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Predictive Value of Serum Hepcidin Levels for the Risk of Incident End-Stage Kidney Disease in Patients with Chronic Kidney Disease: The KNOW-CKD

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Keywords
Biomarker · Chronic kidney disease · End-stage kidney disease · Hepcidin

Abstract

Introduction: Despite the pivotal role of hepcidin in the development of anemia among the patients with chronic kidney disease (CKD), the association between serum hepcidin levels and CKD progression has been never investigated. We here hypothesized that elevation in serum hepcidin levels might be associated with the risk of incident end-stage kidney disease (ESKD) among the patients with pre-dialysis CKD. ***Methods:*** A total of 2,109 patients with pre-dialysis CKD at stages 1 to pre-dialysis 5 were categorized into the quartiles by serum hepcidin levels. The study outcome was incident ESKD. The median duration of follow-up was 7.9 years. ***Results:*** The analysis of the baseline characteristics revealed that unfavorable clinical features were in general associated with higher serum hepcidin levels. The cumulative incidence of ESKD was significantly differed by serum hepcidin levels, with the highest incidence in the 4th quartile ($p < 0.001$, by log-rank test). Cox regression analysis demonstrated that, compared to the 1st quartile, the risk of incident ESKD is significantly increased in the 4th quartile (adjusted hazard ratio 1.372, 95% confidence interval 1.070–1.759). Penalized spline curve analysis illustrated a linear, positive correlation between serum hepcidin levels and the risk of incident ESKD. Subgroup analyses revealed that the association is significantly more prominent in the patients with advanced CKD (i.e., estimated glomerular filtration rate <45 mL/min/1.73 m^2). ***Conclusion:*** Elevation in serum hepcidin levels is significantly associated with the risk of incident ESKD among the patients with pre-dialysis CKD.

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Introduction

Hepcidin is a peptide primarily produced by hepatocyte and in a small quantity by macrophages and adipocytes [1–3]. The gene, hepcidin antimicrobial peptide (*HAMP*), is initially translated into an 84 amino acid pre-pro-hepcidin, which is post-translationally modified to a 60 amino acid pro-hepcidin, and finally to a mature C-terminal 25 amino acid peptide, hepcidin [4]. Beyond the discovery of hepcidin as an antimicrobial peptide in 2000 [1, 5], studies reported that mutations of HAMP lead to severe iron overload and hemochromatosis [6, 7]. Mechanistically, hepcidin binds to and induces degradation of ferroportin, a transmembrane iron exporter protein. As ferroportin is critical for iron absorption via duodenal cells and iron mobilization from the storage in macrophages and hepatocytes, hepcidin is the master regulator for systemic iron homeostasis, ultimately contributing to the development of anemia [8, 9].

Anemia is a common complication in the patients with chronic kidney disease (CKD), especially among those at advanced stages, affecting up to 60% of the patients with non-dialysis CKD [10, 11]. The pathogenesis of anemia in CKD is multifactorial, including decrease in erythropoietin (EPO) production due to reduced functional nephron mass, absolute and/or relative iron deficiency, and inflammation [8, 12]. Intriguingly, all of these are closely related to the function of hepcidin. As EPO suppresses the upregulation of hepcidin [13], reduced EPO production in patients with CKD results in elevated serum hepcidin levels. Inflammatory cytokines, such as interleukin-6 (IL-6), are well-known stimulators of hepcidin expression [14]. Further, the renal clearance of circulating hepcidin is also interfered with among the subjects with reduced glomerular filtration rates [15]. These all together promote elevation in serum hepcidin levels, leading to the development of anemia in CKD associated with inefficient iron metabolism [12]. Indeed, hepcidin is now acknowledged as a major culprit of the anemia in CKD, and novel therapeutics for renal anemia adopt serum hepcidin levels as a surrogate marker [16, 17].

However, despite the pivotal role in the development of anemia, the association between serum hepcidin levels and hard end points in CKD, such as initiation of renal replacement therapy, major adverse cardiac events, and all-cause mortality, is currently elusive. The prognostic value of serum hepcidin levels in combination of N-terminal pro-brain type natriuretic peptide (NT-proBNP) or neutrophil gelatinase-associated lipocalin (NGAL) has been previously evaluated in certain clinical contexts [18–20] but not in patients with CKD. Therefore, here we investigated the association between serum hepcidin levels and the risk of end-stage kidney disease (ESKD) among the patients with pre-dialysis CKD.

Methods

Study Design

The KNOW-CKD (KoreaN Cohort Study for Outcome in Patients With Chronic Kidney Disease) is a prospective cohort study that enrolled the patients with CKD at stages 1 to pre-dialysis 5 from nine tertiary hospitals in South Korea between 2011 and 2016 (NCT01630486 at http://www.clinicaltrials.gov) [21]. The study was designed and conducted according to the Declaration of Helsinki. The study protocol was reviewed and approved by the Institutional Review Board at each participating center, as previously described [22–24]. All the participants voluntarily provided the informed consent. Each participating center closely monitored the participants during the follow-up period to report major events. The reported study outcomes were cross-checked by the collaborating investigators. Among a total of 2,238 patients who were initially recruited, after excluding those lacking the baseline measurement of serum hepcidin levels (n = 98), and those lacking the data on follow-up duration (n = 3), a total of 2,109 patients were finally included for the analyses (Fig. 1). The study observation period ended on March 31, 2022, for the median duration of 7.940 years.

Data Collection from Participants

The baseline data of the participants on demographics, anthropometrics, and medical history were recorded according to the study protocol [21]. Blood and urine samples were obtained following an overnight fasting and were analyzed in the central laboratory (LabGenomics, Seongnam, Korea). Estimated glomerular filtration rate (eGFR) was calculated by CKD Epidemiology Collaboration (CKD-EPI) equation using serum creatinine level, as previously described [25]. CKD stages were defined by eGFR according to the Kidney Disease: Improving Global Outcomes (KDIGO) guideline [26]. Echocardiographic examinations were conducted by the cardiologists at each participating center, who were blinded to the clinical data, according to standard approach [27].

