C-reactive protein to albumin ratio and risk of incident metabolic syndrome in community-dwelling adults: longitudinal findings over a 12-year follow-up period

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ABSTRACT

C-reactive protein to albumin ratio and risk of incident metabolic syndrome in community-dwelling adults: longitudinal findings over a 12-year follow-up period

Aim: The CRP-to-albumin (CRP/Alb) ratio has emerged as a novel biomarker for various inflammatory diseases. This study aimed to evaluate the association between the CRP/Alb ratio and incident metabolic syndrome (MetS) with a large-sample, community-based Korean cohort over a 12-year follow-up period.

Materials and Methods: Among 10,030 participants, a total of 6,205 participants aged 40 to 69 years without MetS were selected from the Korean Genome and Epidemiology Study (KoGES). The baseline CRP/Alb ratio was divided into quartiles. The definition of newly developed MetS was the one proposed by the 2009 Joint Interim Statement of Circulation. Hazard ratios (HRs) with 95% confidence intervals (CIs) for incident MetS were calculated using multivariable Cox proportional hazards regression models after adjusting for potentially confounding variables.

Results: During the 12-year follow-up period, MetS developed in 2,535 subjects (40.9%, 2,535/6,205) with an incidence rate of 5.6-11.9 (over 2 years). Compared to the reference first quartiles, the HRs (95% CIs) of incident MetS in the second, third, and fourth quartiles increased in a dose-response manner. Compared to the reference quartile, the HRs (95% CIs) of the incidence of MetS for the second, third, and fourth quartiles of CRP/Alb ratio were 1.12 (0.99-1.27), 1.24 (1.11-1.40), and 1.51 (1.34-1.69) after adjusting for age, sex, smoking status, alcohol intake, physical activity, total cholesterol, mean arterial pressure, HOMA-IR, and total energy intake.

Conclusions: High CRP/Alb ratio at baseline may be a useful surrogate indicator of future incident MetS.

Key words: CRP-to-albumin ratio; metabolic syndrome; inflammation; insulin resistance;

I. INTRODUCTION

Metabolic syndrome (MetS) is a cluster of cardiometabolic abnormalities, including visceral obesity, high blood pressure, glucose intolerance, and atherogenic dyslipidemia. Individuals with MetS tend to be more susceptible to cardiovascular disease (CVD), type 2 diabetes, and various cancers, all of which are significant causes of mortality.[1,2] The global prevalence of MetS has exhibited an upward trajectory over recent decades.[3] Given the economic and health burden created by MetS, early identification of individuals at higher risk for developing MetS is a high public health priority.[4] The pathophysiology of MetS remains unclear; however, a growing body of evidence has shown that low-grade inflammation concomitant with oxidative stress and insulin resistance play important roles in the development of MetS.[5,6]

C-reactive protein, acute-phase response, is secreted by the liver in response to a variety of inflammatory cytokines. Recent studies have shown that a higher CRP level is positively related with the incidence of MetS even within the normal CRP range[7,8]. Serum albumin is a protein primarily synthesized by the liver that is decreased in cases of malnutrition and inflammation[9] and is elevated in cases of over-nutrition[10]. Previous studies have been conducted to investigate the relationship of serum albumin level with MetS; however, results of these studies have been inconsistent. Some observational studies have shown a connection between higher albumin levels in healthy adults and an increased risk of developing MetS [11,12], but other longitudinal studies have concluded that change in serum albumin concentration is inversely associated with risk of incident MetS [13].

Recently, the CRP-to-albumin (CRP/Alb) ratio has emerged as a novel biomarker for predicting mortality and disease prognosis among critically ill patients with severe sepsis or cancer[14,15]. Furthermore, recent research has unveiled a correlation between CRP/Alb ratio and various inflammatory diseases, such as Crohn's disease[16], rheumatoid arthritis[17], and polycystic ovary syndrome[18]. However, there remains a gap in understanding as no

extensive prospective cohort studies have tested for a longitudinal relationship between the CRP/Alb ratio and the development of MetS. Therefore, we prospectively examined the association between the CRP/Alb ratio and incident MetS using a large, community-based Korean cohort observed over 12 years.

