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Short Communication
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Can Intravenous Iron be Accurately Dosed in Kidney Disease?

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Short Communication

In order to reduce the transfusion requirement of patients with renal anaemia, and on the background of concern in regard to excessive use of erythropoiesis Stimulating Agents (ESA) [1], intravenous iron currently plays a major role in these patients [2]. Yet it is unclear how best to dose iv iron, in order to both maximise efficacy whilst limiting potential toxicity [3]. We therefore attempted to develop an algorithm which would predict haemoglobin and ferritinlevels 6 weeks following their first administration of iv ferrous carboxymaltose (FCM; according to the manufacturer's guidelines).

Data were collected for patients with non-dialysis chronic kidney disease between 2012 and 2015. Patients were excluded from evaluation if ESA dose had changed within 3 months of iron administration. The resulting N=554 patients had a mean age of 64 years, 313 (56.5%) were female, and 186 (33.6%) diabetic; 67 (12.1%) had functioning transplants and 145 (26.2%) were treated with ESA. Median baseline eGFR was 22 ml/min (IQR: 15-32) and CRP was 4mmol/L (IQR: 3-7). As per manufacturer's guidelines, FCM was dosed according to weight, with a minimum of 500 mg administered, increasing in increments of 100 mg to a maximum of 1000 mg as a single dose; 351(63.4%) patients received this highest dose. Median FCM dose per kg body weight was 13.2 mg (IQR: 11.1-14.2). Following iron administration, mean (±SD) haemoglobin rose from 101.1±10.8 g/L to 110.4±11.9 g/L ($p<0.001$ by paired t-test), and the median serum ferritin concentration rose from 78 ng/ml (IQR: 35-138) to 428 ng/ml (IQR: 284-587) ($p<0.001$ by Wilcoxon's test).

Multivariable linear regression analyses where then performed to identify independent predictors of Hb and Ferritin levels 6 weeks post FCM administration. A backwards stepwise approach was

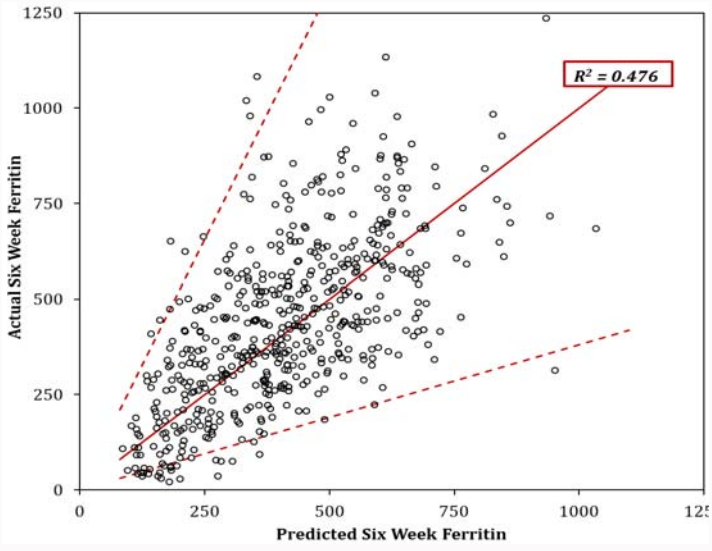

Figure 1: Accuracy of ferritin model.
The red line represents the target for the model, whilst the dashed lines are the 95% prediction intervals. The final model was as follows: predicted 6 week ferritin= 2^x, where x = 3.543 +0.459*[log2baseline ferritin (ng/ml)] +0.004*[age] +0.011*[baseline haemoglobin (g/L)] +0.076*[FCM dose (mg/kg)]-0.182*[male].

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Table 1: Multivariable regression analyses.
Table 1A: Haemoglobin concentration following intravenous FCM.