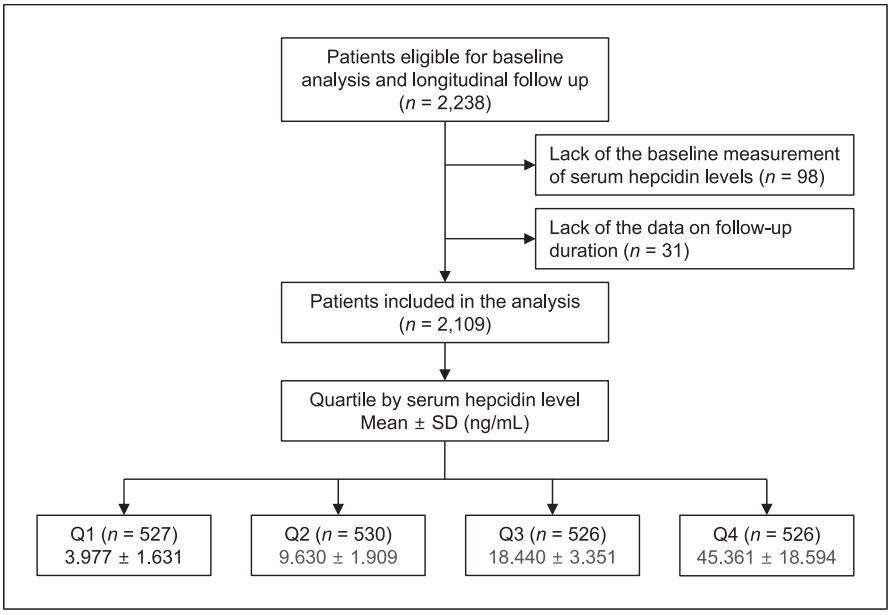

Fig. 1. Flow diagram of the study participants. Q1, 1st quartile; Q2, 2nd quartile; Q3, 3rd quartile; Q4, 4th quartile; SD, standard deviation.

Determination of Serum Hepcidin Levels

Serum hepcidin levels were measured at the central laboratory using an ELISA (enzyme-linked immunosorbent assay) kit (DRG Diagnostics, Marburg, Germany) [21, 28], according to the manufacturer's instructions. The intra- and inter-assay coefficients of variation were 2.1–9.9% and 11.5–14.6%, respectively. Due to the detection limit of 80 ng/mL at the maximum level, higher levels were recorded as 80 ng/mL [28].

Exposure and Study Outcome

The participants were categorized into quartiles by serum hepcidin levels: Q1, Q2, Q3, and Q4 (Fig. 1). The study outcome was incident ESKD, which included initiation of dialysis or kidney transplantation.

Statistical Analysis

Continuous and categorical variables of the baseline characteristics by serum hepcidin levels were compared using one-way analysis of variance and the χ^2 test, respectively. The cumulative incidence of the study outcome was visualized by Kaplan-Meier survival curves and subsequently compared using the log-rank test. The last visiting date was used as the censoring date for those with follow-up loss. To determine the independent association between serum hepcidin levels and the risk of ESKD, Cox proportional hazard regression models were adopted. The models were adjusted for the potential confounders as the following: model 1 reported unadjusted hazard ratios (HRs); model 2 was adjusted for age and gender; model 3 was additionally adjusted for medical history, such as age-adjusted Charlson Comorbidity Index, primary cause of CKD, smoking status, and medications (e.g., angiotensin converting enzyme inhibitors and angiotensin receptor blockers, diuretics, statins, and antiplatelet/anticoagulant agents), and anthropometric data, including body mass index (BMI) and systolic blood pressure (SBP). Model 4 was finally further adjusted for the baseline laboratory data, including hemoglobin, albumin, high-density lipoprotein cholesterol (HDL-C), fasting glucose, 25-hydroxyvitamin D (25[OH]D), high-sensitivity C-reactive protein (hs-CRP), CKD stages, spot urine protein-to-creatinine ratio (PCR), left ventricular mass index, and left ventricular ejection fraction. Participants with any missing data were excluded from primary analyses. The results of Cox regression analyses were reported with HRs and 95% confidence intervals (CIs). The linear correlation between serum hepcidin levels (as a continuous variable) and the risk of ESKD was illustrated by the penalized spline curve. To prove the robustness of the primary findings, we planned sensitivity analyses. First, participants were re-categorized by serum hepcidin levels into tertiles and quintiles, instead of quartiles, for Cox regression analyses. Second, the cause-specific HRs for the study outcome was assessed, where the death events before reaching the study outcome were considered a competing risk and treated as censoring. Third, the model was further adjusted for the use of erythropoiesis-stimulating agents (ESAs) in addition to model 4. Lastly, any missing values in the primary analyses were replaced using multiple imputation to repeat the Cox

Table 1. Baseline characteristics of study participants by serum hepcidin levels

	Serum hepcidin levels				*p* value
	Q1	Q2	Q3	Q4	
Follow-up duration, years	7.581±2.767	7.357±2.771	6.733±2.934	6.884±2.979	<0.001
Age, years	51.334±12.603	53.653±12.580	53.785±11.719	55.443±11.702	<0.001
Male	259 (49.1)	330 (62.3)	351 (66.7)	346 (65.8)	<0.001
Age-adjusted CCI					<0.001
0–3	93 (17.6)	124 (23.5)	139 (26.4)	176 (33.5)	
4–5	96 (18.2)	117 (22.2)	100 (19.0)	105 (20.0)	
6–7	206 (39.1)	174 (33.0)	157 (29.8)	128 (24.3)	
≥8	3 (0.6)	5 (0.9)	4 (0.8)	2 (0.4)	
Primary cause of CKD					<0.001
DM	101 (19.2)	77 (14.6)	92 (17.5)	70 (13.3)	
HTN	28 (5.3)	31 (5.9)	34 (6.5)	45 (8.6)	
GN	333 (63.2)	296 (55.8)	273 (51.9)	201 (38.2)	
TID	117 (22.2)	129 (24.3)	152 (28.9)	217 (41.3)	
PKD	64 (12.1)	82 (15.5)	89 (16.9)	92 (17.5)	
Others	13 (2.5)	23 (4.3)	12 (2.3)	16 (3.0)	
Smoking status					<0.001
Nonsmoker	323 (61.4)	285 (54.0)	260 (49.4)	254 (48.3)	
Ex-smoker	56 (10.6)	84 (15.9)	105 (20.0)	93 (17.7)	
Current smoker	147 (27.9)	159 (30.1)	161 (30.6)	179 (34.0)	
Medication					
ACEi/ARBs	436 (82.9)	454 (85.8)	459 (87.3)	453 (86.1)	0.219
Diuretics	137 (26.0)	152 (28.7)	171 (32.5)	213 (40.5)	<0.001
Statins	234 (44.5)	267 (50.5)	307 (58.4)	289 (54.9)	<0.001
Antiplatelets/ anticoagulants	160 (30.4)	131 (24.8)	153 (29.1)	153 (29.1)	0.192
Iron replacement	30 (5.7)	66 (12.5)	76 (14.4)	134 (25.4)	<0.001
ESAs	8 (1.5)	27 (5.1)	36 (6.8)	88 (16.7)	<0.001
BMI, kg/m^2	24.150±3.509	24.625±3.264	25.036±3.502	24.486±3.257	0.001
SBP, mm Hg	125.606±15.357	127.739±15.088	128.471±16.556	129.232±17.397	0.002
DBP, mm Hg	76.756±11.087	77.147±10.195	77.348±11.528	76.759±11.688	0.785
Laboratory findings					
Hemoglobin, g/dL	13.056±1.857	13.275±1.808	13.047±2.114	11.949±2.026	<0.001
Iron, μg/dL	88.008±37.026	94.522±33.189	97.483±35.971	90.213±34.112	<0.001
Transferrin saturation (%)	28.125±12.408	31.366±11.121	33.472±11.673	33.562±12.383	<0.001
Ferritin, ng/mL	57.672±57.243	100.646±6.725	138.068±85.096	252.823±198.438	<0.001
Albumin, g/dL	4.175±0.380	4.220±0.400	4.184±0.430	4.116±0.486	0.002
Total cholesterol, mg/dL	176.096±36.751	176.074±38.253	177.436±41.411	167.697±40.031	<0.001
HDL-C, mg/dL	52.974±16.559	50.274±14.335	48.690±15.989	45.481±14.230	<0.001
LDL-C, mg/dL	96.812±30.119	98.205±30.945	99.400±33.300	93.329±32.745	0.019
TG, mg/dL	150.232±98.658	155.352±100.937	169.029±103.919	156.083±93.406	0.024
Fasting glucose, mg/dL	106.131±33.989	111.896±38.657	113.865±46.617	111.440±38.390	0.007
25(OH)D	18.527±7.913	18.202±8.302	17.871±7.375	16.955±7.999	0.01
hs-CRP, mg/dL	0.500 [0.020, 23.590]	0.540 [0.030, 60.200]	0.700 [0.050, 52.700]	0.800 [0.100, 68.000]	<0.001
Spot urine ACR, mg/g	308.303 [0.698, 10,099.950]	269.350 [1.337, 11,669.720]	376.963 [1.199, 12,586.840]	498.187 [1.585, 11,204.430]	<0.001
Spot urine PCR, g/g	0.412 [0.008, 15.558]	0.370 [0.005, 19.489]	0.507 [0.011, 20.585]	0.675 [0.011, 16.745]	<0.001

