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ORIGINAL ARTICLE

The hidden interplay between sex and adverse outcomes in incident dialysis patients: the role of aortic calcification

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ABSTRACT

Background. Research on the sex disparity in the prognosis of chronic kidney disease (CKD), particularly among those who are newly initiating dialysis, is limited and inconclusive. This study aimed to investigate the associations between sex, and all-cause mortality and major cardiovascular adverse events (MACE), with a particular focus on the presence of aortic calcification (AC).

Methods. We conducted a *post hoc* analysis of 1459 incident dialysis patients included in this prospective cohort study. The primary outcome of interest was all-cause mortality, and the secondary endpoint was a composite of MACE.

Results. During a median follow-up period of 3.55 years, 362 (269 male and 93 female) patients died and 477 (342 male and 135 female) patients developed MACE. The risks for all-cause mortality [hazard ratio (HR) 0.61, 95% confidence interval (CI) 0.47–0.79] and MACE (HR 0.74, 95% CI 0.60–0.93) were lower in females than in males. This finding was robust across multiple sensitivity analyses and most subgroups. Moreover, the associations between sex and adverse outcomes were significantly modified by AC status at dialysis initiation (P for interaction $<.05$). Specifically, among patients without AC, females exhibited lower risks for all-cause mortality (HR 0.45, 95% CI 0.29–0.69; $P < .001$) and MACE (HR 0.67, 95% CI 0.49–0.93; $P = .015$), whereas no differences were observed for all-cause mortality (HR 0.82, 95% CI 0.59–1.15; $P = .256$) or MACE (HR 0.80, 95% CI 0.59–1.10; $P = .174$) among patients with AC.

Conclusions. In patients with renal failure receiving dialysis, AC abolished the survival and cardiovascular protection observed in female versus male patients. This finding supports the need for greater awareness of the AC burden in female dialysis patients.

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GRAPHICAL ABSTRACT

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The hidden interplay between sex and adverse outcomes in incident dialysis patients: the role of aortic calcification

In the general population, it is broadly accepted that women had a longer life expectancy than men. However, sex disparity in the prognosis of CKD, especially among those who newly started dialysis, is limited and conflicting.

Methods

Patients:
1459 incident dialysis CKD patients

Aim:
To compare the risk of all-cause death and major cardiovascular adverse event (MACE) in women (n=477) vs. men (n=982)

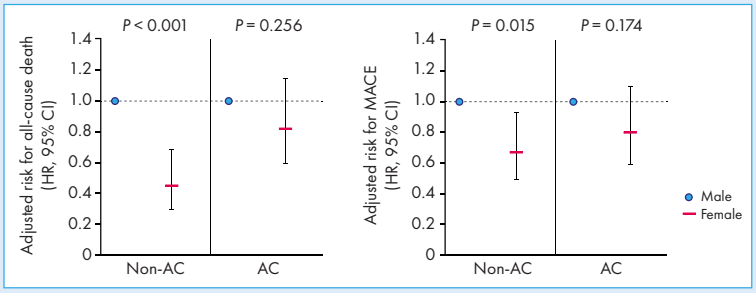
Endpoint:
All-cause mortality composite of MACE

Results

Follow up: 3.55 years
Endpoint:
Died 362, MACE 477

Adjusted death risk
Female: HR 0.61
(95% CI 0.47–0.79)

Adjusted MACE risk
Female: HR 0.74
(95% CI 0.60–0.93)



Conclusion: In patients with renal failure receiving dialysis, AC abolishes the survival and cardiovascular protection seen in female vs. male patients. This finding supports the need for greater awareness of AC burden in women.

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Keywords: all-cause death, aortic calcification, cardiovascular events, incident dialysis, sex disparities

KEY LEARNING POINTS

What was known:

- In the general population, it is broadly accepted that women consistently have a longer life expectancy than men do.
- Sex disparity in the prognosis of CKD, especially among those who newly started dialysis, is limited and conflicting.

This study adds:

- This study adds new evidence that female patients with renal failure receiving dialysis have a lower risk of all-cause death and MACE compared with males.
- This is the first study to examine the potential interaction of sex with AC on clinical outcomes. We found that the female advantage in survival and cardiovascular risk disappeared among patients with AC at the start of dialysis.

Potential impact:

- The study findings indicate the need for greater awareness of AC burden in female dialysis patients.
- This awareness is important to support sex-specific risk assessment strategies and therapeutic interventions to target the management of CKD in the context of cardiovascular disease prevention.

INTRODUCTION

Chronic kidney disease (CKD) is estimated to affect approximately 9.4%–13.4% of the global population, representing a major social and economic health burden worldwide [1, 2]. Although there have been substantial advancements in medical therapy in recent decades, the prevalence and mortality rates of CKD remain alarmingly high. It has been reported that CKD has risen to the 11th leading cause of death globally, with all-age CKD-related rates of mortality increasing by 64.1% between 1990 and 2019 [2, 3]. Notably, the global age-standardized CKD mortality rate is approximately 30% lower in women than in men (15.8 vs 21.6 per 100 000 persons) [1, 4]. Thus, to facilitate the implementation of targeted and individualized treatment strategies by clinicians, obtaining sex-specific data on the prognosis of CKD is imperative.

