Original Article
Association between C-reactive protein and mortality in peritoneal dialysis patients: a meta-analysis

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Abstract: Objective: The aim of this study was to evaluate the association between C-reactive protein (CRP) levels and all-cause mortality and cardiovascular disease mortality in patients undergoing peritoneal dialysis (PD). Methods: A systematic literature search up to March 2016 was performed in PubMed, Web of Science and the Cochrane Library. Hazard ratio (HR) with 95% confidence interval (CI) for all-cause mortality and cardiovascular disease mortality was extracted from each study. The pooled analysis was performed using the random-effect model by Rev Man 5.3 software. Results: Eighteen studies on CRP involving a total of 3869 PD patients were included in this meta-analysis. The combined analysis revealed that CRP levels were significantly positively associated with all-cause mortality (HR 1.04, 95% confidence interval: 1.02-1.06, P=0.0003) and cardiovascular disease mortality (HR 2.54, 95% confidence interval: 1.08-5.94, P=0.03) in peritoneal dialysis patients. Furthermore, statistically significant heterogeneity was found. The results for subgroup analysis of geographic region, study type, sample size and CRP type were consistent with the result about CRP levels and all-cause mortality. Conclusions: Elevated level of CRP was significantly associated with higher risks of all-cause and cardiovascular disease mortality in PD patients. Early detection of CRP levels in peritoneal dialysis patients is likely to identify patients at increased risk of mortality.

Keywords: C-reactive protein, mortality, peritoneal dialysis, meta-analysis

Introduction

End-stage renal disease (ESRD) has become a major public health problem worldwide. The global average prevalence of ESRD patients on dialysis was 215 per million population [1], and the total number of dialysis patients in 2010 was estimated to be close to two million [2]. Peritoneal dialysis (PD) is a popular treatment modality for ESRD patients, which has a flexible schedule, convenience of home therapy and increased freedom from the patient's perspective [3]. Despite technological advances and optimization of dialysis programs, complications such as cardiovascular events, inflammation, malnutrition and reduced residual kidney function increase the risk of mortality in PD patients. Cardiovascular disease is a leading cause of death in PD patients, according to various national and regional registries [4-7], which may be caused by chronic inflammation. In order to improve the clinical outcomes in PD

patients, it is important to identify potentially diagnostic markers to explore survival prediction and treatment strategies.

C-reactive protein (CRP) is an important inflammatory marker and it is associated with an increased risk of experiencing myocardial infarction and sudden cardiac death in apparently healthy subjects [8]. As an acute-phase reactant, CRP is also considered to be an important risk factor for pancreatic cancer, atherosclerosis, myocardial and ischemic stroke [9-11]. It has been reported that up to 30-50% of PD patients have increased CRP levels [12, 13], and both a reduction of residual renal function and peritoneal clearance were associated with CRP levels [14, 15].

Several previous studies have reported that elevated CRP levels predicted higher mortality risks in PD patients [16, 17]. Despite intensive studies in the past, the impact of CRP on the

Figure 1. Flow chart of study selection.
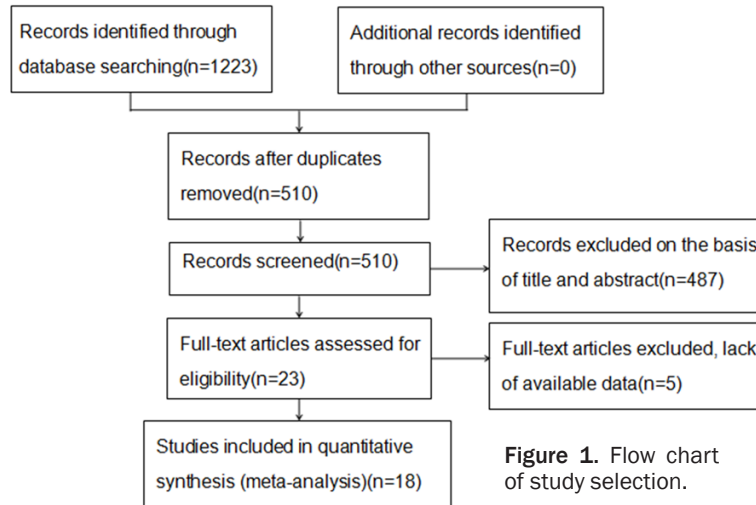
patients; (3) report associations between CRP and mortality; (4) provide sufficient information to analyze risk ratio (RR) estimates (or odds ratio (OR) estimates in cross-sectional studies) or hazard ratios (HR) estimates with their 95% confidence interval (CI). The exclusion criteria included: (1) animal and autopsy studies; (2) review articles or letters; (3) duplicate data set on the same patient populations.