2. MATERIALS AND METHODS

2.1. Study population

We utilized data derived from the Korean Genome and Epidemiology Study (KoGES) Ansan and Ansung study. The dataset used in this Ansan-Ansung cohort study can be provided after review of the research plan by the Korea Disease Control and Prevention Agency (KDCA, https://www.kdca.go.kr/index.es?sid=a3). The KoGES is a comprehensive prospective cohort investigation initiated by the KDCA with the aim of examining the prevalence and risk factors associated with chronic diseases in the Korean population. KoGES comprises eight distinct prospective cohort studies, which are categorized into population-based and gene-environment model studies. The Ansan and Ansung Study, a part of KoGES, is one of the population-based cohort studies within this framework and involves individuals residing in the community and individuals recruited from the national health examinee registry.

The Ansan and Ansung Study targeted men and women in the age range of 40 to 69 years at the study's outset and residing either in an urban area (Ansan) or a rural area (Ansung). Data collection for this cohort commenced with the baseline survey conducted in 2001-2002 and has been conducted biennially through 2013-2014. During the baseline survey (in 2001-2002), a total of 10,030 individuals, consisting of 5,012 Ansan residents and 5,018 Ansung residents, were recruited. Among the 10,030 participants in the baseline study, we excluded 2,769 (27.6%) participants because of their meeting the diagnostic criteria for MetS on the baseline survey or missing data. These criteria were based on the definition of MetS proposed by the 2009 Joint Interim Statement of

Circulation. Then we excluded 952 participants with missing data at the follow-up examinations. Also, we excluded 104 participants with CRP > 10 mg/L or white blood cell (WBC) > 11,000 cells/μL from this study due to the possibility of the presence of current infection or inflammatory disorder. The remaining 6,205 individuals, 3,095 men and 3,110 women, were included in the baseline study.

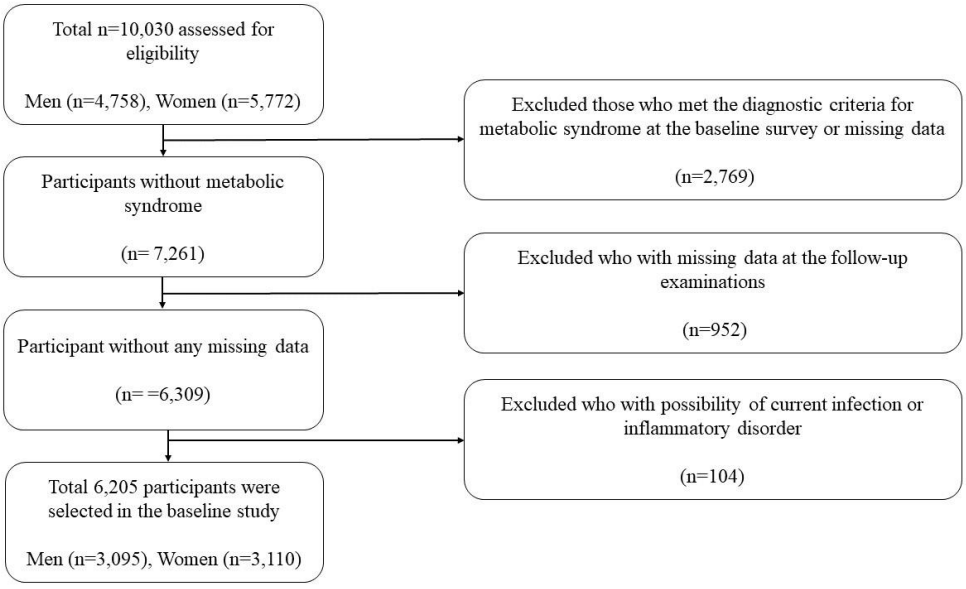

Figure 1. Flow chart for selection of the study population.

Informed consent was obtained from all participants, and participation in our study was voluntary. Our study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the Korean Health and Genomic Study at the Korea National Institute of Health. Detailed information on KoGES has been published in previous reports.[19] The Ansan-Ansung study protocol was reviewed and approved by the Institutional Review Board of the Korea Centers for Disease Control and Prevention, and all participants in that study provided written informed consent. This study was approved by the Institutional Review Board of Gangnam Severance Hospital (IRB number: 3-2018-0348).

