Abstract: Upstroke time (UT), measured from the foot-to-peak peripheral pulse wave, is a merged parameter used to assess arterial stiffness and target vascular injuries. In this study, we aimed to investigate UT for the prediction of cardiovascular and all-cause mortality in patients with chronic kidney disease (CKD). This longitudinal study enrolled 472 patients with CKD. Blood pressure, brachial pulse wave velocity (baPWV), and UT were automatically measured by a Colin VP-1000 instrument. During a median follow-up of 91 months, 73 cardiovascular and 183 all-cause mortality instances were recorded. Multivariable Cox analyses indicated that UT was significantly associated with cardiovascular mortality (hazard ratio (HR) = 1.010, *p* = 0.007) and all-cause mortality (HR = 1.009, *p* < 0.001). The addition of UT into the clinical models including traditional risk factors and baPWV further increased the value in predicting cardiovascular and all-cause mortality (both *p* < 0.001). In the Kaplan–Meier analyses, UT ≥ 180 ms could predict cardiovascular and all-cause mortality (both log-rank *p* < 0.001). Our study found that UT was a useful parameter in predicting cardiovascular and all-cause mortality beyond the traditional risk factors and baPWV.

Keywords: upstroke time; pulse wave velocity; blood pressure; mortality; chronic kidney disease
abnormalities, such as decreased adiponectin and polymorphism of vitamin D receptors, are also associated with mortality in dialysis patients [11,12]. Some biomarkers of inflammation and endothelial dysfunction, such as asymmetric dimethylarginine, are also useful predictors for mortality in dialysis populations [2,13–15].

Traditional atherosclerotic risk factors, including coronary artery disease, smoking, hypertension, diabetes, and congestive heart failure, have strong impacts on mortality in CKD patients [16–18]. Nontraditional atherosclerotic risk factors, such as increased arterial stiffness, are significantly associated with cardiovascular and all-cause mortality in patients with early to advanced CKD and sequential end-stage renal disease [19–24]. High blood pressure, progressive arterial calcification, and attenuated vascular compliance are associated with increased arterial stiffness and the presence of atherosclerotic cardiovascular disease [25]. Vascular endothelial growth factors, norepinephrine, and proinflammatory cytokines are also significantly associated with atherogenesis in patients with CKD and end-stage renal disease [2,13,26–28]. Progressive arterial stiffness increases, in terms of increased brachial-ankle pulse wave velocity (baPWV), are also associated with increased mortality in patients with CKD [29].

The upstroke time (UT) is measured from the initial notch to the peak of the peripheral arterial pulse wave. In recent studies, UT was not only used as a diagnostic tool for peripheral artery disease and target organ damage but also as a predictor of cardiovascular and all-cause mortality [30–32]. However, the relationship of UT with mortality in CKD patients is still unknown. Therefore, we aim to explore the survival impact of UT among CKD patients.

2. Materials and Methods

2.1. Study Subjects and Design

All study participants were enrolled from patients booked for echocardiographic examinations at Kaohsiung Municipal Siaogang Hospital from March 2010 to March 2012 due to suspected ischemic heart disease, heart failure, hypertension, abnormal cardiac physical examination, a survey for dyspnea, a pre-operative cardiac function survey, and so on. Patients classified in stages 3, 4, and 5 CKD (based on the estimated glomerular filtration rate (eGFR) level (30 to 59, 15 to 29, and <15 mL/min/1.73m²) with kidney damage lasting for more than 3 months) were included [33]. As the value of UT had a beat-to-beat variation in patients with atrial fibrillation (n = 6) and severe aortic stenosis (n = 2) might have a significant impact on the value of UT, we excluded such patients [34,35]. In addition, we also excluded patients with end-stage renal disease receiving renal replacement therapies (n = 4). In total, 472 patients joined this study (Figure 1).

2.2. Ethics Statement

The study protocol was approved by the Institutional Review Board of Kaohsiung Medical University Hospital, and all enrolled patients gave written, informed consent to participate in the study (KMUHIRB-E(I)-20190415, 6 March 2020).

2.3. Blood Pressure, baPWV, and UT Measurements

Blood pressures, baPWV, and UT were measured by an instrument (Colin VP1000, Komaki, Japan) in all participants in the supine position after at least 10 min rest [18,36,37]. Detailed measurements of blood pressures and baPWV were published in our previous studies [18,38]. Briefly, the baPWV was counted as the traveled distance of the pulse wave divided by the passage time of the pulse wave from the brachial to tibial arteries. The UT was also automatically calculated as the time interval from foot-to-peak of the ankle arterial pulse wave in each participant (Figure 2). After obtaining the bilateral values, the higher values of blood pressures, baPWV, and UT were used for further analyses [30].
Figure 1. Flowchart of the study protocol.

Figure 2. The upstroke time was automatically calculated from the foot-to-peak of peripheral pulse wave.

2.4. Collection of Clinical Characteristics, Medical, and Laboratory Data

The clinical characteristics and medical profiles, including the age, gender, history of smoking, hypertension, diabetes mellitus, congestive heart failure, coronary artery disease, and cerebrovascular disease were obtained from the medical records. The body mass index was calculated as a standard ratio of weight (kilograms) divided by the square of height (meters). The medications taken during this study period, including angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), β-blockers, calcium channel blockers (CCBs), and diuretics, were also reviewed from the medical records. Standard laboratory data for fasting blood samples and serum creatinine were measured by an automatic analyzer (Roche Diagnostics, Mannheim, Germany). The value of eGFR was calculated using the four variable equations from the Modification of Diet in Renal Disease study [33].
2.5. Definition of Cardiovascular and All-Cause Mortality

All study participants were followed-up until December 2018. Survival information and causes of death were obtained from the official death certificate and final confirmation by the Ministry of Health and Welfare. The causes of death were classified by the International Classification of Diseases 9th Revision. The causes of cardiovascular mortality were defined as deaths due to cerebral vascular disease, ischemic heart disease, myocardial infarction, heart failure, valvular heart disease, and atherosclerotic vascular disease.

