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Combinations of valvular calcification and serum alkaline phosphatase predict cardiovascular risk among end-stage kidney disease patients

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ABSTRACT

Background: Valvular calcification (VC) refers to the calcified valvular remodeling associated with kidney dysfunction, especially end-stage kidney disease (ESKD). ESKD patients with VC had significantly higher cardiovascular risk than those without. Factors interacted with VC regarding prognostic prediction in this population were seldom investigated. We aimed to examine the potential synergetic effects of VC and alkaline phosphatase (Alk-P) on ESKD patients' cardiovascular risk and mortality.

Methods: ESKD patients undergoing hemodialysis were prospectively enrolled from a medical center in 2018. We identified patients with echocardiography and available serum Alk-P levels. Cox proportional hazard regression was performed to analyze the risk of major adverse cardiovascular events (MACEs), cardiovascular and overall mortality among 4 participant groups (with or without VC versus low or high Alk-P levels). The models were further adjusted for age, sex, and clinical variables.

Results: Of the 309 ESKD patients, 38, 46, 112, and 113 had no VC with low Alk-P, no VC with high Alk-P, VC with low Alk-P, and VC with high Alk-P, respectively. After adjusting for age and sex, patients with VC and high Alk-P had a higher risk of developing MACE, cardiovascular and overall mortality (HR, 3.07, 3.67, 3.65; 95% CI 1.38–6.84, 1.1–12.24, 1.29–10.36, respectively). Patients with VC and high Alk-P remained at higher risk of MACE (HR, 2.76; 95% CI 1.17–6.48) than did those without VC and with low Alk-P.

Conclusion: Serum Alk-P could be used to identify a subgroup of ESKD patients with elevated cardiovascular risk among those with VC.

1. Introduction

Valvular calcification (VC) is characterized by the deposition of calcium apatite in the cardiac valves accompanied by valvular remodeling. The prevalence of VC is between 0.4 % in the general population and 1.7 % in older adults [1]. The incidence of VC of the aortic valve is nearly 5 per 1000 individuals per year [2], with a higher incidence of 3.3 % annually among those with end-stage kidney disease (ESKD) [3]. The proportion of patients affected by VC is much greater among those with chronic kidney disease (CKD), and more than half of ESKD patients under chronic dialysis have VC [4,5]. An analysis using the Framingham Heart Study cohort revealed that patients with CKD had a 60 % higher risk of VC than did those without [6]. The age of VC onset is significantly younger in CKD patients than in the general population. Previous studies have shown that risk factors for VC in patients with ESKD older age, longer dialysis vintage, greater inflammatory cytokine levels, hyperphosphatemia, and higher levels of calcium-phosphate products [5,7].

The pathobiology of VC is complex. Aging-associated VC is

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; Alk-P, alkaline phosphatase; ANOVA, analysis of variance; ARB, angiotensin receptor blocker; BMD, bone mineral density; CI, confidence interval; CKD, chronic kidney disease; CKD-EPI, chronic kidney disease – epidemiology collaboration; CKD-MBD, chronic kidney disease-mineral bone disorder; eGFR, estimated glomerular filtration rate; ELISA, enzyme-linked immunosorbent assay; ESKD, end-stage kidney disease; HR, hazard ratio; LA, left atrial; MACE, major adverse cardiovascular event; PTH, parathyroid hormone; VC, valvular calcification.

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frequently related to chronic and passive calcified degeneration of cardiac valves, but recent studies have reshaped this theory by demonstrating the influences of inflammation, the metabotoxic milieu, and prof-fibrotic stimuli [8]. In a uremic environment, VC is recognized as a manifestation of CKD-mineral bone disorder (CKD-MBD). Valvular interstitial cells may undergo aberrant phenotypic differentiation toward an osteoblast-like status, resulting in active secretion of calcium-containing osteoid into valvular tissues [9]. High extracellular phosphate, a prevalent complication in ESKD patients, is an instrumental driver of such pathology, akin to the pathophysiology in uremic vascular calcification [10].

VC exerts a variety of pathophysiological influences. Aortic VC leads to left ventricular outflow obstruction, increases ventricular loading and oxygen consumption, and culminates in myocardial hypertrophy and fibrosis. Mitral VC stiffens mitral leaflets and distends the left atrium, causing arrhythmia, pulmonary congestion, and heart failure. The sequelae of VC tend to be more severe among patients with ESKD, as this population suffers from a disproportionately high number cardiovascular events due to the presence of atypical cardiovascular risk factors [11]. Among patients under chronic peritoneal dialysis, VC was shown to increase the risk of cardiovascular events and morality by 2- to 3-fold, especially among those with more severe inflammation [12]. Results from studies of CKD patients generally agree with these findings.

