Abdominal aorta calcification predicts cardiovascular but not non-cardiovascular outcome in patients receiving peritoneal dialysis
A prospective cohort study

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Abstract
Abdominal aorta calcification (AAC) is associated with worse clinical outcomes in dialysis patients. However, the long-term prognostic values of AAC to cardiovascular (CV) and non-CV mortality in patients starting peritoneal dialysis (PD) remain unknown. This study is aimed to analyze the predictive power of AAC to CV and non-CV mortality in PD patients. We prospectively enrolled 123 patients undergoing PD. All patients received quantitative analysis of AAC via abdominal computer tomography at enrollment. The AAC ratio was measured by the area of the whole aorta affected by aortic calcification above the iliac bifurcation. The CV mortality and non-CV mortality during the follow-up period were investigated using the Cox proportional hazard model and time-dependent receiver operating characteristic (ROC) analysis. After median 6.8 (interquartile range, 3.6–9.2) years of follow-up, there were 18 CV mortality, 24 non-CV mortality and 42 total mortality. The age and AAC ratio were significantly higher in CV mortality group compared with others without CV mortality. In time-dependent ROC analysis, AAC had excellent predictive power of CV mortality (AUC:0.787) but not non-CV mortality (AUC:0.537). The best cutoff value of AAC ratio to predict CV mortality was 39%. In addition, AAC was not associated with non-CV mortality but remained to be a significantly predictor of CV mortality after adjusted with clinical covariates in different Cox proportional hazard models. AAC has excellent prognostic value of CV mortality but is unable to predict non-CV mortality in patients undergoing PD.

Keywords: abdominal aorta calcification, cardiovascular mortality, non-cardiovascular mortality, peritoneal dialysis

1. Introduction
Cardiovascular (CV) disease is an important global issue, especially in dialysis patients. It is the leading cause of deaths in end-stage renal disease (ESRD) patients[1] which accounting for up to 40% of deaths among these patients during the first 3 years of dialysis.[2] In addition, CV mortality in ESRD patients is about 10 to 20 times higher compared with general population.[3] The impact of cardiovascular disease on patients starting dialysis has recently received increasing attention.[2-4]

The atherosclerosis-related vascular complication is the most common cause of CV disease. Once atherosclerosis develops, the atheromatous plaque or fibrous fatty plaque forms with calcium deposition will cause narrowing the blood vessel lumen and weakening the media which cause coronary artery disease, stroke and peripheral artery disease.[4,5] The CV events associated with atherosclerosis are more often fatal in patients with chronic kidney disease than in individuals without chronic kidney disease.[6] In addition to CV mortality, non-CV mortality was also increased to the same extent as mortality from CV disease.[2,7] Accurate risk assessment for future CV events can help clinician to guide clinical management[8] and the accurate tool to predict the long-term outcomes is still lacking.

Abdominal aorta calcification (AAC) is a good clinical tool to evaluate the atherosclerosis occurring in abdominal aorta and is a marker of subclinical atherosclerotic disease. It correlates with symptomatic coronary artery disease[9] and is also highly predictive of subsequent CV outcomes in general popul-
There were several studies showed that AAC could predict CV outcomes in patients under hemodialysis but the data, especially the long-term data, for patients under peritoneal dialysis (PD) was still limited. In addition, previous studies of AAC were mostly focused on CV outcomes and total mortality instead of non-CV mortality. The role of AAC in prediction of mortality from non-CV diseases in dialysis patients has not yet been reported. In this prospective cohort study, we aimed to analyze the long-term predictive values of AAC to CV and non-CV mortality in PD patients.

2. Methods

2.1. Patients

We prospectively enrolled 123 patients who undergoing PD for more than 3 months since February 2009. Pregnant women, patients with clinical signs of active infection, and those with a prior renal transplant were excluded. The baseline characteristics, medical history and medication usage were carefully recorded, and biochemical parameters were tested during initial evaluation. All patients provided written informed consent. This study was approved by the Institutional Review Board of National Taiwan University Hospital (approval numbers NTUH-REC No. 200808062R and NTUH-REC No. 201007080R).

