Association between cold dialysis and cardiovascular survival in hemodialysis patients

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Abstract

Background. Higher cardiovascular mortality has been noted in patients with chronic kidney disease (CKD). CKD patients are also known to have impaired energy expenditure but the role of energy expenditure in cardiovascular disease is not yet known. Furthermore, the association between cold dialysis (CD) and clinical outcomes in hemodialysis patients is unclear.
Methods. This was a single-center retrospective cohort study consisting of two groups: a CD group with dialyze temperature <35.5°C and a standard dialysis (SD) group with dialyze temperature between 35.5 and 37°C. The end points of the study were overall mortality, cardiac mortality and non-cardiac mortality. The study analyzed the associations between dialyze temperature and long-term survival in CD and SD groups. Propensity score analysis was used to control for intergroup baseline differences.

Results. Baseline characteristics of both groups were similar. Kaplan–Meier analysis showed that CD was significantly associated with a lower risk for overall mortality (P = 0.006) and cardiac mortality (P = 0.023) but not for non-cardiac mortality or infectious mortality. After multivariate Cox regression analysis, adjusting for propensity scores and other possible confounding factors, CD remained a significant beneficial factor for overall mortality (P = 0.050) and cardiac mortality (P = 0.034).

Conclusion. Our studies show that CD is significantly and independently associated with a lower risk for overall mortality and cardiac mortality.

Keywords: chronic kidney disease; cold dialysis; hemodialysis; survival

Introduction

The number of patients with end-stage renal disease (ESRD) is increasing daily throughout the world. The care of these patients presents a great burden and has become a global public health problem [1]. Hemodialysis patients have a higher risk of mortality, with a mortality rate as high as 15–20% as reported by previous studies [2, 3]. Cardiovascular disease (CVD) is common in ESRD patients [4], followed by infection and stroke [5]. Thus, reducing cardiovascular mortality is an important issue for nephrologists that care for ESRD patients.

The causes underlying the higher frequency of CVD in dialysis patients are complex and multifactorial. The prevalence of traditional risk factors, such as diabetes and hypertension, is higher among hemodialysis patients than in the general population. In addition, there are several metabolic and hemodynamic disturbances that can modify cardiovascular risk. Furthermore, there is increasing evidence that uremia-related factors, such as anemia, hypoalbuminemia, divalent ion abnormality, higher fibroblast growth factor 23 [6, 7], hyperhomocysteinemia [8] and oxidative stress [9], contribute to the more common occurrence of CVD in hemodialysis patients [4, 5, 10, 11]. In addition, impaired energy expenditure in chronic kidney disease (CKD) patients may also be associated with CVD and higher risk of mortality [12, 13].

A group of hemodialysis patients has been undergoing regular treatment with cold dialysis (CD) for several years. These patients receive CD either for hemodynamic instability [14], intractable puritus [15, 16], or for increased comfort. CD has also been shown to cause energy loss by the extracorporeal circuit [17], and exposure to cold dialyze may activate brown adipose tissue [18], thereby increasing whole-body energy expenditure via thermogenesis.

Although exposure of hemodialysis patients to cold dialyze occurs intermittently, this treatment occurs regularly over long periods of time, sometimes up to decades. Therefore, it is of interest to study the effects of CD on hemodialysis patients who have impaired energy expenditure and increased risk of cardiovascular mortality. This specific population offers the possibility to observe the effects of CD on their clinical outcome.

The question arises as to whether regular CD is associated with a better clinical outcome in hemodialysis patients. We hypothesized that prolonged exposure to lower temperature dialyze may improve cardiovascular mortality in hemodialysis patients. To answer this question, we conducted a retrospective study to analyze long-term clinical outcomes in hemodialysis patients using different dialyze temperatures.