Table 1 (continued)

	Serum hepcidin levels				*p* value
	Q1	Q2	Q3	Q4	
Creatinine, mg/dL	1.451±0.873	1.553±0.824	1.833±1.164	2.448±1.392	<0.001
eGFR, mL/min/1.73 m^2	60.819±32.464	55.531±29.423	48.835±28.499	36.114±23.919	<0.001
CKD stages					<0.001
Stage 1	136 (25.8)	98 (18.5)	71 (13.5)	35 (6.7)	
Stage 2	122 (23.1)	113 (21.3)	104 (19.8)	59 (11.2)	
Stage 3a	88 (16.7)	108 (20.4)	90 (17.1)	60 (1.4)	
Stage 3b	101 (19.2)	121 (22.8)	107 (20.3)	114 (21.7)	
Stage 4	65 (12.3)	77 (14.5)	132 (25.1)	178 (33.8)	
Stage 5	15 (2.8)	13 (2.5)	22 (4.2)	80 (15.2)	

Values for categorical variables are given as number (percentage); values for continuous variables as mean ± standard deviation or median [interquartile range]. 25(OH)D, 25-hydroxyvitamin D; ACEi/ARBs, angiotensin converting enzyme inhibitor and/or angiotensin receptor blockers; ACR, albumin-to-creatinine ratio; BMI, body mass index; CKD, chronic kidney disease; DBP, diastolic blood pressure; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; ESAs, erythropoiesis-stimulating agents; GN, glomerulonephritis; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; HTN, hypertension; LDL-C, low-density lipoprotein cholesterol; PCR, protein-to-creatinine ratio; PKD, polycystic kidney disease; Q1, 1st quartile; Q2, 2nd quartile; Q3, 3rd quartile; Q4, 4th quartile; SBP, systolic blood pressure; TG, triglyceride; TID, tubulointerstitial disease.

regression analyses. Pre-defined subgroup analyses were also implemented to examine if the association between serum hepcidin levels and the risk of ESKD is differed across specific clinical settings. These subgroups were defined by age (either <60 or ≥60 years), gender (male or female), BMI (<23 or ≥23 kg/m^2), eGFR (either <45 or ≥45 mL/min/1.73 m^2), and spot urine ACR (either <300 or ≥300 mg/g). Two-tailed *p* values below 0.05 were deemed statistically significant. All statistical analyses were executed using SPSS for Windows version 22.0 (IBM Corp., Armonk, NY, USA) and R software (version 4.1.1; R Project for Statistical Computing, Vienna, Austria).

Results

Baseline Characteristics

The baseline characteristics of the study participants were described by serum hepcidin levels (Table 1). Higher serum hepcidin levels were significantly related to shorter duration of follow-up, older ages, higher frequency of male gender, higher Charlson Comorbidity Index score, higher frequency of diabetes mellitus as a primary cause of CKD, higher frequency of smoking history, more prevalent use of diuretics, statins, iron replacement, and ESAs, and higher SBP. Higher serum hepcidin levels were also related to lower hemoglobin, transferrin saturation, albumin, total cholesterol, HDL-C, and 25(OH)D levels and to higher ferritin, triglycerides, spot urine PCR, and creatinine levels. Accordingly, higher serum hepcidin levels were significantly associated with more advanced CKD stages of the participants. In the echocardiographic examination, left ventricular mass index, E/e' (the ratio of the early transmitral blood flow velocity to early diastolic velocity of the mitral annulus), left atrium diameter, posterior wall thickness, interventricular wall thickness, and left ventricular end-diastolic diameter positively correlated with serum hepcidin levels (online suppl. Table S1; for all online suppl. material, see https://doi.org/10.1159/000542057). In the overall, higher serum hepcidin levels were in general associated with more severe comorbid conditions at the baseline.

