Association of Body Weight Variability with Adverse Cardiovascular Outcomes in Patients with Pre-Dialysis Chronic Kidney Disease

Sang Heon Suh 1, Tae Ryom Oh 1, Hong Sang Choi 1, Chang Seong Kim 1, Eun Hui Bae 1, Sue K. Park 2,3,4, Yong-Soo Kim 5, Yeong Hoon Kim 6, Kyu Hun Choi 7, Kook-Hwan Oh 8, Seong Kwon Ma 1,* and on behalf of the KoreaN Cohort Study for Outcomes in Patients with Chronic Kidney Disease (KNOW-CKD) Investigators †

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Abstract: To investigate the association of body weight variability (BWV) with adverse cardiovascular (CV) outcomes in patients with pre-dialysis chronic kidney disease (CKD), a total of 1867 participants with pre-dialysis CKD from Korean Cohort Study for Outcomes in Patients With Chronic Kidney Disease (KNOW-CKD) were analyzed. BWV was defined as the average absolute difference between successive values. The primary outcome was a composite of non-fatal CV events and all-cause mortality. Secondary outcomes were fatal and non-fatal CV events and all-cause mortality. High BWV was associated with increased risk of the composite outcome (adjusted hazard ratio (HR) 1.745, 95% confidence interval (CI) 1.065 to 2.847) as well as fatal and non-fatal CV events (adjusted HR 1.845, 95% CI 1.136 to 2.996) and all-cause mortality (adjusted HR 1.861, 95% CI 1.101 to 3.145). High BWV was associated with increased risk of fatal and non-fatal CV events, even in subjects without significant body weight gain or loss during follow-up periods (adjusted HR 2.755, 95% CI 1.114 to 6.813). In conclusion, high BWV is associated with adverse CV outcomes in patients with pre-dialysis CKD.

Keywords: all-cause mortality; body weight variability; cardiovascular events; chronic kidney disease

1. Introduction

Patients with chronic kidney disease (CKD) are likely to have experienced body weight fluctuations. Body weight (BW) loss associated with malnutrition–inflammation is
prevalent even before the commencement of renal replacement therapy [1,2] and increases mortality [3]. Several factors are associated with appetite impairment in patients with CKD, which further contributes to protein-energy wasting [4]. Conversely, BW gain associated with excess extracellular fluid is also common in patients with CKD, resulting in accelerated coronary artery calcification [5] and increased all-cause mortality [6]. The prevalent use of diuretics in CKD patients further impose the likelihood of body weight variability (BWV) [7]. As these conditions are not mutually exclusive, it could be assumed that a considerable portion of patients with CKD may experience fluctuations in their BW during the progression of CKD, rather than persistent gain or loss of BW. Nevertheless, the clinical impact of BWV in patients with pre-dialysis CKD has not been established.

BWV is an emerging predictor of adverse cardiovascular (CV) outcomes in various clinical contexts, although its probable association with health outcomes has long been suggested in general population [8]. A prospective cohort study reported that BWV is associated with all-cause mortality, and, in a subgroup with body mass index (BMI) < 25 kg/m² at the baseline, is also associated with increased risks of incident diabetes mellitus (DM) [9,10] and atrial fibrillation [11] in general population. A recent nationwide cohort study reported that BWV is associated with increased risks of myocardial infarction, stroke, and all-cause mortality in patients with type 2 DM [12,13] and in patients with in non-alcoholic fatty liver disease [14]. Fluctuation in BW is associated with a higher rate of cardiovascular (CV) events independent of traditional cardiovascular risk factors in patients with coronary artery disease (CAD) [15,16]. The association between BWV and CV outcomes, however, remains to be elucidated in patients with CKD.

We here investigated the association of BWV with CV outcomes in patients with pre-dialysis CKD. As the patients with CKD are prone to experience BW gain or loss during the course of the disease, we analyzed the association between BWV and longitudinal changes of BW in patients with CKD. We also analyzed the association of BWV with CV outcomes in patients without significant BW gain or loss during follow-up periods.

