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Authors
Rattanasompattikul, Manoch
Molnar, Miklos Z.
Zaritsky, Joshua J.
et al.

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Association of malnutrition–inflammation complex and responsiveness to erythropoiesis-stimulating agents in long-term hemodialysis patients

Manoch Rattanasompattikul1,2,9,*
  Miklos Z. Molnar1,3,4,*
  Joshua J. Zaritsky5
  Parta Hatamizadeh1,2
  Jennie Jing1
  Keith C. Norris6
  Csaba P. Kovesdy7,8
  and Kamyar Kalantar-Zadeh1,10

1Harold Simmons Center for Chronic Disease Research and Epidemiology, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, CA, USA,
2Division of Nephrology and Hypertension, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, CA, USA,
3Institute of Pathophysiology, Semmelweis University, Budapest, Hungary,
4Division of Nephrology, Department of Medicine, University Health Network, University of Toronto, Toronto, Ontario, Canada,
5Department of Pediatrics, David Geffen School of Medicine, UCLA, Los Angeles, CA, USA,
6Department of Medicine, Charles Drew University, Los Angeles, CA, USA,
7Division of Nephrology, Memphis Veterans Affairs Medical Center, Memphis, TN,
8Division of Nephrology, University of Tennessee Health Science Center, Memphis, TN, and
9Division of Nephrology, University of Tennessee Health Science Center, Memphis, TN and
10Division of Nephrology & Hypertension, University of California Irvine, School of Medicine

Keywords: erythropoietin-stimulating agent (ESA) therapy, hemoglobin, inflammatory marker, malnutrition–inflammation complex, responsiveness to ESAs

Correspondence and offprint requests to: Kamyar Kalantar-Zadeh, E-mail: kkz@uci.edu

*These two authors contributed equally.

ABSTRACT

Background. Protein-energy wasting, inflammation and refractory anemia are common in long-term hemodialysis patients. A decreased responsiveness to erythropoiesis-stimulating agents (ESA) is often the cause of the refractory anemia. We hypothesized that the malnutrition–inflammation complex is an independent predictor of decreased responsiveness to ESAs in hemodialysis patients.

Methods. This cohort study of 754 hemodialysis patients was examined for an association between inflammatory and nutritional markers, including the malnutrition–inflammation score (MIS) and responsiveness to ESA. Cubic spline models were fitted to verify found associations.

Results. The mean ±SD age of patients was 54 ± 15 years, 53% were diabetic and 32% blacks. MIS was worse in the highest quartile of ESAs responsiveness index (ERI, ESA dose divided by hemoglobin) when compared with 1st quartile (6.5 ± 4.5 versus 4.4 ± 3.4; P < 0.001). Both C-reactive protein (log CRP) (β = 0.19) and interleukin-6 (log IL-6) (β = 0.32) were strong and independent predictors of ERI using multivariate linear regression. Serum albumin (β = −0.30) and prealbumin levels (β = −0.14) were inversely associated with ERI. Each 1 SD higher MIS, higher CRP and lower albumin were
associated with 86, 44 and 97% higher likelihood of having highest versus three lowest ERI quartiles in fully adjusted models [odds ratio (and 95% confidence interval) of 1.86 (1.31–2.85), 1.44 (1.08–1.92) and 1.97 (1.41–2.78)], respectively. Cubic splines confirmed the continuous and incremental nature of these associations.

Conclusions. Malnutrition–inflammation complex is an incremental predictor of poor responsiveness to ESAs in hemodialysis patients. Further studies are needed to assess whether modulating inflammatory or nutritional processes can improve anemia management.

INTRODUCTION

Protein-energy wasting (PEW) and inflammation are closely associated in patients on maintenance hemodialysis (MHD) [1, 2]. Chronic inflammation is common in uremic patients, in part because of genetic predisposition [3, 4], but also because of factors related to the decreased glomerular filtration rate (GFR) and to the dialysis procedure itself [5, 6]. An association between inflammation, nutrition and anemia has been reported in hemodialysis patients [7]. Moreover, in the National Health and Nutrition Examination Survey (NHANES) III population, Eustace et al. [8] found an association between the risk of having an increased CRP level with decreasing estimated GFR. Inflammation is an important cause of uremic cachexia, and baseline serum C-reactive protein (CRP) level independently predicts a decrease in fat mass over time in patients on maintenance dialysis [9]. The recognition of the link between inflammation and malnutrition resulted in the description of a syndrome called malnutrition–inflammation complex syndrome (MICS) or PEW [10].