Association between Serum Hepcidin Levels and the Risk of Incident ESKD

Kaplan-Meier survival curve analysis visualized that the cumulative incidence of ESKD was significantly differed by serum hepcidin levels ($p < 0.001$, by log-rank test), with the highest incidence in Q4 (Fig. 2). Cox proportional hazard models to address the independent association between serum hepcidin levels and the risk of incident ESKD demonstrated that, compared to Q1, the risk of incident ESKD is significantly increased in Q4 (adjusted HR 1.372, 95% CI: 1.070–1.759) (Table 2). Every 1 log increase in serum hepcidin levels was associated with significant elevation of the risk of incident

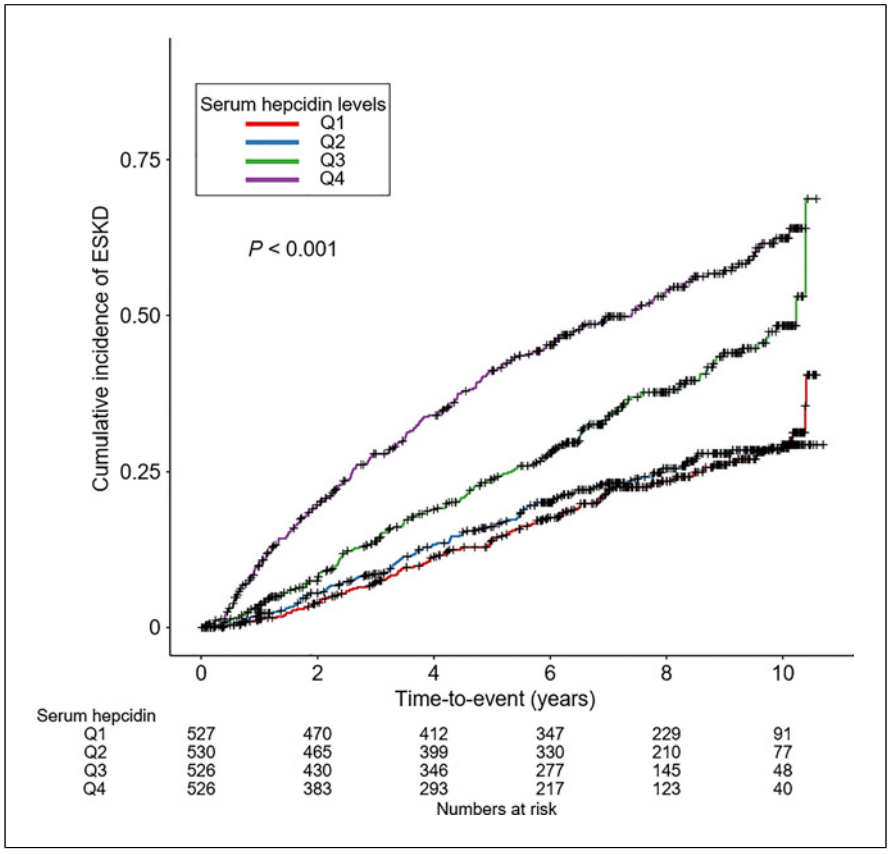

Fig. 2. Kaplan-Meier survival curve for cumulative incidence of ESKD by serum hepcidin levels. *p* value by log-rank test. ESKD, end-stage kidney disease; Q1, 1st quartile; Q2, 2nd quartile; Q3, 3rd quartile; Q4, 4th quartile.

Table 2. HRs for the incident ESKD by serum hepcidin levels

Outcome	Serum hepcidin levels, ng/mL	Events, *n* (%)	Model 1		Model 2		Model 3		Model 4	
			HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Incident ESKD	Q1 0.010–6.610	121 (23.0)	Reference		Reference		Reference		Reference	
	Q2 6.620–13.300	122 (23.0)	1.026 (0.784, 1.344)	0.850	1.031 (0.800, 1.328)	0.813	1.005 (0.779, 1.296)	0.968	1.094 (0.826, 1.448)	0.532
	Q3 13.400–25.000	173 (32.9)	1.741 (1.360, 2.230)	<0.001	1.751 (1.384, 2.215)	<0.001	1.633 (1.287, 2.073)	<0.001	1.119 (0.864, 1.449)	0.395
	Q4 25.100–80.000	256 (48.7)	2.940 (2.333, 3.706)	<0.001	2.935 (2.355, 3.659)	<0.001	2.511 (2.006, 3.142)	<0.001	1.372 (1.070, 1.759)	0.013
	Per 1 log increase	N/A	1.622 (1.482, 1.775)	<0.001	1.630 (1.497, 1.773)	<0.001	1.492 (1.372, 1.624)	<0.001	1.125 (1.031, 1.228)	0.008

Model 1, unadjusted model. Model 2, model 1 + adjusted for age and gender. Model 3, model 2 + adjusted for age-adjusted Charlson Comorbidity Index, primary cause of CKD, smoking status, medication (ACEi/ARBs, diuretics, statins, and antiplatelets/anticoagulants), BMI, and SBP. Model 4, model 3 + adjusted for hemoglobin, albumin, HDL-C, fasting glucose, 25(OH)D, hs-CRP, CKD stages, spot urine PCR, LVMI, and LVEF. CI, confidence interval; ESKD, end-stage kidney disease; HR, hazard ratio; Q1, 1st quartile; Q2, 2nd quartile; Q3, 3rd quartile; Q4, 4th quartile.

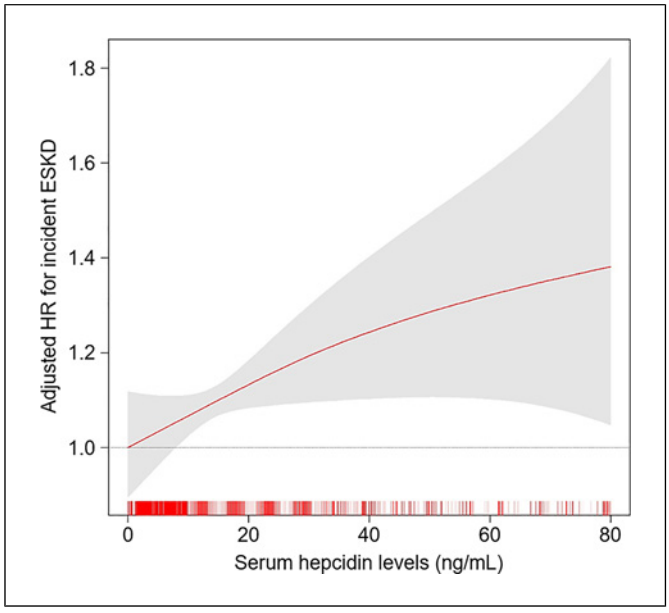

Fig. 3. Penalized spline curve of serum hepcidin levels on the risk of ESKD. Adjusted HR of serum hepcidin levels as a continuous variable for the risk of ESKD is depicted. The model was adjusted for age, gender, age-adjusted Charlson Comorbidity Index, primary causes of CKD, smoking status, medication (ACEi/ARBs, diuretics, statins, antiplatelets/anticoagulants), BMI, SBP, hemoglobin, albumin, HDL-C, fasting glucose, 25(OH)D, hs-CRP, CKD stages, spot urine PCR, LVMI, and LVEF. ESKD, end-stage kidney disease; HR, hazard ratio.

ESKD (adjusted HR 1.125, 95% CI: 1.031–1.228). Penalized spline curve analysis illustrated a linear, positive correlation between serum hepcidin levels and the risk of incident ESKD (Fig. 3).

