Yu *et al. Nutrition Journal* (2025) 24:7
https://doi.org/10.1186/s12937-025-01072-1

Nutrition Journal

RESEARCH Open Access

Association of iron deficiency with kidney outcome and all-cause mortality in chronic kidney disease patients without anemia

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Abstract

Background Iron deficiency is prevalent in patients with chronic kidney disease (CKD), even in those without anemia. However, the effects of iron deficiency on CKD progression and all-cause mortality in non-dialysis-dependent CKD (NDD-CKD) patients without anemia remain incompletely understood.

Methods This multicenter retrospective nationwide cohort study included adult patients with non-anemia NDD-CKD from 24 hospitals across China. The study investigated the associations between serum ferritin or transferrin saturation (TSAT) levels and the risks of CKD progression and all-cause mortality.

Results Among 18,878 patients with NDD-CKD, 9,989 patients were included in the kidney outcome analysis, and 18,481 patients in the all-cause mortality analysis. Of the patients with the measurement, 2,450 (27.2%) had ferritin levels ≤ 100ng/mL and 2,440 (13.1%) had a TSAT level ≤ 20%. Compared with patients with TSAT level of > 20%, those with TSAT level of ≤ 20% had significantly higher risks of CKD progression (adjusted hazard ratio [aHR]: 1.66, 95% confidence intervals [CI]: 1.16–2.37; $P = 0.005$) and all-cause mortality (aHR: 2.21, 95% CI: 1.36–3.57; $P = 0.001$). The robustness of results was supported by subgroup analyses. However, there was no significant association found between ferritin levels and the risk of CKD progression or all-cause mortality ($P > 0.05$).

Conclusion Iron deficiency was prevalent in NDD-CKD patients without anemia, and TSAT could be a modifiable risk factor of CKD progression and all-cause mortality. The screening of iron biomarkers, especially TSAT, in the early stage of NDD-CKD is important to assess and improve prognosis.

Keywords Iron deficiency, Serum ferritin, Transferrin saturation, Chronic kidney disease, Anemia

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Introduction

Chronic kidney disease (CKD) is a significant contributor in the increasing morbidity and mortality associated with noncommunicable diseases. From 1990 to 2017, the global prevalence of CKD across all-age groups increased by 29.3%, while the mortality rate from CKD rose by 41.5% [1]. Apart from the traditional risk factors, such as hypertension, hyperglycemia and proteinuria, many non-traditional risk factors are believed to influence the progression of CKD [2]. It is crucial for patients with early-stage CKD to identify modifiable risk factors to prevent the progression of CKD and premature death.

Iron is an essential component of hemoglobin and myoglobin, playing a vital role in various cellular mechanisms such as DNA synthesis, enzymatic processes, and mitochondrial energy generation [3]. Consequently, iron deficiency is associated with numerous pathophysiological conditions, such as anemia, heart failure, and cancer. While previous studies focused mainly on iron deficiency as a potentially modifiable etiology of anemia, it is now recognized as a distinct clinical condition [4]. Recent studies have highlighted that many CKD patients may have iron deficiency even in the absence of anemia [5–9]. The detection of iron deficiency in CKD patients without anemia requires additional support from clinical evidence. However, existing studies have focused on the impact of iron deficiency in anemic CKD patients, with limited evidence on the consequences of iron deficiency in CKD patients without anemia [10–17].

In this large multicenter retrospective cohort study of non-dialysis-dependent CKD (NDD-CKD) patients without anemia, we investigated the association between iron deficiency, as determined by the level of serum ferritin or transferrin saturation (TSAT), and the risks of CKD progression and all-cause mortality.

Methods

Study population

This study is a large multicenter retrospective cohort study that used deidentified data from the China Renal Data System (CRDS), including patients from 24 hospitals across China from January 1, 2000, to December 31, 2022 [18].

The study enrolled hospitalized adult patients (aged ≥ 18 years) with CKD who underwent at least one serum ferritin test or TSAT test in the CRDS. CKD was defined based on one of the following criteria: International Statistical Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes, estimated glomerular filtration rates (eGFR) less than 60 ml/min/1.73 m^2 for more than 3 months, or at least two abnormal urine protein tests for more than 3 months. eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI) [19]. Abnormal urine protein was defined as one of the following: qualitative urine protein detection greater than 1+, 24-hour urine protein quantitation > 0.3 g, or urine albumin to creatinine (UACR) > 300 mg/g. If the TSAT test was not available, the TSAT (expressed as a percentage) was calculated using the formula: serum iron concentration (μmol/L) * 100 / total iron binding capacity (TIBC, μmol/L). Patients had either ferritin or TSAT, or both, were included in the study. Baseline was defined as the first hospitalization with available ferritin or TSAT.

Exclusion criteria included the absence of eGFR data or eGFR < 30 ml/min/1.73 m^2 during the baseline period (defined as the first hospitalization with available iron indicators); history of kidney transplantation or dialysis before or at baseline; acute kidney injury (AKI) within 90 days before admission or during the hospitalization; pregnancy, anemia (defined based on ICD-10-CM codes or a hemoglobin less than 130 g/L in male or 120 g/L in non-pregnant female) [20], anti-anemic preparations (including iron, vitamin B, folic acid, and erythropoiesis-stimulating agents (ESAs) treatment), transfusion, or other hematologic disorders within 90 days before admission or during the hospitalization. Patients with iron excess, defined as serum ferritin concentration over 500 ng/mL at baseline, were also excluded [21].