Data extraction and quality assessment

survival in PD patients remains unclear. There are also contradictory results indicating insignificant links between CRP and clinical outcomes in patients undergoing PD therapy [18, 19].

Therefore, it is necessary to undertake a systematic meta-analysis to investigate whether CRP could predict mortality in PD patients. By extracting data from the latest and the maximum range of studies, we analyzed the predictive value of CRP for clinical outcome.

Material and methods

Search strategy

A systematic literature search up to March 2016 was performed in PubMed, Web of Science and the Cochrane Library. Search terms and key words: 'C-reactive protein', 'mortality' and 'peritoneal dialysis'. No language restrictions were imposed. The titles and abstracts were scanned to exclude clearly irrelevant studies. The full texts of the remaining articles were read to determine whether they contained information on the topic of interest. Furthermore, a manual search was performed to identify additional published studies by checking all the references.

Inclusion and exclusion criteria for literatures

Two authors independently assessed the eligibility of studies. The inclusion criteria included: (1) prospective, retrospective or cross-sectional study design; (2) present levels of CRP in PD

The data of studies was extracted independently by two authors (SH and ZB) and any questions or discrepancies were resolved by discussion and consensus. The following data were collected: the first author's name, year of publication, location in which the study was performed, study participants' age range, sample size, study design, duration of PD (months), outcomes (all-cause and cardiovascular disease mortality), study quality score, HR estimates of elevated level of CRP, as well as their 95% confidence interval (CI). We assessed non-randomized studies' quality using the Newcastle-Ottawa quality assessment scale. We evaluated quality of studies in meta-analysis based on three items: patient selection, comparability of groups and ascertainment of outcome [20]. If a study provided several risk estimates, the most completely adjusted estimate was collected.

Statistical analyses

The extracted data were analyzed by using Review Manager 5.3 software analysis (Cochrane Collaboration, Copenhagen, Denmark). The generic inverse variance weighting method (DerSimonian and Laird random-effects model) [21] was used to test the overall effect of crude and adjusted hazard ratios (HRs). Heterogeneity was investigated by x^2 test (P<0.1), and I^2 statistic was used to quantify its impact [22]. Publication bias was assessed using the funnel plot with the Egger's bias indicator test [23]. Sensitivity analyses were conducted by using a stepwise process to assess the robustness.

Table 1. Characteristics of studies on CRP and mortality in peritoneal dialysis patients