Sensitivity and Subgroup Analyses

Upon re-categorizing participants by serum hepcidin levels into tertiles or quintiles, compared to the 1st tertile and quintile, the risk of incident ESKD was significantly higher in the 3rd tertile (adjusted HR 1.265, 95% CI: 1.013–1.579) and in the 5th quintile (adjusted HR 1.481, 95% CI: 1.124–1.951) (online suppl. Table S2). After censoring the death events prior to the onset of ESKD, the risk of incident ESKD was still significantly increased in Q4, compared to Q1 (adjusted HR 1.373, 95% CI: 1.041–1.810) (Table 3). Additional adjustment for the use of ESAs did not significantly alter the primary result (adjusted HR for Q4 1.344, 95% CI: 1.045–1.729) (online suppl. Table S3). Even, after replacing missing values by multiple imputation methods, the risk of incident ESKD remained significantly increased in Q4, compared to Q1 (adjusted HR 1.289, 95% CI: 1.019–1.631) (Table 4). Subgroup analyses demonstrated that the association between serum hepcidin levels and the risk of incident ESKD was significant in the subjects with eGFR <45 mL/min/1.73 m^2 but not in those with eGFR ≥45 mL/min/1.73 m^2 (p for interaction = 0.023). The other variables, such as age, gender, BMI, and albuminuria, did not significantly modified the association between serum hepcidin levels and the risk of incident ESKD (Table 5).

Discussion

In the present study, we discovered that elevation in serum hepcidin levels is significantly associated with increased risk of incident ESKD among the patients with pre-dialysis CKD. We believe that the robustness of the finding is convincing because the sensitivity analyses, including competing risk analysis and multiple imputation, yielded the comparable result to that of the primary analysis. Furthermore, subgroup analyses suggest that the association is significantly more prominent in the patients with advanced CKD (eGFR <45 mL/min/1.73 m^2).

The vast majority of the studies on hepcidin have highlighted its biological function as an inhibitor of ferroportin [29, 30] or as an antimicrobial peptide [31, 32]. Yet the clinical implication of serum hepcidin levels on the overall prognosis has been largely neglected. Only a few studies focused on the prognostic value of serum hepcidin levels [18–20], none of which evaluated the potential as a predictor of CKD progression. In addition, the previous studies analyzed the predictive role of hepcidin in combination of other biomarkers, such as NGAL and NT-proBNP [18–20]. Therefore, it is a fining of novelty that elevation in serum hepcidin levels is independently associated with risk of incident ESKD among the patients with pre-dialysis CKD.

It is still uncertain whether hepcidin directly result in kidney damage in the natural course of CKD. Deletion of *Hamp* gene obviously alleviated anemia and prevented growth retardation in a murine model of adenine-induced CKD [33], while the comparison of kidney functions did not demonstrate any significant differences between wild type and knockout mice. Similarly, even though the overexpression of hepcidin in a human kidney cell line increased the intracellular iron contents, no definitive data of cellular damage such as cell death and fibrosis have been presented [34]. Thus, currently available evidence does not support that hepcidin directly accelerates CKD progression. On the other hand, it does

Table 3. Cause-specific HRs for the incident ESKD by serum hepcidin levels

Outcome	Serum hepcidin levels	Model 1		Model 2		Model 3		Model 4	
		HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Incident ESKD	Q1	Reference		Reference		Reference		Reference	
	Q2	1.054 (0.821, 1.354)	0.678	1.031 (0.801, 1.328)	0.813	1.005 (0.778, 1.299)	0.968	1.094 (0.802, 1.491)	0.571
	Q3	1.785 (1.420, 2.243)	<0.001	1.751 (1.388, 2.208)	<0.001	1.633 (1.283, 2.079)	<0.001	1.118 (0.825, 1.515)	0.471
	Q4	3.035 (2.446, 3.767)	<0.001	2.936 (2.354, 3.661)	<0.001	2.511 (1.988, 3.171)	<0.001	1.373 (1.041, 1.810)	0.025
	Per 1 log increase	1.652 (1.510, 1.808)	<0.001	1.630 (1.488, 1.785)	<0.001	1.493 (1.360, 1.637)	<0.001	1.125 (1.022, 1.239)	0.016

Model 1, unadjusted model. Model 2, model 1 + adjusted for age and gender. Model 3, model 2 + adjusted for age-adjusted Charlson Comorbidity Index, primary cause of CKD, smoking status, medication (ACEi/ARBs, diuretics, statins, and antiplatelets/anticoagulants), BMI, and SBP. Model 4, model 3 + adjusted for hemoglobin, albumin, HDL-C, fasting glucose, 25(OH)D, hs-CRP, CKD stages, spot urine PCR, LVMI, and LVEF. CI, confidence interval; ESKD, end-stage kidney disease; HR, hazard ratio; Q1, 1st quartile; Q2, 2nd quartile; Q3, 3rd quartile; Q4, 4th quartile.

Table 4. HRs for the incident ESKD by serum hepcidin levels after multiple imputation

Outcome	Serum hepcidin levels	Model 1		Model 2		Model 3		Model 4	
		HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Incident ESKD	Q1	Reference		Reference		Reference		Reference	
	Q2	1.054 (0.820, 1.356)	0.680	1.031 (0.800, 1.328)	0.813	0.991 (0.768, 1.278)	0.945	1.047 (0.788, 1.390)	0.754
	Q3	1.785 (1.414, 2.253)	<0.001	1.751 (1.384, 2.215)	<0.001	1.599 (1.261, 2.028)	<0.001	1.143 (0.887, 1.474)	0.302
	Q4	3.035 (2.442, 3.770)	<0.001	2.935 (2.355, 3.659)	<0.001	2.524 (2.018, 3.158)	<0.001	1.289 (1.019, 1.630)	0.034
	Per 1 log increase	1.653 (1.516, 1.797)	<0.001	1.630 (1.497, 1.773)	<0.001	1.496 (1.375, 1.627)	<0.001	1.118 (1.030, 1.213)	0.008

Model 1, unadjusted model. Model 2, model 1 + adjusted for age and gender. Model 3, model 2 + adjusted for age-adjusted Charlson Comorbidity Index, primary cause of CKD, smoking status, medication (ACEi/ARBs, diuretics, statins, and antiplatelets/anticoagulants), BMI, and SBP. Model 4, model 3 + adjusted for hemoglobin, albumin, HDL-C, fasting glucose, 25(OH)D, hs-CRP, CKD stages, spot urine PCR, LVMI, and LVEF. CI, confidence interval; ESKD, end-stage kidney disease; HR, hazard ratio; Q1, 1st quartile; Q2, 2nd quartile; Q3, 3rd quartile; Q4, 4th quartile.

not seem likely either that hepcidin may play a compensatory role against CKD progression. Although hepcidin demonstrated a kidney-protective role in a murine model of experimental urinary tract infection [32], the context should be apart from CKD. Collectively, it is postulated that the functional role of hepcidin in the progression of CKD is minor and is mostly limited to the development of renal anemia.