Despite the importance of VC in ESKD patients, very few reports have addressed whether there are factors that interact with VC regarding outcome influences. Alkaline phosphatase (Alk-P), a hydrolase residing in multiple body tissues, functions primarily in skeletal mineralization [13]. Higher Alk-P levels were predictive of greater mortality in ESKD patients, independent of hepatic diseases status, supporting its prognostic importance in this population [14]. In addition, the Alk-P level has been shown to interact with risk factors for mortality such as oxidative stress markers in patients with ESKD [15]. These findings prompted us to investigate whether Alk-P status might modulate the effects of factors that influence VC in this population. We hypothesized that VC and serum Alk-P level jointly play a role in predicting cardiovascular risk and mortality in patients with ESKD. Using medical records from a well-maintained cohort of ESKD patients, we employed multivariate analysis to answer this research question.

2. Methods

2.1. Procedures and study design

This study was a retrospective analysis of a prospectively assembled cohort, with study procedures described previously [16]. In brief, ESKD patients under chronic hemodialysis (>3 months of treatment), defined as having an estimated glomerular filtration rate (eGFR) < 15 mL/min/1.73 m^2 based on the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) formula, were prospectively enrolled from the dialysis unit of our hospital between Oct 1st and December 31st, 2018. The patients underwent echocardiographic examinations by board-certified cardiologists who were blinded to the study design during the study period, and we investigated whether VC was present. The presence of VC was defined as bright refringent lesions with a thickness > 1 mm over the mitral or aortic leaflet or annulus on echocardiography [17,18]. Serum Alk-P levels were measured using an enzyme-linked immunosorbent assay (ELISA) (Cat. 10410B, Innovation Scientific Ltd., Australia). The final cohort for analysis remained after application of the following exclusion criteria: the absence of echocardiographic valvular calcification or serum Alk-P test results (Fig. 1).

Following enrollment, we recorded the following patient clinical features: age, sex, body weight, dialysis vintage (duration of dialysis), comorbidity profile (cardiovascular, metabolic, and other organs), laboratory data (hemogram, nutrition and metabolic indices, liver function parameters, electrolyte and mineral-related hormones), dialysis clearance, and medication regimens. Regarding medication use, we documented anti-hypertensives, anti-hyperlipidemic agents (statins), glucose-lowering drugs (oral anti-diabetics and insulin/analogs), anticoagulants, and those affecting mineral bone disorders (calcitriols and phosphate binders), according to a previous report [19,20]. We also noted echocardiographic indices involving the heart and great vessels (aortic root and inferior vena cava diameter) in addition to VC status. Participants were prospectively followed up for the development of prespecified study outcomes, death, or the end of follow-up on December 31, 2021, should any happened first.

2.2. Outcomes

The primary outcome of this study was major adverse cardiovascular events (MACEs), defined as cardiovascular mortality, coronary revascularization for any reason, non-fatal myocardial infarction/unstable angina, non-fatal stroke, or hospitalization for heart failure. For secondary outcomes, we focused on cardiovascular mortality (due to myocardial infarction, arrythmia, stroke, aortic dissection, aneurysmal rupture, cardiac tamponade, or pulmonary embolism), and all-cause mortality.

2.3. Statistical analysis

To determine the optimal cut-off threshold for categorizing patients,

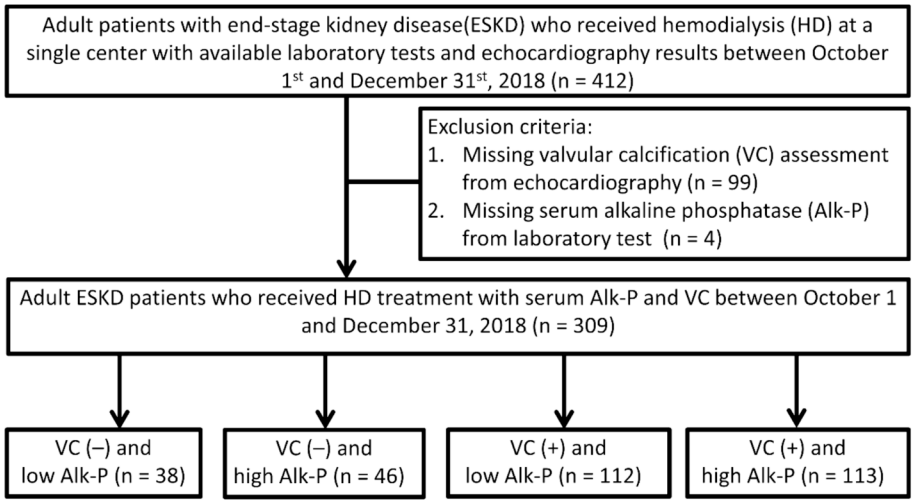

Fig. 1. Flowchart of patient selection. *Alk-P, alkaline phosphatase; ESKD, end-stage kidney disease; HD, hemodialysis; VC, valvular calcification.*