2. Materials and Methods

2.1. Study Designs and Data Collection from Participants

The Korean Cohort Study for Outcomes in Patients With Chronic Kidney Disease (KNOW-CKD) is a nationwide prospective cohort study involving 9 tertiary-care general hospitals in Korea [17]. Korean patients with CKD from stage 1 to pre-dialysis stage 5, who voluntarily provided informed consent were enrolled. The study was conducted in accordance with the principles of the Declaration of Helsinki, and the study protocol was approved by the institutional review boards of participating centers. A total of 2238 subjects were longitudinally followed up. (Figure 1). After excluding those lacking the baseline measurement of BW, and those with the number of body weight measurement during follow-up periods less than three, 1867 subjects were finally included for the analyses. The median follow-up duration was 6.155 years. Demographic information was collected from all eligible participants, including age, gender, comorbid conditions, and medication history (angiotensin-converting enzyme inhibitor/angiotensin II receptor blockers (ACEi/ARBs), diuretics, total number of antihypertensive drugs). Venous samples were collected following overnight fasting, to determine hemoglobin, albumin, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglyceride, fasting glucose, high-sensitivity C-reactive protein (hs-CRP), 25(OH) vitamin D and creatinine levels at the baseline. Estimated glomerular filtration rate (eGFR) was calculated by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [18]. The urine albumin-to-creatinine ratio (UACR) was measured in random, preferably second-voided, spot urine samples. The 24 h urine protein excretion was also determined.
2.2. Determination of BWV

BW was measured at 0, 6, and 12 months and then yearly thereafter up to 8 years. The median number of BW measurement was 6 times. Intra-individual BWV between visits was determined by average successive variability (ASV), defined as the average absolute difference between successive values [9,10,15,16]. The 1st, 2nd and 3rd, and 4th quartiles were defined as low, moderate, and high BWV, respectively (Figure 1).

2.3. Estimation of the Rate of Longitudinal BW Change during Follow-Up Periods

The rate of longitudinal BW change for each individual were estimated using a regression model and expressed as the slope (kg/year) [19]. The 1st, 2nd and 3rd, and 4th quartiles were defined as a decrease, maintenance, and increase of BW, respectively (Supplemental Table S1).

2.4. Study Outcomes

The primary outcome was a composite of non-fatal CV events and all-cause mortality. Raw numbers for the composite outcome by enrollment sites subgroups are summarized in Supplemental Tables S2 and S3, respectively. Secondary outcomes were fatal and non-fatal CV events and all-cause mortality. CV events, either fatal or non-fatal, included any coronary artery event (unstable angina, myocardial infarction, or coronary intervention/surgery), hospitalization for heart failure, ischemic or hemorrhagic stroke, incident peripheral arterial disease, and symptomatic arrhythmia.

2.5. Statistical Analysis

Continuous variables were expressed as mean ± standard deviation or median [interquartile range]. Categorical variables (e.g., current smoking status) were expressed as number of participants and percentage. For descriptive analyses, Student’s T-test or one-way analysis of variance and \( \chi^2 \) test were used for continuous and categorical variables, respectively. The correlation between the BWV and BW slope was established by curve estimation regression analysis. Multinomial logistic regression models were analyzed to
address the association between BWV and longitudinal BW change, where the models were
adjusted for age, gender, Charlson comorbidity index, history of DM, smoking history, BMI,
systolic blood pressure (SBP), diastolic blood pressure (DBP), medications (ACEi/ARBs,
diuretics, total number of antihypertensive drugs), hemoglobin, albumin, HDL-cholesterol,
triglycerides, fasting serum glucose, hs-CRP, 25(OH) vitamin D levels, eGFR, and 24 h urine
protein. The results of multinomial logistic regression models were presented as odd ratios
(ORs) and 95% confidence intervals (CIs). To assess the association between BWV and
the outcomes, Cox proportional hazard regression models were analyzed. Patients lost to
follow-up were censored at the date of the last visit. We adjusted age, gender, Charlson co-
morbidity index, history of DM, smoking history, BMI, SBP, DBP, medications (ACEi/ARBs,
diuretics, total number of antihypertensive drugs), hemoglobin, albumin, HDL-cholesterol,
triglycerides, fasting serum glucose, hs-CRP, 25(OH) vitamin D levels, eGFR, and 24 h urine
protein. The results of Cox proportional hazard models were presented as hazard ratios
(HRs) and 95% CIs. Statistical significance was defined as $p < 0.05$. Data were analyzed
using IBM SPSS statistical analysis software for Windows, version 22.0 (IBM Corp).