Nevertheless, based on our finding, the elevation in serum hepcidin levels is an independent predictor of CKD progression. Although hepcidin critically contributes to the development of renal anemia by alteration of iron metabolism, the expression of hepcidin is regulated by diverse factors, one of which is inflammation [8, 9, 12]. IL-6, by activation of STAT3 (signal transducer and activator of transcription 3), directly upregulates the transcription of hepcidin [14, 35, 36]. Alternatively, it is also well known that the reduced renal production of EPO in patients with CKD results in unopposed hepcidin expression [37]. Because both

Table 5. HRs for the incident ESKD by serum hepcidin levels in various subgroups

	Serum hepcidin levels	Events, *n* (%)	Unadjusted HR (95% CIs)	*p* for interaction	Adjusted HR (95% CIs)	*p* for interaction
Age <60 years	Q1	78 (21.0)	Reference	0.506	Reference	0.371
	Q2	74 (22.0)	1.130 (0.822, 1.554)		0.995 (0.697, 1.421)	
	Q3	116 (33.2)	2.011 (1.508, 2.682)		0.995 (0.717, 1.380)	
	Q4	150 (47.8)	3.193 (2.426, 4.203)		1.180 (0.859, 1.620)	
Age ≥60 years	Q1	43 (27.6)	Reference		Reference	
	Q2	48 (24.7)	0.877 (0.581, 1.324)		0.907 (0.552, 1.492)	
	Q3	57 (32.2)	1.370 (0.921, 2.036)		1.145 (0.726, 1.807)	
	Q4	106 (50.0)	2.575 (1.804, 3.674)		1.411 (0.935, 2.131)	
Male	Q1	68 (26.3)	Reference	0.025	Reference	0.165
	Q2	77 (23.3)	0.884 (0.638, 1.225)		1.091 (0.751, 1.585)	
	Q3	107 (30.5)	1.382 (1.019, 1.875)		1.331 (0.947, 1.870)	
	Q4	156 (45.1)	2.281 (1.714, 3.036)		1.608 (1.162, 2.224)	
Female	Q1	53 (19.8)	Reference		Reference	
	Q2	45 (22.5)	1.259 (0.846, 1.873)		0.893 (0.575, 1.386)	
	Q3	66 (37.7)	2.459 (1.711, 3.535)		0.623 (0.407, 0.955)	
	Q4	100 (55.6)	4.422 (3.163, 6.181)		0.869 (0.575, 1.313)	
BMI <25 kg/m^2	Q1	79 (23.7)	Reference	0.466	Reference	0.693
	Q2	75 (24.7)	1.100 (0.802, 1.509)		1.089 (0.762, 1.556)	
	Q3	86 (31.3)	1.587 (1.169, 2.155)		0.946 (0.669, 1.339)	
	Q4	151 (48.9)	3.053 (2.324, 4.012)		1.157 (0.843, 1.587)	
BMI ≥25 kg/m^2	Q1	42 (21.9)	Reference		Reference	
	Q2	47 (21.4)	1.030 (0.678, 1.566)		1.120 (0.696, 1.801)	
	Q3	86 (34.7)	2.093 (1.441, 3.040)		1.375 (0.908, 2.081)	
	Q4	103 (48.4)	3.059 (2.128, 4.398)		1.741 (1.138, 2.665)	
eGFR ≥45 mL/min/ 1.73 m^2	Q1	25 (7.6)	Reference	0.037	Reference	0.023
	Q2	13 (4.3)	0.647 (0.330, 1.271)		0.501 (0.222, 1.126)	
	Q3	27 (10.7)	1.908 (1.093, 3.330)		1.713 (0.873, 3.361)	
	Q4	9 (6.5)	0.976 (0.453, 2.105)		0.625 (0.240, 1.629)	
eGFR <45 mL/min/ 1.73 m^2	Q1	96 (48.0)	Reference		Reference	
	Q2	109 (47.4)	1.012 (0.769, 1.331)		1.242 (0.914, 1.688)	

Table 5 (continued)

	Serum hepcidin levels	Events, *n* (%)	Unadjusted HR (95% CIs)	*p* for interaction	Adjusted HR (95% CIs)	*p* for interaction
	Q3	146 (53.3)	1.402 (1.083, 1.815)		0.988 (0.742, 1.316)	
	Q4	247 (63.8)	1.939 (1.530, 2.455)		1.405 (1.078, 1.833)	
Spot urine ACR <300 mg/g	Q1	29 (11.3)	Reference	0.939	Reference	0.557
	Q2	32 (11.9)	1.113 (0.672, 1.841)		1.388 (0.786, 2.451)	
	Q3	37 (16.1)	1.891 (1.160, 3.082)		1.261 (0.717, 2.220)	
	Q4	54 (27.0)	2.981 (1.864, 4.693)		1.808 (1.070, 3.055)	
Spot urine ACR ≥300 mg/g	Q1	91 (34.3)	Reference		Reference	
	Q2	87 (35.4)	1.133 (0.844, 1.520)		0.950 (0.681, 1.326)	
	Q3	132 (46.0)	1.652 (1.264, 2.159)		0.872 (0.643, 1.182)	
	Q4	198 (63.7)	2.996 (2.334, 3.846)		1.067 (0.795, 1.431)	

The model was adjusted for age, gender, age-adjusted Charlson Comorbidity Index, primary causes of CKD, smoking status, medication (ACEis/ARBs, diuretics, statins, antiplatelets/anticoagulants), BMI, SBP, hemoglobin, albumin, HDL-C, fasting glucose, 25(OH)D, hs-CRP, CKD stages, spot urine PCR, LVMI, and LVEF at the baseline. ACR, albumin-to-creatinine ratio; BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HR, hazard ratio; Q1, 1st quartile; Q2, 2nd quartile; Q3, 3rd quartile; Q4, 4th quartile.

inflammation and impaired EPO production are remarkable features of advanced CKD, it seems reasonable that the elevation in serum hepcidin levels is a reflection of deteriorating kidney function and may predict the risk of incident ESKD.

