

Differential association of serum levels of hepcidin and iron indexes with anemia according to the severity of anemia and kidney function in non-dialysis chronic kidney disease patients

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Abstract

Background and objectives: There have been no studies regarding on the differential associations of hepcidin and iron indexes with anemia, according to the severity of anemia and kidney function in non-dialysis chronic kidney disease (CKD) patients.

Methods: We used baseline data of a multicenter prospective cohort study. After excluding 561 patients who have used erythropoietin stimulating agents or iron, or who are missing data on hemoglobin, hepcidin or iron metabolism, 1677 patients were included for the analysis.

Results: In multivariate logistic regression, serum ferritin was not associated with anemia, while serum levels of TSAT and hepcidin-25 were significantly associated with anemia. In patients with estimated glomerular filtration rate (eGFR) ≥ 45 ml/min/1.73m², only serum TSAT was associated with hemoglobin < 13 g/dl (OR 0.96, $P < 0.001$) and hemoglobin < 11.5 g/dl (OR 0.96, $P = 0.019$), whereas only serum hepcidin-25 was related to hemoglobin < 11.5 g/dl (OR 1.03, $P < 0.001$) and hemoglobin < 10.0 g/dl (OR 1.03, $P = 0.002$) in patients with eGFR < 45 ml/min/1.73m². The predictive power of TSAT for anemia was larger than those of hepcidin-25 and ferritin in patients with eGFR ≥ 45 ml/min/1.73m², while the predictive power of hepcidin-25 for anemia was the largest among the three studied factors, particularly in patients with eGFR < 45 ml/min/1.73m².

Conclusion: Only TSAT and hepcidin were associated with anemia in patients with preserved and decreased kidney function, respectively, while ferritin was not related to anemia in non-dialysis CKD patients. Hepcidin-related anemia was more severe than anemia associated with TSAT.

Background

- Recently, iron metabolism has been highlighted as another factor in anemia of CKD. Ganz T. JASN. 2007;18(2):394-400
- However, the role of iron indexes (TSAT and ferritin) in anemia of CKD has been doubtful. Stancu S et al. AJKD. 2010;55(4):639-647
- Hepcidin can be a better biomarker in anemia of CKD than conventional iron indexes since it is more fundamental. Ganz T. Blood. 2011;117(17):4425-4433.

Methods

Patients

- Participants of KNOW-CKD cohort enrolled during 2011-2016

Definition

- eGFR by MDRD equation
- Hepcidin by cELISA
- Anemia defined by < 13 g/dl; < 11.5 g/dl; < 10.0 g/dl

Statistical analysis

- Univariate analysis: chi-square test, One-way ANOVA
- Multivariate analysis: Logistic regression analysis
- Comparative study: Delong's test for AUC comparison, Category-free NRI

Results

Baseline characteristics of the study participants

	Total (n = 1,677)
Age (years)	53.0 \pm 12.4
Male sex	65.4
Cause of CKD	
Diabetic nephropathy	22.7
Glomerulonephritis	32.6
Hypertensive nephropathy	21.2
Others	23.5
Fasting glucose (mg/dl, n = 1673)	110.9 \pm 39.8
eGFR (ml/min/1.73m ²)	54.8 \pm 30.2
Hemoglobin (g/dl)	13.2 \pm 1.9
Serum TSAT (%)	31.9 \pm 11.9
Serum hepcidin-25 (ng/ml)*	11.8 (6.2–21.5)
Serum ferritin (ng/ml)*	92.2 (51.6–164)
hsCRP (mg/l, n = 1597)*	0.6 (0.2–1.6)
UPCR (g/g, n = 1648)*	0.4 (0.1–1.4)