Materials and methods

Cohorts

In this retrospective study, patients undergoing maintenance hemodialysis at Chang Gung Memorial Hospital at Keelung from 1993 to 2007 were reviewed. All patients received regular 4 h hemodialysis treatment, thrice weekly for at least 3 months. The 3 months were chosen for the patients who were stable after this period. Blood flow rate was ~200–350 mL/min, and dialyze flow rate was ~500 mL/min. CD was defined as dialyze temperature <35.5°C for >3 h per dialysis treatment. Patients using dialyze temperatures between 35.5 and 37°C were defined as the standard dialysis (SD) cohort. Most patients (~85%) underwent high-efficiency dialysis with a dialyze temperature between 36.0°C and 36.5°C. Patients who received a constant dialyze temperature were excluded from the study. The hemodialysis prescription policy for CD remained unchanged throughout the observation period. There were 910 patients enrolled in the study: 165 patients in the CD group and 745 patients in the SD group. The study focused on the association of CD and the long-term survival between CD and SD groups for a mean follow-up period of 47.6 ± 39.4 months. The patients started CD at a mean time of 6.1 ± 20.9 months after starting regular dialysis (Table 1).

Study design

The study was a single-center retrospective dynamic cohort study designed to analyze the effect of treatment with cold dialyze on the survival of dialysis patients. The patients were divided into two groups as defined above. Basic demographic data were collected for both study groups, including age, gender, presence of diabetes, nutritional status [body mass index (BMI) and normalized protein catabolic rate (nPCR)], dialysis vintage, the year of starting dialysis, primary cause of ESRD and presence of hepatitis B or C. In addition, initial fluid status parameters and cardiothoracic ratio (CT ratio), obtained by chest radiography, were also recorded at the start of the study. Baseline hematological, biochemical, hemodynamic and dialysis-related parameters were also collected. Overall mortality, cardiac mortality, non-cardiac mortality and infectious mortality were analyzed and compared between CD and SD groups. The study was terminated on 31 December 2008, and the patients left our dialysis program, shifted to peritoneal dialysis or received transplantation. Patient information was censored. Cardiovascular death was defined as the patient dying from heart failure, coronary artery disease, arrhythmia or sudden death. Infection-related death was defined as the patient dying due to infection. Study information was obtained from medical records with expert assessments. This study was approved by the Institutional Review Board (IRB) of the Chang Gung Memorial Hospital.

Laboratory assays and hemodynamic factors

Laboratory parameters that were measured included levels of serum creatinine, blood urea nitrogen (BUN), hemoglobin, albumin, high-sensitivity C-reactive protein (hs-CRP), ferritin, corrected calcium (cCa), phosphate,
intact parathyroid hormone (iPTH), lipid profiles (cholesterol and triglyceride) and alkaline phosphatase (Alk-P). In addition, parameters reflecting urea clearance, including the urea reduction rate (URR) and the Kt/V value (single pool Kt/V) [19], were analyzed to determine the efficacy of dialysis treatment. Blood samples were collected before and after each dialysis session, performed according to recommended procedures for dialysis in the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative guidelines [20]. Serum creatinine, BUN, hemoglobin, hs-CRP, ferritin, cCa, phosphate, cholesterol, triglycerol and Alk-P were determined using standard autoanalyzers. Serum iPTH levels were measured using a commercially available radioimmunoassay kit (Scantibodies Laboratory, Santee, CA). In addition, hemodynamic factors, including systolic blood pressure (SBP) before hemodialysis (pre-SBP), SBP after hemodialysis (post-SBP), diastolic blood pressure (DBP) before hemodialysis (pre-DBP), DBP after hemodialysis (post-DBP), difference in SBP before and after hemodialysis (ΔSBP) and difference in DBP before and after hemodialysis (ΔDBP), were obtained. Intra-dialytic hypotension was defined as a fall in systolic or mean arterial blood pressure of >20 mmHg and resulting in clinical symptoms [21].

