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Original Paper

Dose-Response Between Cardiovascular Risk Factors and Cardiovascular Mortality Among Incident Peritoneal Dialysis Patients

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Key Words
Cardiovascular diseases • Mortality • Peritoneal dialysis • Risk factor

Abstract
Background/Aims: Traditional cardiovascular (CV) risk factors (RFs) and their management targets may not be applicable to specific medical subpopulations, particularly dialysis patients. This study aimed to evaluate the dose-response association between measurements of RFs, cardiovascular mortality, and potential metabolic targets among Chinese patients initializing peritoneal dialysis (PD). ***Methods:*** Risk-set sampling was applied to two population based 1:10 case-control studies of incident PD patients, matched by age, sex and the year of initialisation of PD: a main sample (204 cases and 2,040 controls) and a replication sample (81 cases and 810 controls). The dose-response association between continuous measurements of CV RFs (blood pressure, fasting glucose, body mass index, total cholesterol, phosphate and ejection fraction) at baseline and the 2-year CV mortality were analyzed using conditional Logistic regression. The final threshold was chosen based upon a significant break in the regression coefficients and achievement of the minimum Bayesian information criterion (BIC). ***Results:*** A linear relationship was identified between fasting glucose and CV mortality. Non-linear associations between other measurements and CV mortality suggested potential metabolic treatment intensification thresholds as <145/92mmHg for blood pressure, <1.70mmol/L for phosphate, 24 kg/m^2 for body mass index, 4.6mmol/L for total cholesterol, and >60% for ejection fraction respectively. ***Conclusion:*** Our findings highlight the potential importance of more intensive glucose management, anti-hypertensive treatment and dietary management

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among PD patients. We recommend that the clinical relevance of these epidemiological associations be tested using randomized controlled trials of multifaceted interventions.

Introduction

Chronic kidney disease (CKD) has become a worldwide heath problem [1]. In particular, end-stage renal disease (ESRD) triggers premature mortality and is a substantial health economic burden [2]. It has been estimated that more than 10.8% of Chinese adults (around 130 million) have CKD with dialysis needed at some point in their lives [3]. The Chinese medical insurance scheme has now increased its coverage, making dialysis, especially peritoneal dialysis (PD), more affordable among Chinese patients with ESRD [4]. The leading cause of mortality among people accepting PD is cardiovascular disease (CVD) [5]. CVD risk factors in the general population have been well-investigated, and include hypertension, obesity, dyslipidaemia, diabetes, and smoking [6]. However, it has become increasingly clear that these CVD risk factors must be interpreted in the context of any comorbidities [7]. For example, hyperphosphatemia is very common and often poorly controlled among patients with ESRD, but is less common in the general population [8].

Therefore, findings from the general population may not be applicable to specific medical subpopulations, particularly dialysis patients [5]. Previous studies have examined the association between individual CVD risk factors, especially hypertension, and all-cause mortality in patients with prevalent haemodialysis or PD [7, 9] . However, there have been no studies to investigate the association between all of the well-established CVD risk factors and CVD mortality among patients initialising PD. As a result, the potential metabolic targets for such CVD risk factors remain uncertain. This aim of this study was to estimate potential thresholds for intensifying clinical management by examining the dose-response association between continuous measurements of all well-established CVD risk factors (modifiable and non-modifiable) and CVD mortality among patients undergoing PD in the Henan Peritoneal Dialysis Registry (HPDR).

Materials and Methods

Data Setting

Briefly, the HPDR is operated under the auspices of the Department of Nephrology, the First Affiliated Hospital of Zhengzhou University and provides an independent audit and analysis of renal care in Henan, China. During the study period, information was prospectively collected electronically from all renal units across Henan. Data arriving at the HPDR are subjected to an algorithm which identifies suspicious values, which are then further verified and corrected where necessary by contacting the renal unit.

Study population

This study was designed as two population based case-control samples: a main study and a replication study. Both cases and controls used in the main study (attending the First Affiliated Hospital of Zhengzhou University) and those in the replication study (attending the other renal clinics across the province) were derived from adults aged more than 18 years, commencing PD between 2007-2014. Ethics approval was granted by the Clinical Research Ethics Committee of the First Affiliated Hospital of Zhengzhou University.

Case definition

Cases were defined as deceased patients, on the HPDR, with CVD as the cause of death based on the diagnosis on death certificate. Patients who died of any cause, underwent transplant or whose kidney function recovered within 90 days after initialisation of dialysis were excluded (n=16) to avoid the reverse causal association between risk factors and early outcome [10]. We considered the death date to be the index date for cases.

Control selection

We selected 10 population controls for each case within the main study and the replication study, matched for age, sex and the year of initialisation of PD. We selected controls using risk-set sampling. Controls were assigned an index date to that of corresponding cases.

Exposure Definition

Systolic blood pressure (SBP), diastolic blood pressure (DBP), body mass index (BMI), total cholesterol as the measurements of well-established risk factors were selected as exposures in our study. Hyperphosphatemia is a particularly important CVD risk factor among patients with kidney disease [11] and is routinely recorded among patients on dialysis [12]. Therefore, phosphorus as the measurement was selected as an exposure in our study. Although not a CVD risk factor, ejection fraction (EF) as a prognostic factor was included in the analysis because of its likely important predictive value of CVD mortality. All exposures were measured at the beginning of PD by standard methods, reviewed by 2 clinicians and recorded in HPDR.

Covariates

We also obtained data on other CVD risk factors (as listed in Table 1), which can be associated with CVD risk factors to allow adjustment for confounding. These data were measured at the time when patients started PD treatment.

Statistical analysis

Conditional logistic regression models were applied to conduct the comparison within the matched risk set for categorical variables, and mix-effect models were used for continuous variables with adjustment for age, gender and year of initialisation of PD treatment. Because we used risk-set sampling strategy to select controls, the odds ratios estimated the incidence rate ratios [13].