The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) defined the hyporesponsiveness to erythropoiesis-stimulating agents (ESA) as the presence of at least one of the following three conditions: (i) a significant decrease in hemoglobin level at a constant ESA dose; (ii) a significant increase in the ESA dose requirement to preserve a certain hemoglobin level or (iii) a failure to raise the hemoglobin level to >11 g/dL despite an ESA dose equivalent to erythropoietin >500 IU/kg/week [11]. Although anemia has been associated with increased rates of death and complications in patients with chronic kidney disease (CKD) who are undergoing dialysis and in those not undergoing dialysis [12, 13], a reduced hematopoietic response to ESAs has also been associated with an increased risk of an adverse outcome [14–18]. Additionally, previous studies have shown an association between erythropoietin resistance and mortality among CKD patients [19, 20]. It has been suggested that the dose of ESA is a frequently neglected confounder for the association between hemoglobin and mortality in randomized trials and that the variable ESA requirements may potentially and plausibly generate confounding by indication [21].

Several studies revealed the association between ESAs responsiveness index (ERI) and nutrition and inflammatory markers in hemodialysis patients [22–26]. Wei et al. [27] studied 44 peritoneal dialysis patients and found that patients who need EPO ≥ 150 U/kg/week had higher CRP and lower serum albumin. Another recent large cohort study, which measured CRP in 1754 hemodialysis patients found that patients in the upper CRP quartiles were more likely to be older, recently hospitalized, have a catheter as vascular access, have lower albumin, hemoglobin and transferrin saturation levels and receive higher ESA doses [28]. In our prior smaller study of only 385 patients from the first 12 months of our current cohort [The Nutritional and Inflammatory Evaluation in Dialysis (NIED) study], we found differences in levels of inflammatory markers across increments of ESA dose per kilogram; however, we did not examine systematically ERI over a longer period of time [29]. Larger national cohort studies did examine more elaborate nutritional and inflammatory markers such as pro-inflammatory cytokines and their associations with ESA hyporesponsiveness [30, 31]. Moreover, novel techniques of illustrating trends and incremental associations have not been used previously.

In the current study, we assessed the association between inflammatory and nutritional markers and ERI in 754 patients over a 5-year period (2001–06) using a combination of logistic regressions with cubic spline modeling. We hypothesized that higher levels of inflammatory markers and lower levels of nutritional markers, representing worse malnutrition–inflammation complex, are independent predictors of ERI in patients on MHD.

MATERIALS AND METHODS

Patient population

We studied MHD patients who participated in the NIED study [29]. The original NIED cohort consisted of 754 patients who were recruited from a population base of more than 3000 MHD outpatients treated in eight DaVita maintenance dialysis clinics in Southern California during a period of 6 years. To be included in the study, patients had to be at least 18 years old and receiving outpatient hemodialysis for at least 8 weeks. Patients were excluded if they had an acute infection or had a life expectancy of <6 months. The study was approved by the relevant institutional review committees and all subjects gave informed consent prior to being enrolled in the study. The medical records for each subject were thoroughly reviewed by a collaborating physician in the study. Information such as underlying kidney disease, cardiovascular disease history and other illnesses was abstracted.

Erythropoietin therapy and responsiveness to ESA

In all seven dialysis facilities, precise documentation of the administered doses of recombinant human erythropoietin or epoetin alfa (Epogen) (ESA) and iron was available. The total dose of ESA (U/week) among all 754 MHD patients of this analysis was calculated over the first 13-week (3 month) interval after patients entered the 5-year (7/2001–6/2006) cohort. The average weekly ESA dose then was calculated by dividing the total 3-month dose by 13. For those patients who missed more than 1 week of dialysis treatment or who left the cohort before the end of the third month (because of death,
transplant), the average ESA dose/week was calculated using the actual numbers of weeks they contributed to the cohort. ESA responsiveness (resistance) index was defined as the average weekly ESA dose divided by the average blood hemoglobin as described by Gunnell et al. [32] to normalize the amount of required ESA for the degree of severity of anemia. Most nephrologists were not aware of the periods in which this analysis was conducted. We assumed that all nephrologists treated the anemia of their MHD patients according to NKF-DQG guidelines [33], i.e. to achieve a targeted hemoglobin of 11–12 g/dL (110–120 g/L) and/or a hematocrit of 33–36%.