Factor	Coefficient (95% CI)	p-Value
Pre-Treatment Hb (g/L)	0.70 (0.64, 0.76)	<0.001
Log_2 Pre-Treatment Ferritin(ng/ml)	-2.94 (-3.44, -2.45)	<0.001
Pre-Treatment CRP (mg/L)	-0.13 (-0.21, -0.05)	0.001
ESA (Yes)	3.20 (1.63, 4.78)	<0.001

Results are from a multivariable regression analysis, with haemoglobin concentration 6 weeks following FCM administration as the dependent variable. A backwards stepwise approach was used to exclude non-significant variables. Factors not included in the final model were Dose per Kg (p=0.771), Sex (p=0.643), Age (p=0.822), Transplant versus non-transplant (p=0.412) and eGFR (p=0.189).

Table 1B: Ferritin concentration following intravenous FCM.

Factor	Coefficient (95% CI)*	p-Value
Log_2 Pre-Treatment Ferritin (ng/ml)	37.5% (33.4%, 41.7%)	<0.001
Pre-Treatment Hb (per 10 g/Ls)	8.0% (3.9%, 12.3%)	<0.001
FCM Dose (mg/kg)	5.4% (3.4%, 7.4%)	<0.001
Age (per decade)	2.7% (0.2%, 5.3%)	0.033
Sex (Male)	-11.8% (-19.4%, -3.6%)	0.006

Results are from a multivariable regression analysis, with log_2 [Ferritin concentration 6 weeks following FCM administration] as the dependent variable. A backwards stepwise approach was used to exclude non-significant variables. Factors not included in the final model were ESA (p=0.627), CRP (p=0.593), eGFR (p=0.321), Diabetes (p=0.333) and Transplant versus non-transplant (p=0.183).
*The coefficients from the model were anti-logged, and converted into percentage increases in six week Ferritin for a one unit increase in the factor (unless stated otherwise).
Bold p-Values are significant at p<0.05.

used to derive the final model. Ferritin values followed a skewed distribution, hence log_2-transformations were applied to improve model fit. The resulting coefficients from the model of ferritin were then anti-logged, and converted into percentage increases, to simplify their interpretation.

Post-treatment haemoglobin values to be positively associated with the baseline haemoglobin levels, and with the use of ESA (the dose of which had remained unchanged, as described above). Post-treatment haemoglobin levels were also found to be negatively associated with baseline CRP and ferritin concentrations, and higher in diabetics (Table 1A). Interestingly, the weight-adjusted dose of iron was *not* a significant predictor of post-treatment haemoglobin in the final model (p=0.771), nor was it significant on univariate correlation analysis (Spearman's Rho: -0.026, p=0.541).

Post-treatment ferritin values were positively associated with baseline ferritin levels, baseline haemoglobin concentration, weight-adjusted FCM dose, age and female gender (Table 1B). Because this model included FCM dose as a predictor, we were interested to investigate the accuracy of the model by comparing actual and predicted post-treatment ferritin levels (Figure 1). Although the model explained a moderate amount of the post-treatment ferritin variability (R^2: 0.476), 95% prediction intervals were wide.

In conclusion, although the purpose of this study was to attempt to develop an algorithm which may aid iron dosing in CKD, we were unable to do so. Yet a number of important implication stem from this work. Specifically, a number of predictor variables showed an association with serum ferritin levels following iron administration, suggesting that consideration of these may aid dosing when addressed at the level of a large *population*. This is not without merit. Yet further evaluation demonstrated that the accuracy of the model is insufficient to allow its use as a prediction tool for dosing *individual* patients. This serves as a reminder that 'population-level' associations do not necessarily imply predictive utility for individual patients. Nevertheless, future re-evaluation taking into account repeated FCM dosing and measures may enable refinement of the algorithm; there is data emerging to suggest this may facilitate ESA dosing in patients with dialysis-dependent renal disease [4].

Another important observation from the analysis was that the weight-adjusted dose of iron was not a significant predictor of post-treatment haemoglobin level. Although at first sight counter-intuitive, in fact the FIND-CKD study also showed a poor correlation between dose and haemoglobin increment [2]. This is likely a reflection of the supraphysiological amounts of iron administered parenterally, suchthat maximal iron uptake is accomplished even at the lower range of dosing. Thus adequate haemoglobin increments may result from lower FCM dosing than currently undertaken, and this too has important clinical and economic implications.

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