Statistical analysis

Continuous variables are expressed as mean ± SD. For normally distributed continuous variables, two-tailed Student’s unpaired t-tests were employed to evaluate differences between means. Differences between groups of categorical variables were analyzed by the chi-square test or Fisher’s exact test. A propensity score approach was also used by employing a logistic regression model to compute the probability of being assigned to either treatment group. Firstly, a multinomial logistic regression was fitted with treatment as the outcome and factors that may be related to the clinical decision behind prescribing CD or SD treatment and was used to calculate the propensity score. Factors such as age, gender, comorbidity of diabetes, pre-SBP, ΔSBP, the year of starting dialysis, nutrition status, including BMI and serum albumin, may all be related to the prescription of CD or SD treatment and were used to calculate propensity scores. The model was then used to estimate predicted probabilities of being assigned to either treatment group. Finally, all primary and secondary analyses were conducted with multiple propensity scores as covariates. Patients’ survival curves were derived from Kaplan–Meier analysis and were compared by the Cox–Mantel log-rank test. Mortality was considered as an end point in all–cause mortality survival analyses. Cardiac mortality was considered as an end point and mortality due to other causes were censored in the cardiac mortality survival analyses. Non-cardiac mortality was also considered as an end point, with cardiac mortality being censored in non-cardiac mortality survival analyses. Infectious mortality was also treated as an end point and mortality due to other causes was censored in infectious mortality survival analyses. Patient survival was analyzed by entering propensity scores into the Cox proportional hazards model to control for covariates. The Cox proportional hazards model was applied to identify prognostic factors associated with outcomes, while statistically significant variables from univariate analyses and propensity scores were adjusted in Model 1 (Table 2). Further adjustment of factors associated with CVD in Model 2 and factors associated with inflammation and dialysis efficacy in Model 3 was also carried out. P < 0.05 was considered to be statistically significant. All analyses were performed using a commercially available statistical software package, SPSS version 15.0 for Windows (SPSS, Chicago, IL).

Results

Study subjects

The age of our cohort of patients was 58.3 ± 15.0 years, and there was no significant difference in age between CD patients and SD patients (57.4 ± 14.5 versus 59.6 ± 14.5 years, P = 0.084) (Table 1). Regarding gender distribution, 44% were male, and there was a similar distribution between CD and SD groups (41 versus 45%, P = 0.307). The presence of diabetes was 42% in our cohort of patients, with no significant difference being noted between CD and SD groups (46 versus 41%, P = 0.259). The CD group had a significantly higher BMI than did the SD group (23.4 ± 3.9 versus 22.1 ± 3.7, P = 0.002). However, the normalized protein catabolic rate (nPCR) was not significantly different between the two cohorts (1.13 ± 0.37 versus 1.06 ± 0.36, P = 0.058). There were no significant differences between groups regarding vascular access, dialysis vintage,
the starting year of hemodialysis and cause of ESRD. With respect to the epidemiology of chronic hepatitis, no significant differences regarding hepatitis B and hepatitis C infection were noted between the CD and SD groups. In total, 239 patients were lost during the follow-up period, with the missing data accounting for 16% (27/165) and 28% (212/745) of the CD and SD groups, respectively. In our CD group of patients, 46 patients received dialyzate temperature <35°C and 119 patients received dialyzate temperature between 35 and 35.5°C.

Clinical characteristics of the study patients

There were no significant differences in serum BUN and creatinine levels between CD and SD patients (Table 3). Similarly, hemoglobin, albumin, hs-CRP, ferritin, cCa, iPTH, cholesterol and Alk-P levels were not significantly different between the two groups. However, CD patients had significantly higher levels of phosphate and triglycerol. Dialysis-related parameters, including Kt/V and URR, were similar in the two groups. Regarding hemodynamic factors, post-SBP was significantly lower in CD patients than in SD patients, but pre-SBP, pre-DBP, post-DBP, and ADBP were similar between the two groups. The occurrence of intra-dialytic hypotension was similar in CD and SD groups.