Researchers in many medical disciplines are increasingly aware that manifestations of disease differ between women and men [5–7]. It is broadly accepted that women in the general population consistently have a longer life expectancy than men do, largely due to the differences in sex hormone levels, lifestyle, social behaviour and so on [8, 9]. However, the available research data on the impact of sex on health outcomes in patients with CKD is limited and conflicting, particularly among those receiving dialysis. A meta-analysis of 46 cohorts, including 2 051 158 patients from five continents, suggested that female patients tended to have a lower risk of all-cause mortality and cardiovascular mortality than males did, across all levels of estimated glomerular filtration rate (eGFR) [10]. Conversely, Lim *et al.* [11] recently reported that female patients undergoing dialysis had higher all-cause mortality rates but lower incidence rates of cardiovascular death than male patients. The differences between these studies could be attributed to variations in the study design and patient characteristics, especially cardiovascular profiles, including blood pressure (BP) levels, coronary calcium and left ventricular hypertrophy. These factors are critical, as demonstrated by Borrelli *et al.* [12], who reported that the cardiovascular protection observed in female patients with CKD disappeared in those with higher BP levels. Therefore, a better understanding of sex disparity in poor outcomes related to the potential interactive effects between sex and cardiovascular health risk factors is important to support dialysis management and develop strategies to mitigate potential inequities in access to care for this vulnerable population.

Aortic calcification (AC) is a prevalent complication of CKD and serves as an independent contributor to increased cardiovascular disease (CVD) and mortality risk in this patient group [13, 14]. Extensive evidence suggests that sexual dimorphism influences various aspects of AC, from epidemiology and risk factors, to pathophysiology [15, 16]. Recent studies have provided valuable insight into the modifying effect of AC on the association between sex and several clinical outcomes in the general population [17, 18]. However, to date, no study has addressed this issue in the context of patients with CKD. In a large cohort of patients with renal failure who initiated dialysis, we investigated the associations between sex, all-cause mortality and major cardiovascular adverse event (MACE), with a particular focus on the presence of AC, with the aim, at least in part, of filling the research gaps in this field.

MATERIALS AND METHODS

Date sources and study population

This study is a secondary analysis of patients from the Aichi Cohort Study of Prognosis in Patients Newly Initiated into Dialysis (AICOPP) study (identifier: UMIN000007096), which is available in the Figshare public dataset [19]. The details of this cohort have been described previously [20]. In brief, this multicentre prospective cohort study recruited a consecutive sample of 1889 patients aged 20 years or older with kidney failure who initiated maintenance dialysis at 17 dialysis centres in Japan between October 2011 and September 2013. The exclusion criteria were as follows: (i) patients who had been on dialysis for <90 days or had withdrawal from maintenance dialysis (n = 389); (ii) patients with an absence of baseline chest X-ray radiographs (n = 11); and (iii) patients with missing data for important variables including age, sex, body mass index (BMI) and eGFR at baseline (n = 26). Patients with missing or incorrect follow-up data were also excluded (n = 4). Finally, we included 1459 incident dialysis patients in this analysis (Supplementary data, Fig. S1).

This study was conducted according to the amended Declaration of Helsinki. Given that the distinct original study protocols was approved by the ethical committees of each AICOPP group facility (No. 20110823–3), and informed consent was obtained from all patients by the original cohort studies, it was no longer required for this secondary study.

Data acquisition

Baseline characteristics reported to the clinical research center of the AICOPP at the time of dialysis initiation included sociodemographics (age, sex and BMI), comorbidities (prevalent coronary artery disease, stroke and diabetes, etc.), medication history [renin–angiotensin system inhibitors (RASi), phosphate binders, vitamin D receptor activator (VDRA) and steroid] and dialysis modality (haemodialysis or peritoneal dialysis), etc. AC was evaluated by an experienced radiologist using chest X-ray. Physical function was assessed by trained nurses at dialysis initiation using the Barthel Index (BI), which includes the following 10 activities: feeding, transferring, grooming, toileting, bathing, walking, climbing stairs, dressing, bowel continence and bladder continence [21, 22]. Total BI scores range from 0 to 100, with higher scores indicating greater physical functional independence. Blood samples were drawn from each research centre before the first dialysis session. Blood pressure and laboratory parameters, including haemoglobin, albumin, calcium, C-reactive protein (CRP), intact parathyroid hormone (iPTH), creatinine, potassium, phosphorus and calcium, were measured using automated and standardized methods. The eGFR was estimated using the CKD Epidemiology Collaboration equation.

Outcome ascertainment

The primary outcome of interest was all-cause mortality, and the secondary endpoints were the composite of MACE and individual components of MACE. All-cause mortality was defined as death from any cause. MACE were defined as a composite of cardiovascular death and nonfatal cardiovascular events. Cardiovascular events were defined as any of the following: heart failure requiring hospitalization, acute coronary syndrome (unstable angina, myocardial infarction or coronary intervention/surgery), stroke, aortic disease or peripheral artery disease requiring surgery or hospitalization. Cardiovascular death was defined as death due to cardiovascular events or sudden cardiogenic death. The follow-up time was calculated as the time from the start of dialysis to the occurrence of study outcomes, withdrawal, loss to follow-up or the end of follow-up (30 September 2016), whichever occurred first. The events and the date of occurrence were thoroughly recorded and collected from the medical records.

Statistical analysis

Continuous data were presented as the means (standard deviation) for variables with a normal distribution or as medians (interquartile range) for variables with a non-normal distribution. Categorical variables were reported as the number with the corresponding percentage. To analyse the differences among the study groups, the unpaired t-test, the chi-square test and the Kruskal–Wallis test were used, as appropriate. Among the 1459 selected patients, most variables had complete data or a

Table 1: Baseline characteristics of incident dialysis patients overall and stratified by sex.

