especially pronounced in women. Our findings motivate future work to investigate the combined effects of several risk factors to measure sarcopenia prevalence and to construct prediction models for screening population with high sarcopenia risk.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2019.09.007.

Table 4
Post-hoc analysis of the AUC of platelet counts and white blood cell counts for sarcopenia.

	AUC (SE, 95% CI)			P-value*		
	Platelet counts	WBC counts	Platelet counts and WBC counts	P vs W	W vs WP	P vs WP
Men						
Unadjusted	0.508 (0.015, 0.479–0.536)	0.555 (0.013, 0.529–0.582)	0.557 (0.014, 0.530–0.583)	0.026	0.820	0.008
Model 1[a]	0.735 (0.012, 0.721–0.748)	0.741 (0.012, 0.727–0.754)	0.741 (0.012, 0.728–0.754)	0.144	0.858	0.061
P-value[†]	0.228	0.028	0.022			
Model 2[b]	0.737 (0.012, 0.723–0.750)	0.744 (0.012, 0.731–0.757)	0.745 (0.012, 0.731–0.758)	0.074	0.923	0.028
P-value[†]	0.173	0.008	0.005			
Model 3[c]	0.756 (0.012, 0.743–0.769)	0.759 (0.011, 0.738–0.783)	0.759 (0.011, 0.739–0.784)	0.057	0.899	0.048
P-value[†]	0.040	0.051	0.028			
Women						
Unadjusted	0.561 (0.013,0.536–0.586)	0.617 (0.012, 0.593–0.642)	0.621 (0.012, 0.597–0.644)	< 0.001	0.312	< 0.001
Model 1[a]	0.784 (0.009, 0.773–0.794)	0.790 (0.009,0.779–0.800)	0.792 (0.009, 0.781–0.802)	0.085	0.061	0.004
P-value[†]	0.004	< 0.001	< 0.001			
Model 2[b]	0.784 (0.010, 0.773–0.795)	0.790 (0.010, 0.780–0.801)	0.793 (0.010, 0.782–0.803)	0.062	0.063	0.003
P-value[†]	< 0.001	< 0.001	< 0.001			
Model 3[c]	0.790 (0.010, 0.779–0.800)	0.794 (0.010, 0.874–0.805)	0.796 (0.010, 0.786–0.807)	0.138	0.039	0.050
P-value[†]	< 0.001	< 0.001	< 0.001			

AUC, area under the curve; 95% CI, 95% confidence interval; P, platelet counts; W, white blood cell counts;
[a] Model 1: adjusted for age.
[b] Model 2: adjusted for age, smoking, and alcohol intake.
[c] Model 3: adjusted for age, smoking, alcohol intake, hypertension, dyslipidemia, number of chronic diseases.
* Post-hoc analyses were conducted using the DeLong's method.
[†] *P*-value: without platelet counts, white blood cell counts, platelet counts, and white blood cell counts vs with platelet counts, white blood cell counts, platelet counts, and white blood cell counts.

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Authorship

H-S Lee, H-S Kim, and Y-J Kwon: conception and design of the study, or acquisition of data, or analysis and interpretation of data, drafting the article, and revising it critically for important intellectual content, I-H Koh: analysis and interpretation of data, or revising it critically for important intellectual content, All authors: final approval of the version to be submitted.

Declaration of competing interest

Hye-Sun Lee, Il-Hyun Koh, Hyoung Sik Kim, and Yu-Jin Kwon declare that they have no conflict of interest.

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