This study utilized two datasets for distinct analytical purposes. The dataset for the analysis of kidney disease progression excluded patients without repeated eGFR measurement after discharge. The dataset for the analysis of all-cause mortality excluded patients without identifiable information from the national electronic cause-of-death reporting system of the China Center for Disease Control and Prevention [22].

The study protocol was approved by the Medical Ethics Committee of Nanfang Hospital, Southern Medical University. Patient informed consent was waived due to the retrospective nature of the study. The study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline [23].

Clinical variables

Iron status was categorized as either iron deficiency or iron replete according to the Kidney Disease: Improving Global Outcomes (KDIGO) guideline [20]. Iron deficiency was defined as TSAT level ≤20% or serum ferritin concentration ≤100 ng/mL.

Baseline laboratory variables were measured during the first eligible hospitalization (baseline period). Prescription use was determined by having at least one prescription of medications according to the Anatomical Therapeutic Chemical classification system within 90 days before admission and during hospitalization. The comorbidities were diagnosed based on ICD-10-CM codes before discharge.

Study outcome

The primary outcome was the progression of CKD, defined as a composite of a sustained decrease in eGFR of > 40% from baseline (excluding the occurrence of AKI) or the development of end-stage kidney disease (ESKD, eGFR < 15 ml/min/1.73 m^2 or the need for maintenance dialysis or kidney transplantation). Follow-up was terminated when patients reached the study outcome or when their last available serum creatinine measurement was recorded, whichever came first.

The secondary outcome was all-cause mortality, which was determined using records from the national electronic cause-of-death reporting system [22]. Follow-up started at discharge and continued until the event of death or the last date recorded in the electronic medical record, whichever came first.

Statistical analysis

Baseline clinical characteristics were summarized and presented as the median (interquartile range [IQR]) for continuous variables or frequency (percentage) for categorical variables. Group comparisons were conducted using the Kruskal-Wallis H test for continuous variables and χ^2 test or Fisher's exact test for categorical variables. Clinical variables with a missing proportion < 20% were assumed to be missing at random and were imputed using random forest [24].

The study utilized the Kaplan-Meier method to estimate cumulative incidences of study outcomes. All outcomes were analyzed as time-to-event outcomes. Cox proportional hazards models were used to assess associations between iron status and outcomes. For progression of CKD, the analyses were adjusted for sex, age, eGFR, proteinuria, albumin, C-reactive protein (CRP), hemoglobin, total cholesterol, Charlson score, diabetes, hypertension, cardiovascular and cerebrovascular disease, liver disease, cancer, statins, and renin-angiotensin-aldosterone system (RAAS) inhibitors. In the case of all-cause mortality, the analyses were adjusted for similar factors but excluded hemoglobin, statins and RAAS inhibitor. Subgroup analysis was conducted to validate the robustness of the findings, stratified by age (> 65 and ≤65 years), sex, diabetes, hypertension, and CRP (> 10 and ≤10 mg/L). All tests were two-tailed, and *P* values < 0.05 were considered statistically significant. The analyses were performed using R (version 4.0.3).

Results

Baseline characteristics of study population

Among the 18,878 eligible patients with non-anemic NDD-CKD, a total of 9,989 patients were included in the study to assess the association of iron deficiency with kidney disease progression, while 18,481 patients were included to assess the association of iron deficiency with all-cause mortality (Fig. 1). The baseline characteristics of CKD progression dataset are summarized in Table 1. Of the 8,995 patients with ferritin measurement, the median serum ferritin concentration was 176.2 (IQR, 93.2, 285.0) ng/mL, and the median age was 57 years, with 40.5% being female. Comparing with patients with ferritin levels > 100 ng/mL, 2,450 (27.2%) patients with ferritin levels ≤ 100 ng/mL were younger, had a higher proportion of female, lower eGFR levels, and lower hemoglobin concentration. Among the 2,440 (24.43%) patients with TSAT measurements, 320 (13.1%) had a level of TSAT ≤ 20%. Patients with TSAT levels ≤ 20% were more likely to be female, with lower levels of proteinuria and hemoglobin.

The characteristics of the all-cause mortality analysis set are summarized in Table 2. Among the 18,481 patients included in the analysis, 4,730 (25.59%) had TSAT measurements, and 1,866 (10.1%) patients died during a median follow-up of 45.4 (IQR, 18.6 to 70.7) months.

Serum ferritin, TSAT and CKD progression

During a median follow-up of 18.4 (IQR, 6.6 to 35.5) months, a total of 1,151 (11.5%) patients experienced CKD progression. The cumulative incidence of CKD progression is presented in Fig. 2A-B. Compared to patients with ferritin levels > 100 ng/mL, patients with serum ferritin ≤100 ng/mL showed no significant association with CKD progression (adjusted hazard ratio [aHR], 1.11; 95% confidence intervals [CI], 0.96–1.29; *P* = 0.170). For TSAT levels, patients with TSAT levels of ≤20% had a 66% higher risk of CKD progression compared to those with TSAT levels > 20% (aHR, 1.66; 95% CI, 1.16–2.37; *P* = 0.005) (Table 3).

Serum ferritin, TSAT and all-cause mortality

The cumulative incidence of all-cause mortality is illustrated in Fig. 2C-D. After adjusting for covariates, patients with ferritin levels of ≤100 ng/mL showed no significant association with the risk of all-cause mortality (aHR, 1.10; 95% CI, 0.99–1.23; *P* = 0.087) compared to those with ferritin levels > 100 ng/mL. However, patients with TSAT levels ≤20% had a higher risk of all-cause mortality (aHR, 2.21; 95% CI, 1.36–3.57; *P* = 0.001) than those with TSAT levels > 20% (Table 3).

