Patterns of C-reactive Protein and Mortality in Dialysis Patients

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MONDO: Monitoring Dialysis Outcomes

Introduction

Markers of inflammation, such as C-reactive protein (CRP), are associated with increased mortality risk in the general population [1] and in hemodialysis (HD) patients [2]. We showed previously a rise of CRP in chronic HD patients before death (Figure 1) [3]. This finding was independent of gender and region of the world. Since CRP is a marker of both chronic inflammation and acute infections and because there is considerable intra-individual variability [4], monitoring of CRP for risk assessment in HD patients has been questioned. Here we explore the association of CRP levels and of CRP variability with mortality risk.

Methods

The MONDO consortium consists of HD databases from North and South America, Europe, and Asia. We assessed the concentration of CRP and CRP-variability within the first year (baseline) in incident HD patients who survived >365 days and observed survival in the following 365 days. CRP means and coefficients of variation (CoV) were calculated for patients who had ≥ 4 CRP measurements in their baseline period. Routine CRP measurements for this analysis were available from patients in Europe only. Patients were grouped into tertiles of baseline CRP and CRP-CoV, respectively. A Cox-proportional hazards model was constructed to assess hazard ratios (HR) for mortality adjusted for age, sex, diabetes, and the first year means of weight, blood pressure, weight gain, and albumin.

Results

CRP was available in a total of 9918 incident patients, 3822 from Germany and 6096 from 15 other European countries, including 10 in (South-) Eastern Europe (Table 1). Based on a mean of 8 CRP values (range 4-12) obtained in the course of the first year on dialysis, levels ≥ 7.7mg/L were associated with increased mortality risk in the following year (Figure 2). Notably, when average CRP was medium or high, low variability, as indicated by a low coefficient of variation (CoV), was associated with higher risk than high variability of CRP. This suggests that, for the same average CRP level, stable elevation of CRP confers the same or even higher risk than multiple acute increases of CRP, as would occur with repeated infections or episodes of inflammation.

Conclusion

Elevated CRP levels are known to be associated with increased mortality risk in HD patients. Interestingly, not only absolute levels of CRP but also CRP variability is associated with mortality risk. It is those patients with relatively steady elevations (i.e., low CRP variability) that seem at greatest risk for mortality. Taken together with previous observations of a rise in CRP prior to death, monitoring of longitudinal trends of CRP is likely to offer important information for risk prediction in HD patients.

Table 1: Baseline characteristics of patients initiating dialysis. All continuous variables are presented as mean (95% CI)

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Age [y]</th>
<th>% Male</th>
<th>% Diabetic</th>
<th>Albumin [g/dL]</th>
<th>Post-dialysis weight [kg]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europe</td>
<td>6096</td>
<td>61.3</td>
<td>58.7</td>
<td>21.7</td>
<td>3.86 (3.84-3.88)</td>
</tr>
<tr>
<td>Germany</td>
<td>3822</td>
<td>61.8</td>
<td>59.7</td>
<td>43.1</td>
<td>3.48 (3.47-3.50)</td>
</tr>
</tbody>
</table>

Figure 2: Hazard Ratios of mortality associated with CRP-elevation and CRP-variability, respectively. Levels of CRP were grouped into low (< 7.7mg/L), medium (7.7 – 18.7 mg/L) and high (> 18.7 mg/L), respectively. Similarly, CoV was grouped into low (< 0.74%), medium (0.74 – 1.21%) and high (>1.21%). Hazard ratios were adjusted for age, sex, diabetes, blood pressure, weight gain, and albumin. Ref: reference; P values denote statistical significance for comparison with reference group.