First author	Year	Location	Age (years)	Sample size	Study design	Duration (months)	Outcome	HR (95% CI)	Study quality
Ates K 24	2005	Turkey	18-74	97	P	33.9	ACM	1.06 (1.02-1.11)	7
Avram MM 25	2005	US	55	66	RP	49	ACM	1.03 (1.01-1.05)	7
Balafa O 26	2011	Netherlands	52.6	257	P	3.9	ACM	2.46 (1.15, 5.25)	7
Chung SH 27	2003	Sweden	24-85	117	RP	20.7	ACM	1.69 (1.16-2.47)	6
Fine A 28	2002	Canada	19-81	170	RP	NR	CVDM	1.5 (0.72-3.11)	6
Han SS 29	2010	Korea	18-84	291	RP	2.1	CVDM	6.04 (2.33-15.69)	6
Herzig KA 13	2001	Australia	25-78	50	P	1.2-140.4	ACM &CVDM	2.10 (0.80-5.40) 6.0 (0.8-43)	7
Liu SH 17	2014	Taiwan	48.6	402	Cro	73.6	ACM	1.014 (1.003-1.026)	7
Noh H 30	1998	Korea	49.0	105	P	43.5	ACM	1.1923 (1.0125-1.404)	7
Paniagua R 31	2003	Mexico	NR	75	P	2.04-20.5	CVDM	6.23 (1.01-52.89)	7
Perez Fontan M 32	2005	Spain	7-87	565	RP	1-125	ACM	1.25 (1.05-2.55)	6
Szeto CC 33	2007	China	NR	405	RP	49.7	ACM	1.112 (1.037-1.193)	7
Tung CW 34	2015	Taiwan	52.14	78	P	37.76	ACM	1.11 (1.001-1.22)	7
Wang AY 35	2003	China	55	246	P	4-151	ACM &CVDM	1.02 (1.01-1.04) 1.03 (1.01-1.05)	8
Westhuyzen J 36	2005	Australia	Non-sur:71 Sur:60.6	46	P	Non-sur:3-14 Sur:4.0-13.5	ACM	1.081 (1.007-1.160)	7
WUJingjing 37	2014	China	28-87	230	Cro	6-12	ACM	0.988 (0.977-1.000)	6
Zalunardo NY 38	2007	UK	58.9	209	P	2.4-19.2	ACM	1.79 (1.05-3.07)	5
ZHONG Hui 39	2012	China	DN:63 Non-DN:45	460	RP	DN:11.48 Non-DN:11.1	ACM	1.015 (0.983-1.049)	6

Abbreviation: P, prospective; RP, retrospective; Cro, cross-sectional; NR, not-reported; ACM, all-cause mortality; CVDM, cardiovascular disease mortality; HR, hazard ratio; CI, confidence intervals.
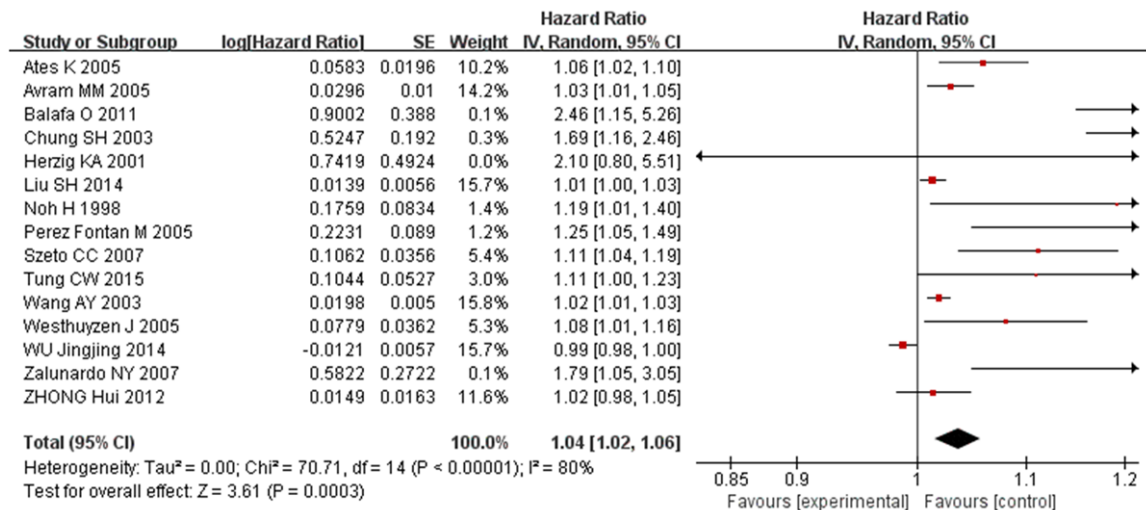

Figure 2. Forest plot showing the association between CRP levels and all-cause mortality in peritoneal dialysis patients.