Missing information was as follows: BMI (10.51%), phosphate (10.23%), albumin (9.92%), total protein (12.75%), total cholesterol (14.53%), low density lipoprotein (14.58%), high density lipoprotein (14.52%), triglyceride (14.52%), fasting glucose (15.26%), SBP (2.26%), and DBP (2.23%). We used multiple imputation to replace missing values by using a chained equation approach based on all candidate predictors. We created 15 imputed datasets for missing variables that were then combined across all datasets by using Rubin's rule to obtain estimations.

The associations between the continuous measurements and the risk of CVD mortality were estimated using a linear model, restricted cubic spline models with 3-5 equally spaced knots determined for the levels of these continuous exposures, and a quadratic spline model. The restricted cubic spline model with 3 equally spaced knots was chosen as the best –fit model for the dose-response curves because of its minimum Bayesian information criterion (BIC) compared with other models. A linear test was used in the restricted cubic spline model to test the linearity of the relationship. The break-point test [14] was carried out to target the potential thresholds (P_5 to P_{95} of measurements) by incorporating the piecewise term into the cubic spline model. The threshold with a significant break in the regression coefficients and achieving the minimum BIC was chosen as the final threshold. The 95% CI of the threshold was obtained from 1000 bootstrap samples.

Two sets of sensitivity analyses were implemented to observe the association between continuous measures and risk of cardiovascular mortality. First, all analyses were carried out in the continuous measurement data-rich range (covering > 95% people). Second, using a 'rule-out' approach [15], we estimated how strongly a single unmeasured binary confounder would need to be associated with continuous and cardiovascular mortality to fully explain our findings [15].

All analyses were performed using STATA (STATA/MP 15.0 StataCorp, College Station, TX, USA). All P values were calculated using two-tailed tests and a P value < 0.05 was taken to indicate statistical significance.

Table 1. Characteristics of cases with cardiovascular mortality and controls from patients with peritoneal dialysis in Henan Peritoneal Dialysis Registry dataset, 2007-2015. Categorical variables present as count (percentage) and continuous variables present as median (inter-quartile range). -* indicates age and gender are matched between case and control and there is no need to test the difference