2.6. Statistical Analysis

All variables were presented as percentages or mean ± standard deviation. After the normality of continuous variables was determined using the Kolmogorov–Smirnov test, appropriate parametric and nonparametric tests were used. Differences between two categorical variables were analyzed by the Chi-square test. The time to mortality events were modeled using the Cox proportional hazards model with forward selection. Before multivariable analysis, we performed a collinearity test. Due to the high collinearity between systolic blood pressure and pulse pressure, only pulse pressure was selected for the multivariable analysis. We conducted two multivariable models. The variables in model 1 included the significant clinical variables in the univariable analysis except for systolic blood pressure and baPWV, and the variables in model 2 included the significant clinical variables in the univariable analysis except for systolic blood pressure and UT. The incremental values of baPWV and UT were studied over a clinical model to assess the risk for mortality events by calculating the improvement in the global Chi-square. The best cut-off value of UT for the prediction of cardiovascular and all-cause mortality was determined by a receiver operating characteristic curve. A Kaplan–Meier survival plot was calculated from the baseline to time of mortality events and compared using the log-rank test. The statistical significance was defined as a p value less than 0.05. Statistical analysis was performed using SPSS version 22.0 (SPSS, Chicago, IL, USA).

3. Results

3.1. Baseline Characteristics in All Participants

The difference of clinical characteristics between patients with and without all-cause mortality is shown in all-cause mortality in Table 1. Patients with all-cause mortality had an older age, a higher prevalence of diabetes, cerebrovascular disease, and congestive heart failure, a higher pulse pressure, heart rate, fasting glucose, baPWV, and UT, a higher percentage of using diuretics and advanced CKD (eGFR < 30 mL/min/1.73m²), and a lower body mass index, total cholesterol, and eGFR.

3.2. Major Predictors of All-Cause and Cardiovascular Mortality in Study Patients

During the follow-up period (median 91 months), 73 cardiovascular mortality and 183 all-cause mortality instances were recorded. Table 2 shows the predictors of cardiovascular and all-cause mortality in univariate analysis. Increased cardiovascular mortality was significantly associated with increased age, heart rate, serum fasting glucose, baPWV, and UT (hazard ratio (HR) = 1.015; 95% confidence interval (CI) = 1.010 to 1.020; p < 0.001), decreased body mass index and eGFR, and the presence of diabetes, coronary artery disease, cerebrovascular disease, and congestive heart failure. Increased all-cause mortality was significantly associated with increased age, systolic blood pressure, heart rate, serum fasting glucose, baPWV, and UT (HR = 1.014, 95% CI= 1.011 to 1.017; p < 0.001), decreased body mass index, total cholesterol, and eGFR, the presence of diabetes, cerebrovascular disease, and congestive heart failure, and the use of diuretics.
Table 1. Comparison of the clinical characteristics between patients with and without all-cause mortality.

| Variables                      | Patients with All-Cause Mortality | Patients Without All-Cause Mortality | p Value * | All Patients (n = 472) | p Value ** |
|--------------------------------|-----------------------------------|--------------------------------------|-----------|------------------------|-----------|
| Age (years)                    | 72.4 ± 11.4                       | 63.3 ± 11.6                          | <0.001    | 66.8 ± 12.4            | <0.001    |
| Male gender (%)                | 54.6                              | 49.1                                 | 0.243     | 51.3                   |           |
| Smoking history (%)            | 8.2                               | 11.3                                 | 0.303     | 10.1                   |           |
| Diabetes mellitus (%)          | 49.2                              | 28.7                                 | <0.001    | 36.7                   |           |
| Hypertension (%)               | 77.0                              | 75.1                                 | 0.627     | 75.8                   |           |
| Coronary artery disease (%)    | 23.6                              | 17.0                                 | 0.078     | 19.6                   |           |
| Cerebrovascular disease (%)    | 15.1                              | 4.0                                  | <0.001    | 8.1                    |           |
| Congestive heart failure (%)   | 25.2                              | 4.4                                  | <0.001    | 12.0                   |           |
| Systolic blood pressure (mmHg) | 146 ± 25                          | 140 ± 20                             | 0.013     | 142 ± 22               | 0.001     |
| Pulse pressure (mmHg)          | 69 ± 18                           | 61 ± 13                              | <0.001    | 78 ± 13                | <0.001    |
| Heart rate (beats/min)         | 73 ± 15                           | 69 ± 12                              | 0.003     | 70 ± 13                | <0.001    |
| Body mass index (kg/m²)        | 25.4 ± 4.1                        | 26.6 ± 4.0                           | 0.001     | 26.1 ± 4.1             | 0.005     |

Antihypertensive medication

- ACEI (%): 12.6, 8.0, 0.100, 9.7
- ARB (%): 47.5, 55.0, 0.113, 52.1
- β blocker (%): 42.1, 45.5, 0.468, 44.2
- Calcium channel blocker (%): 43.7, 48.8, 0.282, 46.8
- Diuretics (%): 46.7, 31.0, 0.001, 37.1

Laboratory parameters

- Fasting glucose (mg/dL): 125.4 ± 51.0, 112.4 ± 40.3, 0.007, 116.9 ± 44.7, <0.001
- Triglyceride (mg/dL): 151.5 ± 101.1, 153.0 ± 102.6, 0.693, 152.5 ± 102.0, <0.001
- Total cholesterol (mg/dL): 183.0 ± 40.7, 194.1 ± 41.2, 0.008, 190.1 ± 41.3, 0.022
- eGFR < 30 mL/min/1.73 m² (%): 35.3 ± 15.9, 45.9 ± 13.4, <0.001, 41.8 ± 15.3, <0.001
- baPWV (cm/s): 2128.1 ± 599.4, 1776.1 ± 356.5, <0.001, 1912.6 ± 496.0, <0.001
- Upstroke time (ms): 177.4 ± 47.6, 150.3 ± 28.0, <0.001, 160.8 ± 39.1, <0.001

Abbreviations. ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin II receptor blocker; baPWV: brachial-ankle pulse wave velocity; eGFR: estimated glomerular filtration rate. * p value for two group comparison; ** p value for Kolmogorov-Smirnov test.