3. Results

3.1. Baseline Characteristics

The baseline characteristics of study participants were described by BWV (Table 1). The mean age was highest in subjects with low BWV, and lowest in subjects with high BWV. The gender distribution was not significantly different among the groups. Charlson comorbidity index was higher in subjects with high BWV. Detailed presentation of Charlson Comorbidity Index components by BWV is summarized in Supplement Table S4, which revealed that the frequency of cerebrovascular disease and diabetes with organ damage was significantly higher in the subjects with high BWV. The frequency of the subjects with previous medical history of DM was highest in the subjects with high BWV, and lowest in the subjects with low BWV. The frequencies of other medical history, such as CAD and arrhythmia were not significantly different among the groups. Smoking status did not differ across the groups either. BMI, waist circumference, and SBP were highest in the subjects with high BWV, and lowest in the subjects with low BWV. The subjects with high BWV were significantly likely to take no less than 3 antihypertensive drugs at the baseline. Serum albumin level was highest in the subjects with moderate BWV. Serum triglyceride and fasting glucose levels were highest in the subjects with high BWV, and lowest in the subjects with low BWV. Conversely, 25(OH) vitamin D level was highest in subjects with low BWV, and lowest in subjects with high BWV. The 24 h urine protein and UACR in random urine were lowest in in the subjects with moderate BWV. Hemoglobin, total cholesterol, LDL-cholesterol, HDL-cholesterol, hs-CRP levels were not significantly different among the groups. In contrast, eGFR was highest in the subjects with high BWV, and lowest in the subjects with low BWV. Accordingly, the distribution of CKD stages across the groups was significantly different. Collectively, high BWV was in large associated with unfavorable clinical features, with an exception of eGFR, which could be attributed to significantly higher BMI in subjects with high BWV and a relevant limitation of creatinine-based estimation of glomerular filtration rate.

Table 1. Baseline characteristics of study participants by BWV.

|                | Low                  | Moderate             | High                 | $p$ Value |
|----------------|----------------------|----------------------|----------------------|-----------|
| Follow-up duration (year) | 5.510 ± 2.025         | 6.024 ± 1.721         | 6.024 ± 1.785         | <0.001    |
| Age (year)     | 54.889 ± 10.969       | 54.035 ± 11.603       | 51.442 ± 13.726       | <0.001    |
| Male           | 278 (59.3)            | 556 (59.5)            | 299 (64.4)            | 0.161     |
3.2. High BWV Is Associated with Adverse CV Outcomes in Patients with Pre-Dialysis CKD