Main Dataset	Case (n=204)	Control (n=2,040)	P-value
Age, years	63 (47 to 74)	63 (46 to 74)	-*
Female gender, n (%)	87 (42.7)	870 (42.6)	-*
History of cardiovascular diseases, n (%)	95 (46.6)	981 (48.1)	0.003
History of diabetes mellitus, n (%)	70 (34.3)	597 (29.3)	<0.0001
Primary Glomerular Disease, n (%)	69 (34.3)	558 (27.4)	<0.0001
Taking antihypertensive treatment, n (%)	178 (87.4)	1860 (91.2)	<0.0001
Taking lipid -lowering treatment, n (%)	77 (37.6)	842 (41.3)	<0.0001
Taking glucose -lowering treatment, n (%)	56 (27.4)	690 (33.8)	<0.0001
Haemoglobin, g/L	90.7 (79.0 to 102.0)	95.0 (81.0 to 108.0)	<0.0001
Packed cell volume	0.7 (0.3 to 26.4)	18.4 (0.3 to 29.1)	<0.0001
Reticulocyte, %	54.2 (19.8 to 85.0)	36.4 (4.4 to 64.2)	<0.0001
Phosphate, mg/dl	1.7 (1.4 to 2.1)	1.6 (1.3 to 2.0)	<0.0001
Albumin, g/L	30.6 (26.0 to 34.3)	33.0 (28.8 to 36.9)	<0.0001
Total iron binding capacity , μmol/L	52.0 (32.3 to 68.4)	50.0 (33.2 to 66.7)	<0.0001
FeTIBC, mmol/L	23.1 (5.6 to 46.6)	29.2 (16.2 to 59.6)	<0.0001
Creatinine, μmol/L	806.9 (596.0 to 976.0)	731.2 (562.0 to 932.0)	<0.0001
BUN, mmol/L	20.3 (17.0 to 26.0)	19.9 (15.7 to 24.5)	<0.0001
estimated Glomerular Filtration rate, mL/min/1.73 m^2	5.7 (4.5 to 7.5)	6.0 (4.5 to 8.0)	<0.0001
Calcium, mmol/l	1.8 (1.6 to 2.2)	2.2 (2.0 to 2.4)	<0.0001
Transferrin, mg/dl	266.8 (105.0 to 579.2)	258.5 (100.0 to 521.3)	0.0007
Total protein, g/L	55.7 (50.3 to 59.4)	58.0 (52.0 to 63.0)	<0.0001
Prealbumin, mg/L	273.0 (171.2 to 375.5)	273.5 (182.0 to 364.0)	0.7973
Total Cholesterol, mmol/L	4.4 (3.5 to 5.2)	4.0 (3.7 to 5.3)	<0.0001
Triglyceride, mmol/L	1.3 (1.0 to 1.8)	1.3 (1.0 to 2.1)	<0.0001
High density lipoprotein, mmol/L	1.2 (1.0 to 1.5)	1.2 (1.0 to 1.4)	<0.0001
Low density lipoprotein, mmol/L	2.6 (1.9 to 3.5)	2.5 (1.6 to 3.2)	<0.0001
Fasting glucose, mmol/L	5.2 (4.2 to 6.5)	5.0 (4.3 to 6.0)	<0.0001
Sodium, mEq/L	138.0 (135.2 to 141.4)	138.5 (136.4 to 142.0)	<0.0001
C-reaction protein, mg/dl	6.5 (1.3 to 18.6)	5.3 (0.4 to 17.5)	<0.0001
Body mass index, kg/m^2	23.0 (21.2 to 25.2)	22.2 (20.2 to 24.8)	<0.0001
Systolic blood pressure, mmHg	143.0 (135.0 to 155.0)	140.0 (130.0 to 152.0)	<0.0001
Diastolic blood pressure, mmHg	84.0 (80.0 to 90.0)	82.0 (80.0 to 90.0)	<0.0001
Ejection Fraction, %	57 (49 to 64)	60 (54 to 65)	<0.0001
Continuous ambulatory peritoneal dialysis, %	134 (65.5)	1,461 (71.6)	<0.0001
Replication Dataset	Case (n=81)	Control (n=810)	
Age, years	61 (45to 71)	61 (44 to 72)	
Female gender, n (%)	32 (39.5)	324 (40.0)	
History of cardiovascular diseases, n (%)	40 (49.4)	406 (50.1)	0.3630
History of diabetes mellitus, n (%)	32 (39.7)	230 (28.4)	<0.0001
Primary Glomerular Disease, n (%)	31 (38.0)	270 (33.3)	<0.0001
Taking antihypertensive treatment, n (%)	70 (86.1)	720 (88.9)	<0.0001
Taking lowering-lipid treatment, n (%)	28 (34.7)	328 (40.5)	<0.0001
Taking lowering-glucose treatment, n (%)	20 (24.6)	245 (30.2)	<0.0001
Haemoglobin, g/L	91.0 (82.0 to 102.0)	95.0 (81.0 to 108.0)	<0.0001
Packed cell volume	3.2 (0.3 to 27.6)	18.4 (0.3 to 29.1)	<0.0001
Reticulocyte, %	52.0 (19.4 to 85.0)	34.0 (2.0 to 60.4)	<0.0001
Phosphate, mg/dl	1.7 (1.4 to 2.1)	1.6 (1.3 to 2.0)	<0.0001
Albumin, g/L	30.9 (25.7 to 34.5)	33.5 (29.4 to 37.0)	<0.0001
Total iron binding capacity , μmol/L	52.0 (30.0 to 73.9)	49.8 (32.8 to 65.6)	<0.0001
FeTIBC, mmol/L	23.4 (8.1 to 55.5)	29.4 (16.8 to 60.8)	<0.0001
Creatinine, μmol/L	758.8 (550.0 to 929.7)	712.0 (533.8 to 917.0)	<0.0001
BUN	20.3 (16.6 to 26.6)	19.8 (15.6 to 24.4)	<0.0001
estimated Glomerular Filtration rate, mL/min/1.73 m^2	1.4 (0.3 to 3.0)	1.6 (0.5 to 3.5)	<0.0001
Calcium	2.0 (1.9 to 2.1)	2.0 (1.9 to 2.2)	<0.0001
Transferrin, mg/dl	325.0 (142.0 to 635.9)	256.9 (88.8 to 547.6)	<0.0001
Total protein, g/L	55.9 (51.6 to 59.4)	58.0 (52.3 to 63.4)	<0.0001
Prealbumin, mg/L	282.7 (164.4 to 400.0)	273.0 (181.0 to 357.0)	<0.0001
Total Cholesterol, mmol/L	4.4 (3.7 to 5.2)	4.5 (3.7 to 5.2)	<0.0001
Triglyceride, mmol/L	1.2 (0.9 to 1.8)	1.3 (1.0 to 2.1)	<0.0001
High density lipoprotein, mmol/L	1.2 (1.0 to 1.5)	1.2 (1.0 to 1.4)	<0.0001
Low density lipoprotein, mmol/L	2.4 (1.7 to 3.2)	2.6 (1.9 to 3.5)	<0.0001
Fasting glucose, mmol/L	5.4 (4.6 to 6.9)	5.0 (4.3 to 5.8)	<0.0001
Sodium, mEq/L	138.6 (135.0 to 141.7)	139.0 (136.5 to 142.0)	<0.0001
C-reaction protein, mg/dl	6.0 (1.3 to 18.5)	5.4 (0.4 to 17.4)	<0.0001
Body mass index, kg/m^2	22.2 (20.1 to 24.2)	22.9 (21.1 to 25.2)	<0.0001
Systolic blood pressure, mmHg	145.0 (130.0 to 155.0)	140.0 (130.0 to 155.0)	<0.0001
Diastolic blood pressure, mmHg	84.0 (80.0 to 90.0)	82.0 (78.0 to 90.0)	<0.0001
Ejection Fraction, %	54.0 (48.0 to 64.0)	60.0 (55.0 to 65.0)	<0.0001
Continuous ambulatory peritoneal dialysis, %	54 (66.3)	569 (70.2)	<0.0001

Results

Table 1 shows the patient characteristics for the 204 cases and 2, 040 population controls in the main sample, and for the 81 cases and 810 controls in the replication sample. Diabetes mellitus (34.3% and 39.7% in the main and replication sample respectively), primary glomerular disease (34.3% and 38.0% respectively) were more common among cases than controls (for diabetes mellitus: 29.3% and 28.4% respectively; for primary glomerular disease: 27.4% and 33.3% respectively). Existing CVD, antihypertensive treatment, lipid-lowering treatment, and anti-diabetes treatment were less common among cases than controls. Reticulocytes, phosphate, total iron binding capacity (TIBC), creatinine, blood urea nitrogen (BUN), transferrin, total cholesterol, low density lipoprotein, fasting glucose, C-reactive protein (CRP), BMI, SBP and DBP were higher in cases than controls. Haemoglobin, packed cell volume, albumin, Fe-TIBC, estimated Glomerular Filtration Rate (eGFR), calcium, total protein, pre-albumin, sodium and EF were lower in cases than controls. The proportion undertaking continuous ambulatory peritoneal dialysis (CAPD) was lower among cases (65.5% and 66.3% in the main and replication samples respectively) than controls (71.6% and 70.2% respectively).