Results

Studies and data included in this meta-analysis

A total of 1223 relevant citations were retrieved on initial search strategy. Of these, 713 duplicates were excluded. After screening the titles and abstracts, 487 articles were excluded because they were review articles or irrelevant to the current study. 5 publications were excluded for lacking of available data. As a result, this meta-analysis was carried out for 18 citations involving a total of 3869 patients [13, 17, 24-39], including 2 cross-sectional studies, 7 retrospective and 9 prospective studies (**Figure**

Table 2. Summary risk estimates of the association between CRP and all-cause Mortality in peritoneal dialysis patients

Subgroup	No. Of Studies	Samples	HR (95%) CI	Heterogeneity test P	I^2 (%)^	References
All studies	15	3333	1.04 1.02-1.06	P<0.0001	80	[13, 17, 24-27, 30, 32-39]
Geographic region						
Asia group	8	2023	1.03 1.01-1.05	P<0.0001	82	[17, 24, 30, 33-35, 37, 39]
Non-Asia group	7	1310	1.19 1.06-1.33	P=0.0006	75	[13, 25-27, 32, 36, 38]
Study type						
Pros group	8	1088	1.08 1.02-1.14	0.002	70	[13, 24, 26, 30, 34-36, 38]
Non-Pros group	7	2245	1.07 1.01-1.12	0.002	76	[17, 25, 27, 32, 33, 37, 39]
Sample size						
<100	5	337	1.05 1.02-1.09	0.16	39	[13, 24, 25, 34, 36]
≥100	10	2996	1.03 1.0-1.05	P<0.0001	83	[17, 26, 27, 30, 32, 33, 35, 37-39]
CRP type						
Ordinary CRP group	11	2147	1.08 1.03-1.13	P<0.0001	84	[13, 24-27, 30, 32, 33, 36-38]
Hs-CRP group	4	1186	1.02 1.01-1.03	0.34	11	[17, 34, 35, 39]

Abbreviation: Pro, prospective; Retro, retrospective; HR, hazard ratio; CI, confidence intervals; ^I^2 is interpreted as the proportion of total variation across studies that are due to heterogeneity rather than chance.
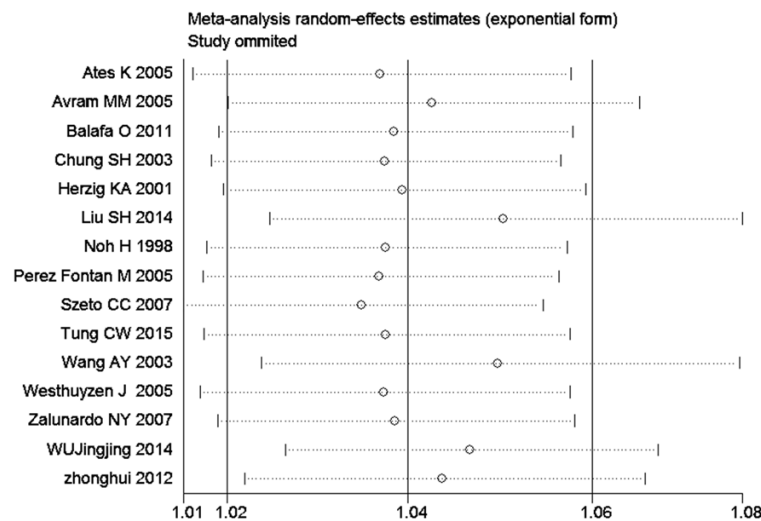

Figure 3. The stability of the study on association between CRP levels and all-cause mortality was detected through sensitivity analysis.

Association between CRP levels and all-cause mortality

The pooled HRs of all-cause mortality were shown in **Figure 2**. Findings in individual studies were controversial. 11 studies on the association of CRP with all-cause mortality showed a positive association and the association was not statistically significant in 4 studies. Overall, the association between CRP and all-cause mortality was significantly positive and the pooled HR was 1.04 (95% CI: 1.02-1.06), with significant heterogeneity between studies (P< 0.00001, I^2=80%).

1). The main characteristics of extracted reports were summarized in **Table 1**. These studies were published between 1998 and 2015. Two studies were performed in Oceania, three in North America, four in Europe and nine in Asia. The sample sizes ranged from 46 to 565 with a mean of 215 individuals. 13 studies investigated CRP and all-cause mortality, 3 studies for cardiovascular disease mortality and 2 studies reported both of them. The study quality scores ranged from 5 to 8.