2.2. Outcomes

These patients were prospectively followed in our peritoneal dialysis center after enrollment. The causes of mortality from CV and non-CV diseases were carefully recorded during follow-up. CV mortality was defined as mortality due to acute coronary syndrome, peripheral artery disease, sudden cardiac death (SCD), life threatening arrhythmia (ventricular tachycardia/ventricular fibrillation), progressive heart failure, ischemic and hemorrhagic stroke. SCD was defined as cardiac arrest occurring suddenly and within 1h of witnessed symptom onset. The patients suffered from other causes of death were categorized as the non-CV mortality. The patients who received renal transplantation were censored in this study.

2.3. Outcomes predictor

AAC ratio is the predictor of interest in this study. AAC was measured by the standard 64-multiple detector computed tomography (MDCT) scan (LightSpeed VCT, GE Healthcare, Milwaukee, WI) in all subjects. The calcified area was calculated based on an attenuation range of >150 Hounsfield units using image analysis software (ImageJ, version 1.45, National Institutes of Health, Bethesda, MD). The percentages of the area of the whole aorta affected by aortic calcification were calculated from the images of 4 consecutive slices just above the iliac bifurcation level. The images were reviewed independently by 2 radiologists who were blinded to the patients’ clinical characteristics.

2.4. Covariates

The baseline demographic data, biochemistry analysis and echocardiogram including HbA1c, serum creatinine, PD KT/V, lipid profiles, serum electrolytes, C-reactive protein (CRP) and left ventricular ejection fraction (LVEF) were also analyzed as covariates in this study.

2.5. Echocardiography

Transthoracic echocardiography (iE33 xMATRIX Echocardiography System, Philips, Amsterdam, Netherlands) was performed in all patients and LVEF was measured by M-mode measurements or long-axis area-length method in accordance with the recommendations of the American Society of Echocardiography.

2.6. Statistical analysis

Data were expressed as mean ± standard deviation for normally distributed data which were tested by Kolmogorov-Smirnov test. Comparisons of data between groups were made by the independent t test. Differences between proportions were calculated by the Chi-square test or Fisher’s exact test. Cox regression analysis was used to explore the associations between variables and outcomes. Significant determinants in univariable Cox regression analysis (P < .05), including age, LVEF, AAC ratio, were then tested in multivariable Cox regression analysis with stepwise subset selection to identify independent predictors of outcomes. The discrimination abilities of AAC to CV, non-CV and total mortality were assessed using the time-dependent receiver operating characteristic (ROC) curve analysis. The optimal cutoff point of the AAC ratio with the highest area under curve (AUC) to predict CV mortality was obtained by multiple comparisons of Cox regression probability. The Kaplan-Meier survival curves according to the cutoff were plotted and log-rank tests were used for comparison. The predicted probability of an event in the Cox model was obtained using the ‘phreg’ procedure in SAS version 9.4 (SAS Institute, Cary, NC). The optimal cutoff point of a marker in the survival analysis was determined using R version 3.6.1 (R Development Core Team) and the “survminer” package (Version 0.4.6 updated on Sep 3, 2019). Other analyses were done using SPSS version 25 for Windows (SPSS Inc., IL, USA). The significance level of the statistical analysis was set at .05.

3. Results

3.1. Patients (Table 1)

After median 6.8 (interquartile range, 3.6–9.2) years follow-up, there were 18 CV mortality, 24 non-CV mortality and 42 total mortality. The cumulative CV mortality, non-CV mortality and total mortality were 20.4%, 26.6%, 41.6%, respectively. The causes of CV mortality including 7 life threatening arrhythmia, 3 cardiogenic shock, 7 sudden death and 1 hemorrhagic stroke. The causes of non-CV mortality were mainly sepsis, especially peritonitis, except 1 patient with lung adenocarcinoma.