we first evaluated the distribution of serum Alk-P levels among all patients. After selecting the cutoff, the patients were divided into four groups according to the presence/absence of VC and high/low serum Alk-P levels. We first compared the 4 groups with respect to patient age, body weight, dialysis vintage, and laboratory data using one-way analysis of variance (ANOVA) (for normally distributed variables) or the Kruskal-Wallis test (for skewed distributed variables) as appropriate. To compare of sex, comorbidities, and medication use, we used the Chi-square (for normally distributed variables) or Fisher's exact test (for skewed distributed variables), as appropriate. After follow-up, the incidence of primary and secondary outcomes was used to construct Kaplan-Meier survival or event-free curves according to groups, followed by between-group comparison using the log-rank test. We then used Cox proportional hazard regression analysis to analyze the risk of MACEs among patients in the 4 groups using those with VC and high Alk-P as the reference group. Models were adjusted for age, sex, and further clinical variables as a sensitivity analysis. For all analyses, $p < 0.05$ was considered statistically significant.

3. Results

A total of 412 patients with ESKD undergoing chronic hemodialysis were enrolled during the study period (Fig. 1). After applying the exclusion criteria, the remaining 309 patients with available VC assessment and serum Alk-P results were selected for subsequent analysis (Fig. 1). The distribution of serum Alk-P levels (mean ± standard deviation, 75.6 ± 39.0 IU/L; median 65 IU/L) among all patients is shown in **Supplementary Fig. 1A**. We then chose the median value as the cutoff value for determining high or low serum Alk-P levels, yielding 150 (48.5 %) patients with low and 159 (51.5 %) with high Alk-P levels, respectively. We then used echocardiographic VC status (225 [72.8 %] present and 84 [27.2 %] absent) to divide the patients into 4 groups. No VC with low Alk-P, n = 38 (12.3 %), no VC with high Alk-P, n = 46 (14.9 %), VC with low Alk-P, n = 112 (36.2 %), and VC with high Alk-P, n = 113 (36.6 %) (Table 1). The distribution of Alk-P according to VC status is shown in **Supplementary Fig. 1B**.

Clinical and echocardiographic features among participant groups.

ESKD patients with VC were significantly older than those without, regardless of Alk-P level ($p < 0.001$) (Table 1). Those with high Alk-P had a significantly higher proportion of females ($p = 0.028$) and longer duration of dialysis ($p = 0.003$) than those with low Alk-P, regardless of VC status. In contrast, those without VC and low Alk-P had the highest body weight of the 4 groups ($p = 0.009$). As for the comorbidity profile, there were no significant differences in cardiovascular, metabolic, and other organ morbidities between the 4 groups, except for a higher prevalence of coronary artery disease in patients with VC and low or high Alk-P ($p = 0.019$) (Table 1). Analysis of laboratory data showed that patients with low Alk-P, regardless of VC status, had significantly higher transferrin saturation ($p = 0.003$), higher albumin ($p < 0.001$), lower aluminum ($p = 0.018$) and parathyroid hormone ($p < 0.001$) levels than did those with high Alk-P (Table 1). On the other hand, patients with VC and high Alk-P had significantly lower triglyceride ($p = 0.004$) and phosphate ($p = 0.043$) levels than did those in the other 3 groups. Analysis of medication use showed that patients without VC and with high Alk-P had a significantly higher prevalence of receiving angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEi/ARB); those with high Alk-P, regardless of VC status, more frequently received calcitriol (Table 1).

The echocardiographic findings of the patients are shown in Table 2. Participants without VC and low Alk-P levels had a significantly lower left atrial (LA) diameter, whereas those with VC and high Alk-P levels had the highest LA diameter ($p = 0.01$). Patients with VC and low Alk-P levels had significantly lower left ventricular posterior wall thickness ($p = 0.008$) and relative wall thickness ($p = 0.022$) than did those in the other 3 groups (Table 2).

Table 1
Baseline characteristics of chronic hemodialysis patients according to valvular calcification (VC) and serum Alk-P level. Cut-off point of 65 (n = 309):