Dose-response relationship curves between continuous measurements of risk factors and incidence rate ratio for CVD mortality were derived from the natural cubic spline models with adjustment in Fig. 1 for the main sample and in Fig. 2 for the replication sample. Fasting glucose linearly increased with the adjusted incidence rate ratio for cardiovascular mortality both in the main sample and the replication sample. SBP, DBP, BMI, TC, phosphate and EF were non-linearly associated with the adjusted incidence rate ratio for CVD mortality (linearity test: all $P < 0.0001$) both in the main sample and replication sample.

The threshold was estimated at 145 (143 to 147) mmHg for SBP both in the main sample and replication sample, with decreased adjusted incidence rate ratio for CVD mortality below the threshold and presented stable above the threshold.

The threshold for DBP was estimated at 92 (90 to 94) mmHg both in the main sample and the replication sample, with decreased adjusted incidence rate ratio for CVD mortality below the threshold and presented stable above the threshold in the main sample, comparing with stable risk below the threshold and increased risk above the threshold in the replication sample.

"U" (J)-shapes between three clinical measurements (BMI, TC, and EF) and CVD mortality were identified both in the main sample and replication sample, with a consistently estimated threshold of BMI, TC, and EF estimated at 24 (33 to 26) kg/m^2, 4.6 (4.4 to 4.8) mmol/L, and 60 (58 to 62) %, respectively associated with the lowest adjusted incidence rate ratio for CVD mortality.

The non-linear association between phosphate and risk of CVD mortality was identified both in the main sample and replication sample, with a consistently estimated threshold of 1.70 (1.65 to 1.75) mmol/L. CVD mortality remained stable below the threshold and increased above the threshold in the main sample, compared with decreased CVD mortality below the threshold but stable above the threshold in the replication sample. This linear and non-linear association was also found in the sensitivity analyses modelling the associations within the data rich range (5^{th} percentile to 95^{th} percentile of the above measurements) as shown as Fig. 3 for the main sample and Fig. 4 for the replication sample.

Finally, we estimated that an unmeasured confounder that was 1.4-fold as frequent among patients with hyperglycaemia as those without the condition would need to increase the CVD mortality risk by a factor of twenty or more to fully explain the results, if no increased risk actually existed (Fig. 5).

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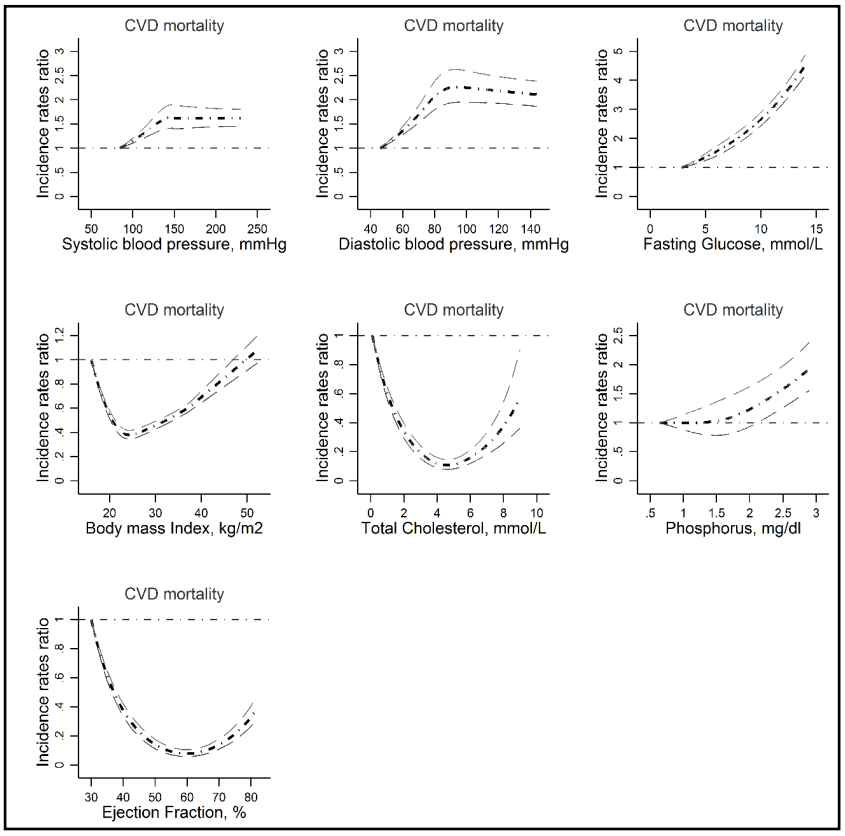

Fig. 1. Adjusted dose-response associations between measurements of cardiovascular risk factors and cardiovascular mortality among incident peritoneal dialysis patients within main dataset.