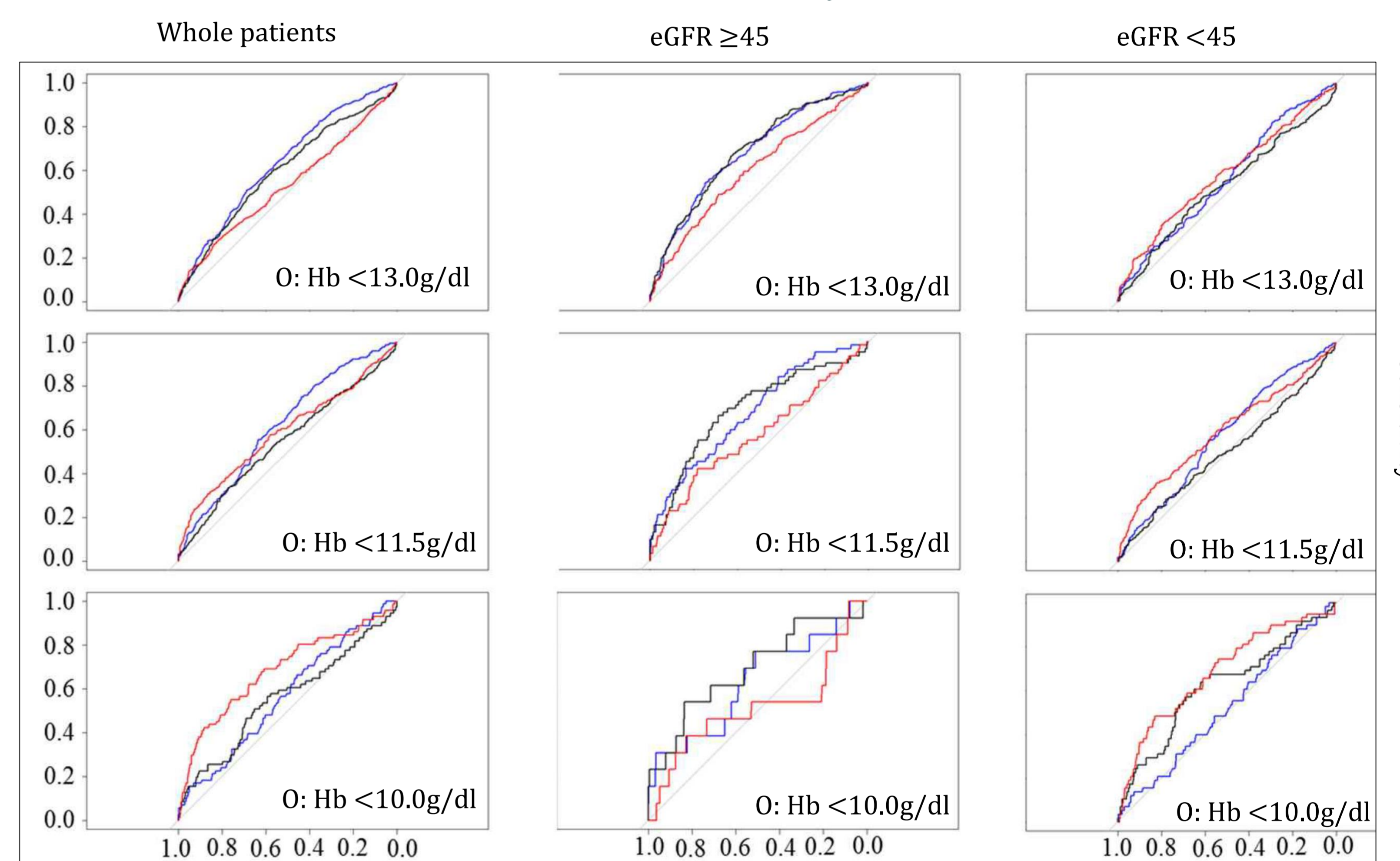
BP, blood pressure; CKD, chronic kidney disease; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; TSAT, transferrin saturation; CRP, C-reactive protein; UPCR, urine protein-to-creatinine ratio. Values are expressed as mean \pm standard deviation for continuous variables and percentage for categorical variables. When there are missing values, the total numbers of patients for each variable is expressed in parenthesis. The missing rates of all variables were less than 5.0%. * meant variables with non-normal distribution which are expressed as median (interquartile range).

Association between the serum levels of hepcidin-25 and iron indexes and the several thresholds of anemia