**Malnutrition inflammation score**

Using the seven components of the conventional Subjective Global Assessment of Nutrition (SGA), a semiquantitative scale with three severity levels, and combining it with three new elements [body mass index (BMI), serum albumin and total iron binding capacity (TIBC) to represent serum transferrin] in an incremental fashion, the so-called malnutrition–inflammation score (MIS) with 10 components has been created [1]. Each MIS component has four levels of severity from 0 (normal) to 3 (very severe). The sum of all 10 MIS components ranges from 0 to 30, denoting increasing degrees of severity. In a prospective study in MHD patients, the MIS was compared with the conventional SGA and its refinements, anthropometry, near-infrared measured body fat percentage, laboratory measures including serum CRP, and 12-month prospective hospitalization and mortality rates [1]. The MIS was found to be a comprehensive scoring system with significant associations with prospective hospitalization and mortality as well as measures of nutrition, inflammation and anemia in MHD patients, and was superior to conventional SGA and to individual laboratory values as a predictor of dialysis outcome and an indicator of MICS. In this study, MHD patients were scored by collaborating renal dietitians who were trained adequately for this purpose. To evaluate the degree of reproducibility, the MIS was reassessed randomly by a physician on a subset of 24 patients without reference to the first MIS evaluation. The correlation coefficient \(r\) between the two MIS assessments was 0.88 denoting a high degree of reproducibility.

**Laboratory tests**

Pre- and post-dialysis blood samples were obtained on a mid-week day that coincided with the day that the required quarterly blood drawings were obtained for testing at the DaVita dialysis facilities. Single-pooled Kt/V was used to represent the weekly dialysis dose. All laboratory studies were performed by DaVita Laboratories (Deland, FL) using automated methods. Serum high-sensitivity CRP was measured using a turbidimetric immunoassay (WPCI, Osaka, Japan; normal range <3.0 mg/L) [34, 35]. Interleukin-6 (IL-6) and tumor necrosis factor-\(\alpha\) (TNF-\(\alpha\)) levels were measured with using immunoassay kits (R&D Systems, Minneapolis, MN; units: pg/mL; normal range: IL-6: <9.9 pg/mL, TNF-\(\alpha\): <4.7 pg/mL) [36, 37]. The CRP, TNF-\(\alpha\) and IL-6 levels were measured in the General Clinical Research Center Laboratories at Harbor UCLA. Serum transthyretin (prealbumin) was measured by immunoprecipitation and plasma homocysteine concentration was measured by high-performance liquid chromatography in the Harbor-UCLA Clinical Laboratories.

**Statistical methods**

The NIED study was a prospective study, while our analyses were cross-sectional using baseline data at the inception of the cohort. Data were summarized using proportions, means [standard deviation (SD)] or medians (inter-quartile range) as appropriate. Categorical variables were compared using \(\chi^2\) tests, and continuous variables were compared using t-tests or the Mann–Whitney U-tests, the Kruskal–Wallis H-tests or analyses of variance, as appropriate. We used Pearson’s and Spearman’s rank-order correlation coefficients for selected analyses where indicated. Multivariate regression analyses including linear and logistic regression were performed to assess the association between inflammatory/nutritional markers and ERI. In our fully adjusted model, we adjusted for age, gender, race, diabetes mellitus, dialysis center, insurance (Medicaid versus others), Kt/V (single pool), blood hemoglobin, serum iron saturation ratio, the Charlson comorbidity score, dialysis vintage and intact parathyroid hormone. The associations were assessed using fractional polynomials and restricted cubic splines. Data analysis was performed using STATA version 11.1 (STATA Corporation, College Station, TX).

**RESULTS**

Table 1 shows the descriptive analyses of all 754 hemodialysis patients among ERI quartile groups. The mean age was 54 ± 15 years, the proportion of males was 53%, 53% were diabetic and the mean dialysis duration time (vintage) was 30 ± 34 months. Consistent with the Southern California location of the dialysis clinics, this study population had a substantial Hispanic contribution of 49%, and 32% of patients were black. Patients with higher ERI had higher MIS, CRP and IL-6 levels and lower levels of nutritional markers such as serum albumin, prealbumin and percentage of lymphocytes.