	VC (−) Low Alk-P	VC (−) High Alk-P	VC (+) Low Alk-P	VC (+) High Alk-P	*p* value
Number of participants	38	46	112	113	
Age (years) [#]	61.16 ± 13.22	64.41 ± 11.83	71.62 ± 11.27	70.65 ± 11.27	<0.001
Gender, Female (%) [†]	16 (42.1)	24 (52.2)	42 (37.5)	64 (56.6)	0.028
Weight (Kg) [§]	64.33 ± 12.66	59.31 ± 14.05	61.90 ± 12.87	60.19 ± 13.49	0.009
Vintage (years) [§]	7.15 ± 7.03	8.75 ± 6.98	6.64 ± 6.54	9.74 ± 7.55	0.003
Comorbidities (%)					
Cardiovascular					
Hypertension[†]	31 (81.6)	35 (76.1)	92 (82.1)	90 (79.6)	0.844
Coronary Artery Disease[†]	13 (34.2)	13 (28.3)	51 (45.5)	60 (53.1)	0.019
PAD[†]	7 (18.4)	14 (30.4)	22 (19.6)	36 (31.9)	0.112
Heart failure[†]	6 (15.8)	8 (17.4)	30 (26.8)	21 (18.6)	0.304
Metabolic					
Type 2 DM [†]	15 (39.5)	20 (43.5)	55 (49.1)	53 (46.9)	0.746
Hyperlipidemia[†]	21 (55.3)	31 (67.4)	57 (50.9)	64 (56.6)	0.304
Other organs					
COPD[†]	1 (2.6)	3 (6.5)	13 (11.6)	13 (11.5)	0.311
Malignancy[‡]	2 (5.3)	4 (8.7)	12 (10.7)	15 (13.3)	0.541
Laboratory data					
Hemogram and related parameters					
Hb (g/dl) [§]	10.84 ± 1.64	10.41 ± 1.24	10.19 ± 1.39	10.32 ± 1.25	0.075
Platelet (x1000/ul) [§]	206.84 ± 49.16	196.32 ± 58.78	184.92 ± 56.93	195.16 ± 61.75	0.170
Ferritin (ng/ml) [§]	545.1 ± 310.17	533.72 ± 234.74	570.04 ± 304.37	528.92 ± 253.14	0.839
TSAT (%)[§]	35.22 ± 15.84	30.29 ± 13.68	33.78 ± 12.66	28.56 ± 11.39	0.003
Nutrition and metabolic					
Albumin (gm/dl) [§]	4.08 ± 0.27	3.83 ± 0.36	3.91 ± 0.34	3.81 ± 0.36	<0.001
Cholesterol (mg/dl) [§]	159.55 ± 34.98	152 ± 34.99	158.24 ± 41.3	155 ± 38.23	0.813
Triglyceride (mg/dl) [§]	163.68 ± 101.04	166.39 ± 167.79	153.16 ± 103.06	121.51 ± 75.26	0.004
Glucose [AC] (mg/dl) [§]	109.89 ± 55.08	120.41 ± 65	109.64 ± 48.33	119.29 ± 60.15	0.520
Uric acid (mg/dl) [§]	6.72 ± 1.88	6.36 ± 1.51	6.1 ± 1.64	6.13 ± 1.57	0.332
Liver function					
A.S.T. (IU/L) [§]	15.68 ± 5.03	16.15 ± 5.99	15.39 ± 4.93	18.06 ± 15.55	0.553
Alkaline-P (IU/L) [§]	49.57 ± 10.95	99.67 ± 54.91	50.33 ± 8.68	99.55 ± 34.32	<0.001
Electrolyte and mineral parameters					
Na (meq/l) [§]	138.65 ± 2.67	137.02 ± 3.12	138.16 ± 2.84	137.53 ± 3.28	0.090
K (meq/l) [§]	4.91 ± 0.58	4.58 ± 0.77	4.64 ± 0.6	4.6 ± 0.63	0.056
iCa (mg/dl) [§]	4.59 ± 0.59	4.57 ± 0.48	4.57 ± 0.47	4.6 ± 0.48	0.839
P (mg/dl) [§]	5.42 ± 1.11	5.16 ± 1.37	5.07 ± 1.28	4.93 ± 1.32	0.043
Al (ng/ml) [§]	6.17 ± 2.02	7.2 ± 3.75	6.2 ± 3.3	7.93 ± 5.19	0.018
PTH (pg/ml) [§]	210.46 ± 179.78	356.96 ± 277.3	193.93 ± 188.06	375.89 ± 337.56	<0.001
Dialysis clearance					
Kt/V (Gotch) [§]	1.34 ± 0.15	1.39 ± 0.15	1.36 ± 0.2	1.42 ± 0.2	0.073
Medication (%)					
Anti-HTN drugs					
ACEI/ARB[†]	21 (55.3)	35 (76.1)	60 (53.6)	56 (49.6)	0.021

(*continued on next page*)

Table 1 (*continued*)

	VC (−) Low Alk-P	VC (−) High Alk-P	VC (+) Low Alk-P	VC (+) High Alk-P	*p* value
B-blockers†	18 (47.4)	28 (60.9)	60 (53.6)	58 (51.3)	0.622
Calcium antagonists (CCB) †	20 (52.6)	31 (67.4)	67 (59.8)	63 (55.8)	0.481
Statins†	16 (42.1)	22 (47.8)	32 (28.6)	44 (38.9)	0.096
OAD†	8 (21.1)	13 (28.3)	44 (39.3)	32 (28.3)	0.120
Insulin and analogues†	5 (13.2)	10 (21.7)	24 (21.4)	23 (20.4)	0.718
Anticoagulants‡	1 (2.6)	3 (6.5)	5 (4.5)	8 (7.1)	0.756
Calcitriol	9 (23.7)	24 (52.2)	31 (27.7)	65 (57.5)	<0.001
Phosphate binders					
Calcium-based†	23 (60.5)	28 (60.9)	68 (60.7)	72 (23.3)	0.968
Non-calcium based†	13 (34.2)	11 (23.9)	22 (19.6)	18 (15.8)	0.111

