ORIGINAL RESEARCH PAPER
Volume - 15 | Issue - 08 | August - 2026 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

# ESTIMATION OF SERUM FERRITIN AND C-REACTIVE PROTEIN LEVELS AS MARKERS OF OXIDATIVE STRESS IN PATIENTS WITH CHRONIC KIDNEY DISEASE UNDERGOING DIALYSIS: A CROSS-SECTIONAL STUDY

Medical Biochemistry

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## ABSTRACT

**Background:** Chronic kidney disease (CKD) is increasingly recognised as a state of persistent inflammation and oxidative stress that intensifies as renal function declines and dialysis is initiated. Serum ferritin and C-reactive protein (CRP), as acute-phase reactants, may serve as accessible surrogate markers of this oxidative-inflammatory burden.**Objectives:** To estimate serum ferritin and CRP levels across CKD stages and evaluate their association with renal function parameters (urea, creatinine, and estimated glomerular filtration rate [eGFR]) in patients with CKD undergoing dialysis.**Methods:** This cross-sectional, STROBE-compliant study included 70 patients with CKD. Serum urea, creatinine, ferritin, and CRP were estimated by standard automated methods, and eGFR was calculated using the CKD-EPI equation. Pearson's correlation and multiple linear regression were used to assess associations between ferritin/CRP and renal function parameters.**Results:** The mean age was 46.84 ± 15.02 years, with a male predominance (57.1%). Most patients (82.9%) were in Stage 5 CKD. Mean serum urea (124.34 ± 72.89 mg/dL) and creatinine (7.42 ± 3.70 mg/dL) were markedly elevated. Mean serum ferritin (560.66 ± 300.15 ng/mL) and CRP (62.45 ± 83.51 mg/L) rose progressively with advancing CKD stage. Ferritin correlated positively with creatinine ($r = 0.512$, $p < 0.001$) and urea ($r = 0.463$, $p < 0.001$), and negatively with eGFR ($r = -0.377$, $p = 0.0049$). On multivariate regression, ferritin ($\beta = -0.0097$, $p = 0.038$) and creatinine ($\beta = -3.0494$, $p < 0.001$) were independent predictors of eGFR ($R^2 = 0.574$).**Conclusion:** Serum ferritin and CRP are markedly and progressively elevated in advancing CKD, most likely reflecting inflammation-driven oxidative stress rather than true iron overload. Ferritin should be interpreted alongside CRP and renal function parameters rather than in isolation, particularly when guiding anemia management in dialysis patients.

## KEYWORDS

Chronic Kidney Disease; Serum Ferritin; C-reactive Protein; Oxidative Stress; Hemodialysis; Estimated Glomerular Filtration Rate

## INTRODUCTION

Chronic kidney disease (CKD) is increasingly understood not merely as a disorder of excretory failure but as a systemic condition in which persistent low-grade inflammation and oxidative stress substantially drive disease morbidity.[1] CKD is defined, per the Kidney Disease: Improving Global Outcomes (KDIGO) framework, as an abnormality of kidney structure or function present for more than three months, classified on the basis of estimated glomerular filtration rate (eGFR) and albuminuria category.[1] As renal function deteriorates, retention of uremic toxins and depletion of endogenous antioxidant reserves promote a pro-oxidant state; once maintenance hemodialysis is initiated, repeated contact of blood with dialyzer membranes, dialysate exposure, and leukocyte activation act as additional, procedure-specific triggers of oxidative and inflammatory activation.[4,5].

Ferritin, principally known as an intracellular iron-storage protein, is simultaneously a positive acute-phase reactant. In CKD and dialysis populations, its serum concentration is influenced not only by true iron stores but substantially by the coexisting inflammatory burden, such that hyperferritinemia in this setting more often signals inflammation than genuine iron overload.[6–8] C-reactive protein (CRP), synthesised by the liver under interleukin-6 stimulation, is a more specific marker of acute-phase inflammation and has been repeatedly linked to cardiovascular risk and mortality in dialysis cohorts.[6] Because both analytes track the same underlying oxidative-inflammatory cascade that accompanies renal failure and dialysis, their combined estimation has been proposed as a practical, low-cost surrogate for oxidative stress burden in CKD, particularly where direct assays of reactive oxygen species or lipid peroxidation products are not routinely feasible.[4,5].

Indian data specifically addressing this relationship remain relatively limited, despite the well-documented tendency for CKD to present at an advanced, often dialysis-dependent stage in Indian tertiary-care settings.[3] Evidence from predominantly non-Indian hemodialysis cohorts supports the concept that hyperferritinemia frequently indicates inflammation rather than iron excess, and that both low and high ferritin values may be independently associated with adverse renal and iron-related outcomes.[7,10] Against this background, the present cross-sectional study was undertaken to estimate serum ferritin and CRP levels across CKD stages in patients undergoing or approaching dialysis, and to evaluate their relationship with conventional renal function parameters — serum urea, creatinine, and eGFR — as an accessible composite indicator of the oxidative-inflammatory state in CKD.