Table 2 shows multivariate linear regression between responsiveness to ESA and relevant nutritional and inflammatory values after adjustment for several important confounders in our fully adjusted model. Both CRP (log CRP) (\(\beta = 0.19\)) and logarithm of IL-6 (log IL-6) (\(\beta = 0.32\)) were strong and independent predictors of ERI using multivariate linear regression. In addition, serum albumin (\(\beta = −0.30\)) and prealbumin levels (\(\beta = −0.14\)) were also found as negative independent predictors of ERI. In addition, a significant, moderate positive correlation was found between ERI and inflammatory markers such as log CRP (\(R = 0.18\)) (Figure 1, upper panel) and log IL6 (\(R = 0.31\)) (Figure 1, lower panel).

Table 3 shows the likelihood of ESA the worst hyporesponsiveness using multivariate logistic regression analyses to compare the highest (worse) versus three lowest quartiles (as reference) of responsiveness to ESA. The likelihood of belonging to the highest ERI quartile compared with three lowest quartiles increased by 86% for every 1 SD higher MIS [odds ratio (OR) = 1.86 95% confidence interval (CI): 1.31–2.85], by 44% for every 1 SD higher of CRP [OR = 1.44 95% CI: 1.08–
Table 1. Descriptive analysis of the demographic and laboratory data of all 754 MHD patients and a comparison among ERI across four quartiles