Potential sources of heterogeneity in the strength of the association between CRP levels and all-cause mortality were examined by conducting subgroup analyses. The associations of CRP with all-causes mortality risk did not differ by geographic region, study type, sample size, CRP type (**Table 2**). Our meta-analysis reported that geographic region (P=0.02) and CRP type (P=0.01) introduced the source of heterogeneity.
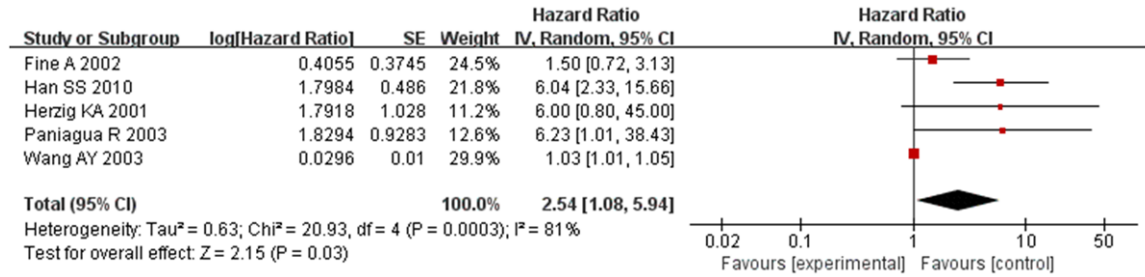
Figure 4. Forest plot showing the association between CRP levels and cardiovascular disease mortality in peritoneal dialysis patients.
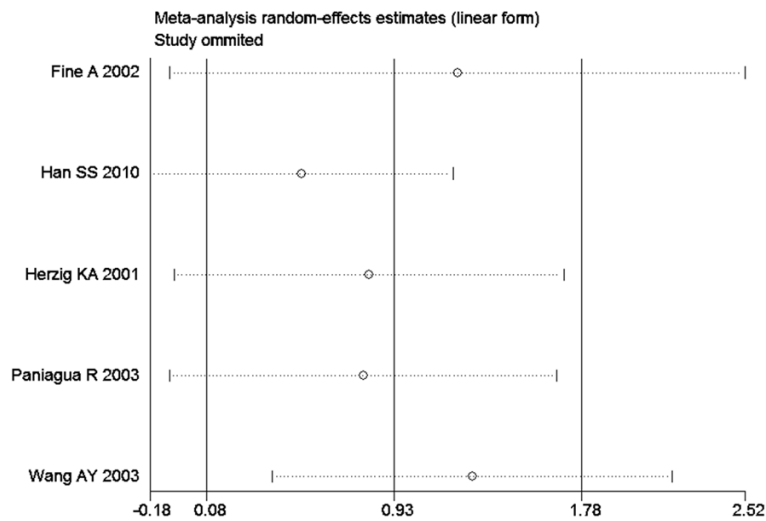

Figure 5. The stability of the study about the association between CRP levels and cardiovascular disease mortality was detected through sensitivity analysis.

We conducted the sensitivity analysis to check if any single study affected the results by omitting one study each time. The results showed that no individual study could change the final pooled results (**Figure 3**), which validated the rationality and reliability of our meta-analysis.

Association between CRP levels and cardiovascular disease mortality

The pooled HRs of cardiovascular disease mortality were shown in **Figure 4**. Results from studies on CRP and cardiovascular disease mortality were inconsistent, with both inverse and positive associations reported. 3 studies showed a positive association and it was not statistically significant in 2 studies. As a result, the association between CRP and cardiovascular disease mortality was significantly positive and the pooled HR was 2.54 (95% CI: 1.08-5.94), with significant heterogeneity between studies (P=0.0003, I^2=81%).

To explore the heterogeneity among studies of CRP with cardiovascular disease mortality, we performed sensitivity analysis by using a step wise process, we determined that most of heterogeneity was accounted for the studies performed by Han SS et al [29] and Wang AY et al [35]. After excluding the two studies, there was no heterogeneity (P=0.20, I^2=38%).

We conducted the sensitivity analysis to check if any single study affected the results by omitting one study each time. The results showed that no individual study could change the final pooled results (**Figure 5**), which validated the rationality and reliability of our meta-analysis.