## MATERIALS AND METHODS

### *Study design and setting*

This was an observational, analytical cross-sectional study conducted in the Department of Biochemistry, in collaboration with the Department of Medicine, at Hind Institute Of Medical Sciences Barabanki, over a period of 18 months. Tests were performed in the Department of Biochemistry, Hind Institute Of Medical Sciences, using CLIA Analyser.

The study was approved by the Institutional Ethics Committee (Ethical no. IEC/2023/1563), and written informed consent was obtained from all participants prior to enrolment, in accordance with the Declaration of Helsinki. Reporting of this study follows the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for cross-sectional studies.[2].

### Study participants

Seventy (n = 70) patients with a clinical and biochemical diagnosis of CKD, aged 18 years and above, attending the nephrology/dialysis unit, were enrolled by consecutive sampling over the study period. CKD was staged according to KDIGO criteria on the basis of eGFR, calculated using the CKD-EPI equation, sustained for more than three months.[1] Patients were categorised as Stage 1 (eGFR ≥90), Stage 2 (60–89), Stage 3A (45–59), Stage 3B (30–44), Stage 4 (15–29) or Stage 5 (<15 mL/min/1.73 m²). Patients with active malignancy, acute infection at the time of sampling, chronic liver disease, or recent (<3 months) blood transfusion or intravenous iron therapy were excluded, since these conditions independently influence ferritin and CRP levels.

### Data sources, variables and measurement

Demographic details (age, sex) were recorded on a structured proforma. A fasting venous blood sample was collected under aseptic precautions from each participant. Serum urea and creatinine were estimated by standard kinetic/enzymatic methods on an automated analyzer. Serum ferritin was measured by chemiluminescence immunoassay (reference range: males 30–350 ng/mL, females 20–250

ng/mL), and serum CRP was measured by immunoturbidimetry (reference range <0.3 mg/L). eGFR was computed from serum creatinine using the CKD-EPI formula.

**Bias**

Measurement bias was minimised by performing all biochemical assays on the same automated platform with internal quality control run alongside each batch. Selection bias was minimised by consecutive enrolment of eligible patients presenting during the study period (Feb 2024 to Aug 2024). Patients with acute-phase states unrelated to CKD (active infection) were excluded to reduce confounding of ferritin and CRP by non-renal causes.

**Study size**

The sample of 70 patients represented all eligible consecutive patients available during the defined study period; no a priori power calculation was performed, a limitation discussed below.

**Statistical methods**

Data were entered in Microsoft Excel and analysed using standard statistical software. Continuous variables are expressed as mean ± standard deviation (SD) and, where distribution was skewed, as median (interquartile range, IQR); categorical variables are expressed as frequencies and percentages. Ferritin, CRP and eGFR were compared descriptively across CKD stages. Pearson's correlation coefficient (r) was used to assess linear associations between ferritin/CRP and urea, creatinine and eGFR. Multiple linear regression was performed with eGFR as the dependent variable and serum ferritin, CRP, urea and creatinine as independent predictors, with the coefficient of determination ($R^2$) reported. A two-tailed p-value <0.05 was considered statistically significant.

## RESULTS

Of the 70 patients enrolled, 40 (57.1%) were male and 30 (42.9%) female, a male-to-female ratio of approximately 1.33:1. The mean age was 46.84 ± 15.02 years (median 49.00 years, IQR 21.00). Age distribution showed a predominance of the 50–69-year group (34 patients, 48.6%), followed by 30–49 years (25, 35.7%) and below 30 years (11, 15.7%). On CKD staging by eGFR, no patient was in Stage 1; 1 (1.4%) was in Stage 2, 2 (2.9%) in Stage 3A, 3 (4.3%) in Stage 3B, 6 (8.6%) in Stage 4, and the majority, 58 patients (82.9%), were in Stage 5 (Table 1).