To address the association of BWV and the study outcomes, Kaplan–Meier survival was analyzed by BWV (Figure 2). The survival curves for the composite outcome (Log rank, *p* = 0.115) and fatal and non-fatal CV events (Log rank, *p* = 0.126) revealed no significant differences among the groups by BWV, whereas the all-cause death-free survival significantly differs among the groups (Log rank, *p* = 0.023). To determine whether BWV is independently associated with CV outcomes in patients with pre-dialysis CKD, Cox proportional hazard regression models were analyzed. (Table 2). Compared to the subjects with moderated BWV, those with high BWV were associated with increased risks of the composite outcome (adjusted HR 1.738, 95% CI 1.065 to 2.847, *p* = 0.027), fatal and non-fatal CV events (adjusted HR 1.845, 95% CI 1.136 to 2.996, *p* = 0.013), and all-cause mortality (adjusted HR 1.861, 95% CI 1.101 to 3.145, *p* = 0.020). In the subgroup analyses (Table 3), high BWV was associated with the composite outcome in the subjects with age ≥60 years (adjusted HR 2.361, 95% CI 1.139 to 4.897, *p* = 0.021), medical history of DM (adjusted HR 2.199, 95% CI 1.091 to 4.431, *p* = 0.028), and total number of antihypertensive drugs ≥3 (adjusted HR 6.172, 95% CI 1.394 to 27.333, *p* = 0.017). Interestingly, both low (adjusted HR 2.542, 95% CI 1.072 to 6.024, *p* = 0.034) and high (adjusted HR 2.545, 95% CI 1.181 to 5.368, *p* = 0.005) BWV were associated with increased risks of the composite outcome in the subjects with age ≥60 years. These findings suggest that BWV may be a useful biomarker for predicting adverse CV outcomes in patients with pre-dialysis CKD.
5.486, \( p = 0.017 \) BWV were associated with the composite outcomes in those without use of diuretics. Low BWV was also associated with the composite outcomes in those with UACR < 300 mg/g (adjusted HR 3.509, 95% CI 1.028 to 11.05, \( p = 0.045 \)). The association of high BWV with fatal and non-fatal CV events (Supplemental Table S5) were also significant in the subjects with age ≥ 60 years (adjusted HR 2.191, 95% CI 1.054 to 4.557, \( p = 0.036 \)), male gender (adjusted HR 1.865, 95% CI 1.020 to 3.412, \( p = 0.043 \)), medical history of DM (adjusted HR 2.300, 95% CI 1.147 to 4.612, \( p = 0.019 \)), BMI ≥ 25 kg/m² (adjusted HR 3.048, 95% CI 1.181 to 7.869, \( p = 0.021 \)), total number of antihypertensive drugs ≥ 3 (adjusted HR 7.993, 95% CI 2.145 to 29.779, \( p = 0.002 \)), and eGFR < 45 mL/min./1.73 m² (adjusted HR 2.195, 95% CI 1.051 to 4.582, \( p = 0.036 \)). Only high BWV were associated with the fatal and non-fatal CV events in those without use of diuretics (adjusted HR 2.515, 95% CI 1.020 to 3.412, \( p = 0.043 \)). In the subgroup analyses for all-cause mortality (Supplemental Table S6), high BWV was associated with increased risk of all-cause mortality only in the subjects with age ≥ 60 years (adjusted HR 2.438, 95% CI 1.324 to 4.499, \( p = 0.004 \)). Taken together, high BWV is significantly associated with adverse CV outcomes in patients with pre-dialysis CKD.

![Figure 2](image-url)  
**Figure 2.** Kaplan–Meier survival curve for the outcomes by BWV. The probability of composite outcome- (a), fatal and non-fatal CV event- (b), and all-cause death- (c) free survivals by BW variability. \( p \) values by Log rank test. Abbreviations: BWV, body weight variability.

| Table 2. Cox proportional hazards regression of BWV for the outcomes. |
|-----------------|-----------------|-----------------|
| **Unadjusted**   | **Adjusted**     |                |
| **HR (95% CIs)** | **\( p \) Value** | **HR (95% CIs)** | **\( p \) Value** |
| **Composite outcome** |                  |                |
| Low BWV          | 1.236 (0.743, 2.057) | 0.414          | 1.444 (0.790, 2.642) | 0.233 |
| Moderate BWV     | Reference         |                | Reference           |        |
| High BWV         | 1.789 (1.195, 2.679) | 0.005          | 1.738 (1.065, 2.847) | 0.027 |
| **Fatal and non-fatal CV events** |                  |                |
| Low BWV          | 1.283 (0.771, 2.133) | 0.337          | 1.593 (0.882, 2.884) | 0.0123 |
| Moderate BWV     | Reference         |                | Reference           |        |
| High BWV         | 1.827 (1.221, 2.735) | 0.003          | 1.845 (1.136, 2.996) | 0.013 |
| **All-cause mortality** |                  |                |
| Low BWV          | 1.008 (0.543, 1.870) | 0.980          | 0.930 (0.493, 1.753) | 0.8223 |
| Moderate BWV     | Reference         |                | Reference           |        |
| High BWV         | 1.702 (1.043, 2.776) | 0.033          | 1.861 (1.101, 3.145) | 0.020 |

Models were adjusted for age, gender, Charlson comorbidity index, history of DM, smoking history, BMI, SBP, DBP, Medications (ACEi/ARBs, diuretics, number of antihypertensive drugs), hemoglobin, albumin, HDL-cholesterol, triglycerides, fasting serum glucose, hs-CRP, 25(OH) vitamin D levels, eGFR, and 24 h urine protein. Abbreviations: BWV, body weight variability; CV, cardiovascular; CI, confidence interval.
Table 3. Cox proportional hazards regression of BWV for the composite outcome in various subgroups.