<table>
<thead>
<tr>
<th></th>
<th>Total ((n = 754))</th>
<th>ERI (quartile 1) ((n = 189)); best responsiveness</th>
<th>ERI (quartile 2) ((n = 188))</th>
<th>ERI (quartile 3) ((n = 189))</th>
<th>ERI (quartile 4) ((n = 188)); worse responsiveness</th>
<th>(P)-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (% men)</td>
<td>53</td>
<td>59</td>
<td>49</td>
<td>55</td>
<td>48</td>
<td>0.09</td>
</tr>
<tr>
<td>Age (year)</td>
<td>54 ± 15</td>
<td>55 ± 15</td>
<td>55 ± 14</td>
<td>53 ± 16</td>
<td>53 ± 14</td>
<td>0.58</td>
</tr>
<tr>
<td>Vintage time (months)</td>
<td>30 ± 34</td>
<td>33 ± 36</td>
<td>27 ± 27</td>
<td>30 ± 37</td>
<td>32 ± 35</td>
<td>0.29</td>
</tr>
<tr>
<td>Ethnicity (Hispanics %)</td>
<td>49</td>
<td>48</td>
<td>53</td>
<td>54</td>
<td>43</td>
<td>0.10</td>
</tr>
<tr>
<td>Race (% black)</td>
<td>32</td>
<td>29</td>
<td>30</td>
<td>29</td>
<td>42</td>
<td>0.01</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>53</td>
<td>59</td>
<td>49</td>
<td>55</td>
<td>48</td>
<td>0.10</td>
</tr>
<tr>
<td>SLE (%)</td>
<td>2</td>
<td>0</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>0.17</td>
</tr>
<tr>
<td>Glomerulonephritis (%)</td>
<td>9</td>
<td>10</td>
<td>7</td>
<td>11</td>
<td>8</td>
<td>0.57</td>
</tr>
<tr>
<td>Polycystic kidney disease (%)</td>
<td>1.5</td>
<td>3</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>0.08</td>
</tr>
<tr>
<td>ESA dose (U/week)</td>
<td>7032 ± 4963</td>
<td>2184 ± 787</td>
<td>4715 ± 832</td>
<td>7837 ± 978</td>
<td>13 415 ± 5113</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ESA dose per weight (U/kg/week)</td>
<td>102 ± 75</td>
<td>32 ± 14</td>
<td>70 ± 26</td>
<td>114 ± 29</td>
<td>187 ± 82</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ESA response index (ESA/Hb)</td>
<td>600 ± 459</td>
<td>177 ± 64</td>
<td>387 ± 64</td>
<td>644 ± 77</td>
<td>1,196 ± 499</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ESA response/wt (ESA/Hb/kg)</td>
<td>8.71 ± 7</td>
<td>2.57 ± 1</td>
<td>5.80 ± 2</td>
<td>9.35 ± 2</td>
<td>16.67 ± 8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MIS</td>
<td>5.1 ± 3.6</td>
<td>4.4 ± 3.4</td>
<td>4.5 ± 3.2</td>
<td>4.5 ± 3.1</td>
<td>6.4 ± 4.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Blood Hb (g/dL)</td>
<td>12.1 ± 0.9</td>
<td>12.4 ± 0.7</td>
<td>12.2 ± 0.8</td>
<td>12.2 ± 0.9</td>
<td>11.4 ± 1.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lymphocyte count (%)</td>
<td>23 ± 8</td>
<td>24 ± 7.5</td>
<td>23 ± 7</td>
<td>23 ± 8</td>
<td>21 ± 8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26 ± 6.1</td>
<td>26 ± 5.1</td>
<td>26 ± 5.4</td>
<td>27 ± 6.1</td>
<td>27 ± 7.3</td>
<td>0.07</td>
</tr>
<tr>
<td>Kt/V (single pool)</td>
<td>1.61 ± 0.31</td>
<td>1.59 ± 0.28</td>
<td>1.62 ± 0.27</td>
<td>1.63 ± 0.35</td>
<td>1.59 ± 0.33</td>
<td>0.50</td>
</tr>
<tr>
<td>nPCR (g/kg/dL)</td>
<td>1.06 ± 0.24</td>
<td>1.03 ± 0.26</td>
<td>1.09 ± 0.24</td>
<td>1.08 ± 0.23</td>
<td>1.04 ± 0.25</td>
<td>0.05</td>
</tr>
<tr>
<td>Serum ferritin (ng/mL)</td>
<td>569 ± 412</td>
<td>590 ± 367</td>
<td>552 ± 414</td>
<td>548 ± 426</td>
<td>546 ± 496</td>
<td>0.72</td>
</tr>
<tr>
<td>Serum iron (ng/mL)</td>
<td>66 ± 27</td>
<td>75 ± 25</td>
<td>67 ± 27</td>
<td>68 ± 25</td>
<td>55 ± 26</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TIBC (mg/dL)</td>
<td>208 ± 40</td>
<td>211 ± 35</td>
<td>210 ± 38</td>
<td>208 ± 36</td>
<td>203 ± 49</td>
<td>0.24</td>
</tr>
<tr>
<td>Iron saturation (%)</td>
<td>32 ± 11</td>
<td>35 ± 11</td>
<td>35 ± 11</td>
<td>31 ± 11</td>
<td>27 ± 10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>3.88 ± 0.38</td>
<td>3.98 ± 0.33</td>
<td>3.94 ± 0.35</td>
<td>3.94 ± 0.32</td>
<td>3.71 ± 0.46</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prealbumin (mg/dL)</td>
<td>28.29 ± 9.6</td>
<td>29.7 ± 9</td>
<td>28.5 ± 10</td>
<td>28.8 ± 9.6</td>
<td>26.14 ± 9.6</td>
<td>0.006</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>80.6 ± 32.3</td>
<td>85.6 ± 32.6</td>
<td>80 ± 36</td>
<td>76.5 ± 27</td>
<td>79.3 ± 32.5</td>
<td>0.23</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>5.62 ± 6.7</td>
<td>4.47 ± 6.4</td>
<td>4.98 ± 5.28</td>
<td>5.56 ± 5.79</td>
<td>7.36 ± 8.94</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IL6 (ng/mL)</td>
<td>17.25 ± 48.29</td>
<td>12.32 ± 46.16</td>
<td>18.77 ± 68.44</td>
<td>12.95 ± 22.33</td>
<td>26.11 ± 55.94</td>
<td>0.03</td>
</tr>
<tr>
<td>TNF-α (ng/mL)</td>
<td>8.57 ± 11.50</td>
<td>7.49 ± 9.29</td>
<td>8.99 ± 12.99</td>
<td>9.17 ± 11.26</td>
<td>9.56 ± 13.99</td>
<td>0.24</td>
</tr>
</tbody>
</table>

Continued
The associations of different inflammatory and nutritional markers with ERI are shown in Figure 2. The association between serum albumin and higher ERI was decremental (Figure 2A). Similar to albumin, lower prealbumin was associated with higher ERI (Figure 2B). In the case of inflammatory markers, lower C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) were associated with higher ERI. This indicates an inverse relationship between these markers and ERI, suggesting a protective effect against inflammation for patients with higher ERI.