**Table 1. Demographic profile and CKD stage distribution of study participants (n = 70)**

| Variable | Category | n | % |
|---|---|---|---|
| Age group (years) | < 30 | 11 | 15.7 |
| | 30–49 | 25 | 35.7 |
| | 50–69 | 34 | 48.6 |
| Sex | Male | 40 | 57.1 |
| | Female | 30 | 42.9 |
| CKD stage (eGFR-based) | Stage 1 (≥90) | 0 | 0.0 |
| | Stage 2 (60–89) | 1 | 1.4 |
| | Stage 3A (45–59) | 2 | 2.9 |
| | Stage 3B (30–44) | 3 | 4.3 |
| | Stage 4 (15–29) | 6 | 8.6 |
| | Stage 5 (<15) | 58 | 82.9 |

Mean age: 46.84 ± 15.02 years (median 49.00, IQR 21.00). Male:Female ratio ≈ 1.33:1. Biochemical parameters (Table 2) confirmed marked renal dysfunction: mean serum urea was 124.34 ± 72.89 mg/dL (reference 15–45 mg/dL) and mean creatinine was 7.42 ± 3.70 mg/dL (reference 0.5–1.2 mg/dL), several-fold above the upper reference limits. Mean serum ferritin was 560.66 ± 300.15 ng/mL, exceeding upper reference limits for both sexes, and mean serum CRP was 62.45 ± 83.51 mg/L, markedly above the reference cut-off of <0.3 mg/L.

**Table 2. Biochemical parameters of study participants (n = 70)**

| Parameter | Mean ± SD | Minimum | Maximum | Reference range |
|---|---|---|---|---|
| Serum urea (mg/dL) | 124.34 ± 72.89 | 30.95 | 367 | 15–45 |
| Serum creatinine (mg/dL) | 7.42 ± 3.70 | 1.17 | 19.6 | 0.5–1.2 |
| Serum ferritin (ng/mL) | 560.66 ± 300.15 | 11.87 | 986 | M: 30–350; F: 20–250 |
| Serum CRP (mg/L) | 62.45 ± 83.51 | 0.3 | 378.9 | < 0.3 |

Stage-wise analysis (Table 3) demonstrated a progressive rise in ferritin and CRP with advancing CKD stage, mirrored by a corresponding decline in eGFR: mean ferritin rose from 190.78 ng/mL in Stage 2 to 611.06 ± 281.95 ng/mL in Stage 5, and mean CRP rose from 0.30 mg/L in Stage 2 to 75.76 ± 90.88 mg/L in Stage 5, while mean eGFR fell from 76.0 to 7.16 ± 2.54 mL/min/1.73 m² over the same range. A non-monotonic dip in ferritin and rise in CRP were observed at Stage 3B, most likely attributable to the very small cell size (n = 3) at this stage.

**Table 3. Stage-wise distribution of serum ferritin, CRP and eGFR among CKD patients**

| CKD stage | Ferritin, ng/mL (Mean ± SD) | CRP, mg/L (Mean ± SD) | eGFR, mL/min/1.73m² (Mean ± SD) |
|---|---|---|---|
| Stage 2 (n=1) | 190.78 ± 0.00 | 0.30 ± 0.00 | 76.00 ± 0.00 |
| Stage 3A (n=2) | 318.49 ± 209.99 | 8.40 ± 10.75 | 47.50 ± 3.54 |
| Stage 3B (n=3) | 124.72 ± 96.71 | 55.80 ± 33.46 | 34.33 ± 1.53 |
| Stage 4 (n=6) | 568.19 ± 322.91 | 23.55 ± 19.22 | 17.17 ± 3.13 |
| Stage 5 (n=58) | 611.06 ± 281.95 | 75.76 ± 90.88 | 7.16 ± 2.54 |

On correlation analysis, serum ferritin showed a statistically significant positive correlation with serum creatinine ($r = 0.512$, $p < 0.001$) and serum urea ($r = 0.463$, $p < 0.001$), and a significant negative correlation with eGFR ($r = -0.377$, $p = 0.0049$). Serum CRP showed weaker, though still significant, positive correlations with creatinine ($r = 0.289$, $p = 0.015$) and urea ($r = 0.248$, $p = 0.035$); its correlation with eGFR ($r = -0.168$, $p = 0.164$) did not reach statistical significance. On multivariate linear regression with eGFR as the dependent variable, serum ferritin ($\beta = -0.0097$, 95% CI −0.019 to −0.001, $p = 0.038$) and serum creatinine ($\beta = -3.0494$, 95% CI −4.226 to −1.873, $p < 0.001$) emerged as independent, significant negative predictors of eGFR, whereas CRP ($\beta = -0.0293$, $p = 0.073$) and urea ($\beta = 0.0383$, $p = 0.254$) did not retain independent significance. The overall model explained 57.4% of the variance in eGFR ($R^2 = 0.574$) (Table 4).