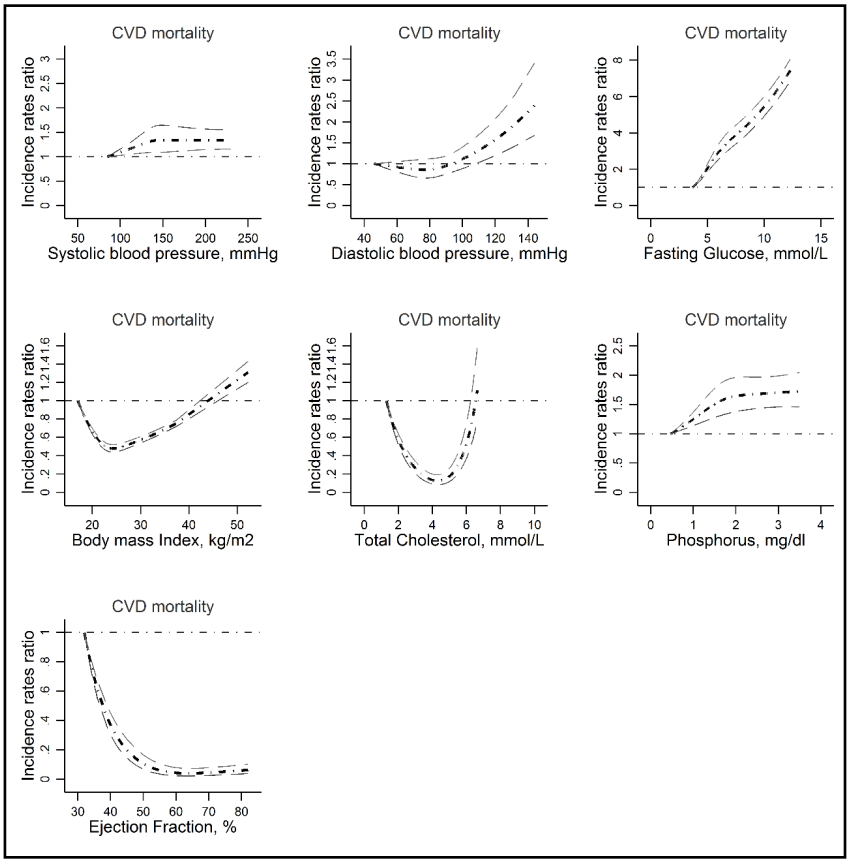

Fig. 2. Adjusted dose-response associations between measurements of cardiovascular risk factors and cardiovascular mortality among incident peritoneal dialysis patients within replication dataset.

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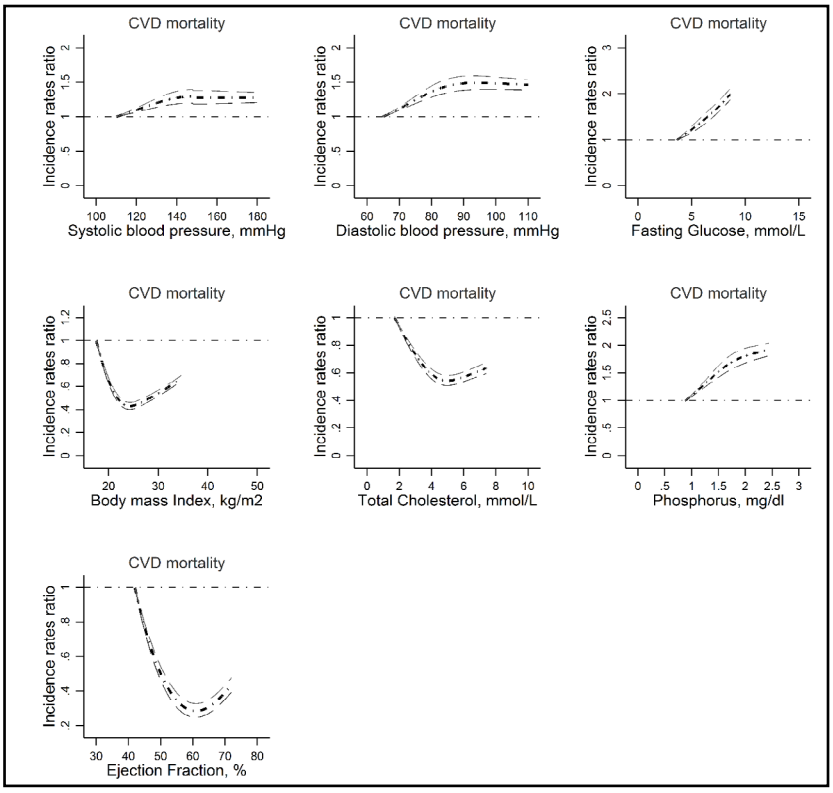

Fig. 3. Adjusted dose-response associations between measurements of cardiovascular risk factors and cardiovascular mortality among incident peritoneal dialysis patients within main dataset:. sensitivity analyses in the data rich zone.

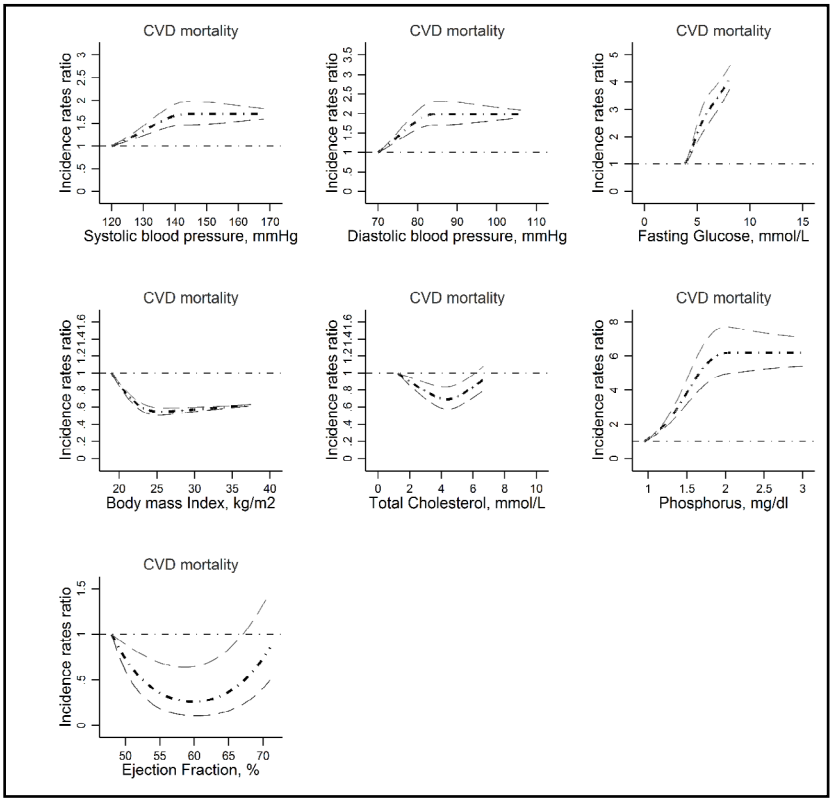

Fig. 4. Adjusted dose-response associations between measurements of cardiovascular risk factors and cardiovascular mortality among incident peritoneal dialysis patients within replication dataset: sensitivity analyses in the data rich zone.