Table 2. Predictors of cardiovascular and all-cause mortality in univariate analysis among all study patients.

| Variables                      | Cardiovascular Mortality | All-Cause Mortality |
|--------------------------------|--------------------------|---------------------|
|                                 | HR (95% CI)              | p Value             | HR (95% CI) | p Value |
| Age (years)                    | 1.067 (1.040, 1.095)     | <0.001              | 1.072 (1.054, 1.090) | <0.001 |
| Gender (male)                  | 0.863 (0.523, 1.423)     | 0.564               | 1.043 (0.760, 1.433) | 0.794 |
| Smoking history (%)            | 1.076 (0.463, 2.497)     | 0.865               | 0.806 (0.456, 1.422) | 0.456 |
| Diabetes mellitus (%)          | 2.292 (1.391, 3.778)     | 0.001               | 1.955 (1.422, 2.687) | <0.001 |
| Hypertension (%)               | 0.707 (0.415, 1.205)     | 0.202               | 1.019 (0.706, 1.471) | 0.919 |
| Coronary artery disease (%)    | 2.184 (1.282, 3.721)     | 0.004               | 1.307 (0.893, 1.914) | 0.169 |
| Cerebrovascular disease (%)    | 3.193 (1.620, 6.297)     | 0.001               | 2.757 (1.753, 4.336) | <0.001 |
| Congestive heart failure (%)   | 5.050 (2.908, 8.771)     | <0.001              | 3.635 (2.487, 5.313) | <0.001 |
| Systolic blood pressure (per 1 mmHg) | 1.007 (0.996, 1.019) | 0.207               | 1.010 (1.002, 1.017) | <0.001 |
| Pulse pressure (per 1 mmHg)    | 1.024 (1.008, 1.040)     | 0.003               | 1.027 (1.017, 1.037) | <0.001 |
| Heart rate (per 1 beats/min)   | 1.023 (1.004, 1.041)     | 0.015               | 1.017 (1.005, 1.029) | 0.005 |
| Body mass index (per 1 kg/m²)  | 0.912 (0.849, 0.979)     | 0.011               | 0.934 (0.893, 0.976) | 0.002 |

Antihypertensive medication

- ACEI: 0.753 (0.273, 2.074), 0.583, 1.195 (0.701, 2.036), 0.513
- ARB: 1.096 (0.663, 1.810), 0.721, 0.835 (0.608, 1.146), 0.264
- β blocker: 1.158 (0.703, 1.905), 0.565, 0.962 (0.699, 1.324), 0.811
- Calcium channel blocker: 0.957 (0.581, 1.576), 0.862, 0.917 (0.667, 1.260), 0.593
- Diuretics: 1.274 (0.766, 2.117), 0.350, 1.670 (1.216, 2.295), 0.002

Laboratory parameters

- Fasting glucose (per 1 mg/dL): 1.007 (1.002, 1.012), 0.007, 1.005 (1.001, 1.008), 0.008
- Triglyceride (per 1 mg/dL): 0.999 (0.996, 1.002), 0.502, 0.999 (0.998, 1.001), 0.597
- Total cholesterol (per 1 mg/dL): 0.994 (0.987, 1.002), 0.127, 0.992 (0.989, 0.997), 0.001
- Baseline eGFR (per 1 mL/min/1.73 m²): 0.979 (0.964, 0.994), 0.006, 0.967 (0.958, 0.976), <0.001
- baPWV (per 10 cm/s): 1.101 (1.007, 1.016), <0.001, 1.013 (1.010, 1.016), <0.001
- Upstroke time (per 1 ms): 1.015 (1.010, 1.020), <0.001, 1.014 (1.011, 1.017), <0.001

Abbreviations. ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin II receptor blocker; baPWV: brachial-ankle pulse wave velocity; CI: confidence interval; eGFR: estimated glomerular filtration rate; HR: hazard ratio.
In Tables 3 and 4, we performed a collinearity test. Both in cardiovascular and all-cause mortality analysis, the values of the variance inflation factors of systolic blood pressure and pulse pressure were greater than four (Table 3). After we withdrew the variable of systolic blood pressure, all values of the variance inflation factors in cardiovascular and all-cause mortality analysis were less than four (Table 4). Due to the high collinearity between systolic blood pressure and pulse pressure, only pulse pressure was selected into the multivariable models.

**Table 3.** Collinear analysis for all continuous variables in cardiovascular and all-cause mortality models.

| Continuous Variables | Variance Inflation Factors in Cardiovascular Mortality Model | Variance Inflation Factors in All-Cause Mortality Model |
|----------------------|--------------------------------------------------------------|--------------------------------------------------------|
| Age (years)          | 1.925                                                       | 1.925                                                  |
| Systolic blood pressure (mmHg) | 4.927                                                      | 4.927                                                  |
| Pulse pressure (mmHg)           | 5.388                                                       | 5.388                                                  |
| Heart rate (beats/min)          | 1.349                                                       | 1.349                                                  |
| Body mass index (kg/m²)          | 1.099                                                       | 1.099                                                  |
| Fasting glucose (mg/dL)          | 1.098                                                       | 1.098                                                  |
| Triglyceride (mg/dL)            | 1.115                                                       | 1.115                                                  |
| Total cholesterol (mg/dL)        | 1.128                                                       | 1.128                                                  |
| Baseline eGFR (mL/min/1.73 m²)   | 1.127                                                       | 1.127                                                  |
| Brachial-ankle pulse wave velocity (per 10 cm/s) | 2.010                                                      | 2.010                                                  |
| Upstroke time (ms)              | 1.546                                                       | 1.546                                                  |

**Table 4.** Collinear analysis for all continuous variables after removing systolic blood pressure in cardiovascular and all-cause mortality models.

| Continuous Variables (After Removing Systolic Blood Pressure) | Variance Inflation Factors in Cardiovascular Mortality Model | Variance Inflation Factors in All-Cause Mortality Model |
|----------------------------------------------------------------|--------------------------------------------------------------|--------------------------------------------------------|
| Age (years)          | 1.560                                                       | 1.560                                                  |
| Pulse pressure (mmHg)           | 1.734                                                       | 1.734                                                  |
| Heart rate (beats/min)          | 1.312                                                       | 1.312                                                  |
| Body mass index (kg/m²)          | 1.094                                                       | 1.094                                                  |
| Fasting glucose (mg/dL)          | 1.090                                                       | 1.090                                                  |
| Triglyceride (mg/dL)            | 1.115                                                       | 1.115                                                  |
| Total cholesterol (mg/dL)        | 1.127                                                       | 1.127                                                  |
| Baseline eGFR (mL/min/1.73 m²)   | 1.127                                                       | 1.127                                                  |
| Brachial-ankle pulse wave velocity (per 10 cm/s) | 1.727                                                      | 1.727                                                  |
| Upstroke time (ms)              | 1.469                                                       | 1.469                                                  |