Characteristics	Total ($n = 1459$)	Female ($n = 477$)	Male ($n = 982$)	P-value
Demographic data				
Age (years)	67.46 (13.07)	68.06 (12.95)	67.17 (13.12)	.220
BMI (kg/m^2)	23.51 (4.40)	23.25 (5.23)	23.64 (3.93)	.112
SBP (mmHg)	152 (26)	150 (26)	152 (26)	.191
Comorbidities (n, %)				
CAD	242 (16.6)	55 (11.6)	187 (19.1)	<.001
Stroke	231 (15.8)	60 (12.6)	171 (17.4)	.018
Diabetes	786 (53.9)	239 (50.1)	547 (55.7)	.044
Cancer	88 (6.0)	23 (4.8)	65 (6.6)	.176
Atrial fibrillation	86 (5.9)	25 (5.3)	61 (6.2)	.458
Aortic calcification	565 (38.7)	199 (41.7)	366 (37.3)	.102
Medication (n, %)				
ACEIs/ARBs	886 (60.8)	275 (57.7)	611 (62.3)	.085
VDRA	403 (27.6)	140 (29.4)	263 (26.8)	.303
Phosphate binders	515 (35.3)	175 (36.7)	340 (34.6)	.439
Steroid	76 (5.3)	28 (5.9)	48 (4.9)	.425
Laboratory parameters				
Haemoglobin (g/dL)	9.37 (1.56)	9.32 (1.62)	9.40 (1.51)	.347
Albumin (g/dL)	3.20 (0.60)	3.21 (0.621)	3.19 (0.58)	.592
Calcium (mg/dL)	8.61 (1.06)	8.71 (1.12)	8.56 (1.02)	.014
Phosphorus (mg/dL)	6.36 (1.88)	6.39 (1.88)	6.34 (1.89)	.649
Intact PTH (pg/mL)	293 (190–439)	336 (199–563)	280 (187–403)	<.001
eGFR (mL/min/1.73 m^2)	5.04 (4.03–6.08)	4.32 (3.61–5.47)	5.38 (4.35–6.34)	<.001
CRP (mg/dL)	0.26 (0.09–1.14)	0.20 (0.06–0.95)	0.30 (0.10–1.24)	.001
Potassium (mmol/L)	4.55 (0.83)	4.45 (0.84)	4.59 (0.82)	.002
BI	100 (95–100)	100 (85–100)	100 (95–100)	.003
Haemodialysis (n, %)	1346 (92.9)	445 (93.7)	901 (92.5)	.412

Data are counts (percentages), means (standard deviation) or median (1st quartile and 3rd quartile) as appropriate.
ACEIs: angiotensin-converting enzyme inhibitors; ARBs: angiotensin II type 1 receptor blockers.

missing data rate <1%, with the exception of iPTH and CRP, which had 11.7% and 6.8% missing data, respectively. In order to minimize the amount of missing data for covariates, iPTH and CRP were converted from continuous to categorical variables using cut-off values of 300 pg/mL and 0.5 mg/dL, and missing data were assigned to a separate category. The incidence rates for each outcome (all-cause mortality and MACE) were calculated per 100 person-years, and the differences between groups were compared with a log-rank test. The Cox proportional hazards models were employed to analyse the associations between exposure factors and each outcome, with adjustment for confounders. Potential confounders were selected based on their association with outcomes or changes >10% in effect estimates. The crude model represents the hazard ratio (HR) with 95% confidence intervals (CIs) without adjustment. Model 1 was adjusted for age and BMI; Model 2 further included comorbid conditions and systolic blood pressure (SBP) levels; Model 3 was adjusted for the variables in Model 2, plus the BI and laboratory parameters; Model 4 (fully adjusted model) further included the use of medications (RASi, phosphate binders, VDRA and steroid) and dialysis modality. Proportional hazards assumptions were tested using Schoenfeld residuals.

Moreover, we examined the effect modification of sex on the primary outcome in prespecified subgroups by age (<65 and ≥65 years), SBP (<155 and ≥155 mmHg), presence of diabetes mellitus and AC. For each subgroup analysis, multiplicative interaction terms were created to test for effect modification. In addition, five sensitivity analyses were conducted in patients receiving haemodialysis and without a history of CVD, previous stroke, previous atrial fibrillation or cancer. Furthermore, receiver operating characteristic (ROC) curve analyses were performed to predict AC in relation to study outcomes. The areas under the ROC curves (AUCs) were calculated by using the DeLong method.

All the statistical analyses were conducted using IBM SPSS Statistics version 21.0 (IBM Corp., Armonk, NY, USA) and MedCal 15.2.1 (MedCalc Software, Ostend, Belgium). A two-tailed $P < .05$ value was considered to indicate statistical significance.

RESULTS

Baseline characteristics

Table 1 presents the baseline demographic, clinical and laboratory details of the cohort by sex. Among the 1459 incident dialysis patients, the mean age was 67.5 years, and 1346 (92.9%) received haemodialysis. The present study included 477 (32.7%) female and 982 (67.3%) male patients. Female patients had lower levels of eGFR, potassium and CRP, and lower BI, but higher levels of serum calcium and iPTH (all $P < .05$). Moreover, compared with males, a lower proportion of females had prevalent coronary artery disease (11.6% vs 19.1%), stroke (12.6% vs 17.4%) and diabetes (50.1% vs 55.7%) at study entry, whereas medication usage of RASi, phosphate binders and VDRA were equally likely in both sexes. No sex differences were found in the mean age, BMI, SBP, haemoglobin or albumin levels at baseline (all $P > .05$). In addition, at baseline, 199 (41.7%) female and 366 (37.3%) male patients were diagnosed with AC separately, but the difference was not statistically significant ($P = .102$, Table 1).

Table 2: Incidence rate for each outcome in overall and stratified by sex in incident dialysis patients.