2.2. Anthropometric and clinical measurements

The participants' body weight and height were measured in light indoor clothing without shoes to the nearest 0.1 cm and 0.1 kg, respectively. Smoking status was divided into three categories: current smokers, ex-smokers, and never smokers. We categorized alcohol consumption as current intake or not. Physical activity was classified into the following three categories: no exercise, irregular exercise (one or two episodes per week) and regular exercise (three or more episodes per week). We defined an episode of exercise as one lasting for at least thirty minutes. The mean arterial BP was calculated: [systolic BP + (2 diastolic BP)]/3. After fasting overnight for at least eight hours, the plasma concentrations of albumin, glucose, triglycerides (TG) and high-density lipoprotein (HDL) cholesterol were measured enzymatically using a 747 Chemistry Analyzer (Hitachi 7600, Tokyo, Japan). The HbA1c level was measured using high-performance liquid chromatography (VARIANT II; Bio-Rad Laboratories, Hercules, CA). The high sensitivity CRP concentration was measured by immunoradiometric assay (ADVIA 1650; Bayer Diagnostics, Tarrytown, NY). The plasma insulin concentration level was assessed by radioimmunoassay (LINCO kit). The formula for calculating the homeostasis model assessment-insulin resistance (HOMA-IR) score was: [fasting insulin (mIU/mL) x fasting glucose (mg/dL)/405].

2.3. Definition of metabolic syndrome

We defined MetS using the definition proposed by the 2009 Joint Interim Statement of Circulation.[20] According to this definition, MetS included any three of the following five conditions: (1) visceral obesity: waist circumference of ≥ 90 cm in men and ≥ 80 cm in women, (2) high blood pressure: systolic blood pressure (BP) of ≥ 130 mm Hg and/or diastolic BP of ≥ 85 mm Hg or patient receiving current hypertension drug treatment, (3) impaired fasting glucose: fasting glucose level of ≥ 100 mg/dL or patient receiving current glucose-lowering drug treatment, (4) high triglyceride levels: triglyceride level of ≥ 150 mg/dL or patient receiving current triglyceride-lowering drug treatment, (5) low HDL cholesterol levels: HDL-C level of < 40 mg/dL in men and < 50 mg/dL in women.

2.4. Statistical analysis

The CRP/Alb ratio (mg/g, %) quartiles were categorized: Q1: ≤ 1.29%, Q2: 1.30-2.84%, Q3: 2.85-4.88% and Q4:≥4.89%. The baseline characteristics of the study population according to CRP/Alb ratio quartiles were compared using one-way analysis of variance (ANOVA) or the Kruskal-Wallis test for continuous variables depending upon the normality of distributions. The Chi-square test was used to compare categorical variables. The continuous data were presented as means (standard deviations, SDs) or medians (interquartile ranges, IQRs). Categorical data are presented as frequencies. The lowest quartile, Q1, was set as a reference group of CRP/Alb ratio values. The hazard ratios (HRs) with 95% confidence intervals (CIs) for incident MetS were then calculated using multivariable Cox proportional hazard regression models after adjusting for potentially confounding variables. The cumulative incidence of MetS was represented using a Kaplan-Meier curve. The log-rank tests were conducted to determine the difference in the cumulative incidence of MetS among the groups. All analyses were conducted using SAS statistical software (version 9.4; SAS Institute Inc., Cary, NC, USA). All statistical tests were two-sided. Statistical significance was set at $P < 0.05$.

3. RESULTS

3.1. Baseline characteristics of the study population

Table 1 shows the baseline characteristics of 6,205 participants without MetS at baseline across the CRP/Alb ratio quartiles. These parameters increased proportionally with increasing CRP/Albumin ratio quartiles: the mean values of cardiometabolic variables, including age, waist circumference, blood pressure, fasting plasma glucose, total cholesterol and the median values of insulin, HOMA-IR, and TG levels. In addition, among lifestyle habits, the proportion of current smokers tended to increase in conjunction with the CRP/Alb ratio quartiles. Moreover, the proportion of participants meeting 2

components of the diagnostic criteria at the baseline survey exhibited a tendency to increase with CRP/Alb ratio quartiles.