Outcomes	Factors	Whole patients (n = 1677)		eGFR ≥ 45 (n = 919)		eGFR < 45 (n = 757)	
		Adjusted OR (95% CI)	P	Adjusted OR (95% CI)	P	Adjusted OR (95% CI)	P
Hb < 13.0 g/dl	TSAT	0.97 (0.96–0.98)	< 0.001	0.96 (0.94–0.98)	< 0.001	0.98 (0.96–1.00)	0.058
	Ferritin	1.00 (0.98–1.02)	0.949	0.99 (0.97–1.02)	0.604	1.02 (0.99–1.04)	0.147
	Hepcidin-25	1.02 (1.00–1.03)	0.009	1.01 (0.99–1.03)	0.454	1.01 (0.99–1.03)	0.279
Hb < 11.5 g/dl	TSAT	0.97 (0.96–0.99)	0.002	0.96 (0.93–0.99)	0.019	0.98 (0.96–1.00)	0.075
	Ferritin	0.98 (0.97–1.00)	0.056	1.00 (0.95–1.05)	0.970	0.99 (0.97–1.01)	0.189
	Hepcidin-25	1.03 (1.02–1.05)	< 0.001	1.01 (0.98–1.05)	0.480	1.03 (1.02–1.05)	< 0.001
Hb < 10.0 g/dl	TSAT	0.96 (0.93–1.00)	0.032	0.92 (0.84–1.01)	0.088	0.97 (0.93–1.00)	0.080
	Ferritin	0.99 (0.97–1.02)	0.656	1.02 (0.92–1.12)	0.700	1.00 (0.98–1.03)	0.762
	Hepcidin-25	1.04 (1.02–1.06)	< 0.001	1.06 (0.98–1.15)	0.154	1.03 (1.01–1.05)	0.002

Hb, hemoglobin; ESA, erythropoietin stimulating agents; OR, odds ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate; TSAT, transferrin saturation. Adjusted OR and its CI were calculated by multivariate logistic regression analysis. The references of TSAT, ferritin and hepcidin-25 were per 1%, per 10 ng/ml, and per 1 ng/ml increase. The unit of eGFR was ml/min/1.73m². Variables associated with anemia defined by several thresholds of hemoglobin levels in univariate logistic regression (age, sex, high income, body mass index, fasting glucose, systolic blood pressure, estimated glomerular filtration rate, total bilirubin, albumin, and urine protein-to-creatinine ratio) were chosen as covariates along with white blood cells and C-reactive protein.

Area under the receiver operator curve of serum levels of hepcidin-25 and iron indexes for anemia defined by several Hb thresholds.



O, outcome; eGFR, estimated glomerular filtration rate; Hb, hemoglobin. Red, blue and black lines designated serum hepcidin-25 levels, transferrin saturation and ferritin, respectively. Columns and rows represented total or subgroup by kidney function and anemia defined by several Hb thresholds, respectively.

Net reclassification improvement between serum levels of hepcidin-25 and iron indexes for the several thresholds of anemia

Outcome	Factor	Whole patients (n = 1677)		eGFR ≥ 45 (n = 919)		eGFR < 45 (n = 757)	
		NRI (95% CI)	P	NRI (95% CI)	P	NRI (95% CI)	P
Hb < 13 g/dl	Hepcidin-25 (ng/ml)		Ref.		Ref.		Ref.
	TSAT (%)	0.26 (0.16–0.35)	< 0.001	0.46 (0.32–0.60)	< 0.001 *	-0.12 (-0.27–0.03)	0.119
	Ferritin (ng/ml)	-0.03 (-0.12–0.07)	0.581	0.55 (0.42–0.68)	< 0.001	-0.24 (-0.38–0.09)	0.001
Hb < 11.5 g/dl	Hepcidin-25 (ng/ml)		Ref.		Ref.		Ref.
	TSAT (%)	0.01 (-0.11–0.13)	0.872	0.46 (0.21–0.71)	< 0.001 †	-0.10 (-0.25–0.05)	0.190
	Ferritin (ng/ml)	-0.31 (-0.43–0.19)	< 0.001	0.52 (0.31–0.74)	< 0.001	-0.31 (-0.46–0.16)	< 0.001
Hb < 10 g/dl	Hepcidin-25 (ng/ml)		Ref.		Ref.		Ref.
	TSAT (%)	-0.40 (-0.64–0.17)	0.001	0.23 (-0.31–0.78)	0.401	-0.55 (-0.82–0.29)	< 0.001
	Ferritin (ng/ml)	-0.60 (-0.84–0.37)	< 0.001	0.34 (-0.16–0.85)	0.182	-0.43 (-0.69–0.16)	0.002

Conclusion

- Only TSAT and hepcidin were associated with anemia in patients with preserved and decreased kidney function, respectively.
- Ferritin was not related to anemia in non-dialysis CKD patients.
- Hepcidin-related anemia was more severe than anemia associated with TSAT.