Table 5 presents the multivariable Cox forward hazards analyses of cardiovascular and all-cause mortality. In model 1, increased cardiovascular mortality was significantly associated with increased age, the presence of coronary artery disease and congestive heart failure, and increased baPWV (HR = 1.011 per 10 cm/s, 95% CI = 1.003 to 1.019, p = 0.008). Meanwhile, increased all-cause mortality was significantly associated with increased age, decreased eGFR, the presence of cerebrovascular disease and congestive heart failure, and baPWV (HR = 1.010 per 10 cm/s, 95% CI = 1.005 to 1.015, p < 0.001). In model 2, increased cardiovascular mortality was significantly associated with increased age, the presence of congestive heart failure, and increased UT (HR = 1.010, 95% CI = 1.003 to 1.017, p = 0.007). Meanwhile, increased all-cause mortality was significantly associated with increased age, decreased eGFR, the presence of cerebrovascular disease and congestive heart failure, and increased UT (HR = 1.009, 95% CI = 1.004 to 1.013, p < 0.001).

From the receiver operating characteristic curve (Figure 3), the best cut-off value of UT was 180 ms with 46.6% sensitivity and 80.7% specificity for the prediction of cardiovascular mortality and 43.2% sensitivity and 88.9% specificity for the prediction of all-cause mortality. Figure 4 shows the Kaplan–Meier curves for cardiovascular-mortality-free and all-cause-mortality-free survival between patients with UT ≥ 180 ms versus UT < 180 ms (both log-rank p < 0.001).
Table 5. Predictors of cardiovascular and all-cause mortality in multivariate analysis among all study patients.

| Variables                  | Cardiovascular Mortality |                      |                      | All-Cause Mortality |                      |                      |
|----------------------------|--------------------------|----------------------|----------------------|---------------------|----------------------|----------------------|
|                            | Model 1 HR (95% CI)      | p Value              | Model 2 HR (95% CI)  | p Value             | Model 1 HR (95% CI)  | p Value             | Model 2 HR (95% CI)  | p Value             |
| Age (per 1 year)           | 1.081 (1.039, 1.124)     | <0.001               | 1.007 (1.035, 1.020) | <0.001              | 1.069 (1.043, 1.094) | <0.001              | 1.070 (1.045, 1.096) | <0.001              |
| Coronary artery disease    | 2.433 (1.257, 4.708)     | 0.008                | 1.523 (0.755, 3.073) | 0.240               | /                    | /                    | /                    | /                    |
| Cerebrovascular disease    | 1.863 (0.747, 4.647)     | 0.182                | 1.782 (0.709, 4.481) | 0.219               | 2.251 (1.222, 4.113) | 0.008               | 2.235 (1.232, 4.054) | 0.008               |
| Congestive heart failure   | 6.776 (3.276, 14.015)    | <0.001               | 5.199 (2.546, 10.617) | <0.001              | 3.056 (1.817, 5.138) | <0.001              | 2.291 (1.379, 3.808) | 0.001               |
| Fasting glucose (per 1 mg/dL) | 1.003 (0.999, 1.007)    | 0.151                | /                    | /                   | 1.003 (0.944, 0.971) | 0.090               | /                    | /                   |
| Baseline eGFR (per 1 mL/min/1.73 m²) | 1.011 (1.003, 1.019) | 0.008                | /                    | /                   | 0.963 (0.950, 0.977) | <0.001              | 0.957 (0.944, 0.971) | <0.001              |
| baPWV (per 10 cm/s)        | 1.010 (1.005, 1.015)     | <0.001               | /                    | /                   | 1.009 (1.004, 1.013) | <0.001              | /                    | /                   |

Abbreviations. baPWV: brachial-ankle pulse wave velocity; CI: confidence interval; eGFR: estimated glomerular filtration rate; HR: hazard ratio.
Kaplan–Meier curves for cardiovascular-mortality-free and all-cause mortality-free survival between patients with UT $\geq 180$ ms versus UT $< 180$ ms (both log-rank $p < 0.001$).

The incremental value of UT in mortality prediction is shown in Figure 5. The variables in the clinical models included the variables that were significant in the multivariable analyses of both model 1 and model 2, except the baPWV and UT. Hence, the variables in the clinical model for cardiovascular mortality prediction included age and the presence of congestive heart failure, and the variables in the clinical model for all-cause mortality prediction included age, eGFR, and the presence of cerebrovascular disease and congestive heart failure. The clinical models could significantly predict the cardiovascular (Chi-square $= 71.145$, $p < 0.001$) and all-cause mortality (Chi-square $= 141.683$, $p < 0.001$). The addition of UT into the clinical models plus baPWV offered an extra benefit in the prediction of cardiovascular (Chi-square increase $23.155$, $p < 0.001$) and all-cause mortality (Chi-square increase $28.439$, $p < 0.001$).

**Figure 3.** The receiver operating characteristic curves for cardiovascular mortality (A) and all-cause mortality (B) prediction in our study patients.

**Figure 4.** Kaplan–Meier analyses for cardiovascular-mortality-free survival (A) and all-cause-mortality-free survival (B) in patients with chronic kidney disease.

The incremental value of UT in mortality prediction is shown in Figure 5. The variables in the clinical models included the variables that were significant in the multivariable analyses of both model 1 and model 2, except the baPWV and UT. Hence, the variables in the clinical model for cardiovascular mortality prediction included age and the presence of congestive heart failure, and the variables in the clinical model for all-cause mortality prediction included age, eGFR, and the presence of cerebrovascular disease and congestive heart failure. The clinical models could significantly predict the cardiovascular (Chi-square $= 71.145$, $p < 0.001$) and all-cause mortality (Chi-square $= 141.683$, $p < 0.001$). The addition of UT into the clinical models plus baPWV offered an extra benefit in the prediction of cardiovascular (Chi-square increase $23.155$, $p < 0.001$) and all-cause mortality (Chi-square increase $28.439$, $p < 0.001$).
Figure 4. Kaplan–Meier analyses for cardiovascular mortality (A) and all-cause mortality (B) in patients with chronic kidney disease.

Figure 5. Incremental models for cardiovascular mortality (A) and all-cause mortality (B) in patients with chronic kidney disease.