Subgroup analysis

Subgroup analyses were conducted by stratifying patients based on age, sex, diabetes, hypertension, and CRP levels. Most stratifications revealed no significant effect modifications on the association between serum ferritin and the risk of all-cause mortality or CKD progression (Supplementary Figs. S1 and S3). However, the association between ferritin and all-cause mortality was insignificant

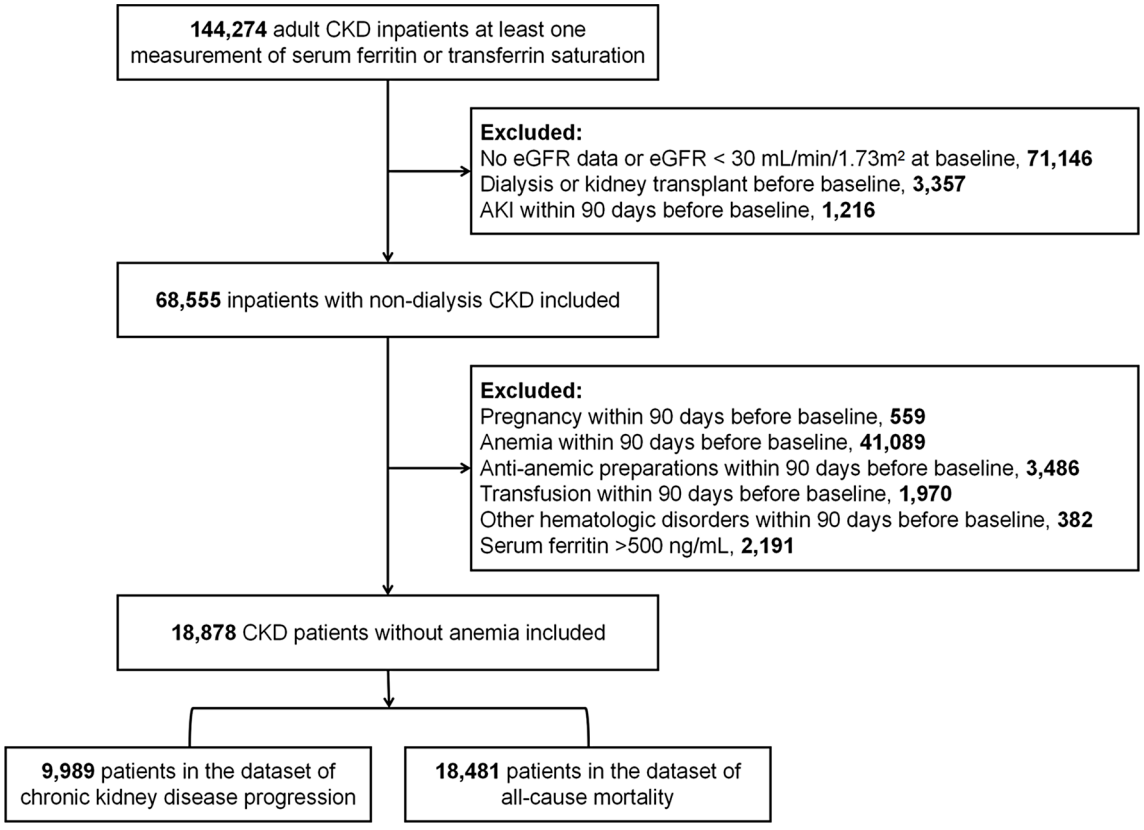

Fig. 1 The flow chart of study cohort inclusion and exclusion. CKD, chronic kidney disease; eGFR, estimated glomerular filtration rates; AKI, acute kidney injury

in females. In males, ferritin levels of ≤100 ng/mL showed a significant 23% increased risk of all-cause mortality (aHR, 1.23; 95% CI, 1.07–1.41; *P* for interaction = 0.026; Supplementary Fig. S3). The association of TSAT with the risk of CKD progression and all-cause mortality remained consistent across various subgroups except for age. In patients aged less than 65 years, the association between TSAT ≤ 20% and the risk of all-cause mortality was significant (aHR, 4.10; 95% CI, 2.22–7.57; *P* for interaction = 0.012; Supplementary Figs. S2 and S4).

Discussion

In this large, multicenter, retrospective cohort study, iron deficiency, characterized by decreased level of serum ferritin or TSAT, was prevalent in NDD-CKD patients without anemia. Our findings indicate that in NDD-CKD patients without anemia, lower TSAT level was associated with higher risks of CKD progression and all-cause mortality. However, we found no significant association between serum ferritin and the risk of CKD progression or all-cause mortality.

Iron deficiency is a prevalent issue, affecting approximately 25% of the general population [11, 25] and 30–45% of CKD patients [26]. Previous studies have found that lower TSAT was associated with cardiovascular hospitalizations and mortality in CKD patients [10–15, 26–28]. However, these studies primarily focused on the association between abnormal iron levels and adverse outcomes in anemic patients. The impact of iron deficiency on CKD progression and all-cause mortality in NDD-CKD subjects without anemia has not been well studied. Moreover, the findings regarding the relationship between iron status and CKD progression were inconsistent [10, 14, 16, 17, 29, 30]. A retrospective study involving 453 veterans with NDD-CKD suggested that higher TSAT levels were associated with higher risk of CKD progression, while lower TSAT or serum ferritin did not show a significant association with CKD progression [9]. In contrast, another observational cohort study including 2,500 patients found a negative correlation between TSAT levels and adverse renal outcomes (renal replacement therapy or a composite of renal replacement therapy plus 50% decline in eGFR) in males and non-anemic patients [17]. These studies were limited by the small sample size and the use of surrogate endpoints. Our large-scale analysis of real-world medical data revealed that lower TSAT level was associated with higher risks of CKD progression and all-cause mortality in NDD-CKD patients without anemia.