Effect of CD on survival: univariate analysis

Survival analysis was performed to determine mortality risk in the CD and SD groups. The median survival time of CD patients was 106.6 months, whereas patients with SD had a median survival time of 75.3 months. Kaplan-Meier analysis showed that CD was significantly associated with a lower risk for overall mortality [hazard ratio, 0.691; 95% confidence interval (CI), 0.531–0.898, P = 0.006; Figure 1]. In addition to CD, younger patients, non-diabetic patients, those with higher albumin and hemoglobin and those with lower hs-CRP, all had a significantly lower risk for overall mortality (Table 4). To determine a possible effect of CD on cardiac-associated survival, cardiac mortality and non-cardiac mortality were considered separately from overall mortality (Table 5). CD was significantly associated with a lower risk for cardiac mortality (hazard ratio, 0.640; 95% CI, 0.436–0.940, P = 0.023; Figure 2). However, CD was not associated with a lower risk for non-cardiac mortality (hazard ratio, 0.741; 95% CI, 0.517–1.062, P = 0.103; Figure 3). Further analysis suggested that CD was not significantly associated with a lower risk for infectious mortality (hazard ratio, 0.911; 95% CI, 0.620–1.337, P = 0.633; Figure 4). Bacteremia rates were similar between CD and SD groups (6.8 versus 4.7%, P = 0.257).

Multivariate analysis

Baseline nutrition status and some laboratory parameters, which could be related to mortality, were not similar in the CD and SD groups. To avoid a possible confounding effect of these factors on survival analyses, overall mortality, cardiac mortality and non-cardiac mortality between CD and SD groups were compared after adjusting for propensity scores and statistically significant variables from univariate analyses, including phosphate and triglycerol. Multivariate Cox regression analysis revealed that CD was significantly associated with a lower overall mortality after adjusting for the variables listed above (hazard ratio, 0.749; 95% CI, 0.573–0.979, P = 0.034; Model 1, Table 4). Further analysis was carried out with adjustments for factors associated with CVD, including hs-CRP, hemoglobin, cholesterol, pre-DBP, post DBP, ADBP and CT ratio, in addition to Model 1 adjustments (Model 2). After adjusting for the possible impact of cardiovascular factors, Model 2 analysis revealed again that CD was significantly associated with better survival (hazard ratio, 0.750; 95% CI, 0.754–0.980, P = 0.035; Model 2, Table 4). Further analysis, with adjustments for factors associated with inflammation and dialysis efficacy, including ferritin, Kt/V and URR, in addition to Models 1 and 2 adjustments, was then performed (Model 3). Furthermore, after adjusting for factors related to inflammation and dialysis efficacy, Model 3 showed that CD was significantly associated with better survival (hazard ratio, 0.743; 95% CI, 0.568–0.972, P = 0.030; Model 3, Table 4). In our serial analysis with multivariate Cox regression, CD was persistently and significantly associated with better survival after adjusting for propensity score and statistically significant variables from univariate analyses (Model 1), for cardiovascular factors (Model 2) and for inflammatory and dialysis efficacy-related factors (Model 3). Thus, our results strongly suggest that CD is significantly associated with a better clinical outcome in hemodialysis patients.
To further emphasize the impact of CD on survival, multivariate Cox regression analysis on cardiac and non-cardiac mortality was performed. Multivariate Cox regression adjusted the propensity score further revealed that CD was persistently and significantly associated with lower cardiac mortality in Model 1 (hazard ratio, 0.653; 95% CI, 0.442–0.966, P = 0.033), Model 2 (hazard ratio, 0.650; 95% CI, 0.440–0.960, P = 0.030) and Model 3 (hazard ratio, 0.656; 95% CI, 0.444–0.970, P = 0.034) adjustment (Table 5). However, there was no significant effect of CD on non-cardiac mortality after adjustment in Model 1, Model 2 or Model 3. Thus, our results strongly suggest an inverse relationship between CD and the occurrence of cardiac mortality.

Discussion

In our dynamic retrospective cohort study, we have shown that CD is associated with lower mortality in patients undergoing maintenance hemodialysis. Patients, who underwent long-term CD for ~12 h/week had longer survival of ~67.0 months compared to 43.4 months in patients undergoing SD. By univariate analysis with Cox regression, CD was significantly associated with lower risk of overall mortality and cardiac mortality. We also studied the association between infectious mortality and CD among patients with non-cardiac mortality and found that there was no correlation between CD and infectious mortality. In order to avoid the confounding influence of many known survival-related factors, multivariate Cox regression, with adjustment for propensity scores and statistically significant variables from univariate analyses, was used. In this multivariate regression analysis, CD

![Fig. 1. Kaplan–Meier analysis of overall patient survival in CD versus SD groups (median survival time was 106.6 versus 75.3 months, respectively, P = 0.006).](https://academic.oup.com/ndt/article-abstract/27/6/2457/1936830)
remained independently related to a lower hazard ratio of overall mortality and cardiac mortality, but not to non-cardiac mortality and infectious mortality.