Groups	No. of events (%)	Person-years	Incidence density (per 100 person-years)	P-value for log rank test
All-cause mortality				.001
Overall	362 (24.8)	4814.38	7.52 (6.76–8.34)	
Female	93 (19.5)	1641.83	5.66 (4.57–6.94)	
Male	269 (27.4)	3172.55	8.48 (7.50–9.56)	
MACE				.001
Overall	477 (32.7)	4080.14	11.69 (10.67–12.79)	
Female	135 (28.3)	1455.17	9.28 (7.78–10.98)	
Male	342 (34.8)	2624.97	13.03 (11.68–14.49)	

Table 3: HRs of sex (female vs male) for each outcomes in overall incident dialysis patients.

	All-cause death		MACE	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Unadjusted model	0.66 (0.53–0.84)	.001	0.71 (0.58–0.87)	.001
Model 1: female vs male	0.61 (0.48–0.77)	<.001	0.68 (0.56–0.83)	<.001
Model 2: female vs male	0.63 (0.49–0.80)	<.001	0.75 (0.61–0.92)	.006
Model 3: female vs male	0.60 (0.47–0.78)	<.001	0.76 (0.61–0.96)	.015
Model 4: female vs male	0.61 (0.47–0.79)	<.001	0.74 (0.60–0.93)	.008

The reference group was the male patients.
Model 1 was adjusted for demographic data (age and BMI).
Model 2 further included comorbid conditions (CAD, diabetes, malignancy, stroke, atrial fibrillation and AC) and SBP levels.
Model 3 further included laboratory parameters (eGFR, calcium, phosphorus, iPTH, potassium, albumin, haemoglobin and CRP) and BI.
Model 4 further included medication usage (ACEIs/ARBs, VDRA, steroid and phosphate binder) and dialysis modality.
CAD: coronary artery disease; ACEIs: angiotensin-converting enzyme inhibitors; ARBs: angiotensin II type 1 receptor blockers.

Survival analyses for all-cause mortality in dialysis patients

During 4814 person-years of follow-up (median follow-up time of 3.55 years), 269 male and 93 female patients died. The crude incidence rate per 100 person-years was 7.52 (95% CI 6.76–8.34) overall, higher in male than in female patients (8.48 vs 5.66; $P < .001$, Table 2). Table 3 shows the associations between sex and clinical outcomes in the proportional hazard models. In the unadjusted Cox regression analysis, females had up to 35% lower risk of all-cause mortality than males did. The risk estimates in female patients remained consistent after progressive adjustment for demographics and clinical comorbid conditions (HR 0.63, 95% CI 0.49–0.80; $P < .001$) as well as laboratory parameters (HR 0.60, 95% CI 0.47–0.78; $P < .001$), and medication usage did not modify the significantly lower risk in females (HR 0.61, 95% CI 0.47–0.79; $P < .001$).

Survival analyses for cardiovascular events in dialysis patients

We further analysed the associations of sex with the prespecified secondary outcomes. MACE occurred in 477 (32.7%) patients, which corresponded to a crude incidence rate of 11.69 (95% CI, 10.67–12.79) per 100 person-years, and the rate was consistently higher in males than in females (13.03 for males vs 9.28 for females; $P = .001$, Table 2). In line with the results of the primary outcome analysis, female dialysis patients experienced a lower risk of MACE than male patients, and the estimates were similar in the unadjusted model and multivariable models adjusted for incremental numbers of covariates (all $P < .05$, Table 3).

Sensitivity and subgroup analysis for all-cause mortality in dialysis patients

To validate our findings, we performed five sensitivity analyses among patients without a history of CVD, without previous stroke, without previous atrial fibrillation, without cancer and receiving haemodialysis. In line with the primary analysis, these results showed that female sex was still associated with a decreased incidence of all-cause mortality (Supplementary data, Fig. S2). Furthermore, subgroup analyses stratified by diabetes mellitus status, age and SBP levels demonstrated similar results (Supplementary data, Fig. S2).

AC changes the female survival advantage in dialysis patients

To obtain further insights into the association between sex and all-cause mortality, we assessed the interaction of sex with each covariate with an interaction term in the fully adjusted model. This analysis allowed us to identify a significant interaction between sex and AC ($P = .044$). We further compared the risk between males and females in patients with and without AC. As compared with male patients, females without AC had a 55% lower risk of all-cause mortality (HR 0.45, 95% CI 0.29–0.69; $P < .001$), a 33% lower risk of MACE (HR 0.67, 95% CI 0.49–0.93; $P = .015$), a 57% lower risk of cardiovascular mortality (HR 0.43, 95% CI 0.22–0.85; $P = .015$) and a 35% lower risk of nonfatal cardiovascular events (HR 0.65, 95% CI 0.48–0.90; $P = .009$). However, once AC was present, these survival advantages in females disappeared (Fig. 1 and Supplementary data, Table S1). In addition, we performed analyses for all-cause mortality among those