In CV mortality analysis, the AAC ratios were significantly higher, 32.6 ± 18.6% in patients died due to CV causes compared with others without CV mortality (including non-CV mortality and survived patients). The patients died from CV causes were also significantly older compared with others without CV mortality. The sex, underling systemic disease, duration of PD before enrollments, medication use at enrollments, biochemical data and left ventricular systolic function were well balanced between 2 groups.
Chol = total cholesterol, LDL = low-density lipoprotein, C-reactive protein, DM = diabetes mellitus, HDL = high-density lipoprotein, HTN = hypertension, LVEF = left ventricular ejection fraction, TC = total cholesterol, T-Chol = total cholesterol, TGs = triglycerides.

3.2. The predictors of CV mortality (Tables 2 and 4)

In univariable Cox regression analysis, older age, lower LVEF, and higher AAC ratio were significant predictors of CV mortality.

### Table 2

| Clinical characteristics of patients with CV mortality or not. | CV mortality (N = 105) | Without CV mortality (N = 110) | P value |
|-------------------------------------------------------------|------------------------|---------------------------------|---------|
| Age, yr                                                     | 59 ± 13                | 53 ± 13                         | .007    |
| BMI                                                        | 24.2 ± 4.0             | 23.2 ± 3.5                      | .270    |
| Male, n (%)                                                 | 6 (33%)                | 47 (48%)                        | .366    |
| DM, n (%)                                                   | 5 (28%)                | 20 (19%)                        | .395    |
| HTN, n (%)                                                  | 17 (94%)               | 92 (88%)                        | .400    |
| ACE or ARB                                                  | 7 (39%)                | 50 (48%)                        | .493    |
| Beta-blocker                                                | 8 (44%)                | 64 (61%)                        | .169    |
| CCB                                                        | 14 (78%)               | 66 (63%)                        | .220    |
| Statin                                                      | 5 (29%)                | 39 (38%)                        | .444    |
| PD duration                                                 | 43 ± 31                | 42 ± 43                         | .931    |
| PD KT/V                                                     | 1.9 ± 0.3              | 1.9 ± 0.4                       | .612    |
| HbA1c, %                                                    | 6.0 ± 0.8              | 5.6 ± 0.9                       | .106    |
| Creatinine, mg/dL                                           | 10.4 ± 2.4             | 11.4 ± 2.8                      | .147    |
| Uric acid                                                   | 7.4 ± 1.1              | 7.0 ± 1.2                       | .164    |
| Tgs, mg/dL                                                  | 179 ± 89               | 207 ± 167                       | .535    |
| T-Chol, mg/dL                                               | 187 ± 40               | 199 ± 47                        | .305    |
| LDL, mg/dL                                                  | 88 ± 41                | 89 ± 37                         | .974    |
| HDL, mg/dL                                                  | 38 ± 11                | 41 ± 12                         | .341    |
| Na, mmol/L                                                  | 135.5 ± 5.7            | 135.5 ± 4.0                     | .971    |
| K, mmol/L                                                   | 3.8 ± 0.7              | 3.9 ± 0.7                       | .746    |
| Ca, mmol/L                                                  | 9.4 ± 1.1              | 9.6 ± 0.9                       | .524    |
| P, mmol/L                                                   | 3.4 ± 1.1              | 5.4 ± 1.3                       | .639    |
| CRP, mg/dL                                                  | 0.9 ± 1.0              | 1.0 ± 2.1                       | .747    |
| LVEF, %                                                     | 60 ± 18                | 68 ± 11                         | .101    |
| AAC, %                                                      | 32.6 ± 18.6            | 12.9 ± 15.3                     | <.001   |

Data are presented as mean ± standard deviation or number (percentage). AAC = abdominal aorta calcification, ACh2L = angiotensin II receptor blockers, BMI = body mass index, CCB = calcium channel blocker, CRP = C-reactive protein, DM = diabetes mellitus, HDL = high-density lipoprotein, HTN = hypertension, LVEF = left ventricular ejection fraction, PD = peritoneal dialysis, T-Chol = total cholesterol, TGs = triglycerides. Every increased 1% of AAC ratio increased 6% risk of CV mortality, (hazard ratio, 1.040; 95% CI, 1.019–1.060). These 3 predictors were then tested in multivariable Cox regression analysis and only AAC ratio remained in the model. Then we adjusted the AAC ratio with age, sex, baseline medication use, DM, HTN and LVEF in 5 different models. The AAC ratio remained to be a significant predictor of CV mortality after adjustment.