MHD, maintenance hemodialysis; AoAC, aortic arch calcification; AVC, aortic valve calcification; DM, diabetes mellitus; PAD, peripheral arterial disease; COPD, chronic obstructive pulmonary disease; A.S.T., aspartate aminotransferase; TSAT, transferrin saturation; Al, aluminum; PTH, parathyroid hormone; ACEI/ARB, angiotensin converting enzyme inhibitor/ angiotensinII receptor blocker; OAD, oral antidiabetic medications.
Data are expressed as n (%) for categorical variables and mean ± standard deviation for continuous variables.
[#] One-way analysis of variance (ANOVA) [§]Kruskal–Wallis test [†]Chi-square test [‡]Fisher's exact test.

Table 2
Echocardiographic findings of chronic hemodialysis patients according to valve calcification (VC) and serum Alk-P level. Cut-off point of 65 (n = 309):

	No VC Low Alk-P (n = 38)	No VC High Alk-P (n = 46)	VC Low Alk-P (n = 112)	VC High Alk-P (n = 113)	*p value*
Aortic root (mm) §	32.23 ± 5.06	31.34 ± 3.95	32.34 ± 4.84	31.67 ± 4.54	0.525
IVS (mm) §	12.03 ± 2.78	12.5 ± 2.46	11.77 ± 2.42	12.54 ± 5.34	0.270
LA diameter (mm) #	39.34 ± 7.47	42.1 ± 7.62	42.59 ± 6.56	44.2 ± 9.07	0.010
LVEDD (mm) #	50.45 ± 8.79	50.4 ± 7.74	50.31 ± 6.52	49.07 ± 8.16	0.564
LVESD (mm) §	33.22 ± 12.01	32.84 ± 9.05	31.29 ± 6.84	30.69 ± 8.83	0.248
LVPW (mm) §	11.43 ± 2.06	11.82 ± 2.43	10.6 ± 2.06	11.35 ± 3.5	0.008
LV mass (g) §	243.73 ± 100.6	252.56 ± 88.27	223.72 ± 73.94	245.87 ± 209	0.293
LVMI§	145.01 ± 56.04	157.05 ± 49.64	135.92 ± 41.86	153.95 ± 134.63	0.112
RWT (mm) §	0.46 ± 0.11	0.48 ± 0.13	0.42 ± 0.1	0.48 ± 0.2	0.022
IVC diameter (mm) §	1.35 ± 0.47	1.46 ± 0.34	1.52 ± 0.37	1.54 ± 0.49	0.199
EF (%)§	65.5 ± 14.51	65.42 ± 13.1	67.76 ± 10.28	67.68 ± 12.64	0.462

HF, heart failure; EF, ejection fraction; DD, diastolic dysfunction; CO, cardiac output; EF, ejection fraction; IVC, inferior vena cava; IVS, interventricular septum; LV, left ventricle; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVH, left ventricular hypertrophy; LVMI, left ventricular mass index; LVPW, left ventricular posterior wall; RWT, relative wall thickness; UCG, echocardiography.
Data are expressed as n (%) for categorical data and as mean ± standard deviation for continuous data. [#]One-way analysis of variance (ANOVA) [§]Kruskal–Wallis test.

3.1. Determining the associations between VC status, Alk-P levels, and outcomes

After more than 3 years of follow up, 121 patients (39.2 %) developed MACEs, while 62 (20.1 %) died of cardiovascular events. Overall, 79 patients (25.6 %) died. Survival analysis includes Kaplan–Meier MACE-free (Fig. 2**A**), cardiovascular survival (Fig. 2**B**), and overall survival curves (Fig. 2**C**). The proportion of patients developing MACEs progressively increased among patients from those without VC and with low Alk-P (18.4 %), without VC and with high Alk-P (30.4 %), with VC and low Alk-P (41.1 %), and with VC and high Alk-P (47.8 %) (log-rank $p = 0.012$). The trend of cardiovascular mortality among the 4 groups followed the same trend, increasing from those without VC and with low Alk-P (7.9 %), without VC and with high Alk-P (17.4 %), with VC and low Alk-P (18.7 %), and those with VC and high Alk-P (26.5 %) (log-rank $p = 0.048$). The overall mortality rates were as follows: patients without VC and with low Alk-P, 10.5 %; without VC and with high Alk-P, 26.1 %; with VC and low Alk-P, 20.5 %; and with VC and high Alk-P, 35.4 % (log-rank $p = 0.006$).