Table 1 Baseline characteristics of chronic kidney disease progression dataset

Characteristics	Ferritin (ng/mL)			*P* value	TSAT (%)			*P* value
	Overall, n = 8,995	≤ 100, n = 2,450	> 100, n = 6,545		Overall, n = 2,440	≤ 20, n = 320	> 20, n = 2,120	
Follow-up, months	18.2 [6.5, 35.6]	18.2 [6.3, 35.4]	18.3 [6.7, 35.6]	0.879	14.9 [4.9, 30.6]	15.1 [4.5, 31.3]	14.9 [5.0, 30.5]	0.905
Age, years	57.0 [44.0, 68.0]	49.0 [37.0, 64.0]	59.0 [48.0, 69.0]	**< 0.001**	51.0 [37.0, 64.0]	49.0 [36.0, 64.0]	51.0 [37.0, 64.0]	0.501
Sex, female, n (%)	3,646 (40.5)	1,574 (64.2)	2,072 (31.7)	**< 0.001**	1,079 (44.2)	198 (61.9)	881 (41.6)	**< 0.001**
Charlson score	4.0 [2.0, 6.0]	3.0 [1.0, 5.0]	4.0 [2.0, 6.0]	**< 0.001**	3.0 [1.0, 4.0]	2.5 [1.0, 4.0]	3.0 [1.0, 4.0]	0.542
Laboratory tests								
Ferritin, ng/mL	176.2 [93.2, 285.0]	58.5 [35.4, 78.8]	231.6 [158.2, 324.0]	**< 0.001**	179.0 [89.5, 286.8]	106.5 [44.3, 257.5]	185.7 [96.1, 289.2]	**< 0.001**
TSAT, %	32.2 [24.6, 41.9]	27.6 [21.0, 36.3]	34.0 [26.8, 43.4]	**< 0.001**	31.4 [24.1, 40.2]	16.5 [13.6, 18.5]	33.5 [27.3, 42.1]	**< 0.001**
Scr, μmol/L	84.0 [65.0, 109.0]	74.0 [58.0, 101.0]	87.0 [69.0, 111.0]	**< 0.001**	91.0 [73.0, 114.2]	93.0 [71.0, 118.2]	91.0 [73.0, 114.0]	0.744
eGFR, ml/min per 1.73m^2	57.0 [44.0, 68.0]	49.0 [37.0, 64.0]	59.0 [48.0, 69.0]	**< 0.001**	51.0 [37.0, 64.0]	49.0 [36.0, 64.0]	51.0 [37.0, 64.0]	0.502
Proteinuria, n (%)								
≥ 1+	4,867 (54.1)	1,475 (60.2)	3,392 (51.8)	**< 0.001**	1,406 (57.6)	165 (51.6)	1,241 (58.5)	**0.004**
Trace	3,567 (39.7)	809 (33.0)	2,758 (42.1)		937 (38.4)	133 (41.6)	804 (37.9)	
NA	561 (6.2)	166 (6.8)	395 (6.0)		97 (4.0)	22 (6.9)	75 (3.5)	
CRP (mg/L), n (%)				**< 0.001**				**< 0.001**
≤ 10	5,536 (61.5)	1,679 (68.5)	3,857 (58.9)		1,900 (77.9)	198 (61.9)	1,702 (80.3)	
> 10	852 (9.5)	127 (5.2)	725 (11.1)		219 (9.0)	76 (23.8)	143 (6.7)	
NA	2,607 (29.0)	644 (26.3)	1,963 (30.0)		321 (13.2)	46 (14.4)	275 (13.0)	
Hb, g/L	139.0 [132.0, 150.0]	135.0 [129.0, 145.0]	141.0 [133.0, 151.0]	**< 0.001**	139.0 [131.0, 149.0]	133.0 [128.0, 141.0]	139.0 [132.0, 149.5]	**< 0.001**
TCHO, mmol/L	4.9 [4.1, 6.0]	4.9 [4.1, 5.9]	4.9 [4.1, 6.0]	0.336	5.1 [4.2, 6.2]	4.9 [4.1, 5.8]	5.2 [4.3, 6.3]	**< 0.001**
ALB, g/L	39.9 [35.6, 43.0]	39.5 [35.2, 42.7]	40.0 [35.8, 43.2]	**< 0.001**	38.8 [34.4, 42.2]	38.6 [35.0, 41.4]	38.8 [34.2, 42.3]	0.999
Comorbidities								
Hypertension, n (%)	4,335 (48.2)	1,010 (41.2)	3,325 (50.8)	**< 0.001**	1,161 (47.6)	161 (50.3)	1,000 (47.2)	0.323
Diabetes, n (%)	2,342 (26.0)	470 (19.2)	1,872 (28.6)	**< 0.001**	502 (20.6)	85 (26.6)	417 (19.7)	**0.006**
Cancer, n (%)	1,094 (12.2)	316 (12.9)	778 (11.9)	0.204	231 (9.5)	29 (9.1)	202 (9.5)	0.871
Liver disease, n (%)	2,747 (30.5)	595 (24.3)	2,152 (32.9)	**< 0.001**	538 (22.0)	75 (23.4)	463 (21.8)	0.568
CVD, n (%)	2,910 (32.4)	593 (24.2)	2,317 (35.4)	**< 0.001**	725 (29.7)	110 (34.4)	615 (29.0)	0.058
PVD, n (%)	2,330 (25.9)	525 (21.4)	1,805 (27.6)	**< 0.001**	438 (18.0)	49 (15.3)	389 (18.3)	0.215
Infection, n (%)	852 (9.5)	172 (7.0)	680 (10.4)	**< 0.001**	169 (6.9)	16 (5.0)	153 (7.2)	0.181
Prescription drugs								
RASi, n (%)	3,767 (41.9)	1,029 (42.0)	2,738 (41.8)	0.906	1,160 (47.5)	155 (48.4)	1,005 (47.4)	0.776
Diuretics, n (%)	1,782 (19.8)	505 (20.6)	1,277 (19.5)	0.256	442 (18.1)	62 (19.4)	380 (17.9)	0.582
Statins, n (%)	3,157 (35.1)	699 (28.5)	2,458 (37.6)	**< 0.001**	914 (37.5)	111 (34.7)	803 (37.9)	0.300
Chemotherapy, n (%)	870 (9.7)	236 (9.6)	634 (9.7)	0.970	202 (8.3)	34 (10.6)	168 (7.9)	0.127