Table 1. Baseline characteristics of study population according to CRP/Alb quartiles

	Total	Q1	Q2	Q3	Q4	P-value[a]
n	6205	1550	1555	1555	1545	
CRP/Alb ratio (mg/g, %)		≤1.29	1.30-2.84	2.85-4.88	≥4.89	
Age (Years)	51.1 (8.6)	49.9 (8.4)	50.1 (8.4)	51.5 (8.7)	52.8 (9.0)	<0.001
Male sex (%)	49.9	47.3	47.5	50.9	53.9	<0.001
Systolic BP (mmHg)	116.7 (17.2)	115.2 (17.0)	115.5 (16.4)	117.6 (17.3)	118.5 (18.3)	<0.001
Diastolic BP (mmHg)	77.6 (11.4)	76.7 (11.5)	77.1 (11.4)	78.1 (11.1)	78.7 (11.5)	<0.001
Mean arterial BP (mmHg)	90.7 (12.6)	89.6 (12.7)	89.9 (12.4)	91.2 (12.5)	92.0 (13.0)	<0.001
Waist circumference (cm)	80.3 (7.8)	78.8 (8.0)	79.5 (7.7)	80.8 (7.6)	80.8 (7.6)	<0.001
BMI (kg/m²)	23.9 (2.8)	23.4 (2.7)	23.7 (2.8)	24.1 (2.8)	24.4 (3.0)	<0.001
FPG (mg/dL)	87.6 (13.9)	88.5 (15.6)	89.1 (15.7)	90.1 (19.2)	88.8 (16.2)	<0.001
Insulin (μU/ml)	6.6 (5.0-8.9)	6.2 (4.6-8.1)	6.7 (6.7-8.8)	7.0 (5.1-9.4)	6.8 (5.2-9.4)	<0.001
HOMA-IR	1.42 (1.06-1.96)	1.31 (0.97-1.47)	1.43 (1.06-1.93)	1.51 (1.10-2.07)	1.48 (1.10-2.04)	<0.001
CRP (mg/dl)	0.13 (0.06-0.22)	0.01 (0.01-0.04)	0.09 (0.08-0.11)	0.17 (0.15-0.19)	0.34 (0.26-0.53)	<0.001
Albumin (g/dl)	4.51 (0.28)	4.52 (0.28)	4.55 (0.28)	4.52 (0.27)	4.47 (0.29)	<0.001
Total cholesterol (mg/dl)	196.4(35.0)	191.8(33.3)	196.5(33.6)	198.2(35.5)	199.4(37.1)	<0.001
Triglyceride (mg/dl)	109 (80-145)	102 (75-134)	106 (79-143)	113 (84-150)	115 (84-155)	<0.001
HDL-cholesterol (mg/dl)	52.4 (11.7)	52.6 (11.7)	51.2 (11.2)	50.7 (11.8)	51.7 (11.6)	<0.001
Current smoker (%)	25.9	22.6	23.4	26.3	27.7	<0.001

Alcohol drinking (%)[b]	50.4	24.4	25.0	25.2	25.3	0.724
Regular exercise (%)[c]	25.8	26.0	26.0	24.4	24.2	0.343
Total energy intake (kcal/day)	1854 (1543-2228)	1883 (1546-2256)	1857 (1573-2258)	1831 (1537-2182)	1847 (1508-2182)	0.045
Nummers of MetS components (%)						<0.001
0	31.4	37.7	34.4	28.7	24.7	
1	37.5	37.4	37.4	39.1	36.3	
2	31.1	24.8	28.2	32.2	39.0	

Abbreviations: CRP, C-reactive protein; Alb, albumin; BP, blood pressure; BMI, body mass index; FPG, fasting plasma glucose; HOMA-IR, homeostatic model assessment for insulin resistance; HDL, high density lipoprotein. Data are expressed as the mean (SD), median (IQR), or percentage. [a]P-values were calculated using ANOVA-test, Kruskal-Walli's test, or chi-square test. [b]Alcohol intake ≥twice/week, [c]Moderate exercise ≥three times/week

3.2. Incidence of metabolic syndrome during the follow-up study and cumulative incidence of metabolic syndrome

Table 2 shows the incidence of MetS during the 12 years of follow-up. During the follow-up period, the incidence rates were calculated biennially. A total of 2,535 individuals (40.9%, 2,535/6,205) developed MetS with the incidence rate per two years ranging from 5.6 to 12.2.

Table 2. Incidence of metabolic syndrome during the follow-up study.