Higher energy expenditure is prominent in ESRD patients treated with CD, with as high as 33% of the estimated resting energy expenditure being noted for each CD procedure in a previous study [17]. Additionally, greater energy expenditure is associated with a lower prevalence of CVD and better survival in the general population [12, 13, 24].

Higher incidence of CVD and mortality among CKD patients undergoing hemodialysis are important issues for nephrologists. Furthermore, CKD patients have been shown to have a lower energy expenditure than the general population [25]. Thus, CD provides a tool for greater energy expenditure in patients with a higher risk for cardiovascular mortality and low energy expenditure.

Since exposure to cold activates brown adipose tissue [18], the benefits of CD may be related to this effect. Brown adipose tissue affects whole-body metabolism, is essential for thermogenesis in human neonates and may regulate susceptibility to weight gain and insulin sensitivity [26–28]. A previous study estimated that as little as 50 g of maximally stimulated brown adipose tissue accounts for up to 20% of daily energy expenditure in adult humans [29]. While it has been suggested that brown adipose tissue is unnecessary in adults, due to their higher basal metabolic rates and greater muscle mass for shivering, recent studies suggest brown adipose tissue is important for both basal and inducible energy expenditure in the form of thermogenesis, mediated by the expression of tissue-specific uncoupling protein (UCP1) in adults [30]. Furthermore, a recent study has identified the importance of brown adipose tissue in adult humans [30]. Thus, activation of brown adipose tissue by cold [18] may increase survival by increasing basal and inducible energy expenditure. Furthermore, a reduction in dialysis-induced myocardial stunning, which may also be associated with CVD and cardiovascular mortality, has been observed with the use of CD [31].

Cold temperatures have also been linked to inflammation. Hypothermia decreases inflammatory cytokine levels and has been associated with compromised host defense and increased infection. Moderate hypothermia delays the induction of pro-inflammatory cytokines in human peripheral blood mononuclear cells [32] and may worsen outcomes during infection by delaying and prolonging cytokine production.

### Table 4. Hazard ratios for overall mortality of hemodialysis patients according to baseline characteristics a

<table>
<thead>
<tr>
<th>Variables</th>
<th>Crude</th>
<th>Model 1 adjusted</th>
<th>Model 2 adjusted</th>
<th>Model 3 adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.052 (1.043–1.061)</td>
<td>&lt;0.001</td>
<td>1.066 (0.871–1.304)</td>
<td>0.537</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.066 (0.871–1.304)</td>
<td>0.537</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2.137 (1.741–2.623)</td>
<td>&lt;0.001</td>
<td>1.002 (0.995–1.008)</td>
<td>0.592</td>
</tr>
<tr>
<td>Hemodialysis duration</td>
<td>1.001 (0.995–1.007)</td>
<td>0.790</td>
<td>1.004 (0.998–1.010)</td>
<td>0.198</td>
</tr>
<tr>
<td>Albumin</td>
<td>0.388 (0.326–0.461)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>0.913 (0.846–0.984)</td>
<td>0.018</td>
<td>0.925 (0.857–0.998)</td>
<td>0.043</td>
</tr>
<tr>
<td>hs-CRP</td>
<td>1.023 (1.014–1.032)</td>
<td>&lt;0.001</td>
<td>1.007 (1.005–1.010)</td>
<td>0.003</td>
</tr>
<tr>
<td>BMI</td>
<td>1.016 (0.739–1.397)</td>
<td>0.087</td>
<td>0.966 (0.929–1.005)</td>
<td>0.000</td>
</tr>
<tr>
<td>Cold hemodialysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.691 (0.531–0.898)</td>
<td>0.006</td>
<td>0.749 (0.573–0.979)</td>
<td>0.034</td>
</tr>
</tbody>
</table>

*HR, hazard ratio. Propensity score was calculated with age, gender, comorbidity of diabetes, pre-SBP, ASBP, the year of starting dialysis and nutrition status, including BMI and serum albumin.