Continuous values are expressed as mean ± SD (range). Count data are expressed as percentages. The cohort includes hemodialysis patients who have been treated with hemodialysis for more than 45 days.

*Categorical variables were compared using χ² tests, and continuous variables were compared using t-tests or Mann–Whitney U-tests, the Kruskal–Wallis H-tests or analyses of variance, as appropriate.

**Table 1. Continued**

<table>
<thead>
<tr>
<th></th>
<th>Total (n = 754)</th>
<th>ERI (quartile 1) (n = 189); best responsiveness</th>
<th>ERI (quartile 2) (n = 188)</th>
<th>ERI (quartile 3) (n = 189)</th>
<th>ERI (quartile 4) (n = 188); worse responsiveness</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intact PTH (mcu/L)</td>
<td>319 ± 341</td>
<td>299 ± 322</td>
<td>279 ± 259</td>
<td>319 ± 314</td>
<td>369 ± 441</td>
<td>0.06</td>
</tr>
<tr>
<td>Charlson comorbidity score</td>
<td>1.9 ± 1.6</td>
<td>1.8 ± 1.6</td>
<td>2 ± 1.6</td>
<td>2 ± 1.6</td>
<td>2 ± 1.7</td>
<td>0.16</td>
</tr>
</tbody>
</table>

Continuous values are expressed as mean ± SD (range). Count data are expressed as percentages. The cohort includes hemodialysis patients who have been treated with hemodialysis for more than 45 days.

**Table 2. Predictors of ERI using multivariate regression analyses (fully adjusted model)**

<table>
<thead>
<tr>
<th></th>
<th>β</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood lymphocyte percentage</td>
<td>−0.214</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MIS</td>
<td>+0.029</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>nPCR</td>
<td>+0.020</td>
<td>0.69</td>
</tr>
<tr>
<td>Serum albumin</td>
<td>−0.301</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum prealbumin</td>
<td>−0.143</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ferritin</td>
<td>+0.103</td>
<td>0.04</td>
</tr>
<tr>
<td>TIBC</td>
<td>−0.226</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum iron</td>
<td>−0.215</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TSAT (%)</td>
<td>−0.084</td>
<td>0.09</td>
</tr>
<tr>
<td>Log CRP</td>
<td>+0.193</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Log IL-6</td>
<td>+0.318</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Log TNF-α</td>
<td>+0.036</td>
<td>0.48</td>
</tr>
<tr>
<td>Intact PTH</td>
<td>+0.151</td>
<td>0.003</td>
</tr>
</tbody>
</table>

*Fully adjusted model adjusted for the value for conventional case-mix features (sex, age, race and presence of diabetes), dialysis center, ZIP code, insurance status (fully Medicaid versus others), Kt/V (single pool), blood hematocrit, the Charlson comorbidity score and dialysis vintage. MIS, malnutrition inflammatory score; TIBC, total iron binding capacity; nPCR, normalized protein catabolic rate; TSAT, transferrin saturation; CRP, C-reactive protein; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α.

**Figure 1**: Scatter diagram showing the association between two inflammatory markers and ERI in 754 long-term hemodialysis patients. Upper panel: logarithm of CRP; and lower panel: logarithm of IL-6.
inhibitors of erythropoiesis. Serum albumin levels and lower number of total and CD4+ non-responders to ESA treatment had higher CRP, lower bition of erythropoiesis by cytokines, such as TNF-α (IFN-γ resistance [39]. In a randomized study by Costa et al. [42], non-responders to ESA treatment had higher CRP, lower serum albumin levels and lower number of total and CD4+ lymphocytes, compared with responders. A recent study [43] examining lymphocyte characteristics in dialysis patients reported that percentages of circulating CD3 and CD4 T-lymphocytes in peritoneal dialysis and MHD patients were significantly lower than in controls. Uremic toxins may cause defects in cell-mediated immunity, and alteration of cellular nutrients may affect lymphocyte function in MHD patients [44]. Other smaller clinical studies reported associations between ERI indices and inflammatory cytokines [45, 46].