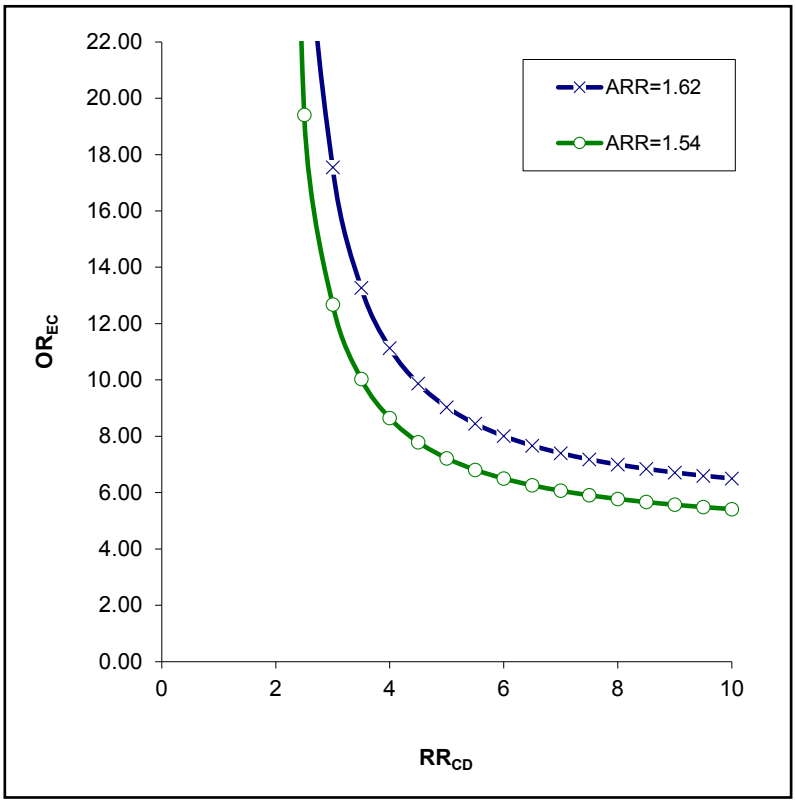

Fig. 5. Required Strength of an Unmeasured Confounder. Sensitivity analysis illustrating how strongly an unmeasured confounder would need to be associated with hyperglycaemia (prevalence ratio for exposure - confounder association, PREC) and cardiovascular mortality (relative risk of the disease in patients with the confounder, RRCD) to fully explain our estimates. We assumed that the prevalence of the confounder was as common as 95% of the population and that 70% of the population with hyperglycaemia. The graphs depict adjusted incidence rate ratio (ARR) associated with the hyperglycaemia (cross line) along with the lower limit of the 95% confidence interval (circle line).

Discussion

The novel findings from this Chinese population based case-control study, was firstly, that conventional CVD risk factors were not the same for patients starting PD treatment as for the general population; secondly that while fasting glucose was linearly associated with an increased risk of CVD mortality; other risk factors (blood pressure, BMI, TC, phosphate and EF) had non-linear relationships with CVD mortality. Thresholds associated with a decreased risk of CVD mortality were identified for SBP (below 145 mmHg), DBP (92 mmHg), and phosphate (1.70 mmol/L). Potential thresholds were identified above and below which risk of CVD mortality increased (24kg/m^2 BMI, 4.6mmol/L total cholesterol, and 60% EF.

Comparison with previous studies

Currently, the potential CVD risk factor thresholds for intensifying clinical management metabolic targets set for patients in pre-dialysis or post-dialysis are generally similar to those for the general population. For example, 140/90 mmHg is the BP control target (despite prior inconsistent findings from the the Kidney Disease Outcomes Quality Initiative (K/DOQI) study where the lowest CVD risk was below 130/80 mmHg [16] and the Korean end-stage renal registry data [17], where the highest CVD mortality risk was found among those with a lower BP <120/80 mmHg. Mixing BP measurement time (pre-dialysis and post-dialysis) and ethnic differences could explain these inconsistent findings. Our study indicated CVD mortality was higher above 145/92 mmHg, suggesting that this could be a potential target for patients treated with PD.

Ahmadi's systematic review among patients with PD treatment suggested that being underweight was associated with higher short-term mortality while being overweight or

obese was associated with lower mortality [18]. Conversely, a meta-analysis among PD patients showed that a BMI of 25-29.9 kg/m^2 and a BMI<18.5 kg/m^2 were both associated with elevated risk of all-cause mortality [19]. However, the dose-response relationship between BMI and risk of CVD mortality has not been evaluated previously. Our study identified a non-linear relationship between BMI and CVD mortality with a threshold of 24 (23 to 26) kg/m^2 associated with lowest risk of CVD mortality, which could be the potential body weight target for Chinese patients initialising PD treatment.

In a PD population in Hong Kong, it was shown that patients with reduced EF (EF<50%) showed an increased risk of cardiac death (relative risk (RR)=2.57) and heart failure (RR=2.25) within four years compared with patients having preserved EF (EF≥50%) [20]: this is consistent with our observations. Moreover, as the first study to reveal a dose-response relationship between EF and CVD mortality, our research suggests an potential EF threshold of 60% as below this (even at 50-60%) we found an increased risk of CVD mortality.