### Table 5. Effect of cold hemodialysis on overall mortality, cardiac mortality and non-cardiac mortality determined by univariate and multivariate Cox regression analysis a

<table>
<thead>
<tr>
<th>Cold hemodialysis</th>
<th>Overall mortality</th>
<th>Cardiac mortality</th>
<th>Non-cardiac mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Univariate analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cold hemodialysis</td>
<td>0.691 (0.531–0.898)</td>
<td>0.006</td>
<td>0.640 (0.436–0.940)</td>
</tr>
<tr>
<td>Multivariate analysis</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Model 1</td>
<td>0.749 (0.573–0.979)</td>
<td>0.034</td>
<td>0.653 (0.442–0.966)</td>
</tr>
<tr>
<td>Model 2</td>
<td>0.750 (0.574–0.980)</td>
<td>0.035</td>
<td>0.650 (0.440–0.960)</td>
</tr>
<tr>
<td>Model 3</td>
<td>0.743 (0.568–0.972)</td>
<td>0.030</td>
<td>0.656 (0.444–0.970)</td>
</tr>
</tbody>
</table>

*HR, hazard ratio. Propensity score was calculated with age, gender, comorbidity of diabetes, pre-SBP, ASBP, the year of starting dialysis and nutrition status, including BMI and serum albumin.
Thus, it seems that hypothermia inhibits the human immune system and compromises its ability to adequately respond to pathogens, whereas febrile temperatures may enhance early activation of host defenses, thereby preventing prolonged exposure to potentially cytotoxic cytokines [33]. However, a recent study has shown that mild hypothermia promotes pro-inflammatory cytokine production in monocytes. Moreover, it has also been shown that mild hypothermia does not increase bacterial proliferation in implanted vascular grafts [34]. Thus, the association between low temperatures and inflammation is still unclear. We found that during the mean study period of 47 months, although serum hs-CRP significantly increased in both groups, the magnitude of increase was not significantly different between the two groups, when measured by one-way analysis of variance (P = 0.609). Similarly, although serum albumin significantly decreased in both groups, the magnitude of the decrease was not significantly different between the two groups (P = 0.137). Thus, our data revealed that long-term exposure to cold dialyrate does not alter serum levels of inflammatory markers. It was also noted that CD was not significantly associated with infectious mortality (P = 0.633), and therefore, our results suggest that exposure to cold might not compromise the immune response in dialysis population. The beneficial effects of CD might be cardiac related as our results revealed a lower cardiac mortality in these patients.

A major limitation of the current study is that the mechanism by which CD lowers the risk of overall mortality could not be determined. Furthermore, these analyses were also limited by their retrospective nature. Propensity score adjustment was therefore used to provide less biased comparisons among the cohorts. In addition, although hypotension may occur during hemodialysis, the effect of CD on hemodynamic stability was not possible to determine. Hemodynamic factors, including SBP and DBP, were all evaluated before and after dialysis in this study revealing that the blood pressure difference before and after dialysis was similar in CD and SD groups. Furthermore, information on the type of dialyzate, dialyzer type, ultrafiltration rate,
pre-dialysis weight and inter-dialytic weight gain was not collected or was difficult to present due to changes with time. However, there were 910 patients in our cohort, which is an adequate amount for analysis of patient outcome. Furthermore, the characteristics of our cohort, with 39% diabetic nephropathy and a mean age of 58.3 ± 15.0, were similar to previous studies of hemodialysis patients [35–37]. Thus, our results may represent common populations undergoing hemodialysis throughout the world.

In summary, our study suggests that CD is significantly and independently associated with a lower risk for overall and cardiac mortality, but not for non-cardiac and infectious mortality. The mechanisms underlying the beneficial effects of CD on the survival of hemodialysis patients are still uncertain.

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Conflict of interest statement. None declared.

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