### Table 3

| The predictors of non-CV mortality (Table 3) |
|---------------------------------------------|
| In univariable Cox regression analysis, older age and longer duration of PD before enrollment were significant predictors of non-CV mortality. Both age and duration of PD were remained in the model after multivariable Cox regression analysis. The AAC was not associated with non-CV mortality (hazard ratio, 1.013; 95% CI, 0.992–1.039).

3.4. The predictive power of AAC to CV and non-CV mortality (Fig. 1 and Table 5)

The time-dependent ROC curve analysis showed that AAC ratio could predict CV mortality and total mortality, AUC:0.787 and AUC:0.685, respectively. However, AAC ratio could not predict the non-CV mortality, AUC:0.537.

### Table 4

| AUC to predict CV mortality after clinical variables adjustments. |
|------------------------------------------------------------------|
| Abdominal aorta calcification (95% CI)                           |
| Model 1                                                          |
| Model 2                                                          |
| Model 3                                                          |
| Model 4                                                          |
| Model 5                                                          |

ACh2L = angiotensin-converting enzyme inhibitor, ARB = angiotensin II receptor blockers, CCB = calcium channel blocker, DM = diabetes mellitus, HTN = hypertension, LVEF = left ventricular ejection fraction.
3.5. The optimal cutoff value for AAC ratio to predict CV mortality (Fig. 2)

We determined the optimal cutoff value for AAC ratio to predict CV mortality using ROC curve analysis. The best cutoff value for AAC ratio was 39% to predict CV mortality (hazard ratio, 8.01; 95% CI, 3.14–20.44). The KM survival curve analysis showed that PD patients with AAC ratio >39% had higher risks of CV mortality compared with other patients with AAC ratio ≤39% (Fig. 2).

4. Discussion

Cardiovascular disease is the leading cause of morbidity and mortality in ESRD patients. In daily practice, predicting the clinical outcomes of PD patients remains to be a challenge. Atherosclerosis-related vascular calcification is commonly observed in dialysis patients and has been highly associated with CV outcomes. There are many risk factors contribute to atherosclerosis and vascular calcification such as age, smoking, hypertension, dyslipidemia, diabetes mellitus, uremia, mineral metabolism particularly hyperphosphatasemia, chronic inflammation, fetuin-A and osteoprotegerin. In the advanced stage of atherosclerosis, the calcium deposit in the vascular wall is frequently observed and can be used for outcomes prediction.

The vascular calcification can be measured from many different sites including coronary arteries, heart valves, carotid arteries, thoracic aorta, abdominal aorta and peripheral arteries. Among all these sites, AAC is one of the best choice due to it can be easily measured with quantitative results and can be used for long-term serial follow-up. AAC tends to progress in ESRD patients during dialysis and it is associated with congestive heart failure, arterial stiffness, effects of renal denervation, autonomic dysfunction and worse heart rate variability. Furthermore, AAC has been reported to predict CV events and mortality in ESRD patients.