Several limitations are to be acknowledged in the current study. First, due to the observational study design, we are not able to confirm the casual relation between serum hepcidin levels and the risk of incident ESKD. Indeed, as hepcidin is a major pathogenic molecule of renal anemia, and as the severity and prevalence of anemia are increased among the patients with more advanced CKD, serum hepcidin levels may be simply elevated in the patients with more severe renal anemia and low eGFR. Yet we rigorously adjusted hemoglobin levels in Cox proportional hazard models to prove the association between serum hepcidin levels and a kidney outcome that is independent of the presence or absence of anemia. Therefore, it is very likely that serum hepcidin levels are a predictor for the risk of incident ESKD. Second, the mechanistic insights on the relation between serum hepcidin levels and CKD progression are lacking in the current study, which mainly analyzed clinical data. However, we included a thorough review on the currently available publications on hepcidin, which strongly indicates a potential role of serum hepcidin levels as a predictor of CKD progression, as discussed above. Third, because the KNOW-CKD is a cohort of Korean patients resident in South Korea, the extrapolation of the result presented in the current study requires a precaution. Nevertheless, provided that the association between serum hepcidin levels and renal prognosis in patients with pre-dialysis CKD has barely been studied so far, the cross-validation of the finding using other CKD cohorts should be required. Fourth, serum hepcidin level was measured only once at the baseline in the current study, while serum hepcidin levels may increase as CKD progresses, as the eGFR significantly decreases as serum hepcidin levels increase (Table 1). Yet, based on this correlation, we assume that the repeated measurement of serum hepcidin levels may more precisely predict the risk of incident ESKD, even though only a single measurement was significantly associated with renal prognosis with the adjustment of the baseline status of kidney function.

In conclusion, we report that elevation in serum hepcidin levels is significantly associated with increased

risk of incident ESKD among the patients with pre-dialysis CKD. It is expected that the measurement of serum hepcidin levels may help early identification of the patients at higher risk of CKD progression.

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Statement of Ethics

The study protocol of the KNOW-CKD was reviewed and approved by the Institutional Review Boards of the participating centers (Seoul National University Hospital [1104–089-359, May 25, 2011], Seoul National University Bundang Hospital [B-1106/129–008, August 24, 2011], Yonsei University Severance Hospital [4–2011-0163, June 2, 2011], Kangbuk Samsung Medical Center [2011–01-076, June 16, 2012], Seoul St. Mary's Hospital [KC11OIMI0441, June 30, 2011], Gil Hospital [GIRBA2553, August 8, 2011], Eulji General Hospital [201105–01, June 10, 2011], Chonnam National University Hospital [CNUH-2011-092, July 5, 2011], and Busan Paik Hospital [11–091, July 26, 2011]). Patients only who voluntarily gave informed consent were enrolled.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

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Data Availability Statement

The data presented in this study are available on request from the corresponding author.

References

1 Krause A, Neitz S, Mägert HJ, Schulz A, Forssmann WG, Schulz-Knappe P, et al. LEAP-1, a novel highly disulfide-bonded human peptide, exhibits antimicrobial activity. FEBS Lett. 2000;480(2–3):147–50. https://doi.org/10.1016/s0014-5793(00)01920-7

2 Liu XB, Nguyen NB, Marquess KD, Yang F, Haile DJ. Regulation of hepcidin and ferroportin expression by lipopolysaccharide in splenic macrophages. Blood Cells Mol Dis. 2005;35(1):47–56. https://doi.org/10.1016/j.bcmd.2005.04.006

3 Bekri S, Gual P, Anty R, Luciani N, Dahman M, Ramesh B, et al. Increased adipose tissue expression of hepcidin in severe obesity is independent from diabetes and NASH. Gastroenterology. 2006;131(3):788–96. https://doi.org/10.1053/j.gastro.2006.07.007

4 Valore EV, Ganz T. Posttranslational processing of hepcidin in human hepatocytes is mediated by the prohormone convertase furin. Blood Cells Mol Dis. 2008;40(1):132–8. https://doi.org/10.1016/j.bcmd.2007.07.009

5 Park CH, Valore EV, Waring AJ, Ganz T. Hepcidin, a urinary antimicrobial peptide synthesized in the liver. J Biol Chem. 2001;276(11):7806–10. https://doi.org/10.1074/jbc.M008922200

6 Matthes T, Aguilar-Martinez P, Pizzi-Bosman L, Darbellay R, Rubbia-Brandt L, Giostra E, et al. Severe hemochromatosis in a Portuguese family associated with a new mutation in the 5'-UTR of the HAMP gene. Blood. 2004;104(7):2181–3. https://doi.org/10.1182/blood-2004-01-0332