The variables in the clinical model for cardiovascular mortality prediction included age and the presence of congestive heart failure. The variables in the clinical model for all-cause mortality prediction included age, estimated glomerular filtration rate, and the presence of cerebrovascular disease and congestive heart failure. In the incremental models, the addition of upstroke time into the clinical models plus brachial-ankle pulse wave velocity (baPWV) resulted in a significant improvement in the predictive value for cardiovascular mortality (A) and all-cause mortality (B) in patients with chronic kidney disease (both \( p < 0.001 \)).

4. Discussion

There were two major findings in the present study. First, increased UT was associated with increased cardiovascular and all-cause mortality in CKD patients. Second, additional consideration of UT might provide an extra benefit in predicting cardiovascular and all-cause mortality beyond the traditional risk factors and baPWV.

Our present study is the first investigation to use UT as a useful parameter in predicting cardiovascular and all-cause mortality in CKD patients. Although the major role of UT on mortality has not been well-understood, some mechanisms might be able to explain the association between the prolongation of UT and poor prognosis. First, UT could be served a surrogate maker for atherosclerotic vascular disease and target organ damage [31,32]. By physiological definition, UT was the time interval from the foot to the peak of the arterial wave. Increased UT was associated with atherosclerotic vascular disease, such as peripheral vascular disease and coronary artery disease [31,32]. Atherosclerosis, the presence of carotid plaques, and coronary artery calcification were significantly correlated with a high mortality rate in CKD patients [39–41]. Consequently, the association between the prolongation of UT and atherosclerosis might explain increased UT as a poor prognostic parameter in CKD patients in the present study. UT, UT per cardiac cycle, and the combination of UT and the ankle-brachial index had a significant influence on the diagnosis of early peripheral artery disease [31,32,42]. Recently, Shoji...
et al. demonstrated that UT was higher in patients with coronary artery disease than in subjects without coronary artery disease. Increased UT was significantly associated with the severity of coronary calcification in elder populations with coronary artery disease [43]. Therefore, the impact of UT on mortality might be through the atherosclerotic processes in CKD populations.

In addition, UT could be a parameter of left ventricular function and geometry [30,44,45]. Abnormal cardiac function, including left ventricular hypertrophy, reduced left ventricular ejection fraction, and increased left ventricular filling pressure and wall stress, have been associated with poor cardiovascular outcomes in patients with CKD [46–48]. Previous studies have shown that increased UT was associated with decreased left ventricular ejection fraction, elevated left ventricular end-diastolic pressure, increased left ventricular systolic wall stress, and left ventricular hypertrophy [30,44,45]. Therefore, the association of increased UT with poor cardiac function and abnormal left ventricular geometry might partially explain why the prolongation of UT and UT ≥ 180 ms were useful in the prediction of increased cardiovascular and all-cause mortality in CKD patients. From previous studies, baPWV was not only a marker for arterial stiffness and left ventricular diastolic function but also a predictor for all-cause mortality [29,36,49–52]. Possible mechanisms of baPWV-associated mortality could be through vascular dysfunction, left ventricular hypertrophy, and left ventricular diastolic dysfunction [20,52]. In our present study, adding UT into a basic clinical model including traditional risk factors plus baPWV could provide an incremental value for the prediction of cardiovascular and all-cause mortality. Hence, the additional consideration of UT might be useful in predicting cardiovascular and all-cause mortality over traditional risk factors and baPWV in patients with CKD.

5. Study Limitations

Our present study had some limitations. First, as the study subjects were already being evaluated for heart disease by echocardiography, the study was susceptible to selection bias, making the findings potentially less-generalized; Second, owing to the study design and ethical concerns, we did not withdraw hypertension medications. Our study result might be affected by these medications; Third, patients with acute renal damage, eGFR > 60 mL/min/1.73m², and end-stage renal disease under hemodialysis or peritoneal dialysis therapies were excluded. Therefore, our study findings cannot be applied to such patients; Fourth, because patients who were excluded did not receive peripheral vascular examination, we could not provide the results of all variable comparisons between those who were excluded and those who were included; Finally, several biomarkers including cardiac natriuretic peptide, C reactive protein, and asymmetric dimethylarginine were lacking in our study, so our present study was limited in providing pathophysiologic evidence of mortality [14,23,28].

6. Conclusions

In this study, we found UT to be a useful parameter for predicting cardiovascular and all-cause mortality in CKD. Additional consideration of UT might provide an extra benefit in predicting cardiovascular and all-cause mortality beyond the traditional risk factors and baPWV.

Author Contributions: Conceptualization, W.-H.L. and P.-C.H.; Data curation, P.-C.H., C.-Y.C. and M.-K.L.; Formal analysis, P.-C.H. and C.-Y.C.; Funding acquisition, Y.-C.C.; Investigation, W.-H.L., Y.-C.C. and S.-C.C.; Methodology, Y.-C.C., S.-C.C. and H.-H.L.; Project administration, S.-C.C. and M.-K.L.; Resources, H.-H.L., M.-K.L. and C.-S.L.; Software, C.-S.L. and H.-M.S.; Supervision, C.-S.L., H.-W.Y., W.-T.L., S.-H.S., T.-H.L. and H.-M.S.; Validation, T.-S.H., W.-C.V., T.-H.L., and H.-W.Y.; Visualization, H.-W.Y., W.-T.L. and S.-H.S.; Writing—original draft, W.-H.L. and P.-C.H.; Writing—review & editing, H.-M.S and T.-H.L. All authors have read and agreed to the published version of the manuscript.

Funding: This study was supported by a grant from Kaohsiung Municipal Siaogang Hospital (kmhk-107-010), Kaohsiung, Taiwan.

Acknowledgments: Mortality data were provided by the Collaboration Center of Health Information Application, Ministry of Health and Welfare, Executive Yuan.