Results are expressed as median [interquartile range] or number (percentage)

Scr: serum creatinine; eGFR: estimated glomerular filtration rates; CRP: C-reactive protein; Hb: hemoglobin; TCHO: total cholesterol; ALB: albumin; CVD: cardiovascular and cerebrovascular disease; PVD: peripheral vascular disease; RASi: renin-angiotensin-aldosterone system inhibitor

The gold standard method for assessing iron stores is the semiquantitative staining of bone marrow iron. However, due to its invasive nature, this test is often not favored in clinical practice. While TSAT and serum ferritin concentration are commonly used tests to diagnose iron deficiency [10], they reflect different aspects of iron status in the body. Serum ferritin assesses the level of storage iron, while transferrin saturation reflects the availability of iron for tissue use [21]. Additionally, serum ferritin levels can be influenced by various pathological conditions such as inflammation, malignancy, and pregnancy [3, 31, 32]. Inflammation can distort interpretation of serum ferritin concentrations, and potentially obscure the diagnosis of iron deficiency [21]. In cases of the functional iron deficiency, characterized by insufficient iron delivery to target tissues and cells, systemic inflammation

Table 2 Baseline characteristics of all-cause mortality dataset

Characteristics	Ferritin (ng/mL)			*P* value	TSAT (%)			*P* value
	Overall, *n* = 16,566	≤ 100, *n* = 4,398	> 100, *n* = 12,168		Overall, *n* = 4,730	≤ 20, *n* = 653	> 20, *n* = 4,077	
Follow-up, months	49.5 [21.1, 73.4]	48.7 [20.3, 72.4]	49.8 [21.6, 73.6]	0.170	25.7 [6.8, 49.5]	21.4 [3.7, 45.3]	26.4 [7.6, 50.0]	**0.002**
Age, years	58.0 [45.0, 69.0]	50.0 [38.0, 66.0]	60.0 [48.0, 70.0]	**< 0.001**	53.0 [39.0, 66.0]	53.0 [38.0, 67.0]	53.0 [39.0, 65.0]	0.965
Sex, female, n (%)	6,834 (41.3)	2,849 (64.8)	3,985 (32.7)	**< 0.001**	2,067 (43.7)	390 (59.7)	1,677 (41.1)	**< 0.001**
Charlson score	4.0 [2.0, 6.0]	3.0 [1.0, 5.0]	4.0 [2.0, 6.0]	**< 0.001**	3.0 [1.0, 4.0]	3.0 [1.0, 4.0]	3.0 [1.0, 4.0]	0.501
Laboratory tests								
Ferritin, ng/mL	177.1 [95.1, 285.3]	58.8 [35.9, 79.3]	229.2 [158.4, 322.6]	**< 0.001**	179.1 [92.0, 283.0]	119.5 [47.5, 253.0]	186.5 [102.3, 288.1]	**< 0.001**
TSAT, %	31.8 [24.2, 40.7]	27.8 [20.6, 37.1]	33.0 [25.9, 42.1]	**< 0.001**	31.3 [24.0, 39.9]	16.8 [13.9, 18.6]	33.3 [27.3, 41.6]	**< 0.001**
Scr, μmol/L	85.0 [65.8, 111.0]	75.0 [58.0, 103.0]	88.0 [69.0, 113.7]	**< 0.001**	91.0 [73.0, 116.0]	94.0 [72.0, 125.0]	91.0 [73.5, 115.0]	0.175
eGFR, ml/min per 1.73m^2	58.0 [45.0, 69.0]	50.0 [38.0, 66.0]	60.0 [48.0, 70.0]	**< 0.001**	53.0 [39.0, 66.0]	53.0 [38.0, 67.0]	53.0 [39.0, 65.0]	0.967
Proteinuria, n (%)				**< 0.001**				**0.004**
≥ 1+	8,594 (51.9)	2,552 (58.0)	6,042 (49.7)		2,453 (51.9)	313 (47.9)	2,140 (52.5)	
Trace	6,890 (41.6)	1,545 (35.1)	5,345 (43.9)		2,093 (44.2)	301 (46.1)	1,792 (44.0)	
