Prognostic role of C-reactive protein and Interleukin-6 in dialysis patients: a systematic review and meta-analysis

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Wei Zhang and Jing He contributed equally to this work.

ABSTRACT

Inflammation may be associated with mortality in dialysis patients. This study aims to summarize the prognostic value of two common inflammatory markers, C-reactive protein (CRP) and Interleukin-6 (IL-6) for dialysis outcome. A total of 109 CRP studies and 22 IL-6 studies were identified from PubMed and EMBASE after systematic searching and assessment. The combined hazard ratios (HRs) of CRP and IL-6 for mortality were analyzed. For all-cause mortality (ACM), both CRP and IL-6 could significantly predict the outcome, with the pooled HRs of 1.142 (95%CI: 1.118-1.166) and 1.152 (95%CI: 1.094-1.214) for CRP and IL-6, respectively. For cardiovascular disease mortality (CVDM), the pooled HR of CRP (1.182, 95%CI: 1.134-1.232) was close to that of IL-6 (1.181, 95%CI: 1.068-1.307). Therefore, elevated levels of CRP or IL-6 were significantly associated with higher ACM and higher CVDM in dialysis patients. The predictive value of the inflammatory biomarkers may be useful in clinical practice.

Key words: C-reactive protein, Dialysis, Interleukin-6, Prognosis

INTRODUCTION

The incidence of end-stage renal disease (ESRD), known as the fifth stage of chronic renal disease, has currently reached one per hundred thousand (1). Patients suffering from ESRD require renal transplant or dialysis therapy including hemodialysis (HD) and peritoneal dialysis (PD). As dialysis patients have high mortality of all-cause or cardiovascular disease, accurate predictive markers should be applied to guide the therapy and to monitor the disease progress. Beyond the traditional biomarkers, including dialysis adequacy, anemia, nutrition biomarkers, and mineral metabolism biomarkers, inflammatory biomarkers have also been introduced to refine outcome prediction, such as C-reactive protein (CRP), TNF-α and interleukins (2, 3). Chronic inflammation is a basic feature of ESRD and is related to an increasing risk of morbidity and mortality in dialysis patients (2, 4, 5). The most widely used inflammatory markers are IL-6 and CRP. Several previous studies suggested elevated CRP or IL-6 levels predicting higher mortality risks in dialysis patients (4, 6-10). However, some other studies showed insignificant links with dialysis outcome and CRP or IL-6, including several studies recruiting a large number of subjects (11-13). Therefore, it is timely and necessary to perform a systematic meta-analysis to globally summarize the prognostic value of CRP and IL-6 in dialysis patients and to address the inconsistencies of the literature. By extracting data from all available studies, we analyzed and compared the predictive value of these two markers for dialysis outcome.

SUBJECTS AND METHODS

We performed this meta-analysis following the guidelines of the Meta-analysis of Observational Studies in Epidemiology group (MOOSE) (14).
Search strategy and quality assessment

To identify the relevant studies, we searched through the online PubMed and EMBASE database from January 1966 to January 2012. Two sets of keywords were set during that process, namely “C-reactive protein and dialysis and (outcome or survival or mortality)” and “IL-6 and dialysis and (outcome or survival or mortality)”. Studies were regarded as eligible when they met the following criteria: (1) they identified the associations between mortality and CRP or IL-6; (2) they were designed retrospectively or prospectively. Articles were excluded based on the following criteria: (1) non-English papers, (2) review articles or letters, (3) absence of key information such as sample size and hazard ratio (HR) data of CRP or IL-6 for mortality. When duplicate studies were retrieved, the studies having reported HRs, or involving more patients (usually the latest), or having longer follow-up duration were included in our systematic review. Thus, the overlap between cohorts and overestimation of the overall HR could be avoided. A flow diagram of the study selection process is presented in Figure 1.

According to a critical review checklist of the Dutch Cochrane Centre proposed by MOOSE, we systematically assessed the quality of all the studies included (14). The key points of the current checklist include (1) clear definition of study population, (2) clear definition of study design, (3) clear definition of disease, (4) clear definition of sample size, (5) clear definition of all-cause mortality (ACM) or cardiovascular disease mortality (CVDM) outcome, and (6) sufficient follow-up duration.

Data extraction and statistical analysis

The key data were extracted from each report, including sample size, follow-up duration, HR of elevated level of CRP or IL-6, as well as their 95% confidence interval (CI) and P value. If the HR value was not available in the text, it was calculated from the total numbers of observed dialysis cases and the numbers of patient deaths in each group or the Kaplan–Meier survival curves (15).

A test of heterogeneity of combined HRs was performed using Cochran’s Q test and Higgins I-squared statistic. The random effect model (Der Simonian and Laird method) was applied in the presence of between-study heterogeneity (P < .05), while the fixed effect model was used if heterogeneity was not observed (P ≥ .05). Publication bias was assessed using the funnel plot with the Egger’s bias indicator test (16). All analyses were performed on Stata: Data Analysis and Statistical Software®V10.1 (http://www stata.com/). StataCorp, Texas, USA.