|                      | Unadjusted | Adjusted | Unadjusted | Adjusted |
|----------------------|------------|----------|------------|----------|
|                      | HR (95% CIs) | p Value | HR (95% CIs) | p Value |
| **Age < 60 years**   |            |          |            |          |
| Low BWV              | 1.811 (0.814, 4.030) | 0.146 | 0.595 (0.183, 1.938) | 0.204 |
| Moderate BWV         | Reference   |          | Reference   |          |
| High BWV             | 1.675 (0.879, 3.195) | 0.117 | 0.782 (0.265, 2.302) | 0.782 |
| **Age ≥ 60 years**   |            |          |            |          |
| Low BWV              | 1.057 (0.541, 2.065) | 0.870 | 1.048 (0.429, 2.559) | 0.919 |
| Moderate BWV         | Reference   |          | Reference   |          |
| High BWV             | 2.089 (1.234, 3.539) | 0.006 | 2.361 (1.139, 4.897) | 0.021 |
| **Male**             |            |          |            |          |
| Low BWV              | 1.853 (0.966, 3.554) | 0.064 | 1.512 (0.632, 3.614) | 0.353 |
| Moderate BWV         | Reference   |          | Reference   |          |
| High BWV             | 1.508 (0.931, 2.440) | 0.095 | 1.723 (0.926, 3.204) | 0.086 |
| **Female**           |            |          |            |          |
| Low BWV              | 0.720 (0.302, 1.719) | 0.460 | 0.275 (0.052, 1.438) | 0.126 |
| Moderate BWV         | Reference   |          | Reference   |          |
| High BWV             | 2.606 (1.187, 5.720) | 0.017 | 0.271 (0.049, 1.490) | 0.133 |
| **CCI ≤ 3**          |            |          |            |          |
| Low BWV              | 0.883 (0.395, 1.978) | 0.763 | 0.879 (0.287, 2.695) | 0.821 |
| Moderate BWV         | Reference   |          | Reference   |          |
| High BWV             | 2.242 (1.231, 4.083) | 0.008 | 1.910 (0.812, 4.496) | 0.138 |
| **CCI ≥ 4**          |            |          |            |          |
| Low BWV              | 1.781 (0.896, 3.542) | 0.100 | 3.855 (1.373, 10.823) | 0.010 |
| Moderate BWV         | Reference   |          | Reference   |          |
| High BWV             | 1.499 (0.841, 2.670) | 0.169 | 1.364 (0.589, 3.157) | 0.469 |
| **DM (–)**           |            |          |            |          |
| Low BWV              | 1.164 (0.539, 2.513) | 0.700 | 2.012 (0.659, 6.143) | 0.220 |
| Moderate BWV         | Reference   |          | Reference   |          |
| High BWV             | 1.952 (1.002, 3.800) | 0.049 | 1.429 (0.531, 3.842) | 0.480 |
| **DM (+)**           |            |          |            |          |
| Low BWV              | 1.304 (0.654, 2.600) | 0.451 | 2.169 (0.762, 6.174) | 0.147 |
| Moderate BWV         | Reference   |          | Reference   |          |
| High BWV             | 1.620 (0.947, 2.769) | 0.078 | 2.199 (1.091, 4.431) | 0.028 |
| **BMI < 25 (kg/m²)** |            |          |            |          |
| Low BWV              | 1.452 (0.785, 2.687) | 0.235 | 2.175 (0.953, 4.965) | 0.065 |
| Moderate BWV         | Reference   |          | Reference   |          |
| High BWV             | 1.891 (1.072, 3.335) | 0.028 | 1.743 (0.813, 3.739) | 0.153 |
| **BMI ≥ 25 (kg/m²)** |            |          |            |          |
| Low BWV              | 0.898 (0.341, 2.367) | 0.829 | 1.203 (0.283, 5.125) | 0.802 |
| Moderate BWV         | Reference   |          | Reference   |          |
| High BWV             | 1.578 (0.863, 2.884) | 0.138 | 2.666 (0.938, 7.579) | 0.066 |
| **Diuretics (–)**    |            |          |            |          |
| Low BWV              | 1.789 (0.928, 3.447) | 0.082 | 2.542 (1.072, 6.024) | 0.034 |
| Moderate BWV         | Reference   |          | Reference   |          |
| High BWV             | 3.037 (1.659, 5.558) | <0.001 | 2.545 (1.181, 5.486) | 0.017 |
| **Diuretics (+)**    |            |          |            |          |
| Low BWV              | 0.824 (0.353, 1.921) | 0.653 | 0.531 (0.148, 1.914) | 0.334 |
| Moderate BWV         | Reference   |          | Reference   |          |
| High BWV             | 1.283 (0.699, 2.355) | 0.422 | 0.956 (0.398, 2.296) | 0.919 |
| **Number of anti-HTN drugs ≤ 2** |            |          |            |          |
| Low BWV              | 1.374 (0.771, 2.450) | 0.281 | 1.822 (0.869, 3.821) | 0.112 |
| Moderate BWV         | Reference   |          | Reference   |          |
| High BWV             | 1.641 (0.983, 2.738) | 0.058 | 1.670 (0.838, 3.328) | 0.145 |
| **Number of anti-HTN drugs ≥ 3** |            |          |            |          |
| Low BWV              | 0.640 (0.187, 2.187) | 0.477 | 1.451 (0.159, 13.227) | 0.741 |
| Moderate BWV         | Reference   |          | Reference   |          |
| High BWV             | 2.374 (1.199, 4.704) | 0.013 | 6.172 (1.394, 27.333) | 0.017 |
| **eGFR ≥ 45 mL/min/1.73 m²** |            |          |            |          |
| Low BWV              | 1.641 (0.624, 4.314) | 0.315 | 0.282 (0.060, 1.326) | 0.109 |
| Moderate BWV         | Reference   |          | Reference   |          |
| High BWV             | 1.956 (1.049, 3.649) | 0.035 | 2.066 (0.855, 4.991) | 0.107 |
| **eGFR < 45 mL/min/1.73 m²** |            |          |            |          |
| Low BWV              | 1.130 (0.609, 2.097) | 0.698 | 1.679 (0.754, 3.741) | 0.205 |
| Moderate BWV         | Reference   |          | Reference   |          |
| High BWV             | 1.822 (1.058, 3.318) | 0.031 | 1.626 (0.775, 3.413) | 0.199 |
Table 3. Cont.