Conflicts of Interest: The authors declare no conflict of interest.
Abbreviations

ACEI angiotensin converting enzyme inhibitor
ARB angiotensin II receptor blocker
baPWV brachial-ankle pulse wave velocity
CI confidence interval
eGFR estimated glomerular filtration rate
HR hazard ratio
UT upstroke time

References

1. Briet, M.; Boutouyrie, P.; Laurent, S.; London, G.M. Arterial stiffness and pulse pressure in ckd and esrd. *Kidney Int.* 2012, 82, 388–400. [CrossRef] [PubMed]
2. Tripepi, G.; Mattace Raso, F.; Sijbrands, E.; Seck, M.S.; Maas, R.; Boger, R.; Witteman, J.; Rapisarda, F.; Malatino, L.; Mallamaci, F.; et al. Inflammation and asymmetric dimethylarginine for predicting death and cardiovascular events in esrd patients. *Clin. J. Am. Soc. Nephrol.* 2011, 6, 1714–1721. [CrossRef] [PubMed]
3. Abd ElHafeez, S.; Tripepi, G.; Stancanelli, B.; Dounousi, E.; Malatino, L.; Mallamaci, F.; Zoccali, C. Norepinephrine, left ventricular disorders and volume excess in esrd. *J. Nephrol.* 2015, 28, 729–737. [CrossRef] [PubMed]
4. Zoccali, C.; Mallamaci, F.; Parlongo, S.; Cutrupi, S.; Benedetto, F.A.; Tripepi, G.; Bonanno, G.; Rapisarda, F.; Fatuzzo, P.; Seminara, G.; et al. Plasma norepinephrine predicts survival and incident cardiovascular events in patients with end-stage renal disease. *Circulation* 2002, 105, 1354–1359. [CrossRef]
5. Enia, G.; Mallamaci, F.; Benedetto, F.A.; Panuccio, V.; Parlongo, S.; Cutrupi, S.; Giacone, G.; Cottini, E.; Tripepi, G.; Malatino, L.S.; et al. Long-term capd patients are volume expanded and display more severe left ventricular hypertrophy than haemodialysis patients. *Nephrol. Dial. Transplant.* 2001, 16, 1459–1464. [CrossRef]
6. Zoccali, C.; Benedetto, F.A.; Mallamaci, F.; Tripepi, G.; Giacone, G.; Cataliotti, A.; Seminara, G.; Stancanelli, B.; Fatuzzo, P.; Seminara, G.; et al. Plasma norepinephrine predicts survival and incident cardiovascular events in patients with end-stage renal disease. *Circulation* 2002, 105, 1354–1359. [CrossRef]
7. Zoccali, C.; Mallamaci, F.; Tripepi, G.; Benedetto, F.A.; Giacone, G.; Cataliotti, A.; Seminara, G.; Stancanelli, B.; Malatino, L.S.; Investigators, C. Prognostic impact of the indexation of left ventricular mass in patients undergoing dialysis. *J. Am. Soc. Nephrol.* 2001, 12, 2768–2774.
8. Zoccali, C.; Benedetto, F.A.; Mallamaci, F.; Tripepi, G.; Giacone, G.; Cataliotti, A.; Malatino, L.S. Left ventricular mass monitoring in the follow-up of dialysis patients: Prognostic value of left ventricular hypertrophy progression. *Kidney Int.* 2004, 65, 1492–1498. [CrossRef]
9. Zoccali, C.; Mallamaci, F.; Maas, R.; Benedetto, F.A.; Tripepi, G.; Malatino, L.S.; Cataliotti, A.; Bellanuova, L.; Boger, R.; Investigators, C. Left ventricular hypertrophy, cardiac remodeling and asymmetric dimethylarginine (adma) in hemodialysis patients. *Kidney Int.* 2002, 62, 339–345. [CrossRef]
10. Tripepi, G.; Benedetto, F.A.; Mallamaci, F.; Tripepi, R.; Malatino, L.; Zoccali, C. Left atrial volume monitoring and cardiovascular risk in patients with end-stage renal disease: A prospective cohort study. *J. Am. Soc. Nephrol.* 2007, 18, 1316–1322. [CrossRef]
11. Zoccali, C.; Mallamaci, F.; Tripepi, G.; Benedetto, F.A.; Wittteman, J.; Malatino, L.; Zoccali, C. Biomarkers of left atrial volume: A longitudinal study in patients with end-stage renal disease. *Hypertension* 2009, 54, 818–824. [CrossRef]
12. Testa, A.; Mallamaci, F.; Benedetto, F.A.; Pisano, A.; Tripepi, G.; Malatino, L.; Thadhani, R.; Zoccali, C. Vitamin d receptor (vdr) gene polymorphism is associated with left ventricular (lv) mass and predicts left ventricular hypertrophy (lvh) progression in end-stage renal disease (esrd) patients. *J. Bone Miner. Res.* 2010, 25, 313–319. [CrossRef] [PubMed]
13. Mallamaci, F.; Tripepi, G.; Cutrupi, S.; Malatino, L.S.; Zoccali, C. Prognostic value of combined use of biomarkers of inflammation, endothelial dysfunction, and myocardial dysfunction in patients with esrd. *Kidney Int.* 2005, 67, 2330–2337. [CrossRef] [PubMed]
14. Zoccali, C.; Bode-Boger, S.; Mallamaci, F.; Benedetto, F.; Tripepi, G.; Malatino, L.; Cataliotti, A.; Bellanuova, I.; Fermo, I.; Frolich, J.; et al. Plasma concentration of asymmetrical dimethylarginine and mortality in patients with end-stage renal disease: A prospective study. *Lancet* 2001, 358, 2113–2117. [CrossRef]

15. Mallamaci, F.; Tripepi, G.; Maas, R.; Malatino, L.; Boger, R.; Zoccali, C. Analysis of the relationship between norepinephrine and asymmetric dimethyl arginine levels among patients with end-stage renal disease. *J. Am. Soc. Nephrol.* 2004, 15, 435–441. [CrossRef] [PubMed]

16. Zoccali, C.; Kramer, A.; Jager, K.J. Chronic kidney disease and end-stage renal disease—a review produced to contribute to the report ‘the status of health in the European union: Towards a healthier Europe’. *NDT Plus* 2010, 3, 213–224. [CrossRef]

17. Fraser, S.D.; Roderick, P.J.; May, C.R.; McIntyre, N.; McIntyre, C.; Fluck, R.J.; Shardlow, A.; Taal, M.W. The burden of comorbidity in people with chronic kidney disease stage 3: A cohort study. *BMC Nephrol.* 2015, 16, 193. [CrossRef]

18. Chen, S.C.; Chang, J.M.; Tsai, Y.C.; Tsai, J.C.; Su, H.M.; Hwang, S.J.; Chen, H.C. Association of interleg bp difference with overall and cardiovascular mortality in hemodialysis. *Clin. J. Am. Soc. Nephrol. CJASN* 2012, 7, 1646–1653. [CrossRef]