Previous studies have suggested that among patients receiving PD, TC was not significantly different between patients with and without CVD mortality [21, 22], which might be due to a non-linear relationship between TC and risk of CVD mortality. In a 10-year Korean cohort of 749 incident PD patients [23], a non-linear relationship between stratified TC concentrations and all-cause mortality was identified, with an potential TC threshold of 180-210mg/dl (4.6-5.4 mmol/L) and lowest risk of all-cause mortality and increased mortality risk for TC below/above this threshold: this is close to our findings of a TC of 4.4-4.8 mmol/L being associated with the lowest risk of CVD mortality. The increased CVD mortality risk was found to be associated with dyslipidaemia among patients starting PD treatment the association was not significant. Similarly, in another Chinese PD cohort PD patients with dyslipidaemia was associated with increased risk of atrial fibrillation, but the association was not significant after adjusting the confounders [24].

In a large longitudinal Taiwan registry dataset, it was found that an increased mortality risk of all-cause mortality was identified among PD patients with phosphate above and below 1.14-1.78mmol/L [25]. In another large prospective multicentre study involving 568 PD patients in the Netherlands [26], it was found that phosphate above 3.5-5.5mg/dl (1.13-1.78 mmol/L) was associated with an increased risk of CVD mortality (RR=2.4) and phosphate below the threshold was associated with slightly increased risk (RR=1.1). In our main sample and in the sensitivity analyses in the data rich range, an increased risk was identified for patients with phosphate above 1.70 mmol/L but risk was stable below the threshold; in our replication sample, risk was actually decreased below the threshold, but still increased above the threshold.

The linear association between fasting glucose and CVD mortality, found in our study is similar to that found in other studies among PD patients without pre-existing diagnosed diabetes [27, 28]. A linear association between fasting glucose and all-cause mortality has also been previously been found among PD patients with pre-existing diabetes [29] and in the general PD population [30]. The linear association between fasting glucose and CVD mortality suggests that PD patients with lower fasting glucose concentration, in spite of having pre-existing diabetes, would be less likely to die due to cardiovascular disease.

Limitations

Our results might be influenced by confounding by unmeasured risk factors, for example, those due to under-recording of pre-existing comorbidities and their duration. The duration of reduced renal function would be a particularly important measure prone to under-estimation. Secondly, we lacked data on lifestyle factors, including smoking, drinking and physical activity. Thirdly, we did not adjust for PD patients' socioeconomic status that would likely impact on PD patients' treatment/management status and their general health status. Finally, the proportion of clinical measurement data that was missing was relatively high requiring multiple imputation, which suggesting that further replication in the external dataset are warranted.

Conclusion

The dose-response relationships between different risk factors and CVD mortality highlight the potential importance of undertaking a randomised controlled trial, testing the impact of reducing hyperglycaemia, alongside using anti-hypertensive treatment to control BP below 140/92 mmHg and strict diet management and phosphate binders treatment to control phosphate below 1.70 mmol/L. Our findings also highlighted a potential target for BMI (24kg/m^2), and total cholesterol (4.6 mmol/L), suggesting that both poor and intensive lifestyle, lipid and cardiac interventions should be applied in Chinese population initialising PD care. Moreover, where EF is above 60%a good prognosis for incident PD population may be predicted. We recommend that the clinical relevance of these epidemiological associations is tested among PD patients using randomized controlled trials of multifaceted interventions.

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Disclosure Statement

The authors declare that they have no competing interests.

References

1 Levin A, Tonelli M, Bonventre J, Coresh J, Donner JA, Fogo AB, Fox CS, Gansevoort RT, Heerspink HJL, Jardine M, Kasiske B, Kottgen A, Kretzler M, Levey AS, Luyckx VA, Mehta R, Moe O, Obrador G, Pannu N, Parikh CR, et al.: Global kidney health 2017 and beyond: a roadmap for closing gaps in care, research, and policy. Lancet 2017;390:1888-1917.

2 Ojo A: Addressing the global burden of chronic kidney disease through clinical and translational research. Trans Am Clin Climatol Assoc 2014;125:229-243; discussion 243-246.

3 Li PK, Chow KM, Van de Luijtgaarden MW, Johnson DW, Jager KJ, Mehrotra R, Naicker S, Pecoits-Filho R, Yu XQ, Lameire N: Changes in the worldwide epidemiology of peritoneal dialysis. Nat Rev Nephrol 2017;13:90-103.

4 Yao Q, Duddington M: Peritoneal dialysis in China. Perit Dial Int 2014;34:S29-30.

5 Vanholder R, Annemans L, Brown E, Gansevoort R, Gout-Zwart JJ, Lameire N, Morton RL, Oberbauer R, Postma MJ, Tonelli M, Biesen WV, Zoccali C, European Kidney Health Alliance: Reducing the costs of chronic kidney disease while delivering quality health care: a call to action. Nat Rev Nephrol 2017;13:393-409.

6 Mehrotra R, Devuyst O, Davies SJ, Johnson DW: The Current State of Peritoneal Dialysis. J Am Soc Nephrol 2016;27:3238-3252.

