BONE MARROW IRON, HEPCIDIN, ERYTHROPOIETIN, INFLAMMATION AND PERIPHERAL IRON INDICES IN RENAL ANEMIA

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INTRODUCTION AND AIMS

Iron deficiency anemia (IDA) and anemia of inflammation (AI) frequently compound renal anemia. Although the distinction between IDA and AI is therapeutically important, peripheral iron indices are not reliable in all cases. We thought to investigate if measurements of hepcidin – the key regulator of iron metabolism – and erythropoietin (Epo) – the key regulator of erythropoiesis – could add useful information to differentiate IDA from AI in renal anemia, using bone marrow (BM) iron as reference.

METHODS

One hundred sixty seven anemic, iron and erythropoietin free, non-dialysis CKD patients entered this prospective single center study. BM examination (aspiration, Perls' stain) was normal in 4 patients, 97 patients had IDA, 65 had AI and 1 had erythrodysplasia. Only IDA and AI patients were retained in the final analysis (N=162; 52% males, median age 67 years, eGFR 14.2mL/min, Hb 9.4g/dL, 23% with diabetes mellitus). Transferrin saturation index (TSAT) was calculated as the percentage of serum iron from total serum iron binding capacity. Serum hepcidin and Epo were measured by ELISA, ferritin, transferrin and C-reactive protein (CRP) by immunoturbidimetric methods. Data are presented as mean (median) and 95% confidence intervals of the mean (median).

RESULTS

Patients with IDA were younger, and had a higher eGFR. In IDA group, anemia was less pronounced and iron indices reflected iron deficiency: higher transferrin, lower TSAT and ferritin. However, only ferritin allowed differentiation, as median TSAT was 18%, below the 20% cut-off recommended for iron deficiency diagnosis. In this IDA group, Epo was higher and hepcidin lower. However, inflammation was similar in both groups.

Investigated parameters in iron deficiency anemia (IDA) and anemia of inflammation (AI)

Parameter	IDA (n=97)	AI (n=65)	P
Age (years)	63 (60-69)	70 (66-74)	0.005
Gender (% male)	49%	55%	0.5
eGFR (mL/min)	18.0 (14.1-22.9)	11.1 (9.4-13.4)	0.001
Hb (g/dL)	9.9 (9.6-10.2)	8.8 (8.4-9.3)	0.0004
Transferrin (mg/dL)	222 (206-237)	194 (177-203)	<0.0001
TSAT (%)	12.5 (10.2-15.3)	18.2 (16.1-22.5)	<0.0001
Ferritin (ng/mL)	110 (93-144)	368 (282-492)	<0.0001
Erythropoietin (mU/mL)	5.2 (4.2-6.4)	4.8 (4.0-6.0)	0.004
Hepcidin (ng/mL)	75.4 (60.5-84.5)	98.7 (88.4-125.0)	0.002
CRP (ng/mL)	7.0 (5.0-10.0)	9.0 (5.0-12.0)	0.6