Results

A total of 838 CRP studies were identified from a primary literature search. After manually screening the titles, abstracts, and key data, 671 records were excluded for not meeting the criteria listed above. Of the 167 reports selected for the detailed assessment, 50 studies were excluded for being duplicated; four studies were excluded for lack of HR (17-20); four studies were excluded for recruiting non-dialysis patients. The final meta-analysis was performed for the remaining 109 CRP studies (6, 8-12, 21-123) (Fig 1A). A similar identification process was performed in 337 studies for IL-6 and 22 studies were finally included (4, 13, 50, 52, 57, 80, 84, 86, 87, 92, 100, 110, 112, 124-132) (Fig 1B). The main features of relevant studies are summarized in Table I. We collected 120 studies including participants from Australia, Belgium, France, Germany, Netherlands, Spain, Sweden, Italy, Serbia, Turkey, Israel, Hong Kong, Taiwan,
TABLE I
SUMMARY TABLE OF THE META-ANALYSIS

<table>
<thead>
<tr>
<th>Study number according to</th>
<th>Total</th>
<th>Origin of population</th>
<th>Disease</th>
<th>Mortality</th>
<th>Subject number</th>
<th>Median Follow-up, months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>America: 22</td>
<td>PD: 14</td>
<td>CVDM: 10</td>
<td></td>
<td>Median: 36</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Asia: 34</td>
<td>Dialysis: 9</td>
<td>ACM &amp; CVDM: 36</td>
<td></td>
<td>Range: 12-69</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Africa: 0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oceania: 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Multiple center: 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-6</td>
<td>22</td>
<td>Europe: 9</td>
<td>HD: 16</td>
<td>ACM: 12</td>
<td>Median: 173</td>
<td>Range: 81-1041</td>
</tr>
<tr>
<td></td>
<td></td>
<td>America: 7</td>
<td>PD: 2</td>
<td>CVDM: 7</td>
<td></td>
<td>Median: 36</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Asia: 6</td>
<td>Dialysis: 4</td>
<td>ACM &amp; CVDM: 3</td>
<td></td>
<td>Range: 12-196</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Africa: 0</td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oceania: 0</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Disease is reported as hemodialysis (HD), peritoneal dialysis (PD), or dialysis.
ACM = all-cause mortality; CVDM = cardiovascular disease mortality.

Table 1

<table>
<thead>
<tr>
<th>Study number</th>
<th>CRP</th>
<th>IL-6</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

Fig. 2 - Forest plots and meta-analysis of studies assessing hazard ratios of high inflammatory levels as compared to low levels. A-B) CRP; C-D) IL-6. Mortality data are reported as all-cause mortality (ACM) (A, C) and cardiovascular disease mortality (CVDM) (B, D).
Fig. 2 - Forest plots and meta-analysis of studies assessing hazard ratios of high inflammatory levels as compared to low levels. A-B) CRP; C-D) IL-6. Mortality data are reported as all-cause mortality (ACM) (A, C) and cardiovascular disease mortality (CVDM) (B, D).

Japan, Korea, Canada, US, Mexico, Brazil, etc. Among them, 109 studies investigated CRP with 95 studies for ACM (n=78585) and 48 studies for CVDM (n=61183); 22 studies dealt with IL-6 with 20 studies for ACM (n=4527) and 10 studies for CVDM (n=3139). Approximately four-fifths of the total studies recruited hemodialysis patients, whereas the others included peritoneal dialysis patients or both. The subject number for each study ranged from 43 to 45390 and median follow-up duration was 36 months.

For studies assessing ACM, there appeared to be heterogeneity among CRP studies and among IL-6 studies, since the P values of both were less than .05. Two inflammatory markers were found to be significantly correlated with ACM, with the pooled HR being 1.142 (95% CI: 1.118-1.166) and 1.152 (95% CI: 1.094-1.214) for CRP and IL-6, respectively (Fig. 2 A, C). Similarly, elevated levels of these inflammatory markers could predict worse CVDM outcome, with the pooled HR being 1.182 (95% CI: 1.134-1.232) and 1.181 (95% CI: 1.068-1.307) for CRP and IL-6, respectively (Fig. 2 B, D). Therefore, both CRP and IL-6 proved to have a prognostic value for ACM and CVDM. Thereafter, publication bias of the studies included was assessed by funnel plots and Egger’s tests as shown in Figure 3 and Table II. To ascertain whether race or genetics influence the results, Asia studies were separated from Western studies. The pooled HRs of CRP for Asia studies were 1.140 (95% CI: 1.095-1.187) and 1.252 (95%: 1.141-1.375) for ACM and CVDM, respectively. The data were close to those of Western studies, which...
Fig. 3 - Funnel plots for studies included in the six meta-analyses. Plots are arranged as follows: A) CRP ACM; B) CRP CVDM; C) IL-6 ACM; D) IL-6 CVDM.