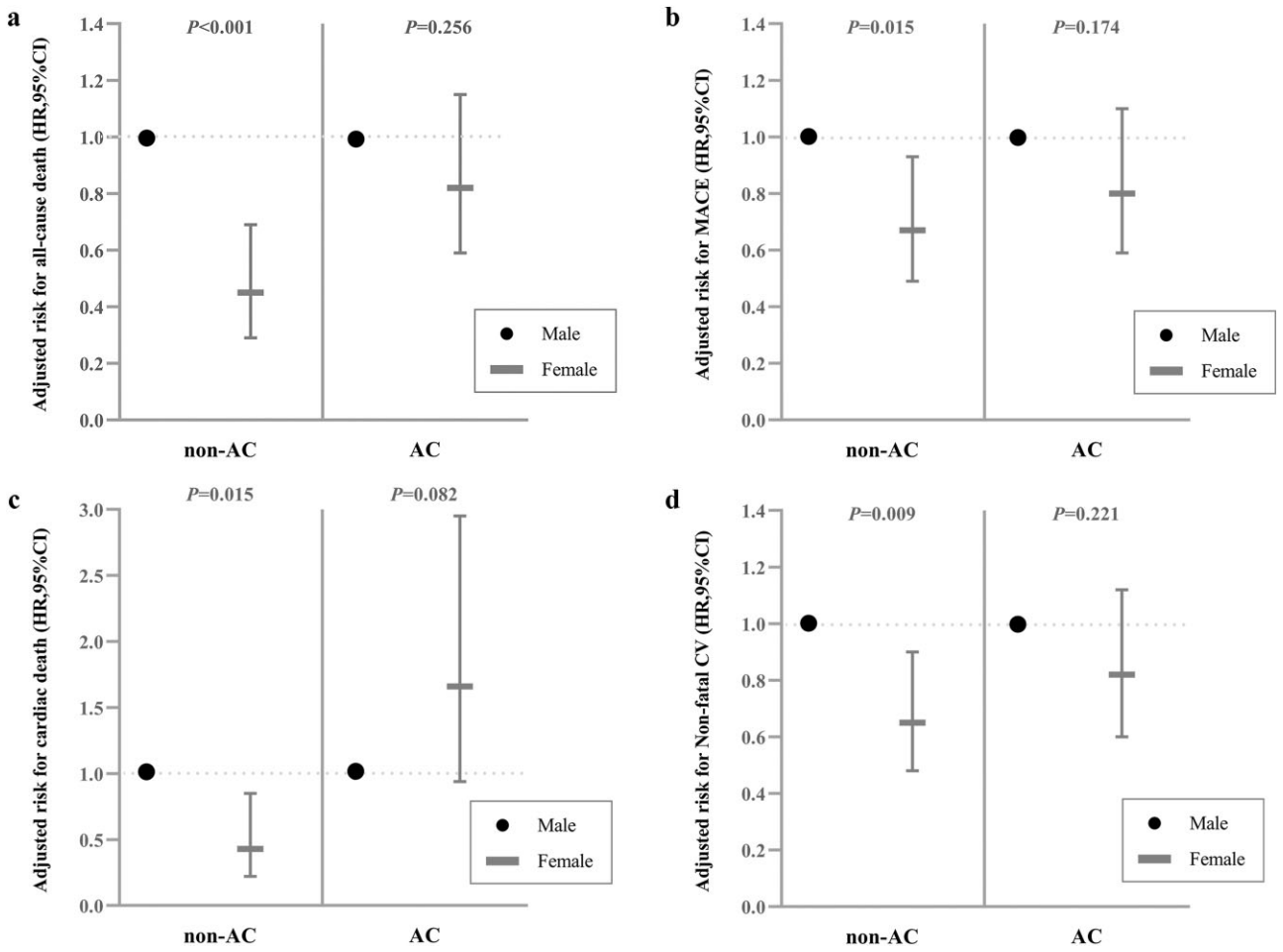

Figure 1: The fully adjusted HRs sex (female vs male) for all-cause mortality (**a**), MACE (**b**), cardiovascular death (**c**) and nonfatal cardiovascular events (**d**) stratified by AC status in incident dialysis patients.

with and without diabetes separately and obtained similar results (Supplementary data, Fig. S3).

For the significant interaction results in the regression analysis, we next subdivided the cohort into four categories based on the presence of AC and sex. As shown in Supplementary data, Table S2, females with AC had multiple cardiovascular risk factors (e.g. old age, history of coronary artery disease and atrial fibrillation, etc.) as compared with those without AC (all $P < .05$). When comparing females and males with AC, we found that females had higher iPTH levels and VDRA medication use but lower BI and eGFR levels. No sex differences were detected with regard to age, BMI, SBP, nutritional markers, prevalence of diabetes, atrial fibrillation or use of phosphate binders or RASi in each subgroup with or without AC (all $P > .05$; Supplementary data, Table S2).

The crude incidence rates of the primary and secondary outcomes were greater in patients with AC, with a steeper increase observed in females (Supplementary data, Table S3). In the crude Kaplan–Meier plots, the presence of AC at dialysis initiation was significantly associated with the progressive risk of all-cause mortality and MACE in both sexes (P-value for log-rank test <.001; Fig. 2). However, after sequential multivariable adjustment, the results of the Cox regression revealed that AC status did not have a significant effect on the adverse clinical outcomes in males (Table 4, all $P < .05$). In contrast, in female patients, the risk of all-cause mortality and MACE were significantly higher in those with AC than in those without AC (Table 4, all $P < .05$).

Finally, we also separately evaluated the prognostic value of AC for clinical outcomes in the male and female patients. For all-cause mortality, the AUCs of AC were 0.67 (95% CI 0.62–0.71) and 0.59 (95% CI 0.56–0.62) in female and male dialysis patients, and the difference was significant (D = 0.077, $P = .017$; Fig. 3). The AUC for MACE was also greater in female patients but did not reach strict statistical significance due to low power (0.60 vs 0.56, $P = .189$; Fig. 3).

DISCUSSION

In this longitudinal cohort of incident dialysis (haemodialysis and peritoneal dialysis) patients, female patients with renal failure experienced a 39% lower risk for all-cause mortality and a 26% lower risk for MACE as compared with male patients, after adjustment for demographics, clinical covariates and current medication usage. Notably, this survival and cardiovascular risk advantage in female patients disappeared once AC was present at the time of dialysis initiation.