7 Roetto A, Daraio F, Porporato P, Caruso R, Cox TM, Cazzola M, et al. Screening hepcidin for mutations in juvenile hemochromatosis: identification of a new mutation (C70R). Blood. 2004;103(6):2407–9. https://doi.org/10.1182/blood-2003-10-3390
8 Agarwal AK, Yee J. Hepcidin. Adv Chronic Kidney Dis. 2019;26(4):298–305. https://doi.org/10.1053/j.ackd.2019.04.005
9 Pagani A, Nai A, Silvestri L, Camaschella C. Hepcidin and anemia: a tight relationship. Front Physiol. 2019;10:1294. https://doi.org/10.3389/fphys.2019.01294
10 Stauffer ME, Fan T. Prevalence of anemia in chronic kidney disease in the United States. PLoS One. 2014;9(1):e84943. https://doi.org/10.1371/journal.pone.0084943
11 Inker LA, Grams ME, Levey AS, Coresh J, Cirillo M, Collins JF, et al. Relationship of estimated GFR and albuminuria to concurrent laboratory abnormalities: an individual participant data meta-analysis in a global consortium. Am J Kidney Dis. 2019;73(2):206–17. https://doi.org/10.1053/j.ajkd.2018.08.013
12 Ganz T, Nemeth E. Iron balance and the role of hepcidin in chronic kidney disease. Semin Nephrol. 2016;36(2):87–93. https://doi.org/10.1016/j.semnephrol.2016.02.001
13 Liu Q, Davidoff O, Niss K, Haase VH. Hypoxia-inducible factor regulates hepcidin via erythropoietin-induced erythropoiesis. J Clin Invest. 2012;122(12):4635–44. https://doi.org/10.1172/JCI63924
14 Nemeth E, Rivera S, Gabayan V, Keller C, Taudorf S, Pedersen BK, et al. IL-6 mediates hypoferremia of inflammation by inducing the synthesis of the iron regulatory hormone hepcidin. J Clin Invest. 2004;113(9):1271–6. https://doi.org/10.1172/JCI20945
15 Malyszko J, Malyszko JS, Pawlak K, Myslinwiec M. Hepcidin, iron status, and renal function in chronic renal failure, kidney transplantation, and hemodialysis. Am J Hematol. 2006;81(11):832–7. https://doi.org/10.1002/ajh.20657
16 Pergola PE, Spinowitz BS, Hartman CS, Maroni BJ, Haase VH. Vadadustat, a novel oral HIF stabilizer, provides effective anemia treatment in nondialysis-dependent chronic kidney disease. Kidney Int. 2016;90(5):1115–22. https://doi.org/10.1016/j.kint.2016.07.019
17 Provenzano R, Besarab A, Sun CH, Diamond SA, Durham JH, Cangiano JL, et al. Oral hypoxia-inducible factor prolyl hydroxylase inhibitor roxadustat (FG-4592) for the treatment of anemia in patients with CKD. Clin J Am Soc Nephrol. 2016;11(6):982–91. https://doi.org/10.2215/CJN.06890615
18 Albert C, Haase M, Albert A, Ernst M, Kropf S, Bellomo R, et al. Predictive value of plasma NGAL:hepcidin-25 for major adverse kidney events after cardiac surgery with cardiopulmonary bypass: a pilot study. Ann Lab Med. 2021;41(4):357–65. https://doi.org/10.3343/alm.2021.41.4.357
19 Elitok S, Kuppe H, Devarajan P, Bellomo R, Isermann B, Westphal S, et al. Urinary neutrophil gelatinase-associated lipocalin/hepcidin-25 ratio for early identification of patients at risk for renal replacement therapy after cardiac surgery: a substudy of the BICARBONATE trial. Anesth Analg. 2021;133(6):1510–9. https://doi.org/10.1213/ANE.0000000000005741
20 Nübel J, Hoffmeister M, Labrenz O, Jost K, Oess S, Hauptmann M, et al. NT-proBNP/urine hepcidin-25 ratio and cardiorenal syndrome type 1 in patients with severe symptomatic aortic stenosis. Biomark Med. 2023;17(10):475–85. https://doi.org/10.2217/bmm-2023-0034
21 Oh KH, Park SK, Park HC, Chin HJ, Chae DW, Choi KH, et al. KNOW-CKD (Korean cohort study for Outcome in patients with Chronic Kidney Disease): design and methods. BMC Nephrol. 2014;15:80. https://doi.org/10.1186/1471-2369-15-80
22 Suh SH, Oh TR, Choi HS, Kim CS, Bae EH, Ma SK, et al. Urinary phosphorus excretion and cardiovascular outcomes in patients with pre-dialysis chronic kidney disease: the KNOW-CKD study. Nutrients. 2023;15(10):2267. https://doi.org/10.3390/nu15102267
23 Suh SH, Oh TR, Choi HS, Kim CS, Bae EH, Ma SK, et al. Association between urinary chloride excretion and progression of coronary artery calcification in patients with nondialysis chronic kidney disease: results from the KNOW-CKD study. Kidney Res Clin Pract. 2023;42(2):251–61. https://doi.org/10.23876/j.krcp.22.072
24 Suh SH, Oh TR, Choi HS, Yang EM, Kim CS, Bae EH, et al. Bone mineral density and all-cause mortality in patients with nondialysis chronic kidney disease: results from KNOW-CKD study. J Clin Med. 2023;12(5):1850. https://doi.org/10.3390/jcm12051850
25 Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604–12. https://doi.org/10.7326/0003-4819-150-9-200905050-00006
26 Levey AS, de Jong PE, Coresh J, El Nahas M, Astor BC, Matsushita K, et al. The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. Kidney Int. 2011;80(1):17–28. https://doi.org/10.1038/ki.2010.483
27 Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for chamber quantification: a report from the American society of echocardiography's guidelines and standards committee and the chamber quantification writing Group, developed in conjunction with the European association of echocardiography, a branch of the European society of cardiology. J Am Soc Echocardiogr. 2005;18(12):1440–63. https://doi.org/10.1016/j.echo.2005.10.005
28 Lee SW, Kim YH, Chung W, Park SK, Chae DW, Ahn C, et al. Serum hepcidin and iron indices affect anemia status differently according to the kidney function of non-dialysis chronic kidney disease patients: Korean cohort study for outcome in patients with chronic kidney disease (KNOW-CKD). Kidney Blood Press Res. 2017;42(6):1183–92. https://doi.org/10.1159/000485865
29 Wallace DF, McDonald CJ, Ostini L, Iser D, Tuckfield A, Subramaniam VN. The dynamics of hepcidin-ferroportin internalization and consequences of a novel ferroportin disease mutation. Am J Hematol. 2017;92(10):1052–61. https://doi.org/10.1002/ajh.24844
30 Billesbølle CB, Azumaya CM, Kretsch RC, Powers AS, Gonen S, Schneider S, et al. Structure of hepcidin-bound ferroportin reveals iron homeostatic mechanisms. Nature. 2020;586(7831):807–11. https://doi.org/10.1038/s41586-020-2668-z
31 Michels K, Nemeth E, Ganz T, Mehrad B. Hepcidin and host defense against infectious diseases. PLoS Pathog. 2015;11(8):e1004998. https://doi.org/10.1371/journal.ppat.1004998
32 Houamel D, Ducrot N, Lefebvre T, Daher R, Moulouel B, Sari MA, et al. Hepcidin as a major component of renal antibacterial defenses against uropathogenic Escherichia coli. J Am Soc Nephrol. 2016;27(3):835–46. https://doi.org/10.1681/ASN.2014101035
33 Akchurin O, Sureshbabu A, Doty SB, Zhu YS, Patino E, Cunningham-Rundles S, et al. Lack of hepcidin ameliorates anemia and improves growth in an adenine-induced mouse model of chronic kidney disease. Am J Physiol Ren Physiol. 2016;311(5):F877–89. https://doi.org/10.1152/ajprenal.00089.2016
34 Pan S, Qian ZM, Cui S, Zhao D, Lan W, Wang X, et al. Local hepcidin increased intracellular iron overload via the degradation of ferroportin in the kidney. Biochem Biophys Res Commun. 2020;522(2):322–7. https://doi.org/10.1016/j.bbrc.2019.11.066
35 Nemeth E, Tuttle MS, Powelson J, Vaughn MB, Donovan A, Ward DM, et al. Hepcidin regulates cellular iron efflux by binding to ferroportin and inducing its internalization. Sci. 2004;306(5704):2090–3. https://doi.org/10.1126/science.1104742
36 Pietrangelo A, Dierssen U, Valli L, Garuti C, Rump A, Corradini E, et al. STAT3 is required for IL-6-gp130-dependent activation of hepcidin in vivo. Gastroenterology. 2007;132(1):294–300. https://doi.org/10.1053/j.gastro.2006.10.018
37 Nakai T, Iwamura Y, Kato K, Hirano I, Matsumoto Y, Tomioka Y, et al. Drugs activating hypoxia-inducible factors correct erythropoiesis and hepcidin levels via renal EPO induction in mice. Blood Adv. 2023;7(15):3793–805. https://doi.org/10.1182/bloodadvances.2023009798