`	Follow-up	n	Incidence cases	Incidence rate per 2 years
2001-2002	Baseline	6205		
2003-2004	2y	5468	737	11.9
2005-2006	4	4590	489	8.9
2007-2008	6	3879	434	9.5
2009-2010	8	3221	475	12.2
2011-2012	10	2821	179	5.6
2013-2014	12	2255	221	7.8

Figure 2 presents the cumulative incidence of MetS according to the CRP/Alb ratio quartiles. The incidence increased proportional to increasing CRP/Alb ratio quartiles (P-value < 0.001).

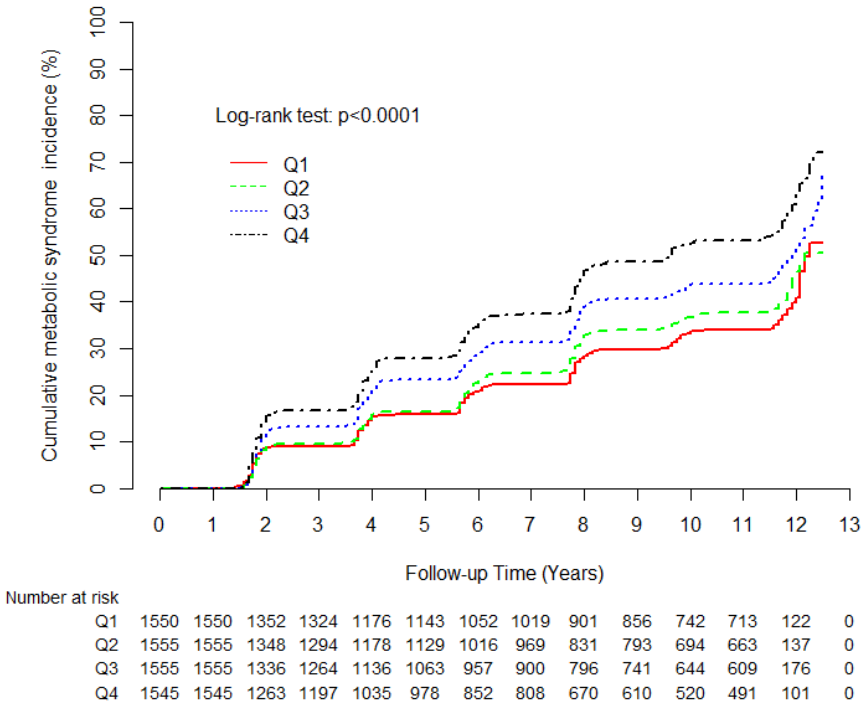

Figure 2. Cumulative incidence of MetS according to CRP/Alb ratio quartiles.

3.3. Multivariate Cox proportional hazard regression analysis

Figure 3 displays the dose-responsive association between CRP/Alb ratio as a continuous variable and incident MetS using Cox proportional hazard spline curve.

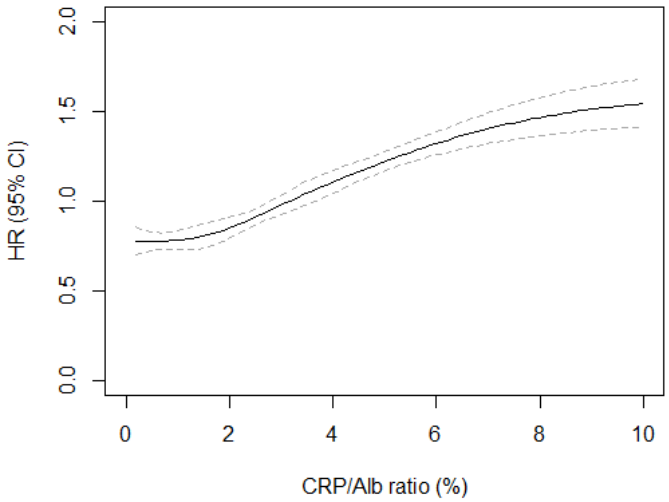

Figure 3. Cox proportional hazard spline curve representing the black line is the hazard ratio for incident MetS according to CRP/Alb ratio and the dotted line is 95% confidence interval for hazard ratio.