NA	1,082 (6.5)	301 (6.8)	781 (6.4)		184 (3.9)	39 (6.0)	145 (3.6)	
CRP (mg/L), n (%)				**< 0.001**				**< 0.001**
≤ 10	10,306 (62.2)	3,058 (69.5)	7,248 (59.6)		3,837 (81.1)	420 (64.3)	3,417 (83.8)	
> 10	1,622 (9.8)	248 (5.6)	1,374 (11.3)		421 (8.9)	164 (25.1)	257 (6.3)	
NA	4,638 (28.0)	1,092 (24.8)	3,546 (29.1)		472 (10.0)	69 (10.6)	403 (9.9)	
Hb, g/L	140.0 [132.0, 150.0]	136.0 [129.0, 145.0]	141.0 [133.0, 151.0]	**< 0.001**	139.0 [131.0, 149.0]	134.0 [128.0, 143.0]	140.0 [132.0, 150.0]	**< 0.001**
GLU, mmol/L	5.5 [4.8, 7.0]	5.3 [4.7, 6.4]	5.6 [4.9, 7.3]	**< 0.001**	5.3 [4.6, 6.6]	5.5 [4.7, 6.8]	5.2 [4.6, 6.5]	**0.001**
TCHO, mmol/L	4.9 [4.1, 5.9]	4.8 [4.0, 5.8]	4.9 [4.1, 5.9]	0.055	5.0 [4.2, 6.1]	4.8 [4.0, 5.7]	5.0 [4.3, 6.1]	**< 0.001**
ALB, g/L	39.9 [35.9, 43.0]	39.6 [35.5, 42.6]	40.0 [36.0, 43.2]	**< 0.001**	39.1 [35.3, 42.4]	38.8 [35.2, 41.7]	39.2 [35.3, 42.5]	0.114
Comorbidities								
Hypertension, n (%)	7,721 (46.6)	1,749 (39.8)	5,972 (49.1)	**< 0.001**	2,155 (45.6)	306 (46.9)	1,849 (45.4)	0.499
Diabetes, n (%)	4,196 (25.3)	835 (19.0)	3,361 (27.6)	**< 0.001**	944 (20.0)	161 (24.7)	783 (19.2)	**0.001**
Cancer, n (%)	1,669 (10.1)	467 (10.6)	1,202 (9.9)	0.171	410 (8.7)	58 (8.9)	352 (8.6)	0.893
Liver disease, n (%)	4,667 (28.2)	975 (22.2)	3,692 (30.3)	**< 0.001**	983 (20.8)	128 (19.6)	855 (21.0)	0.454
CVD, n (%)	5,410 (32.7)	1,118 (25.4)	4,292 (35.3)	**< 0.001**	1,337 (28.3)	219 (33.5)	1,118 (27.4)	**0.001**
PVD, n (%)	4,174 (25.2)	903 (20.5)	3,271 (26.9)	**< 0.001**	821 (17.4)	98 (15.0)	723 (17.7)	0.099
Infection, n (%)	1,374 (8.3)	269 (6.1)	1,105 (9.1)	**< 0.001**	291 (6.2)	27 (4.1)	264 (6.5)	**0.026**
Prescription drugs								
RASi, n (%)	6,686 (40.4)	1,815 (41.3)	4,871 (40.0)	0.157	2,139 (45.2)	302 (46.2)	1,837 (45.1)	0.600
Diuretics, n (%)	3,193 (19.3)	868 (19.7)	2,325 (19.1)	0.377	766 (16.2)	125 (19.1)	641 (15.7)	**0.032**
Statins, n (%)	5,763 (34.8)	1,258 (28.6)	4,505 (37.0)	**< 0.001**	1,688 (35.7)	224 (34.3)	1,464 (35.9)	0.453
Chemotherapy, n (%)	1,286 (7.8)	326 (7.4)	960 (7.9)	0.327	332 (7.0)	57 (8.7)	275 (6.7)	0.078

Results are expressed as median [interquartile range] or number (percentage)

Scr: serum creatinine; eGFR: estimated glomerular filtration rates; CRP: C-reactive protein; Hb: hemoglobin; TCHO: total cholesterol; ALB: albumin; CVD: cardiovascular and cerebrovascular disease; PVD: peripheral vascular disease; RASi: renin-angiotensin-aldosterone system inhibitor

can enhance the synthesis and secretion of ferritin, resulting in serum ferritin levels that remain within the normal range for many patients [33]. On the other hand, TSAT shows better sensitivity than ferritin in detecting iron deficiency [34]. Our study demonstrated that lower TSAT, rather than ferritin levels, was closely associated with higher risks of renal outcome and all-cause mortality in NDD-CKD patients.