19. Tonelli, M.; Wiebe, N.; Cullerton, B.; House, A.; Rabbat, C.; Fok, M.; McAlister, F.; Garg, A.X. Chronic kidney disease and mortality risk: A systematic review. *J. Am. Soc. Nephrol.* 2006, 17, 2034–2047. [CrossRef]

20. Chen, S.C.; Huang, J.C.; Chiu, Y.W.; Chang, J.M.; Hwang, S.J.; Chen, H.C. Prognostic cardiovascular markers in chronic kidney disease. *Kidney Blood Press. Res.* 2018, 43, 1388–1407. [CrossRef]

21. Su, H.M.; Lin, T.H.; Hsu, P.C.; Hsu, P.C.; Lin, Y.C.; Su, H.M.; Hwang, S.J.; Chen, H.C. Abnormally low and high ankle-brachial indices are independently associated with increased left ventricular mass index in chronic kidney disease. *PloS ONE* 2012, 7, e44732. [CrossRef] [PubMed]

22. Zoccali, C.; Mallamaci, F.; Benedetto, F.A.; Tripepi, G.; Parlongo, S.; Cataliotti, A.; Cutrupi, S.; Giacone, G.; Bellanuova, I.; Cottini, E.; et al. Cardiac natriuretic peptides are related to left ventricular mass and function and predict mortality in dialysis patients. *J. Am. Soc. Nephrol.* 2001, 12, 1508–1515. [PubMed]

23. Mallamaci, F.; Zoccali, C.; Tripepi, G.; Benedetto, F.A.; Parlongo, S.; Cataliotti, A.; Cutrupi, S.; Giacone, G.; Bellanuova, I.; Stancanelli, B.; et al. Diagnostic potential of cardiac natriuretic peptides in dialysis patients. *Kidney Int.* 2001, 59, 1559–1566. [CrossRef] [PubMed]

24. Cataliotti, A.; Malatino, L.S.; Jougasaki, M.; Zoccali, C.; Castellino, P.; Giacone, G.; Bellanuova, I.; Tripepi, R.; Seminara, G.; Parlongo, S.; et al. Circulating natriuretic peptide concentrations in patients with end-stage renal disease: Role of brain natriuretic peptide as a biomarker for ventricular remodeling. *Mayo Clin. Proc.* 2001, 76, 1111–1119. [CrossRef]

25. Stancanelli, B.; Malatino, L.S.; Malaponte, G.; Noto, P.; Giuffre, E.; Caruso, A.; Gagliano, C.; Zoccolo, A.M.; Puccia, G.; Castellino, P. Pulse pressure is an independent predictor of aortic stiffness in patients with mild to moderate chronic kidney disease. *Kidney Blood Press. Res.* 2007, 30, 283–288. [CrossRef]

26. Zoccali, C.; Tripepi, G.; Mallamaci, F. Dissecting inflammation in esrd: Do cytokines and c-reactive protein have a complementary prognostic value for mortality in dialysis patients? *J. Am. Soc. Nephrol.* 2006, 17, S169–S173. [CrossRef]

27. Mallamaci, F.; Benedetto, F.A.; Tripepi, G.; Cutrupi, S.; Pizzini, P.; Stancanelli, B.; Seminara, G.; Bonanno, G.; Rapisarda, F.; Fatuzzo, P.; et al. Vascular endothelial growth factor, left ventricular dysfunction and mortality in hemodialysis patients. *J. Hypertens.* 2008, 26, 1875–1882. [CrossRef]

28. Zoccali, C.; Benedetto, F.A.; Maas, R.; Mallamaci, F.; Tripepi, G.; Malatino, L.S.; Boger, R.; Investigators, C. Asymmetric dimethylarginine, c-reactive protein, and carotid intima-media thickness in end-stage renal disease. *J. Am. Soc. Nephrol.* 2002, 13, 490–496.

29. Chen, S.C.; Chang, J.M.; Liu, W.C.; Tsai, Y.C.; Tsai, J.C.; Hsu, P.C.; Lin, T.H.; Lin, M.Y.; Su, H.M.; Hwang, S.J.; et al. Brachial-ankle pulse wave velocity and rate of renal function decline and mortality in chronic kidney disease. *Clin. J. Am. Soc. Nephrol.* 2011, 6, 724–732. [CrossRef]

30. Yu, S.; Lu, Y.; Xiong, J.; Teieiwubai, J.; Chi, C.; Ji, H.; Zhou, Y.; Fan, X.; Zhang, J.; Blacher, J.; et al. Comparison of ankle-brachial index and upstroke time in association with target organ damage: The northern shanghai study. *J. Am. Soc. Hypertens.* 2018, 12, 703–713. [CrossRef]

31. Kiuchi, S.; Hisatake, S.; Watanabe, I.; Toda, M.; Kabuki, T.; Oka, T.; Dobashi, S.; Ikeda, T. Pulse pressure and upstroke time are useful parameters for the diagnosis of peripheral artery disease in patients with normal ankle brachial index. *Cardiol. Res.* 2016, 7, 161–166. [CrossRef] [PubMed]
32. Sheng, C.S.; Li, Y.; Huang, Q.F.; Kang, Y.Y.; Li, F.K.; Wang, J.G. Pulse waves in the lower extremities as a diagnostic tool of peripheral arterial disease and predictor of mortality in elderly chinese. *Hypertension* 2016, 67, 527–534. [CrossRef] [PubMed]

33. Levey, A.S.; Coresh, J.; Bolton, K.; Culleton, B.; Harvey, K.S.; Ikizler, T.A.; Johnson, C.A.; Kausz, A.; Kimmel, P.L.; Kusek, J.; et al. K/doi clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. *Am. J. Kidney Dis.* 2002, 39, S1–S266.