In binominal regression analysis, younger age, lower hepcidin, ferritin and TSAT allowed for IDA from AI differentiation in 38% of cases (p<0.0001). Neither renal function (eGFR), nor inflammation (CRP) seemed to have any influence.
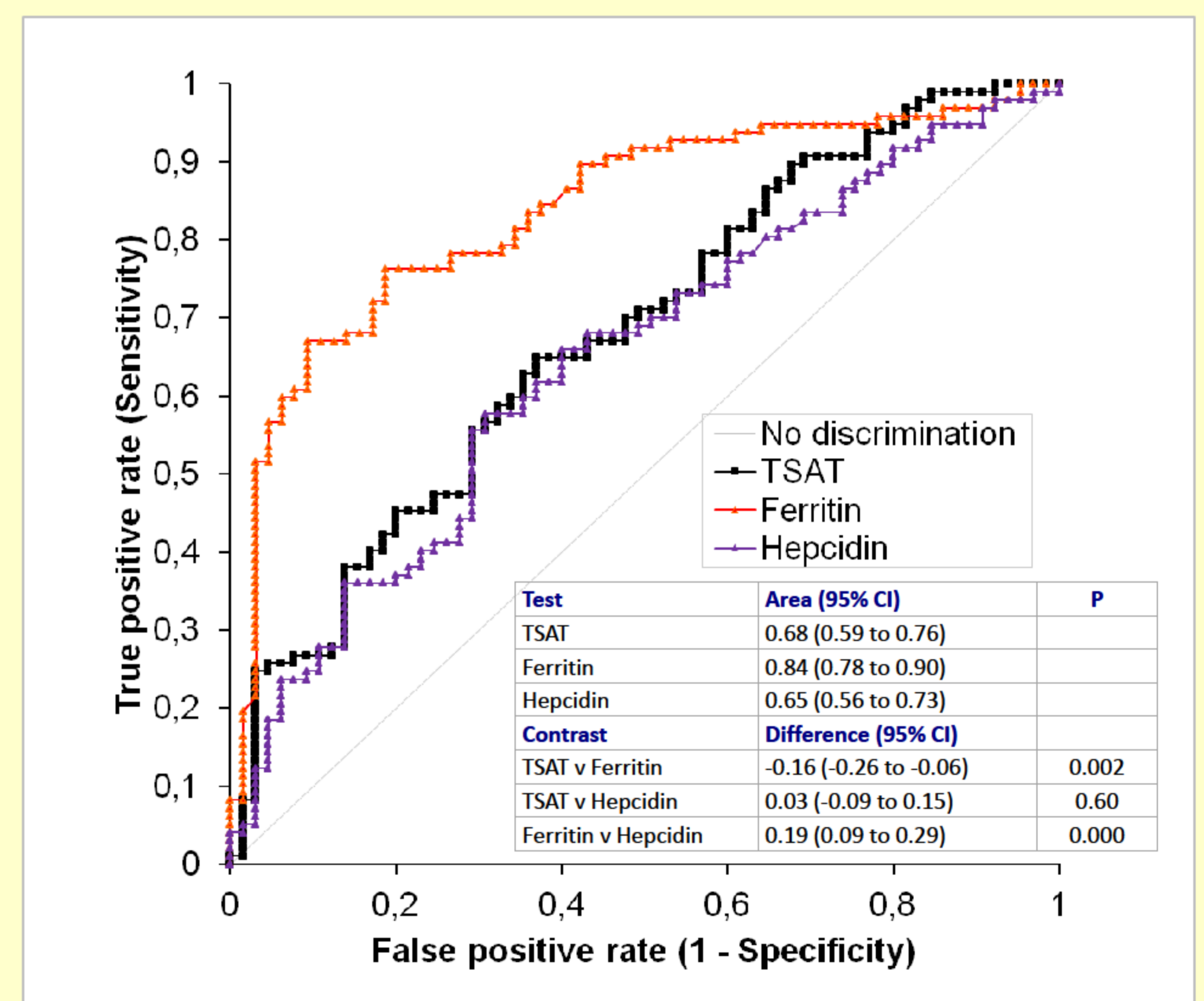
Predictors of IDA (binominal regression)

Predictors	Exp(B) (95% CI)	Sig.
Age	0.95 (0.91-0.98)	0.002
Ln Hepcidin	0.66 (0.42-1.02)	0.06
Ln Ferritin	0.21 (0.11-0.38)	0.000
Ln TSAT	0.35 (0.17-0.74)	0.006
Constant	2.789E7	0.000

The reference category is IDA
Cox&Snell R2 = 0.38 (p=0.000)
Variable(s) entered on step 1: Age, LnGFR, LnHepcidin, LnEpo, LnHb, LnFerritin, Transferrin, LnTSAT, LnCRP.

In receiver operating curve analysis, ferritin had a better accuracy in differentiating IDA from AI than TSAT or hepcidin.

Test	Area (95% CI)	P
TSAT	0.68 (0.59 to 0.76)	
Ferritin	0.84 (0.78 to 0.90)	
Hepcidin	0.65 (0.56 to 0.73)	
Contrast	Difference (95% CI)	
TSAT v Ferritin	-0.16 (-0.26 to -0.06)	0.002
TSAT v Hepcidin	0.03 (-0.09 to 0.15)	0.60
Ferritin v Hepcidin	0.19 (0.09 to 0.29)	0.000

The utility of TSAT, ferritin and hepcidin in differentiating iron deficiency from anemia of inflammation

Cut-off values were 218ng/mL for ferritin (substantially higher than the guideline recommendation), 95ng/mL for hepcidin and 16% for TSAT, but sensitivity and specificity were not impressive: 0.76 (0.67-0.84), 0.65 (0.55-0.74) and 0.65 (0.58-0.77), 0.57 (0.44-0.69), respectively. Thus, ferritin not TSAT or hepcidin had some clinical usefulness.

Best test performance

Parameter	Cut-off	Sensitivity	Specificity	Likelihood ratio (+)	Likelihood ratio (-)
Ferritin (ng/mL)	218	0.76 (0.67-0.84)	0.81 (0.70-0.90)	4.07	0.29
TSAT (%)	16	0.65 (0.55-0.74)	0.63 (0.50-0.75)	1.76	0.56
Hepcidin (ng/mL)	95	0.65 (0.58-0.77)	0.57 (0.44-0.69)	1.58	0.56

CONCLUSIONS

Iron deficiency and anemia of inflammation are prevalent in anemic renal patients, but peripheral iron indices and even hepcidin or erythropoietin measurements are of little help in their differentiation. However, ferritin performed the best.

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Anaemia in CKD 1-5

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