|                    | Unadjusted                     | Adjusted                     |
|--------------------|--------------------------------|------------------------------|
|                    | HR (95% CIs) | p Value | HR (95% CIs) | p Value |
| **Random urine ACR**< 300 mg/g |                   |        |              |        |
| Low BWV            | 1.603 (0.734, 3.501) | 0.237 | 3.059 (1.028, 9.105) | 0.045 |
| Moderate BWV       | 2.150 (1.154, 4.006) | 0.016 | 2.308 (0.977, 5.454) | 0.057 |
| High BWV           | Reference            |        | Reference     |        |
| **Random urine ACR**≥ 300 mg/g |                   |        |              |        |
| Low BWV            | 0.967 (0.485, 1.926) | 0.924 | 0.964 (0.380, 2.447) | 0.939 |
| Moderate BWV       | Reference            |        | Reference     |        |
| High BWV           | 1.464 (0.833, 2.570) | 0.185 | 1.554 (0.690, 3.500) | 0.287 |

Models were adjusted for age, gender, Charlson comorbidity index, history of DM, smoking history, BMI, SBP, DBP, Medications (ACEi/ARBs, diuretics, number of antihypertensive drugs), hemoglobin, albumin, HDL-cholesterol, triglycerides, fasting serum glucose, hs-CRP, 25(OH) vitamin D levels, cGFR, and 24 h urine protein. Abbreviations: ACR, Albumin-to-creatinine ratio; BMI, body mass index; CCI, Charlson comorbidity index; CI, confidence interval; DM, diabetes mellitus; HTN, hypertension; eGFR, estimated glomerular filtration rate.