In 754 MHD patients with comprehensive data of nutritional and inflammatory indicators, high levels of inflammatory markers and low levels of nutritional markers were independent predictors of hyporesponsiveness to ESA. Assuming that nutritional and anti-inflammatory interventions can correct PEW, our findings may have relevant clinical implications in anemia management in CKD patients to optimize the efficacy of ESA treatment.

In this cross-sectional analysis, all inflammatory factors were associated with hyporesponsiveness to ESAs. Chronic inflammation can inhibit erythropoiesis in part through the effects of IL-1, TNF-α, tumor necrosis factor-β and interferon-γ (IFN-γ). These pro-inflammatory cytokines are powerful inhibitors of erythropoiesis in vivo and in vitro [38]. The inhibition of erythropoiesis by cytokines, such as TNF-α and IFN-γ, is also important in the development of erythropoietin resistance [39–41]. In a randomized study by Costa et al. [42], non-responders to ESA treatment had higher CRP, lower serum albumin levels and lower number of total and CD4+ lymphocytes, compared with responders. A recent study [43] examining lymphocyte characteristics in dialysis patients reported that percentages of circulating CD3 and CD4 T-lymphocytes in peritoneal dialysis and MHD patients were significantly lower than in controls. Uremic toxins may cause defects in cell-mediated immunity, and alteration of cellular nutrients may affect lymphocyte function in MHD patients [44]. Other smaller clinical studies reported associations between ERI indices and inflammatory cytokines [45, 46].

Many studies explored the potential mechanism of how a decrease in inflammatory markers can result in increased erythropoietin responsiveness in MHD patients [47]. Attallah et al. performed a randomized, prospective study of MHD patients with unexplained hyperferritinemia and randomly assigned them to receive 300 mg of intravenous vitamin C versus placebo. Hemoglobin levels significantly increased and CRP levels significantly decreased in the treatment group [48]. Statins have been suggested for use in patients with chronic inflammation [47]. Statins are shown to decrease CRP levels irrespective of their effects on lipid levels and may be associated with reduced mortality in patients with ESRD [47, 49]. Chiang et al. [50] evaluated the efficacy of low-dose atorvastatin on ESA hyporesponsiveness and found that ERI decreased in the treatment group.

In the Heart Protection Study (HPS), simvastatin reduced the incidence of major vascular events to a similar

| Table 3. Likelihood of the worst ESA hyporesponsiveness using multivariate logistic regression analyzes to compare the highest (worse) versus three lowest quartiles (as reference) of responsiveness to ESA, known here as ERI |
|---|---|---|
| MIS (for 1 SD ↑) | 1.86 | 1.31–2.85 | <0.001 |
| Serum CRP (for 1 SD ↑) | 1.44 | 1.08–1.92 | 0.01 |
| Log of CRP (for 1 SD ↑) | 1.70 | 1.24–2.33 | 0.001 |
| IL-6 (for 1 SD ↑) | 4.08 | 1.96–8.50 | <0.001 |
| Log of IL-6 (for 1 SD ↑) | 2.18 | 1.58–3.00 | <0.001 |
| TNF-α (for 1 SD ↑) | 1.02 | 0.73–1.44 | 0.89 |
| Log of TNF-α (for 1 SD ↑) | 1.19 | 0.82–1.73 | 0.37 |
| Albumin (for 1 SD ↓) | 1.97 | 1.41–2.78 | <0.001 |
| Prealbumin (for 1 SD ↓) | 1.36 | 0.98–1.82 | 0.07 |
| TIBC (for 1 SD ↓) | 1.55 | 1.14–2.12 | 0.006 |
| %TSAT (for 1 SD ↓) | 1.32 | 0.98–1.79 | 0.07 |
| Ferritin (for 1 SD ↓) | 0.97 | 0.71–1.31 | 0.82 |
| Blood lymphocyte count (for 1 SD ↓) | 1.13 | 1.04–1.23 | 0.005 |

OR and 95% CI for quartile of ERI comparing the odds of highest ERI quartile group (4th ERI quartile group) versus three lowest ERI quartile groups (1st, 2nd and 3rd ERI quartile groups— as reference), adjusted for case-mix (age, gender, race, diabetes mellitus), dialysis center, insurance (Medicaid versus others), Kt/V (single pool), blood hemoglobin, serum iron saturation ratio, the Charlson comorbidity score, dialysis vintage and intact parathyroid hormone using logistic regression analyses.