Body iron homeostasis is a delicate balance regulated by various cellular and systemic processes [35]. Iron serves as a co-factor for hemoproteins and non-heme iron-containing proteins, which are essential for a range of enzymatic functions in living organisms [36, 37]. Hemoproteins play crucial roles in essential biological functions such as oxygen binding and transport (hemoglobin), and cellular respiration (cytochromes). Proteins containing non-heme iron are important for fundamental

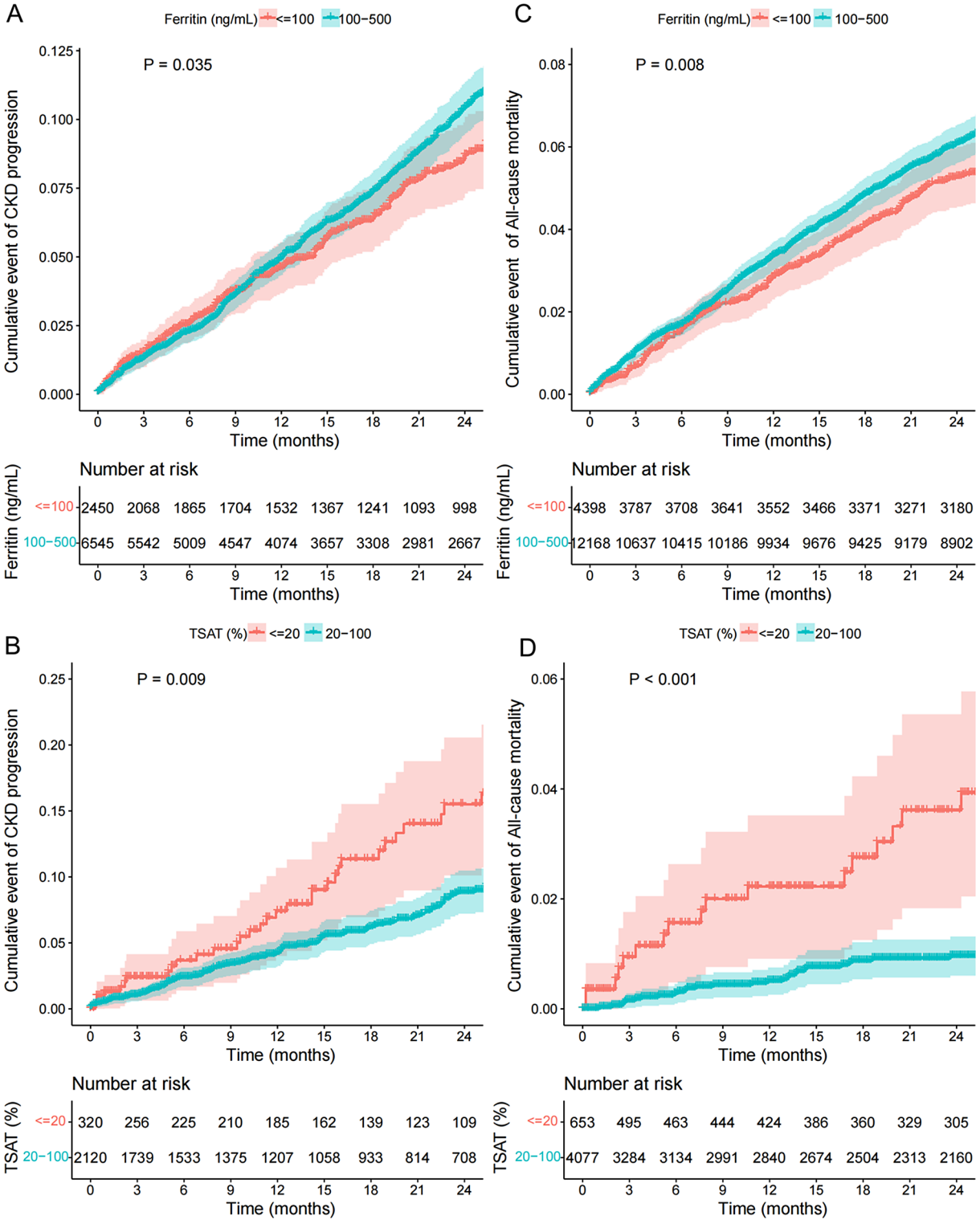

Fig. 2 The Kaplan Meier curves comparing cumulative incidence of chronic kidney disease progression and all-cause mortality. (**A**) Chronic kidney disease progression of different serum ferritin groups. (**B**) Chronic kidney disease progression of different TSAT groups. (**C**) All-cause mortality of ferritin groups. (**D**) All-cause mortality of TSAT groups. TSAT: transferrin saturation

Table 3 Associations of ferritin and TSAT levels with risks for outcomes

	Event/*N* (%)	Crude HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value
Chronic kidney disease progression					
Ferritin (ng/mL)					
≤ 100	248/2,450 (10.1)	0.86 [0.74, 0.99]	**0.035**	1.11 [0.96, 1.29]	0.170
> 100	772/6,545 (11.8)	Reference		Reference	
TSAT (%)					
≤ 20	44/320 (13.8)	1.55 [1.12, 2.15]	**0.009**	1.66 [1.16, 2.37]	**0.005**
> 20	195/2,120 (9.2)	Reference		Reference	
All-cause mortality					
Ferritin (ng/mL)					
≤ 100	432/4,398 (9.8)	0.86 [0.78, 0.96]	**0.008**	1.10 [0.99, 1.23]	0.087
> 100	1403/12,168 (11.5)	Reference		Reference	
TSAT (%)					
≤ 20	29/653 (4.4)	2.75 [1.79, 4.22]	**< 0.001**	2.21 [1.36, 3.57]	**0.001**
> 20	76/4,077 (1.9)	Reference		Reference	

Chronic kidney disease progression: adjusted for sex, age, eGFR, proteinuria, albumin, C-reactive protein, hemoglobin, total cholesterol, Charlson score, diabetes, hypertension, cardiovascular and cerebrovascular disease, liver disease, cancer, statins, and renin-angiotensin-aldosterone system inhibitor