7 Davies SJ: Peritoneal dialysis--current status and future challenges. Nat Rev Nephrol 2013;9:399-408.

8 Kendrick J, Kestenbaum B, Chonchol M: Phosphate and cardiovascular disease. Adv Chronic Kidney Dis 2011;18:113-119.

9 Lo WK: Metabolic syndrome and obesity in peritoneal dialysis. Kidney Res Clin Pract 2016;35:10-14.

10 Emdin CA, Rothwell PM, Salimi-Khorshidi G, Kiran A, Conrad N, Callender T, Mehta Z, Pendlebury ST, Anderson SG, Mohseni H, Woodward M, Rahimi K: Blood Pressure and Risk of Vascular Dementia: Evidence From a Primary Care Registry and a Cohort Study of Transient Ischemic Attack and Stroke. Stroke 2016;47:1429-1435.
11 Kendrick J, Kestenbaum B, Chonchol M: Phosphate and cardiovascular disease. Adv Chronic Kidney Dis 2011;18:113-119.
12 National Institute for Health and Care Excellence: Chronic kidney disease (stage 4 or 5): management of hyperphosphataemia. 2013. https://www.nice.org.uk/guidance/cg157/resources/chronic-kidney-disease-stage-4-or-5-management-of-hyperphosphataemia-pdf-35109636340165.
13 Schmidt M, Christiansen CF, Mehnert F, Rothman KJ, Sorensen HT: Non-steroidal anti-inflammatory drug use and risk of atrial fibrillation or flutter: population based case-control study. BMJ 2011;343:d3450.
14 Yu D, Simmons D: Association between blood pressure and risk of cardiovascular hospital admissions among people with type 2 diabetes. Heart 2014;100:1444-1449.
15 Schneeweiss S: Sensitivity analysis and external adjustment for unmeasured confounders in epidemiologic database studies of therapeutics. Pharmacoepidemiol Drug Saf 2006;15:291-303.
16 Combe C, McCullough KP, Asano Y, Ginsberg N, Maroni BJ, Pifer TB: Kidney Disease Outcomes Quality Initiative (K/DOQI) and the Dialysis Outcomes and Practice Patterns Study (DOPPS): nutrition guidelines, indicators, and practices. Am J Kidney Dis 2004;44:39-46.
17 Jin DC: Dialysis registries in the world: Korean Dialysis Registry. Kidney Int Suppl (2011) 2015;5:8-11.
18 Ahmadi SF, Zahmatkesh G, Streja E, Mehrotra R, Rhee CM, Kovesdy CP, Gillen DL, Ahmadi E, Fonarow GC, Kalantar-Zadeh K: Association of Body Mass Index With Mortality in Peritoneal Dialysis Patients: A Systematic Review and Meta-Analysis. Perit Dial Int 2016;36:315-325.
19 Liu J, Zeng X, Hong HG, Li Y, Fu P: The association between body mass index and mortality among Asian peritoneal dialysis patients: A meta-analysis. PLoS One 2017;12:e0172369.
20 Wang AY, Wang M, Lam CW, Chan IH, Lui SF, Sanderson JE: Heart failure with preserved or reduced ejection fraction in patients treated with peritoneal dialysis. Am J Kidney Dis 2013;61:975-983.
21 Chiang JY, Huang JW, Lin LY, Chang CH, Chu FY, Lin YH, Wu CK, Lee JK, Hwang JJ, Lin JL, Chiang FT: Detrended Fluctuation Analysis of Heart Rate Dynamics Is an Important Prognostic Factor in Patients with End-Stage Renal Disease Receiving Peritoneal Dialysis. PLoS One 2016;11:e0147282.
22 Shi Y, Zheng D, Zhang L, Yu Z, Yan H, Ni Z, Qian J, Fang W: Six-minute walk test predicts all-cause mortality and technique failure in ambulatory peritoneal dialysis patients. Nephrology (Carlton) 2017;22:118-124.
23 Park CH, Kang EW, Park JT, Han SH, Yoo TH, Kang SW, Chang TI: Association of serum lipid levels over time with survival in incident peritoneal dialysis patients. J Clin Lipidol 2017;11:945-954.
24 Shen CH, Zheng CM, Kiu KT, Chen HA, Wu CC, Lu KC, Hsu YH, Lin YF, Wang YH: Increased risk of atrial fibrillation in end-stage renal disease patients on dialysis: A nationwide, population-based study in Taiwan. Medicine (Baltimore) 2016;95:e3933.
25 Liu CT, Lin YC, Lin YC, Kao CC, Chen HH, Hsu CC, Wu MS: Roles of Serum Calcium, Phosphorus, PTH and ALP on Mortality in Peritoneal Dialysis Patients: A Nationwide, Population-based Longitudinal Study Using TWRDS 2005-2012. Sci Rep 2017;7:33.
26 Noordzij M, Korevaar JC, Bos WJ, Boeschoten EW, Dekker FW, Bossuyt PM, Krediet RT: Mineral metabolism and cardiovascular morbidity and mortality risk: peritoneal dialysis patients compared with haemodialysis patients. Nephrol Dial Transplant 2006;21:2513-2520.
27 Chung SH, Han DC, Noh H, Jeon JS, Kwon SH, Lindholm B, Lee HB: High blood glucose independent of pre-existing diabetic status predicts mortality in patients initiating peritoneal dialysis therapy. Int Urol Nephrol 2015;47:1017-1024.
28 Chen KH, Lin JL, Hung CC, Lin-Tan DT, Weng SM, Yen TH, Hsu CW, Yang CW: Impaired fasting glucose association with mortality in nondiabetic patients on maintenance peritoneal dialysis. Am J Med Sci 2011;341:312-317.
29 Park JI, Bae E, Kim YL, Kang SW, Yang CW, Kim NH, Lee JP, Kim DK, Joo KW, Kim YS, Lee H: Glycemic Control and Mortality in Diabetic Patients Undergoing Dialysis Focusing on the Effects of Age and Dialysis Type: A Prospective Cohort Study in Korea. PLoS One 2015;10:e0136085.
30 Zhao C, Luo Q, Xia X, He F, Peng F, Yu X, Huang F: Risk score to predict mortality in continuous ambulatory peritoneal dialysis patients. Eur J Clin Invest 2014;44:1095-1103.