Table 3 shows the results of the multivariable Cox proportional hazard regression analysis for predicting MetS according to CRP/Alb ratio quartiles. In model 1, we accounted for fundamental characteristics which could be obtained without any measurement or laboratory test, considering them as potential confounding factors. In model 2, we incorporated laboratory findings or measurable parameters such as total cholesterol and mean blood pressure, which could influence vascular/metabolic comorbidities. Additionally, in model 3, we included HOMA-IR and total energy intake as an additional confounding variable, recognizing the important role of insulin resistance and dietary pattern in the development of MetS. Compared to the reference first quartiles,

the HRs (95% CIs) for incident MetS in the second, third and fourth quartiles increased in a dose-response manner among all models after adjusting for potential confounding variables. In model 3. compared to the reference quartile, the HRs (95% CIs) of the incidence of MetS for the second, third, and fourth quartiles of CRP/Alb ratio were 1.12 (0.99-1.27), 1.24 (1.11-1.40), and 1.51 (1.34-1.69) after adjusting for age, sex, smoking status, alcohol intake, physical activity, total cholesterol, mean arterial pressure, HOMA-IR, and total energy intake, and protein intake.

Table 3. Hazard ratio and 95% confidence intervals for incident metabolic syndrome by CRP/Alb quartiles.

	Q1	Q2	Q3	Q4
Total, n	1550	1555	1555	1545
New cases of MetS	513	559	675	788
Mean follow-up (years)	8.3 (3.8)	8.1 (3.9)	7.7 (4.0)	7.1 (3.9)
Person-year of follow up	12888	12533	12022	12973
Incidence rate per 1000 person-year	39.8	47.8	56.1	60.7
Model 1	1.00 (ref)	1.11 (0.98-1.25)	1.33 (1.19-1.50)	1.67 (1.49-1.87)
Model 2	1.00 (ref)	1.08 (0.96-1.22)	1.25 (1.12-1.41)	1.57 (1.41-1.76)
Model 3	1.00 (ref)	1.12 (0.99-1.27)	1.24 (1.10-1.40)	1.51 (1.34-1.69)

Model 1: adjusted for age, sex, smoking status, alcohol intake, and physical activity.

Model 2: adjusted for age, sex, smoking status, alcohol intake, physical activity, total cholesterol, and mean arterial pressure.

Model 3: adjusted for age, sex, smoking status, alcohol intake, physical activity, total cholesterol, mean arterial pressure, HOMA-IR, and total energy intake.

Additionally, we have performed ROC and AUROC analyses were performed to compare predictability of MetS using CRP/Alb ratio and CRP, a well-known indicator of MetS risk. Since, the AUROC of CRP/Alb ratio and CRP are not statistically different with the post-hoc P-value of 0.374, CRP/Alb ratio is not better clinical indicator than CRP and another surrogate indicator of MetS risk (data not shown).

4. DISCUSSION

In this large-scale prospective community-based Korean cohort observed over 12 years, we investigated the relationship between the CRP/Alb ratio and the incidence of MetS among Korean adults. To the best of our knowledge, this study is the first to reveal a positive relationship between CRP/Alb ratio and the incidence of MetS regardless of baseline insulin resistance (such as HOMA-IR). This relationship was even present after adjusting for potentially confounding variables.

Our findings are consistent with previous results showing that those with a higher CRP at baseline had a higher risk of incident MetS.[7,8] However, a cross-sectional study conducted in South Korea indicated that high serum albumin levels are also associated with MetS. The associated assumption is that high serum albumin reflects high protein dietary intake.[11] On the contrary, a cross-sectional study in Japan had similar results but also emphasized that elevated serum albumin levels are associated with reduced risk of all-cause and cardiovascular mortality due to the anti-oxidative properties of serum albumin.[12] Also, a longitudinal study demonstrated an inverse relationship between changes in serum albumin levels and incident MetS, suggesting that an increase in serum albumin concentration represents an adaptive response to heightened oxidative stress demands.[13] While CRP serves as an indicator of participants' inflammatory status, serum albumin levels seem to not only reflect nutritional status but also signify the potential anti-oxidative response to chronic inflammation. In this regard, we did not examine CRP or albumin alone; we considered the correlation between CRP and albumin and assumed that CRP/Alb ratio could be a novel marker able to predict incident MetS. Since the

results of the ROC and AUROC analyses showed that the AUROC of CRP/Alb ratio and CRP are not statistically different, we suggest considering CRP/Alb ratio as another indicator, noting that subjects with low albumin and normal CRP, which can result in higher CRP/Alb ratio, may be warned as possible candidate for incident MetS.