MIS, malnutrition inflammatory score; TIBC, total iron-binding capacity; TSAT, transferrin saturation; CRP, C-reactive protein; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α.
proportion irrespective of presenting CRP, albumin or other circulating inflammatory markers concentrations. There was no evidence that CRP modifies the vascular protective effects of statin therapy. Secondary analysis of the JUPITER study also did not record any evidence that the effect of a statin on vascular events differed according to baseline CRP [51, 52]. CRP is positively associated with smoking, diabetes, physical activity, blood pressure, BMI and might not reflect causality. This is supported by genetic–epidemiological studies that showed no increased cardiovascular mortality among people with genetic high CRP. Therefore, CRP has been excluded as a causal factor on the basis of this [53–55]. CRP is most likely a biomarker that predicts cardiovascular mortality. Most likely, it is more important to treat the underlying (low-grade)-inflammation as evidenced by elevated CRP levels.

Activation of monocyte-enhanced release of cytokines can be caused by membrane-induced complement activation, by direct cell–membrane interaction, and by dialysis fluids containing endotoxin [46]. Panichi et al. [56] studied the effects of a vitamin E-coated polysulfone membrane and found that ERI was significantly reduced. Moreover, high-efficiency on-line hemodiafiltration has been shown to improve anemia and to reduce erythropoietin-stimulating agent needs in hemodialysis patients [57]. A significant reduction in plasma CRP and IL-6 levels was also observed. In randomized controlled trials examining the effects of online-produced or filtered ultrapure dialysate on anemia outcomes in MHD patients, ESA doses...
were significantly decreased [46, 58, 59]. These studies raise hope that novel therapies to reduce inflammatory processes may decrease ESA dose requirements.

We also found a negative correlation between measured nutritional markers (% of lymphocyte count, serum albumin, prealbumin, low-density lipoprotein and TIBC) and hyporesponsiveness to ESAs. TNF-α, also known as cachectin, is believed to induce anorexia [60]. Although IL-6 and TNF-α have overlapping effects on food intake, the mechanisms of action are not identical. McCarthy [61] showed that the injection of TNF-α reduced food intake in starved rats, but it did not affect gastric emptying; however, the injection of IL-6 reduced both food intake and gastric emptying. Because both protein-energy malnutrition and inflammation are strongly associated with each other and can change many nutritional measures in the same direction, and because the relative contributions of these two conditions on outcomes in dialysis patients are not yet well defined, the term MICS or malnutrition inflammation atherosclerosis has been suggested to denote the important contribution of both of these conditions to poor dialysis outcome [62, 63].

A limitation of our study is that we did not measure other nutritional deficiencies, which can be limiting factors in the production of red blood cells, such as vitamin B12 and folate. Gastrointestinal or other bleeding episodes may have occurred. Furthermore, we did not evaluate hemoglobinopathies and other hereditary red blood cell abnormalities, which could cause refractory anemia. We did not record other comorbidities such as malabsorption, which could cause nutritional deficiencies. Additionally, we did not record other diseases, which can cause anemia of chronic disease such as malignancies, hypothyroidism and autoimmune diseases other than systemic lupus erythematosus (SLE) and we do not have data about smoking status. Another limitation of this study is the possible inclusion of patients who used angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. These medications can cause anemia by defective erythropoiesis [38]. Moreover, inflammatory markers may fluctuate even month to month in dialysis patients [64]. Since only prevalent hemodialysis patients were included in this study, the study may potentially suffer from survivor bias and the results of this study might be not applicable for incident patients [65, 66].

Strengths of our study include (i) its contemporary nature, because data were obtained in the twenty-first century (2001–06); (ii) uniform laboratory measurements, with all laboratory data obtained from a single facility and (iii) large sample size with several measured inflammatory markers.

CONCLUSIONS

High levels of inflammatory markers and low levels of nutritional markers were independent and significant predictors of hyporesponsiveness to ESA. Further studies are needed to assess whether reducing inflammatory processes in hemodialysis patients can increase the responsiveness to ESAs.

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CONFLICT OF INTEREST STATEMENT

K.K.-Z. is the medical director of DaVita Harbor-UCLA/MFI in Long Beach, CA, USA.

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