Researchers have consistently reported that in the general population, women consistently have a longer life expectancy than men do [8, 9]. However, the literature on sex differences in clinical outcomes among dialysis patients yielded

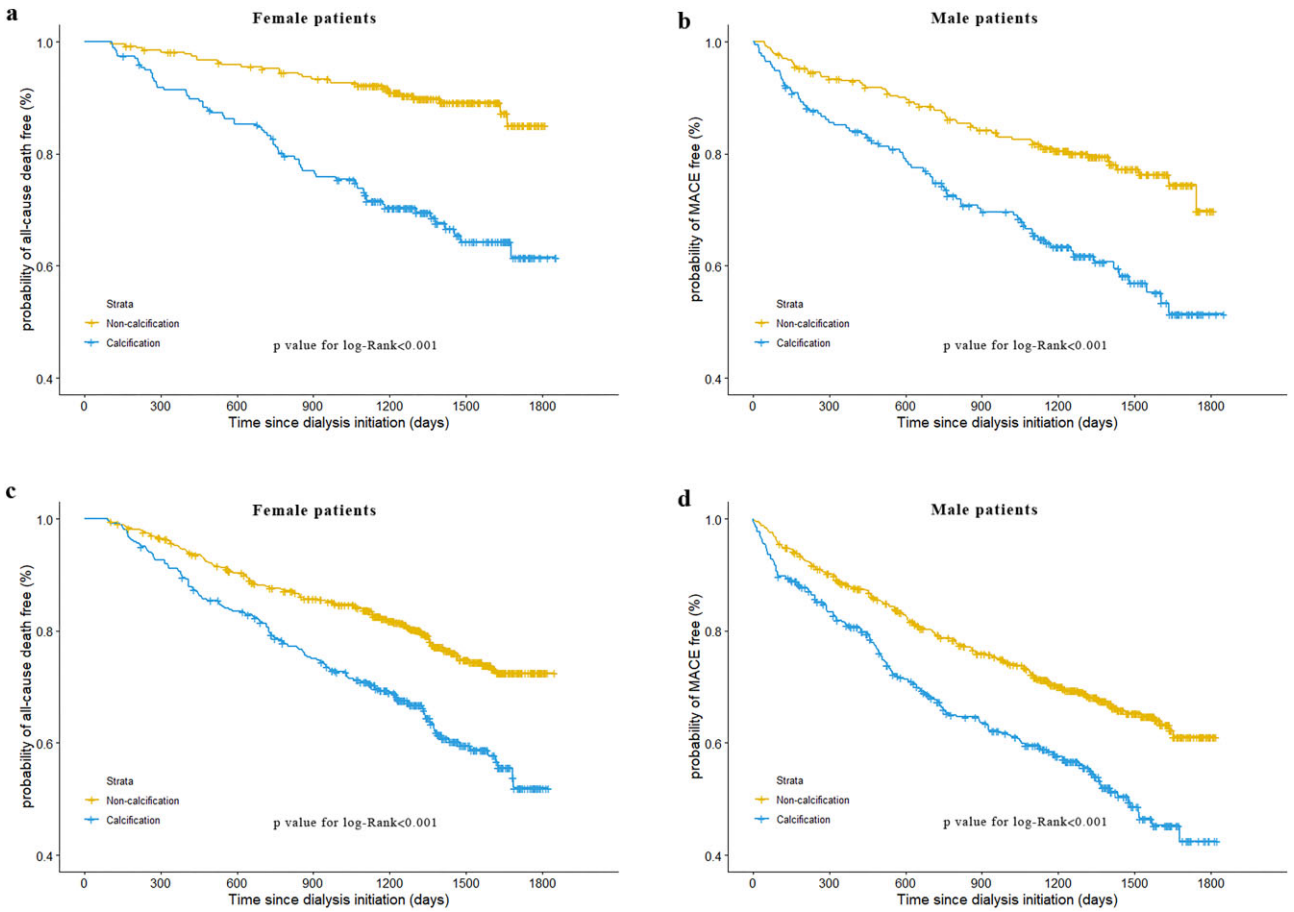

Figure 2: Kaplan–Meier curves for the association between AC and all-cause mortality (**a**, **b**) and MACE (**c**, **d**) in incident dialysis patients, with separate curves for females and males.

Table 4: HRs of AC for each outcomes in female and male dialysis patients.

	Female ($N = 477$)		Male ($N = 982$)	
	All-cause death	MACE	All-cause death	MACE
Unadjusted model	3.53 (2.27–5.47), $P < .001$	2.13 (1.52–3.00), $P < .001$	1.87 (1.47–2.38), $P < .001$	1.67 (1.35–2.06), $P < .001$
Model 1: AC vs non-AC	1.89 (1.18–3.04), $P = .009$	1.85 (1.26–2.71), $P = .002$	1.10 (0.86–1.42), $P = .454$	1.33 (1.05–1.67), $P = .017$
Model 2: AC vs non-AC	1.60 (0.99–2.60), $P = .058$	1.50 (1.02–2.22), $P = .041$	1.06 (0.82–1.38), $P = .652$	1.17 (0.92–1.48), $P = .201$
Model 3: AC vs non-AC	1.70 (1.03–2.81), $P = .037$	1.90 (1.26–2.87), $P = .002$	1.17 (0.90–1.52), $P = .248$	1.16 (0.91–1.48), $P = .228$
Model 4: AC vs non-AC	1.77 (1.06–2.95), $P = .029$	1.89 (1.25–2.88), $P = .003$	1.24 (0.95–1.62), $P = .122$	1.23 (0.96–1.58), $P = .098$