3.3. High BWV Is Associated with Adverse CV Outcomes Even in Patients without BW Gain or Loss during Follow-up Periods

To determine the association between BWV and the rate of longitudinal BW change, multinomial logistic regression models were analyzed (Supplemental Table S7), which demonstrated a robust correlation of high BWV with both BW decrease (adjusted OR 2.310, 95% CI 1.661 to 3.213, \( p < 0.001 \)) and BW increase (adjusted OR 2.642, 95% CI 1.912 to 3.652, \( p < 0.001 \)). Inversely, low BWV was associated with reduced risks of either BW decrease (adjusted OR 0.429, 95% CI 0.300 to 0.614, \( p < 0.001 \)) or BW increase (adjusted OR 0.541, 95% CI 0.384 to 0.763, \( p < 0.001 \)). However, the scatter plot for the correlation of the rate of longitudinal BW change and BWV (Supplemental Figure S1) visualized that a substantial portion of the subjects experience only a limited range of longitudinal BW change, but concurrently show visit-to-visit BWV (i.e., scatter plots condensed in the midline with a distribution along the Y-axis direction). Therefore, we decided to unveil the association of high BWV with adverse CV outcomes in the subjects without BW gain or loss (i.e., the subjects with BW maintenance) during follow-up periods (\( n = 930 \)). The analyses of Cox proportional hazard regression models (Table 4) demonstrated that high BWV is associated with increased risk of fatal and non-fatal CV events in patients with BW maintenance during follow-up periods (adjusted HR 2.755, 95% CI 1.114 to 6.813, \( p = 0.028 \)), suggesting that fluctuations in BW impose an independent risk of CV events even in the absence of longitudinal BW change.

Table 4. Cox proportional hazards regression of BWV for the outcomes in subjects with BW maintenance during follow-up periods.

|                    | Unadjusted                     | Adjusted                     |
|--------------------|--------------------------------|------------------------------|
|                    | HR (95% CIs) | p Value | HR (95% CIs) | p Value |
| **Composite outcome** |                   |        |              |        |
| Low BWV            | 1.580 (0.733, 3.406) | 0.243 | 1.878 (0.701, 5.029) | 0.210 |
| Moderate BWV       | 1.754 (0.872, 3.528) | 0.115 | 2.239 (0.816, 6.148) | 0.118 |
| High BWV           | Reference            |        | Reference     |        |
| **Fatal and non-fatal CV events** |                   |        |              |        |
| Low BWV            | 1.762 (0.846, 3.669) | 0.130 | 2.430 (0.958, 6.166) | 0.062 |
| Moderate BWV       | 1.838 (0.913, 3.698) | 0.088 | 2.755 (1.114, 6.813) | 0.028 |
| High BWV           | Reference            |        | Reference     |        |
| **All-cause mortality** |                   |        |              |        |
| Low BWV            | 1.729 (0.716, 4.179) | 0.224 | 1.530 (0.580, 4.037) | 0.390 |
| Moderate BWV       | 1.377 (0.438, 4.324) | 0.584 | 1.111 (0.309, 3.999) | 0.871 |

Models were adjusted for age, gender, Charlson comorbidity index, history of DM, smoking history, BMI, SBP, DBP, Medications (ACEi/ARBs, diuretics, number of antihypertensive drugs), hemoglobin, albumin, HDL-cholesterol, triglycerides, fasting serum glucose, hs-CRP, 25(OH) vitamin D levels, cGFR, and 24 h urine protein. Abbreviations: CI, confidence interval.
To figure out the impact of the baseline BMI in the subjects with high BWV, the subjects with high BWV were further divided into those with BMI 20 to 24.9 \(\text{kg/m}^2\) (i.e., near normal BMI) vs. those with BMI < 20 \(\text{kg/m}^2\) or \(\geq 20 \text{kg/m}^2\) (i.e., relatively underweight or obese) (Supplemental Table S8). Intriguingly, only the subjects with high BWV and BMI < 20 \(\text{kg/m}^2\) or \(\geq 20 \text{kg/m}^2\) were associated with increased risk of the composite outcome (adjusted HR 2.149, 95% CI 1.107 to 4.173, \(p = 0.024\)), fatal and non-fatal CV events (adjusted HR 2.286, 95% CI 1.180 to 4.426, \(p = 0.014\)), and all-cause mortality (adjusted HR 2.124, 95% CI 1.101 to 4.095, \(p = 0.025\)), indicating a significant impact of the baseline BMI in addition to BWV on the prognosis of the patients with pre-dialysis CKD.

