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Ultrafiltration rate and interleukin-6 levels are independent predictors of erythropoietin resistance in chronic hemodialysis patients

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Background and Aims: Anemia is common in patients under regular hemodialysis therapy. Despite treatment with erythropoiesis-stimulating agents (ESA), hypo-responsiveness to this therapy can occur (refractory cases). We studied the association between ESA resistance in hemodialysis patients and potential causes of ineffective treatment, including nutritional, iron metabolism, and inflammatory variables, and dialysis related parameters.

Method: We performed a cross-sectional study involving 289 hemodialysis patients. Ultrafiltration rate adjusted to weight (UFR/W), urea reduction ratio (URR) and Kt/V were obtained for the session where blood samples were collected. Blood analyses were performed by using automated technology or by enzyme-linked commercialized immunoassays, as previously described [1]. Erythropoietin (EPO) resistance index (ERI) was calculated by the formula: EPO dose per week (IU)/body weight (kg)/hemoglobin (g/dL).

Results: The mean age of patients was 68.7 years (± 13.6), 240 patients (83%) were under ESA prescription and 186 (64.4%) were receiving intravenous iron. The median (interquartile range) for ERI was 7.1 (3.7–11.7) IU/kg/g/dL, and for median transferrin saturation (TSAT) was 21.9 (16.8–28.5) %. ERI was positively correlated with levels of soluble transferrin receptor (sTfR, $r = 0.556$, $P = 7.8 \times 10^{-21}$; Fig. 1), interleukin (IL)-6 ($r = 0.196$, $P = 0.002$), pentraxin 3 ($r = 0.192$, $P = 0.003$), C-reactive protein ($r = 0.130$, $P = 0.043$) and UFR/W values ($r = 0.135$, $P = 0.037$) and inversely correlated with body mass index ($r = -0.179$, $P = 0.005$) and levels of iron ($r = -0.382$, $P = 9.2 \times 10^{-10}$), TSAT ($r = -0.340$, $P = 6.8 \times 10^{-8}$), hepcidin ($r = -0.197$, $P = 0.002$) and albumin ($r = -0.166$, $P = 0.010$). By performing multivariate linear regression analysis (after normalization of non-normally distributed data), levels of sTfR ($\beta = 0.487$, $P < 0.001$), iron ($\beta = -0.176$, $P = 0.003$), and IL-6 ($\beta = 0.111$, $P = 0.035$), and UFR/W values ($\beta = 0.168$, $P = 0.001$) were independent predictors of ERI. When iron repleted patients (ferritin ≥ 100 $\mu\text{g/L}$ and TSAT $\geq 20\%$) receiving EPO therapy were analyzed separately ($n = 138$), sTfR and UFR/W were kept in the regression model as predictors of ERI ($\beta = 0.504$, $P < 0.001$ and $\beta = 0.207$, $P = 0.006$, respectively); within these patients, those with UFR/W > 10 ml/h/kg presented higher ERI than those below 10 ml/h/kg (Fig. 2).

Conclusion: Besides lower iron, raised UFR/W and IL-6 are independently associated with hypo-responsiveness to ESA. sTfR seems to be a valuable tool to access ESA-driven erythropoiesis in hemodialysis patients, particularly in iron repleted patients. Our results support the idea that the modulation of inflammation and UFR prescription can improve anemia management.

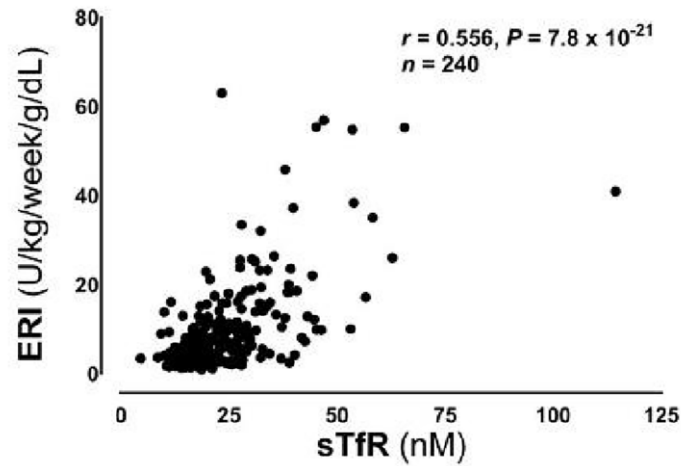


Figure 1: Correlation between erythropoietin resistance index (ERI) values and levels of soluble transferrin receptor (sTfR) in hemodialysis patients. r , Spearman's rank correlation coefficient. $P < 0.05$ was considered as statistically significant.

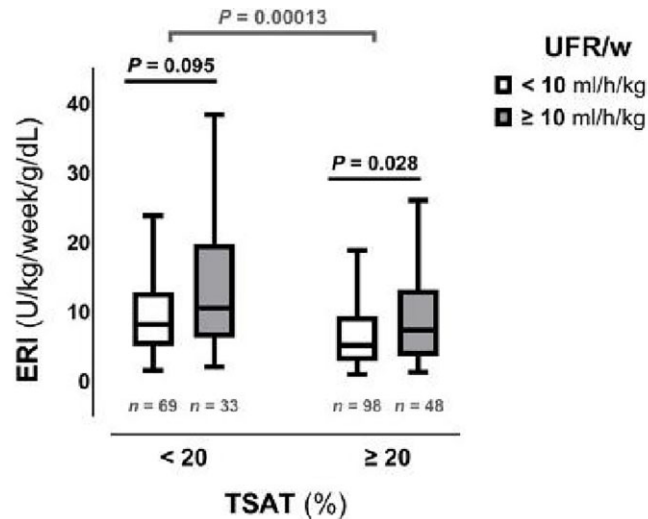


Figure 2: Erythropoietin resistance index (ERI) values in hemodialysis patients according to transferrin saturation (TSAT) and ultrafiltration rate adjusted to weight (UFR/W) cut-off values. The interquartile range is represented by the boxes, with the upper and lower edges denoting the 75th and 25th percentiles, respectively. The median levels are shown by the central horizontal lines inside the boxes. Differences between groups were evaluated by using the Mann-Whitney U test. $P < 0.05$ was considered as statistically significant.