The reference group was the patients without AC.
Model 1 was adjusted for demographic data (age and BMI).
Model 2 further included comorbid conditions (CAD, diabetes, malignancy, stroke and atrial fibrillation) and SBP levels.
Model 3 further included laboratory parameters (eGFR, calcium, phosphorus, iPTH, potassium, albumin, hemoglobin and CRP) and BI.
Model 4 further included medication usage (ACEIs/ARBs, VDRA, steroid and phosphate binder) and dialysis modality.
CAD: coronary artery disease; ACEIs: angiotensin-converting enzyme inhibitors; ARBs: angiotensin II type 1 receptor blockers.

inconsistent conclusions. The findings of our present study align with those of a recent report from the Q-cohort study [23], which indicated a 50% reduced risk of all-cause mortality in female compared with male dialysis patients. The results of the Q-cohort study were obtained in patients on maintenance haemodialysis with a median dialysis duration of 5 years [23]. Consequently, our data extend the observation in prevalent haemodialysis patients to incident dialysis patients. In contrast, another recent study from the Australia and New Zealand Dialysis and Transplant (ANZDATA) Registry, which included 50 000

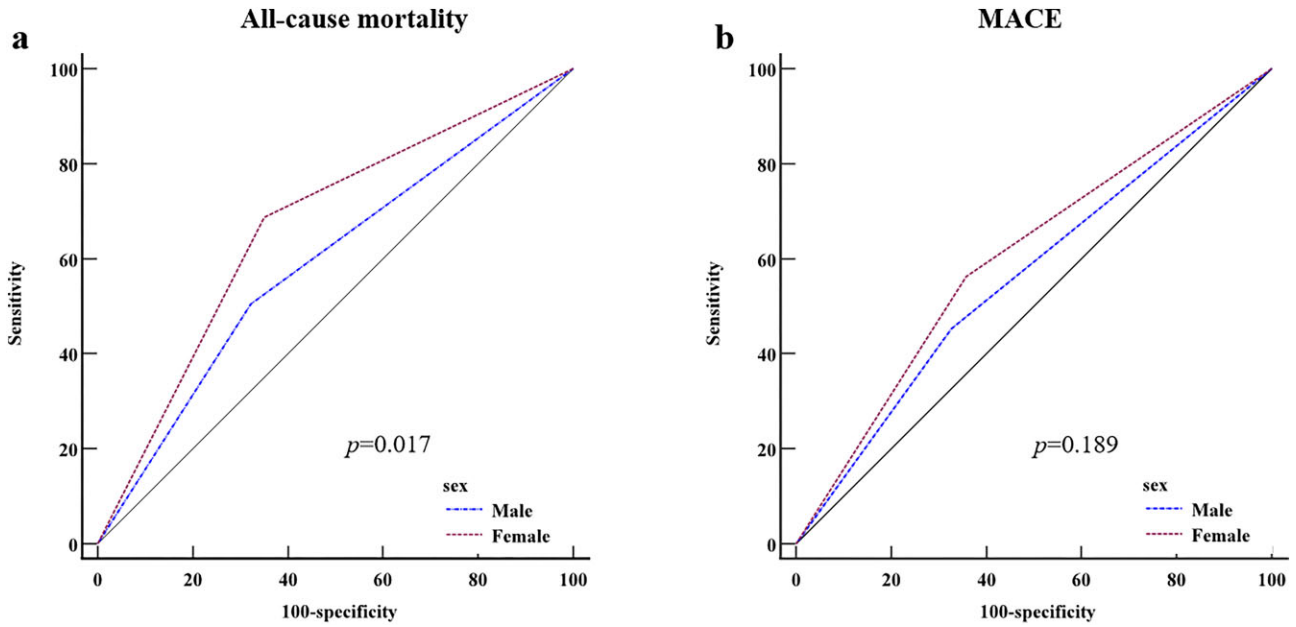

Figure 3: The predictive performance of AC for all-cause mortality (**a**) and MACE (**b**) between females and males.

incident dialysis patients, reported opposite results by showing that female dialysis patients exhibited slightly higher all-cause mortality risk than males did (adjusted HR 1.08, 95% CI 1.05–1.11) in the first 5 years after dialysis initiation [11]. The discrepancy between these studies might be due to the heterogeneity in the study design, patient demographics, sample size, study period and ethnicity. It is noteworthy that patients in the ANZDATA study had a higher all-cause mortality rate than our cohort (22 vs 7.85 per 100 person-years), which was also higher than the 10.6 per 100 person-years reported in the Dialysis Outcome and Practice Patterns Study (DOPPS) [24]. In another nationwide cohort study conducted in Korea, with similar mortality rate to our study (6.4/100 person-years in females and 8.3/100 person-years in males), the authors reached similar conclusions that the survival advantage of females in the general population was maintained in dialysis patients [25]. In addition, some important variables, such as SBP, coronary calcification and inflammatory markers, were not adjusted in the ANZDATA study due to a lack of available data, which might have substantially modified the association between sex and mortality, as the authors mentioned in their discussion section.

Cardiovascular disease is the leading cause of death in patients with CKD, accounting for approximately one half of all deaths [26]. Our study showed that female dialysis patients had a reduced risk of the composite of CVD death and nonfatal CVD events. This finding is in accordance with the results of the ANZDATA registry study, which reported a 10% lower risk of CVD mortality in female compared with male patients on dialysis, with this survival advantage increasing as the dialysis time was prolonged [11]. Similarly, a large systematic review and meta-analysis of 48 studies involving 99 822 (51 069 male and 48 753 female) patients with kidney failure demonstrated that male patients exhibited a 13% elevated risk of CVD mortality, with similar effect estimates found in haemodialysis patients and non-dialysis-dependent CKD patients [27].