4. Discussion

In the present study, we discovered that high BWV is significantly associated with adverse CV outcomes in patients with pre-dialysis CKD. We also demonstrated that BWV is associated with longitudinal of BW gain or loss in patients with CKD. Importantly, we proved that high BWV is associated with adverse CV outcomes, even in patients without significant BW gain or loss during follow-up periods.

In the current study, we found that BWV is associated with both longitudinal BW gain and loss in patients with CKD, rather than a unidirectional association toward BW gain or BW loss. This suggests the multifaceted nature of the progression in the body composition during the course of CKD. Indeed, a recent cohort study reported that both BW gain and loss are associated with adverse outcomes in patients with pre-dialysis CKD [19]. Meanwhile, in the present study, we primarily highlighted on the visit-to-visit fluctuation in BW, rather than longitudinal trends in BW, provided that several events that promote BW gain or loss may differ among each follow-up visit, in which case the BWV should be high, even though the BW slope might be blunted. Therefore, a potential strength of BWV over longitudinal BW change may be a sensitive detection of vulnerable subjects who are at high risk of CV events. In this context, it is of interest to note that high BWV is associated with adverse CV outcomes, even in patients with BW maintenance during follow-up periods, as this suggests a prognostic impact of BWV independent of longitudinal BW change.

It is intriguing that, although high BWV was robustly associated adverse outcomes, low BWV was also associated with high risk of the composite outcome in certain clinical contexts (e.g., urine ACR < 300 mg/g). We speculate that this results from the complex nature of homeostasis in body composition during the course of CKD, which may justify BWV to some degree. Indeed, in the present study, the risks of adverse outcomes were almost consistently lowest in subjects with ‘moderate’, but not ‘low’, BWV. The precise mechanism of how a moderate, not low, degree of BWV predicts the best outcomes in patients with pre-dialysis CKD should be further elucidated.

The mechanism of how BWV is associated with adverse CV outcomes is another remaining question. One possible explanation is the association of BWV and coronary artery calcification (CAC), although the association has not been validated yet. Previous studies reported that central adiposity is strongly associated with CAC in general population [20] and in CKD patients [21,22]. Inversely, malnutrition–inflammation is associated with a higher CAC score in diabetic CKD patients [23], as well as in patients with chronic dialysis [24,25]. As BWV is a sensitive read-out of conditions associated with BW gain or loss in CKD population, we speculate that BWV may predict the risk of CAC, delineating its association with adverse CV outcomes. Another explanation is the association of BWV and heart failure (HF). It has been reported that the fluctuations in BW [26] or anthropometric indices [27], such as BMI and the waist-to-hip ratio, and BW and is associated with increased mortality in patients with HF. As the renal function of the subjects in those studies is relatively reserved, the association of BWV and HF should be further evaluated.

There are a number of limitations in this study. First, we are not able to clarify the causal relationship between high BWV and adverse CV outcomes, because of the observational nature of the current study. Second, despite the clear impact of high BWV on the adverse CV outcomes, the precise mechanism should be further addressed. Third, as
this cohort study enrolled only ethnic Koreans, a precaution is required to extrapolate the
data in the present study to other populations. Fourth, there is a potential risk of multiple
testing burden in the current study, as the multiple outcomes have been analyzed.

In conclusion, we report that high BWV is significantly associated with adverse CV
outcomes in patients with pre-dialysis CKD. Our results suggest that BWV is associated
with longitudinal of BW gain or loss in patients with CKD, while high BWV is associated
with adverse CV outcomes, even in patients without BW gain or loss during follow-
up periods.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/nu13103381/s1, Table S1: Baseline characteristics of study participants by BW slope. Table
S2: Raw numbers for the composite outcome by enrollment sites. Table S3: Raw numbers for the
composite outcome by subgroups. Table S4: Charlson Comorbidity Index components of study
participants by BWV. Table S5: Cox proportional hazards regression of BWV for the fatal and non-fatal
CV events in various subgroups. Table S6: Cox proportional hazards regression of BWV for all-cause mortality in various subgroups. Table S7: Multinomial logistic regression of BWV for longitudinal BW change. Table S8: Cox proportional hazards regression of BMI in addition to BWV for the outcomes. Figure S1: Scatter plot for the correlations of BW slope with BWV.

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Seoul National University College of Medicine, Byung-Joo Park, Sue Kyung Park, and Juyeon Lee.
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