34. Boiteau, G.M.; Bourassa, M.G.; Allenstein, B.J. Upstroke time ratio. A new concept in di differentiation and subvalvular aortic stenosis. *Am. J. Cardiol.* 1963, 11, 319–326. [CrossRef]

35. Chen, S.C.; Lee, W.H.; Hsu, P.C.; Lin, M.Y.; Lee, C.S.; Lin, T.H.; Voon, W.C.; Lai, W.T.; Sheu, S.H.; Su, H.M. Association of brachial-ankle pulse wave velocity with cardiovascular events in atrial fibrillation. *Am. J. Hypertens.* 2016, 29, 348–356. [CrossRef]

36. Lee, W.H.; Hsu, P.C.; Chu, C.Y.; Chen, S.C.; Lee, H.H.; Chen, Y.C.; Lee, M.K.; Lee, C.S.; Yen, H.W.; Lin, T.H.; et al. Association of renal systolic time intervals with brachial-ankle pulse wave velocity. *Int. J. Med. Sci.* 2018, 15, 1235–1240. [CrossRef]

37. Chang, L.H.; Hvu, C.M.; Chu, C.H.; Won, J.G.S.; Chen, H.S.; Lin, L.Y. Upstroke time per cardiac cycle is associated with cardiovascular prognosis in type 2 diabetes. *Endocr. Pract.* 2019, 25, 1109–1116. [CrossRef]

38. Su, H.M.; Lin, T.H.; Hsu, P.C.; Lee, W.H.; Chu, C.Y.; Chen, S.C.; Lee, C.S.; Voon, W.C.; Lai, W.T.; Sheu, S.H. Association of bilateral brachial-ankle pulse wave velocity difference with peripheral vascular disease and left ventricular mass index. *PloS One* 2014, 9, e88331. [CrossRef]

39. Szeto, C.C.; Chow, K.M.; Woo, K.S.; Chook, P.; Ching-Ha Kwan, B.; Leung, C.B.; Kam-Tao Li, P. Carotid intima media thickness predicts cardiovascular diseases in chinese predialysis patients with chronic kidney disease. *J. Am. Soc. Nephrol.* 2007, 18, 1966–1972. [CrossRef]

40. Zanoli, L.; Lentini, P.; Briet, M.; Castellino, P.; House, A.A.; London, G.M.; Malatino, L.; McCullough, P.A.; Mikhailidis, D.P.; Boutouyrie, P. Arterial stiffness in the heart disease of ckd. *J. Am. Soc. Nephrol.* 2019, 30, 918–928. [CrossRef]

41. Chen, J.; Budoff, M.J.; Reilly, M.P.; Yang, W.; Rosas, S.E.; Rahman, M.; Zhang, X.; Roy, J.A.; Lustigova, E.; Nessel, L.; et al. Coronary artery calcification and risk of cardiovascular disease and death among patients with chronic kidney disease. *JAMA Cardiol.* 2017, 2, 635–643. [CrossRef] [PubMed]

42. Hashimoto, T.; Ichihashi, S.; Iwakoshi, S.; Kichikawa, K. Combination of pulse volume recording (pvr) parameters and ankle-brachial index (abi) improves diagnostic accuracy for peripheral arterial disease compared with abi alone. *Hypertens. Res.* 2016, 39, 430–434. [CrossRef] [PubMed]

43. Shoji, T.; Okada, S.; Ohno, Y.; Nakagomi, A.; Kobayashi, Y. High upstroke time of arterial pulse wave is an independent predictor for the presence and severity of coronary artery disease in older population. *J. Hypertens.* 2017, 35, e99. [CrossRef]

44. Manolas, J.; Krayenbuehl, H.P. Comparison between apexcardiographic and angiographic indexes of left ventricular performance in patients with aortic incompetence. *Circulation* 1978, 57, 692–698. [CrossRef] [PubMed]

45. Colan, S.D.; Borow, K.M.; MacPherson, D.; Sanders, S.P. Use of the indirect axillary pulse tracing for noninvasive determination of ejection time, upstroke time, and left ventricular wall stress throughout ejection in infants and young children. *Am. J. Cardiol.* 1984, 53, 1154–1158. [CrossRef]

46. Chen, S.C.; Huang, J.C.; Tsai, Y.C.; Chen, L.I.; Su, H.M.; Chang, J.M.; Chen, H.C. Body mass index, left ventricular mass index and cardiovascular events in chronic kidney disease. *Am. J. Med. Sci.* 2016, 351, 91–96. [CrossRef]

47. Di Lullo, L.; Gorini, A.; Russo, D.; Santoboni, A.; Ronco, C. Left ventricular hypertrophy in chronic kidney disease patients: From pathophysiology to treatment. *Cardiorenal Med.* 2015, 5, 254–266. [CrossRef]

48. Chen, S.C.; Chang, J.M.; Tsai, Y.C.; Huang, J.C.; Chen, L.I.; Su, H.M.; Hwang, S.J.; Chen, H.C. Ratio of transmitral e-wave velocity to early diastole mitral annulus velocity with cardiovascular and renal outcomes in chronic kidney disease. *Nephron. Clin. Pract.* 2013, 123, 52–60. [CrossRef]

49. Su, H.M.; Lin, T.H.; Lee, C.S.; Lee, H.C.; Chu, C.Y.; Hsu, P.C.; Voon, W.C.; Lai, W.T.; Sheu, S.H. Myocardial performance index derived from brachial-ankle pulse wave velocity: A novel and feasible parameter in evaluation of cardiac performance. *Am. J. Hypertens.* 2009, 22, 871–876. [CrossRef]
50. Chen, S.C.; Chang, J.M.; Liu, W.C.; Tsai, J.C.; Chen, L.I.; Lin, M.Y.; Hsu, P.C.; Lin, T.H.; Su, H.M.; Hwang, S.J.; et al. Significant correlation between ratio of brachial pre-ejection period to ejection time and left ventricular ejection fraction and mass index in patients with chronic kidney disease. *Nephrol. Dial. Transplant.* **2011**, *26*, 1895–1902. [CrossRef]

51. Hsu, P.C.; Lin, T.H.; Lee, C.S.; Chu, C.Y.; Su, H.M.; Voon, W.C.; Lai, W.T.; Sheu, S.H. Impact of a systolic parameter, defined as the ratio of right brachial pre-ejection period to ejection time, on the relationship between brachial-ankle pulse wave velocity and left ventricular diastolic function. *Hypertens. Res.* **2011**, *34*, 462–467. [CrossRef] [PubMed]

52. Hsu, P.C.; Tsai, W.C.; Lin, T.H.; Su, H.M.; Voon, W.C.; Lai, W.T.; Sheu, S.H. Association of arterial stiffness and electrocardiography-determined left ventricular hypertrophy with left ventricular diastolic dysfunction. *PLoS ONE* **2012**, *7*, e49100. [CrossRef] [PubMed]