All-cause mortality: adjusted for sex, age, eGFR, proteinuria, albumin, C-reactive protein, hemoglobin, total cholesterol, Charlson score, diabetes, hypertension, cardiovascular and cerebrovascular disease, liver disease, and cancer

cellular processes such as gene regulation, DNA synthesis, and cell proliferation [37]. Therefore, iron deficiency, whether inherited or acquired, can significantly affect the function of various organs, especially major iron-utilizing and recycling organs. The kidney is actively involved in systemic iron homeostasis as it reabsorbs filtered iron to prevent its excretion in the urine [35]. Furthermore, iron is essential for the high metabolic demands of renal cells, which are rich in mitochondria and actively participate in oxidative reactions [38]. Studies on pregnant rats with prenatal iron deficiency suggest that iron is important for nephrogenesis and physiological renal function [35, 39, 40]. These mechanisms may contribute to increased risks of CKD progression among NDD-CKD patients with iron deficiency without anemia. However, the effects of iron deficiency on the kidney are not fully understood, highlighting the need for further research to clarify the impact of iron deficiency on kidney function.

This study has several strengths. Firstly, it is one of the largest studies to assess the association between iron deficiency and CKD progression as well as all-cause mortality in the NDD-CKD patients without anemia. Secondly, robust kidney outcomes were utilized to analyze the relationship between iron deficiency and CKD progression. For all-cause mortality, information was sourced from the national electronic cause-of-death reporting system of the China Center for Disease Control and Prevention, which has undergone extensive validation [22]. Thirdly, adjustments were made for important potential confounders, such as comorbidities, concomitant medications, CRP levels, and hemoglobin concentration.

Nevertheless, our study has several limitations that must be acknowledged. Firstly, the retrospective and observational design of our study did not allow us to confirm causal relationship between iron deficiency and defined outcomes. Secondly, despite adjusting for numerous key variables in the models, some confounders might remain unadjusted. For example, the impact of inflammation could not be accurately assessed, as some inflammatory markers were not measured in many patients in this study. Thirdly, TSAT measurements were unavailable for the majority of study patients, particularly those without anemia. Consequently, the analysis of the relationship between TSAT levels and the risk of CKD progression was restricted to patients with available TSAT measurements. This limitation may partially affect the generalizability of our findings. However, despite the relatively small sample size, a significant association between TSAT levels and the risk of CKD progression was observed. This underscores the importance of screening TSAT levels in CKD patients, including those without anemia. Fourthly, our reliance on single baseline values of ferritin and TSAT may not have captured the effect of exposure duration, potentially leading to misclassification of the primary exposure due to fluctuations in ferritin and TSAT levels over time. Lastly, the predominantly Chinese sample in our study limits the generalizability of our findings to other ethnic populations.

Conclusion

In conclusion, our study suggested that TSAT might be a modifiable risk factor of CKD progression in NDD-CKD patients without anemia. It is recommended to include screening for iron biomarkers, particularly TSAT, in the early stage of NDD-CKD to improve the prognosis of patients. Furthermore, well-designed randomized clinical trials are necessary to confirm the impact of timely iron supplementation treatment on renal outcomes and

all-cause mortality in CKD patients. The findings offer valuable clinical evidence for the monitoring and management of iron status in early-stage NDD-CKD patients.

Abbreviations

CKD	Chronic kidney disease
NDD-CKD	Non-dialysis-dependent CKD
TSAT	Transferrin saturation
CRDS	China Renal Data System
eGFR	Estimated glomerular filtration rates
ICD-10-CM	International Statistical Classification of Diseases, Tenth Revision, Clinical Modification
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration equation
UACR	Urine albumin to creatinine
TIBC	Total iron binding capacity
AKI	Acute kidney injury
ESAs	Erythropoiesis-stimulating agents
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
KDIGO	Kidney Disease: Improving Global Outcomes
ESKD	End-stage kidney disease
IQR	Interquartile range
CRP	C-reactive protein
RAAS	Renin-angiotensin-aldosterone system
aHR	Adjusted hazard ratio
CI	Confidence intervals

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12937-025-01072-1.

Supplementary Material 1

Acknowledgements
The authors thank the staff and participant centers of the China Renal Data System (CRDS) for their important contributions.

Author contributions
Conceptualization: SN, XX and HXY; Methodology: HXY; Software: HXY; Validation: XS, ZXG, FL and HXY; Formal Analysis: HXY; Investigation: MZP, SC, CXS, HXY, FL and RXC; Resources: SN and XX; Data Curation: SYZ and HXY; Writing: All authors; Funding Acquisition: SN and XX. Writing – Review & Editing: All authors; Visualization: HXY and XS; Supervision: SN and XX; the CRDS Study Investigators, contributed to the data acquisition.

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Funding
This study is supported by grants from the National Key R&D Program of China (2021YFC2500200 and 2021YFC2500204 to Dr X, Xu), the National Natural Science Foundation of China (81970586 and 81770683 to Dr X, Xu, 81900626 to Dr S, Nie). The funder was not for profit and has no role in the data collection, analysis, or interpretation; trial design; patient recruitment; or any aspect pertinent to the study.

Data availability
The data used and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and patient consent
The study protocol was approved by the Medical Ethics Committee of Nanfang Hospital, Southern Medical University (approval number: NFEC-2023-409), which waived the requirement for informed patient consent.

Informed consent
Written informed consent for participation was not required for this retrospective analysis in accordance with the national legislation and the institutional requirements.

Competing interests
The authors declare no competing interests.

Received: 16 August 2024 / Accepted: 2 January 2025
Published online: 15 January 2025

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