Previous studies have evaluated the potential influence of AC and sex on clinical outcomes in patients without CKD. A comprehensive database analysis of 63 215 asymptomatic patients revealed that the presence of AC was associated with a 1.3-fold increased risk of CVD in females compared with males [17]. Similarly, in a prospective study of 4503 adults with diabetes, Wong *et al.* [28] demonstrated that over a median follow-up of 11.5 years, coronary artery calcification was a stronger risk factor for CVD and total mortality in females than in males. Moreover, the results of the sCORE COVID-19 registry study, which included 1683 patients with confirmed COVID-19 infection, showed that females were less hospitalized than males and had more favourable outcomes; however, the protective effect of sex was found to be diminished in female individuals with coronary calcification [18]. To the best of our knowledge, our study is the first to demonstrate that the female advantage in survival protection is lost in dialysis patients with AC, and the adverse impact of AC on mortality and MACE is higher for females than for males. A series of analyses supported these findings, including: (i) a significant interaction between AC and sex for all-cause mortality (P for interaction $<.05$); (ii) in the subgroup of patients with AC, no sex difference in all-cause mortality or MACE was found (Fig. 1); (iii) when non-AC was used as a reference, the incidence of adverse outcomes was greater among those with AC in both sexes, but the increased risk was evident only in female dialysis patients (Table 4); and (iv) the AUCs of AC in predicting all-cause mortality and MACE were higher in female than in male dialysis patients (Fig. 3). The findings of this study indicated the need for greater awareness of AC burden in female dialysis patients, which is crucial for the development of sex-specific risk assessment strategies and therapeutic interventions aimed at addressing CKD management in the context of CVD prevention.

AC represents a significant burden in patients with CKD, with a prevalence of 37% in males and 42% in females in our cohort. Although we did not observe a significant sex difference in most age groups, females aged 65 years were more likely to have AC than males of similar age (Supplementary data, Fig. S4). This might be related to the dramatic drop in oestrogen levels. A number of animal studies have provided evidence that

oestrogens prevent AC by reversing transforming growth factor activity and suppressing local inflammatory signalling [29]. Nevertheless, the safety and efficacy of oestrogen supplementation in reducing AC and improving patient prognosis remain controversial [30]. In addition, our study showed that female dialysis patients with AC exhibited the highest proportion of physical frailty, as defined by a BI score <100, which might partly explain the higher risk of death and cardiovascular events observed in this group. Moreover, physical frailty has been shown to worsen cardiovascular outcomes and mortality in patients with CKD [31, 32], with corresponding improvements in outcomes observed among those who are more physically active [33]. It is noteworthy that a recent study from a large US cohort demonstrated that, when given the same dose of physical activity, females derived greater benefits than males did [34]. These findings suggest that encouraging patients to participate in regular leisure-time activities may be an effective strategy for improving their prognosis, especially for female patients with AC. In addition, the relative excess of survival and CVD risk associated with AC in women might be the result of a treatment bias in favour of men [35, 36]. As observed in our study, a slightly higher proportion of men received RASi treatment (62.3% of males vs 57.7% of females, Table 1). Moreover, several studies based on the general population–based studies have found that AC offers incremental value over traditional risk scoring systems for cardiovascular risk stratification [37], and statin initiation [38] and maintenance [39] in primary prevention, particularly in females; thus future studies are warranted to examine this association in patients with CKD.

Some limitations should be noted. First, after we stratified by sex and AC, the sample size of each group was relatively small, and future studies with larger sample sizes are urgently required. Second, our study cohort consisted entirely of Asians, and that the results should therefore be generalized with caution to other ethnic groups. Third, since there is still no consensus on the optimal timing of dialysis initiation for patients with end-stage kidney disease, the time was comprehensively determined by attending physicians in the present study, and there was a lead-time bias between men and women patients. However, we thoroughly adjusted for the eGFR levels at dialysis initiation. In addition, although recruiting incident rather than prevalent dialysis cases can largely mitigate bias favouring surviving patients, we must acknowledge that potential informative censoring bias still exists. For example, our decision to exclude patients who withdrew from maintenance dialysis may introduce bias into our results, as these patients likely have extremely poor outcomes, particularly in terms of mortality. Finally, due to the inherent nature of observational studies, potential biases are inevitable. Although we have adjusted as many important variables as possible for analysis, residual confounders (such as the use of statin and other cardioprotective drugs, sex hormone levels, and the severity of AC) may exist and need to be investigated in the future.

In summary, among patients with renal failure who initiated dialysis, females exhibited a reduced risk of all-cause death and cardiovascular events compared with males, regardless of dialysis modality. The presence of AC at the start of dialysis may modify the association between sex and clinical outcomes. AC is associated with an increased risk in females versus males, and the survival and cardiovascular risk advantages of female dialysis patients are markedly diminished in patients with AC. These findings support the need for greater awareness of the AC burden in female dialysis patients.

SUPPLEMENTARY DATA

Supplementary data are available at *Clinical Kidney Journal* online.

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AUTHORS' CONTRIBUTIONS

All authors contributed significantly. L.M.W., Z.T.L. and X.Z.: researched the data, conducted the analysis, and drafted and revised the manuscript. L.M.W. and H.L.J.: contributed to the study design and method, and analysed and interpreted the data. M.W., H.L., M.Y.Y., L.H.H. and Z.M.G.: helped with the statistical analyses and reviewed the database. All the authors have read and approved the final version of this manuscript.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analysed in this study. The dataset supporting the conclusions of this article is available in the https://figshare.com/articles/dataset/9720836.

CONFLICT OF INTEREST STATEMENT

The authors have declared no conflicts of interest.

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