Cho et al. reported that CRP/Alb ratio is also positively related to incident type 2 diabetes among community-dwelling Korean adults without chronic disease.[21] The authors suggested that CRP/Alb ratio reflects oxidative stress that is linked with the pathogenesis of type 2 diabetes, insulin resistance. Karabag et al. reported that elevated CRP/Alb ratio in stable coronary artery disease is associated with extent, severity, and complexity of coronary atherosclerosis.[22] They mentioned that increased CRP/Alb ratio indicates a higher inflammatory status and may be superior to CRP and albumin alone in determining the prevalence and severity of coronary artery disease.

Besides insulin resistance, the specific mechanism by which high CRP/Alb ratio is related to the development of MetS remains unclear. MetS is associated with chronic low-grade inflammation, including oxidative stress. Individuals who are more responsive to inflammation are also more susceptible to developing MetS compared to those not at risk. During inflammation, serum albumin levels naturally exhibit an inverse correlation with CRP levels.[23] Conversely, individuals with high albumin levels, which act as protective proteins against inflammatory reactions[24], compensate for inflammatory conditions and may exhibit a lower CRP/Alb ratio. As a result, individuals with higher serum albumin levels, reflecting an anti-oxidative response to inflammatory conditions that may decrease due to inflammation, may have a reduced risk of developing MetS.

This study has several limitations that should be considered. First, despite its large size, our study was conducted in a Korean population. Therefore, our results may not be generalizable to other ethnic/racial populations. Second, the study population may not represent the general Korean population as the participants were limited to specific geographic regions. Therefore, this study may be subject to selection bias. A third limitation is that the study did not show the effect of sequential change in the CRP/Alb

ratio; we only considered the baseline measurement of the CRP and albumin. Despite these limitations, our findings have clinical implications regarding preventive public health strategies for East Asian patients at high risk of developing MetS.

5. CONCLUSION

In conclusion, a high CRP/Alb ratio predicts future incident MetS that is independent of other associated variables, such as insulin resistance, among community-dwelling Korean adults.

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Abstract in Korean

C-reactive protein 대 Albumin 비율과 지역거주 주민들의 대사증후군 발병위험성; 12년 종단연구

CRP 대 Albumin 비는 다양한 염증 질환의 새로운 생체 지표로 등장하였다. 본 연구에서는 대규모 지역기반 한국 코호트를 이용하여 CRP 대 Albumin 비가 새롭게 발생하는 대사증후군과 연관이 있는지에 대해 12년 추적관찰 결과를 통해 분석하고자 하였다.

본 연구에서는 한국인유전체역학조사사업(KoGES)의 지역사회기반코호트 자료를 사용하였으며, 총 10,030명의 40세 이상 69세 이하의 참가자 중 기반조사에서 대사증후군을 갖고 있지 않은 6,205명이 연구대상으로 포함되었다. 기반조사의 CRP 대 Albumin 비의 4분위 수에 따라 환자군을 4개의 그룹으로 나누었다. 본 연구에서 새롭게 발생한 대사증후군의 정의는 2009 Joint Interim Statement of Circulation에서 발표된 진단기준을 따르기로 하였다. 대사증후군 발생에 대한 위험비(Hazard ratio)와 95% 유의구간(Confidence Interval)은 분석에 영향을 줄 수 있는 변수들을 보정한 다변량 Cox 회귀분석모델을 이용하였다.

12년의 추적관찰기간동안 총 2,535명 (40.9%)에게서 대사증후군이 발생하였으며, 발병률은 매 2년마다 5.6-11.9%로 나타났다. CRP 대 Albumin 비의 4분위 중 1분위 그룹을 기준으로 하여 계산한 위험비는 2, 3, 4분위로 갈수록 비례하여 증가하였다. 가장 높은 4분위에서의 대사증후군 발생 위험비는 1분위를 기준으로 하여 나이, 성별, 흡연여부, 음주여부, 신체활동, TG와 HDL-C, 평균혈압, HOMA-IR, 총 에너지 섭취량 등을 보정한 후 다변량 분석을 진행하였을 때 1.51(1.34-1.69)로 나타났다.

기반조사에서의 CRP 대 Albumin 비는 추후 대사증후군의 발생을 예측할 수 있는 새로운 지표로 활용될 수 있다.

핵심되는 말 : CRP 대 Albumin 비; 대사증후군; 염증; 인슐린 저항성