TABLE II
COMPARISON OF THE PREDICTING VALUE OF CRP AND IL-6 IN DIALYSIS PATIENTS

<table>
<thead>
<tr>
<th></th>
<th>ACM</th>
<th>CVDM</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP HR</td>
<td>1.142 (1.118-1.166)</td>
<td>1.182 (1.134-1.232)</td>
</tr>
<tr>
<td>Heterogeneity, P value</td>
<td>.000</td>
<td>.000</td>
</tr>
<tr>
<td>Model</td>
<td>Random</td>
<td>Random</td>
</tr>
<tr>
<td>Bias, P value</td>
<td>.000</td>
<td>.000</td>
</tr>
<tr>
<td>N</td>
<td>78585</td>
<td>61183</td>
</tr>
<tr>
<td>Study</td>
<td>95</td>
<td>47</td>
</tr>
<tr>
<td>IL-6 HR</td>
<td>1.152 (1.094-1.214)</td>
<td>1.181 (1.068-1.307)</td>
</tr>
<tr>
<td>Heterogeneity, P value</td>
<td>.000</td>
<td>.000</td>
</tr>
<tr>
<td>Model</td>
<td>Random</td>
<td>Random</td>
</tr>
<tr>
<td>Bias, P value</td>
<td>.000</td>
<td>.000</td>
</tr>
<tr>
<td>N</td>
<td>4527</td>
<td>3139</td>
</tr>
<tr>
<td>Study</td>
<td>19</td>
<td>10</td>
</tr>
</tbody>
</table>

ACM = all-cause mortality; CVDM = cardiovascular disease mortality.
were 1.148 (95%CI: 1.118-1.179) and 1.198 (95%CI: 1.136-1.264). Thus, the origin of the population may not impact the predictive role of CRP. Because of the limited study number, IL-6 studies were not stratified into subgroups according to their origin.

**DISCUSSION**

This systemic review and meta-analysis, which recruited 120 studies, showed that CRP and IL-6 could significantly predict all-cause or cardiovascular disease mortality in dialysis patients. However, this meta-analysis had several limitations and the conclusion should be tempered. First, marked heterogeneity of subjects existed in CRP and IL-6 groups. The heterogeneity of the population was probably because of the difference in the baseline characteristics of patients (age, sex, race or country, HD or PD), the cut-off value of CRP and IL-6, the duration of follow-up, and others. To minimize the residual confounding effect caused by the heterogeneity within these studies, a random effect model was applied. Furthermore, publication bias was detected in all four analyses, and this cannot be adequately overcome by currently available statistical techniques. In addition, all four combined HRs were more than one but less than two, empirically considered significantly but not strongly predictive when HR more than 2 was empirically considered as the cut-off for a strong predictor.

In addition to CRP and IL-6, other inflammatory factors such as IL-1, IL-18, TNF-α, and P-selectin, can also predict mortality in dialysis patients (133, 134). However, these markers have limited application in clinical practice because of several disadvantages such as low concentration or short lasting time. To date, CRP and IL-6 are the most widely-used biomarkers for predicting mortality in dialysis patients. Some previous studies have compared the prognostic value of CRP and IL-6 for dialysis outcome. Honda et al reported IL-6 to be a stronger predictor than CRP for ACM and CVDM (50). However, Panichi et al found CRP could strongly predict mortality, while IL-6 could not predict CVDM significantly (86). Interestingly, a recent study reported that the race difference influenced their prognostic value. Noori et al reported comparable HRs (2.4 for CRP, 2.2 for IL-6) in African American and different HRs (1.87 for CRP, 4.13 for IL-6) in whites (80). Our data showed that both CRP and IL-6 had similar predictive value for either ACM or CVDM. A new strategy is to combine several inflammatory biomarkers to improve the predictive accuracy. When a panel of markers (CRP, IL-1β, IL-6, IL-18, and TNF-α) was applied to predict mortality, the HR was much higher than that of a single marker (135). Cohen et al also used a panel of inflammatory cytokines to stratify dialysis patients into pro-inflammatory, anti-inflammatory, and other patients, and they found the pro-inflammatory patients had the highest risk of death (136).

As our meta-analysis suggested that inflammatory markers such as CRP and IL-6 were significant markers for ACM and CVDM in dialysis patients, we recommend that inflammation be monitored regularly. Our data suggested that measuring baseline inflammatory markers could provide information about outcome. Recently, some researchers also suggested monitoring their time-course oscillations. Although the association between longitudinal inflammatory variation and risk prediction has only been examined in a few studies, the repeated elevations of CRP may be more predictive than a single elevation (2). Another important issue is the cut-off value, which defines how high is dangerous. In our meta analysis each of the articles chose a different cut-off, with some of them using median, some using 10 mg/L for CRP, some using 5 mg/L, and some considering CRP variable as continuous but not dichotomy (data not shown). We suggest addressing this inconsistency in future studies.

In summary, our meta-analysis, representing quantified synthesis of eligible studies, showed that both CRP and IL-6 could significantly predict all-cause and CVD mortality in dialysis patients. The critical role of CRP and IL-6 in dialysis prognosis may contribute to their clinical utility.

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Conflict of interest statement: We have no conflict of interest to declare.
REFERENCES


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