We subsequently used Cox proportional hazard regression analysis to investigate the risk factors for MACE, cardiovascular mortality, and overall mortality. In univariate analyses, patients with VC and high Alk-P levels were found to have a significantly higher risk of MACEs during follow-up (hazard ratio (HR), 3.18; 95 % confidence interval (CI), 1.45–6.99), followed by those with VC and low Alk-P levels (HR, 2.6; 95 % CI, 1.17–5.75) than did those without VC and with low Alk-P levels (Table 3). Participants with VC and high Alk-P also had significantly higher cardiovascular mortality (HR, 4.01; 95 % CI, 1.22–13.12) and overall mortality (HR, 4.01; 95 % CI, 1.44–11.22) than those without VC and with low Alk-P. After adjusting for age and sex, patients with VC and high Alk-P still had a significantly higher risk of developing MACE (HR, 3.07; 95 % CI, 1.38–6.84), cardiovascular mortality (HR, 3.67; 95 % CI, 1.1–12.24), and overall mortality (HR, 3.65; 95 % CI, 1.29–10.36) (model 1; Table 3). Further adjustment for variables with significant differences between groups (Table 1) showed that patients with VC and high Alk-P had a significantly higher risk of developing MACE (HR, 2.76; 95 % CI, 1.17–6.48) than did those without VC and with low Alk-P, whereas the differences in the risk of cardiovascular and overall mortality became insignificant (model 2; Table 3).

4. Discussion

In this study, we assembled a cohort of patients with ESKD undergoing chronic hemodialysis and analyzed the risk of MACE, cardiovascular and overall mortality associated with VC and serum Alk-P levels. We found that ESKD patients with calcified valves and a higher serum Alk-P level had significantly higher cardiovascular risk and overall mortality than did those without VC and with low Alk-P level. The observed risk persisted even after adjusting for demographic factors, body weight, dialysis vintage, comorbidities, laboratory indicators of mineral bone metabolism, and medication use. Our findings suggest that serum Alk-P status could further identify a subgroup of ESKD patients with elevated cardiovascular risk among those with VC, supporting the utility of combining VC and Alk-P for risk prediction.

The clinical features of our patients largely matched those of other ESKD populations. The proportion of patients with VC in our study, 72.8 %, approximated that reported for cohorts from Japan (76.5 %)[18] and Hong-Kong (>80 %) [21]. The distribution and median value of serum Alk-P levels also were similar to ESKD patients under chronic dialysis from China (median, 64 IU/L) [22] and Hong Kong (median, 91.9 IU/L) [23]. Thus, we believe that our findings are applicable to patients outside of our study cohort.

Previous studies have already pinpointed a strong association between VC and a 2- to 5-fold higher cardiovascular risk among ESKD patients [21]. However, relatively few examined factors potentially interacting with VC to affect cardiovascular risk. Several attempts have been made before; for example, Wang and colleagues observed that concurrent atherosclerotic vascular disease synergized with VC in elevating cardiovascular and overall mortality [21]. The same group of researchers subsequently found that higher serum C-reactive protein