Discussion

CRP is a non-glycated protein produced by human hepatocytes in response to infection, inflammation or tissue damage [40], and it is the most widely used marker of inflammatory status. In addition to its role as a marker of malnutrition, inflammation, and atherosclerosis (the MIA syndrome), CRP is also associated with morbidity and mortality in population-based studies as well as a risk prediction in patients with chronic kidney disease (CKD) [41, 42]. Ridker PM et al [11] reported that the baseline plasma concentration of C-reactive protein predicts the risk of future myocardial infarction

and stroke. Liu Y et al [43] recruited 835 PD patients and revealed that CRP is a potentially important factor affecting the prognosis of ERSD patients with PD. A systematic review performed by Li Wei-Jie et al [44] identified that CRP is significantly associated with high risks of all-cause and cardiovascular disease mortality in patients with chronic kidney disease.

CRP is a representative acute phase reactant in chronic inflammation. In recent years, an increasing number of studies have shown that CRP was associated with survival of PD patients. However, the impact of this association remains controversial. Several studies have reported that the elevation of CRP is related to the occurrence of cardiovascular events and mortality [16, 17], whereas others demonstrated that CRP is not significantly linked with mortality [18, 19]. This systemic review and meta-analysis involving 3869 participants from 18 published studies showed that CRP could significantly predict all-cause and cardiovascular disease mortality in peritoneal dialysis patients.

Approximately 30-50% of PD patients have increased CRP levels [12, 13]. The association between elevated CRP levels and mortality in PD patients could be explained by several possible mechanisms. First, CRP is an acute-phase protein that is a marker for underlying systemic inflammation. The elevated CRP level may occur in response to vascular damage and the release of proinflammatory cytokines by monocytes and macrophages recruited into early atherosclerotic plague [45]. Second, CRP may directly contribute to vascular injury via immune and vascular cell activation [46], stimulation of monocyte expression of tissue factor [47], and aggregation of degraded low density lipoprotein particles [48]. Third, the elevated serum CRP may also be linked with lower serum albumin level [49, 50], a reduction of residual renal function and peritoneal clearance [24, 28, 51]. The three aspects above are closely related to survival in PD patients [52-54].

Findings from our meta-analysis suggested that the higher CRP levels could increase the risk of all-cause mortality in PD patients. This association was also significant in the subgroup analysis of geographic region, study type, sample size and CRP type. Meanwhile, we found a high degree of heterogeneity in our pooled results about the association between CRP and all-cause mortality. Thus, we used meta-regression to explore the causes of heterogeneity for covariates and the result showed that geographic region and CRP type introduced the source of heterogeneity. Sensitivity analysis was performed by geographic region in the pooled analysis about the association between CRP levels and cardiovascular disease mortality. After excluding two studies that were conducted in Asia, the heterogeneity was removed (I^2=38%), suggesting that geographic region may affect the heterogeneity of the whole research.

However, our study had several limitations and the conclusion should be tempered. First, there was heterogeneity with these studies. To minimize the overall effect caused by the heterogeneity, we used a random-effect model and performed sensitivity and subgroup analyses to investigate potential sources of heterogeneity. Second, the technique of detecting CRP may lack comparability among the studies. Finally, we did not include unpublished studies and it is also possible that we missed some eligible data.

Our meta-analysis also had some advantages. First, a large number of participants involving 3869 PD patients in eighteen observational studies were included in our meta-analysis, providing powerful data to estimate the association between CRP and mortality. Second, all the extracted HRs were obtained from published statistics, which is more reliable than the calculated values from the data in the article. Third, we adopted Begg's funnel plot and Egger's test to assess the publication bias and the results did not show evidence of publication bias.

In summary, the current meta-analysis showed that elevated CRP levels were significantly associated with high risks of all-cause and cardiovascular disease mortality in PD patients. Early detection of CRP levels in peritoneal dialysis patients is likely to identify patients at increased risk of mortality. More studies with strict standardization, long-term follow up and representative populations are needed to further explore the risk stratification in PD patients.

Disclosure of conflict of interest

None.

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