There are 2 main commonly employed methods to quantify AAC including plain abdominal X ray with Kauppila score and CT. The advantage of plain X ray including lower cost and radiation dose but it is difficult to quantify AAC. In contrast, CT can easily quantify AAC with objective and reproducible results. In addition, the abdominal CT is commonly performed to assess other pathologies therefore incidentally available for many patients. Furthermore, CT can clearly recognize the patterns of calcification. In dialysis patients, it is characterized by mineral deposition in the tunica media, in contrast to non-dialysis populations, where calcification predominately deposits in the atheromatous plaque. Previous study supported that CT appeared to be more sensitive than plain X-rays at detecting vascular calcifications in hemodialysis patients. Tsushima et al developed a method to measure the percentage of calcified volume against whole vascular volume using CT and Mori et al also described and validated a new volume-rendering approach to quantify aortic calcification using commercially available software. Currently, CT remains the reference standard in the measurement of AAC. In this study, we used CT to evaluate the ratio of AAC and confirmed its strong predictive value of CV mortality. Even after adjustments with traditional risk factors, AAC remained to be the excellent predictor of CV mortality.

| Table 5 |
| AAC to predict total mortality, CV mortality and non-CV mortality with Cox regression and time-dependent receiver operating characteristic curve analysis. |
| AUC | AUC (95% CI) | P value | AUC (95% CI) | P value |
| Total mortality | 24.4±20.0% | 1.035 (1.018–1.052) | <.001 | 0.685 (0.579–0.792) | .001 |
| CV mortality | 32.6±18.6% | 1.060 (1.033–1.089) | <.001 | 0.787 (0.664–0.910) | <.001 |
| Non-CV mortality | 18.2±15.2% | 1.015 (0.992–1.039) | <.001 | 0.537 (0.401–0.673) | .572 |

Number of events: total mortality, N = 42, CV mortality, N = 18, non-CV mortality, N = 24. AAC = abdominal aorta calcification, AUC = area under curve.
Compared with CV mortality, the studies about the association between non-CV mortality and AAC are limited. At the best of our knowledge, the present study is the first one demonstrating that AAC could not predict the non-CV mortality. Mäkelä et al recently reported that AAC can predict total mortality and CV events in PD patients. Unfortunately, they didn’t report the association between non-CV cause of deaths and AAC. In this study, we also showed that AAC could predict total mortality but the predictive power was mainly contributed from CV mortality. In the present study, instead of AAC, age and duration of PD before enrollment were significant predictors of non-CV mortality. The possible explanation of our finding was that the main causes of non-CV mortality were sepsis, especially peritonitis, and cancer which were not strongly associated with atherosclerosis.

Interestingly, the incidence of non-CV mortality was even higher than CV mortality in PD patients in our study. The data from the European Renal Association-European Dialysis and Transplant Association Registry also supported our finding which showed that the age-adjusted CV mortality in dialysis patients was 8.8 times higher, whereas the non-CV mortality was also increased 8.1 times compared with general population. This emphasizes that in addition to the reduction of CV risk factors to improve CV outcomes, the prevention of non-CV mortality deserves equal attention. In the future, research for the reduction of mortality in dialysis patients should focus on both CV and non-CV causes of death.

There are several limitations to this study. First, this is a small cohort study and all the patients in this study were Taiwanese. The statistic power was limited due to small case number. Further larger clinical studies with different ethnicities enrollment are needed to confirm our findings. Second, the time gap between chronic kidney disease to initiation of PD might also influence the severity of AAC and outcomes which was lacked in current study. Third, our study group is only limited to PD patients, and further studies are needed to elucidate whether the same association between AAC and CV, non-CV mortality also exists in hemodialysis patients or even general population. The risks of non-CV mortality might be different between hemodialysis and PD patients.

5. Conclusion

AAC has excellent prognostic value of long-term CV mortality in PD patients. The predictive power is high even after adjust with multiple clinical variables. However, AAC is not associated with non-CV mortality. Since the non-CV mortality contributed a large portion of total cause of mortality, further studies should focus on the risk assessment and management of non-CV cause of deaths in PD patients.

Author contributions

J.W.H. conceived and designed the experiments. C.H.T., I.J.T. and Y.H.L. analyzed the data. C.H.T and I.J.T. wrote the paper. L.Y.L. and J.W.H. made scientific comments on the manuscript.

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