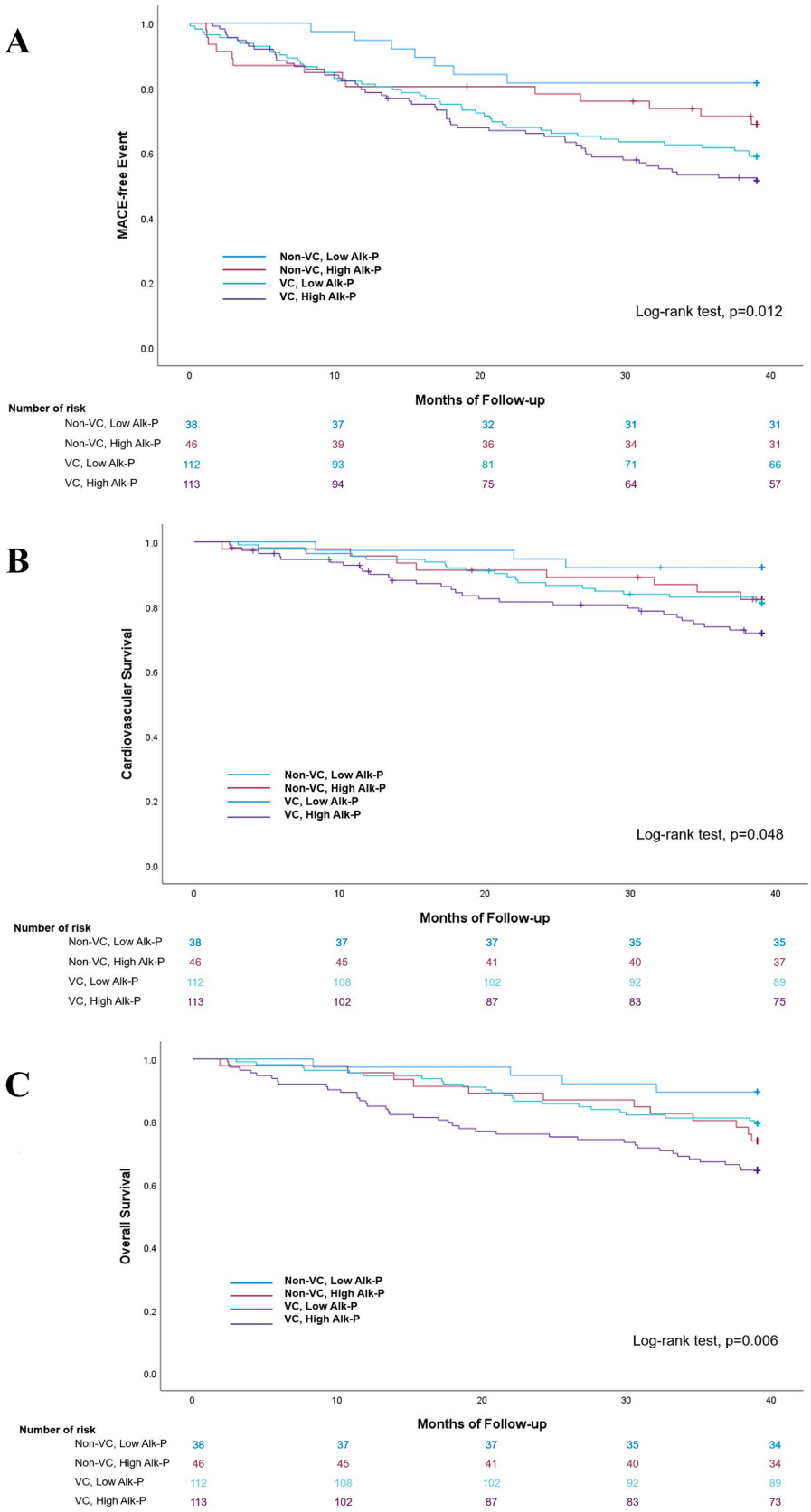

Fig. 2. Kaplan-Meier MACE-free survival (A), cardiovascular survival (B), and overall survival (C) curves based on patients' VC and serum Alk-P levels. *Alk-P, alkaline phosphatase; MACE, major adverse cardiovascular event; VC, valvular calcification.*

Table 3
Cox proportional hazard analysis of outcome events between four groups according to VC and Alk-P (reference group: VC (−) low Alk-P).

Events	Crude		Model 1*		Model 2 **	
	HR (95 % CI)	*p*	HR (95 % CI)	*p*	HR (95 % CI)	*p*
MACEs						
VC (−) high Alk-P	1.86 (0.75–4.60)	0.181	1.95 (0.79–4.85)	0.148	1.67 (0.65–4.30)	0.289
VC (+) low Alk-P	2.60 (1.17–5.75)	0.019	2.13 (0.95–4.80)	0.068	1.85 (0.81–4.21)	0.145
VC (+) high Alk-P	3.18 (1.45–6.99)	0.004	3.07 (1.38–6.84)	0.006	2.76 (1.17–6.48)	0.020
CV mortality						
VC (−) high Alk-P	2.33 (0.62–8.80)	0.211	2.33 (0.62–8.79)	0.212	1.56 (0.39–6.30)	0.532
VC (+) low Alk-P	2.52 (0.75–8.43)	0.135	1.92 (0.56–6.59)	0.299	1.47 (0.42–5.23)	0.548
VC (+) high Alk-P	4.01 (1.22–13.12)	0.022	3.67 (1.10–12.24)	0.034	2.88 (0.80–10.34)	0.105
Mortality						
VC (−) high Alk-P	2.63 (0.85–8.15)	0.094	2.62 (0.84–8.14)	0.096	1.71 (0.52–5.58)	0.376
VC (+) low Alk-P	2.07 (0.72–5.98)	0.179	1.57 (0.53–4.62)	0.416	1.15 (0.38–3.49)	0.800
VC (+) high Alk-P	4.01 (1.44–11.22)	0.008	3.65 (1.29–10.36)	0.015	2.40 (0.80–7.25)	0.121

Model 1*: adjusted for Age and Sex.
Model 2**: adjusted for Age, Sex and variables with significant differences among groups from Table 1.

and lower fetuin-A levels additively increased ESKD patients' risk of MACE and mortality [12]. In addition, echocardiographic VC was found to increase the outcome-predictive efficacy of traditional prognostic factors among ESKD patients [24]. These results clearly show that the cardiovascular risk posed by VC synergizes with that from inflammation and anti-calcific defense machineries among patients with kidney impairment. However, previous studies have failed to evaluate whether further factors are capable of modulating the detrimental effect of VC. In patients with ESKD, serum Alk-P levels were found to be heavily associated with prevalent bone pathologies [3]. Higher Alk-P levels may serve as an indicator of higher bone turnover status and/or low bone mineral density (BMD) in chronic dialysis patients [25]. Therefore, we proposed that ESKD patients with higher Alk-P and concurrent VC might have higher bone turnover, more frequent calcium traffic between tissues, and more severe ectopic calcification, all of which correlate with higher cardiovascular mortality [26]. This hypothesis is consistent with our findings that patients with VC and high Alk-P levels had significantly higher parathyroid hormone (PTH) levels and more commonly received vitamin D for suppressing PTH than did patients in the other 3 groups (Table 1). Moreover, high bone turnover status increases calcium and phosphorus release into the circulation and conditions vascular and valvular tissues to adopt an osteoblast-like phenotype [26–28]. Thus, it is reasonable that VC synergizes with high Alk-P to elevate cardiovascular risk. Importantly, Alk-P may exhibit better outcome predictive ability than PTH, since the former has lower time-averaged variations than the latter [29]. An alternative possibility is that ESKD patients with high Alk-P had relatively lower BMD in addition to VC, predisposing them to frailty and sarcopenia [30]. Frailty is shown to correlate with an increased cardiovascular risk in patients with various levels of kidney function [31], partly accounting for our observations.

Interestingly, we discovered that the cardiovascular risk among patients with VC and low Alk-P levels became insignificant after adjusting for demographic and other clinical features (Table 3). Low turnover status on bone histopathologic examination is traditionally a marker of greater vascular calcification severity and the presence of VC in patients with CKD [32,33]. However, the issue of whether low bone turnover always leads to negative outcomes in ESKD patients has been challenged recently [34], as mediators of such negative influences include not only vascular/valvular pathologies but also malnutrition/inflammation/cachexia syndrome and even diabetes [35]. Our patients with VC and low Alk-P had the most advanced age, low serum albumin levels, and the highest proportion of patients with diabetes (Table 1). We considered that adjusting for these risk mediators might attenuate the adverse effects of low Alk-P levels.

An important potential complication of VC is adverse atrial remodeling and incident atrial fibrillation (AF). A decade-old study already showed that patients with VC had a significantly elevated risk of atrial fibrillation over 16 years of follow-up, mediated partially by left atrial enlargement [36]. Even among those with persistent AF receiving radiofrequency ablation, patients with VC were at further risk of AF recurrence over time [37]. CKD or ESKD patients are particularly prone to developing AF, which in turn may precipitate kidney function decline and constitute a vicious cycle [38]. AF may therefore be an occult mediator of cardiovascular risk associated with VC [39], amenable to correction. However, the use of anticoagulants in this population requires careful adjudication to balance the risk of drug side effects, overdose, and therapeutic needs.

The identification of a subgroup of ESKD patients with VC at particularly high cardiovascular risk is important. Our findings suggest that high serum Alk-P levels, a potential indicator of high bone turnover in addition to VC, increased the cardiovascular risk over that of patients with low bone turnover. Consequently, direct targeting of high turnover status or low BMD in patients with ESKD may bring therapeutic benefits. Indeed, a recent cohort study from Taiwan revealed that anti-osteoporotic medications including bisphosphonate, denosumab, teriparatide, and raloxifene, significantly reduced cardiovascular risk by more than 50 % among patients with CKD [40]. Going further, a previous study suggests that direct inhibition of Alk-P might attenuate vascular calcification in animal models [41], supporting the therapeutic potential of an Alk-P–directed approach.

5. Limitation

This study has several strengths and limitations. Our study may be one of the first few reports to identify important risk factors interacting with VC with regard to cardiovascular risk estimation. The risk associated with VC and high Alk-P persisted after extensive adjustment for potential variables, supporting the robustness of our findings. However, this study had some limitations. First, we did not measure bone-specific or distinct subtypes of Alk-P, whose relationship with bone turnover rate could be more intimate than that of total Alk-P. However, our patients did not have chronic hepatitis at baseline, nor did they have any history of biliary diseases, excluding the possibility of influences caused by other major Alk-P origins. Second, we did not rate the severity of VC and were unable to make inferences about incremental differences resulting from different extents of VC. Finally, our patients were homogeneous in ethnicity, and the extrapolation of our findings to other non-Asian populations may require further validation.

6. Conclusion

We used a cohort of patients with ESKD to determine whether VC status interacted with serum Alk-P levels for cardiovascular risk prediction. We showed that those with VC and higher Alk-P levels had a

significantly higher risk of developing MACEs than those without VC and with low Alk-P levels, whereas the risk associated with VC and low Alk-P disappeared after adjusting for confounders. These results indicate that estimating cardiovascular risk in patients with ESKD would be best accomplished using combinatorial markers, preferably laboratory and image-based markers, instead of assessing VC alone. New strategies that target VC, bone turnover, and Alk-P suppression are emerging, and we expect that these novel approaches will meaningfully reduce cardiovascular risk in patients with ESKD in the coming era.

Availability of data and material

The raw data were available upon reasonable request to the corresponding author.

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Statement of ethics, consent, and permission

This study was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board (IRB) of Shin Kong Wu Ho-Su Memorial Hospital (approval no 20220713R and 20240708R).

CRediT authorship contribution statement

Chia-Ter Chao: Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization. **Min-Tser Liao:** Writing – review & editing, Conceptualization. **Chung-Kuan Wu:** Writing – review & editing, Supervision, Resources, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2024.101505.

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