**Table 4. Correlation of ferritin/CRP with renal function parameters and multivariate regression for predictors of eGFR**

| Analysis | Variable(s) | r or β | p-value |
|---|---|---|---|
| Pearson correlation | Ferritin vs Creatinine | r = 0.512 | < 0.001 |
| | Ferritin vs Urea | r = 0.463 | < 0.001 |
| | Ferritin vs eGFR | r = −0.377 | 0.0049 |
| | CRP vs Creatinine | r = 0.289 | 0.015 |
| | CRP vs Urea | r = 0.248 | 0.035 |
| | CRP vs eGFR | r = −0.168 | 0.164 |
| Multivariate | Serum ferritin | β = −0.0097 | 0.038 |
| | Serum CRP | β = −0.0293 | 0.073 |
| | Serum urea | β = 0.0383 | 0.254 |
| | Serum creatinine | β = −3.0494 | < 0.001 |

## DISCUSSION

CKD is increasingly understood as a state of chronic low-grade inflammation superimposed on progressive nephron loss, in which oxidative stress and acute-phase reactants such as ferritin and CRP both reflect and potentially amplify disease progression.[4,5] Loss of antioxidant reserve, retention of uremic toxins, and — once dialysis is initiated — repeated blood–membrane contact within the extracorporeal circuit collectively sustain this oxidative-inflammatory state, a mechanism well described in dialysis populations.[4,5].

The mean age of the present cohort (46.84 ± 15.02 years) and the predominance of patients in the 50–69-year bracket are consistent with CKD as a disease of accumulating metabolic and vascular insult over decades; a broadly similar age pattern has been reported from other Indian dialysis-oriented cohorts.[3] The male predominance observed here (57.1%, ratio 1.33:1) also mirrors the pattern seen in an Indian hospital-based CKD risk-factor study, in which roughly two-thirds of enrolled patients were male.[3] This disparity has been variously attributed to differences in healthcare-seeking behaviour, occupational

and lifestyle risk exposure, and a possible protective hormonal effect in women.

A striking finding was that 82.9% of patients presented in Stage 5 CKD, with a mean eGFR of only 7.16 mL/min/1.73 m² among these patients — indicating that the great majority of the study population was already dialysis-dependent or imminently so. Late-stage presentation is a recurring theme in hospital-based Indian CKD cohorts and underscores persistent gaps in early screening and nephrology referral in routine practice.[3].

The mean serum ferritin of 560.66 ± 300.15 ng/mL observed in this study falls within the range that several hemodialysis studies have identified as reflecting inflammation-driven hyperferritinemia rather than true iron overload. Kalantar-Zadeh et al. first demonstrated that elevated ferritin in maintenance hemodialysis patients tracks with hospitalisation burden and short-term mortality risk, behaving as an acute-phase reactant rather than a pure iron-store index.[8] Large multinational registry data from the Dialysis Outcomes and Practice Patterns Study have similarly documented a secular rise in population ferritin levels and confirmed its association with adverse outcomes, particularly at the highest strata.[9] The progressive rise in ferritin with advancing CKD stage in the present cohort — reaching a mean of 611.06 ng/mL in Stage 5 — parallels this literature and supports the interpretation that hyperferritinemia here reflects cumulative inflammatory burden rather than simple iron accumulation.

Serum CRP was also markedly elevated (mean 62.45 ± 83.51 mg/L) and rose in parallel with CKD stage, again peaking in Stage 5. Persistent CRP elevation in CKD and dialysis populations has long been linked with accelerated atherosclerosis and adverse cardiovascular outcomes, an association first systematically characterised by Stenvinkel et al. in their description of the malnutrition–inflammation–atherosclerosis complex in chronic renal failure.[6] The oxidative and inflammatory mechanisms underlying this rise — including leukocyte activation, dialyzer bioincompatibility, and loss of antioxidant capacity during hemodialysis — have been extensively reviewed by Liakopoulos et al. and Libetta et al., both emphasising that these processes begin early in CKD and are further amplified once dialysis is initiated.[4-5].

The correlation and regression findings of the present study — a significant positive correlation of ferritin with creatinine and urea, a significant negative correlation with eGFR, and its emergence as an independent predictor of eGFR alongside creatinine — are consistent with a growing body of evidence linking iron-status markers directly to kidney outcomes. In a large cohort, Fujisawa et al. demonstrated that both low and high serum ferritin quartiles were independently associated with an increased risk of kidney disease progression, arguing against a simple linear relationship and supporting the view that ferritin should be interpreted within its inflammatory context rather than as an isolated iron marker.[10] This context-dependent relationship is compatible with the present cross-sectional finding of a negative ferritin–eGFR correlation in a population overwhelmingly composed of advanced, inflamed CKD patients.

Mechanistically, elevated ferritin despite declining renal clearance is best explained by hepcidin-mediated functional iron restriction: hepcidin, itself upregulated by both inflammation and reduced renal clearance, limits the release of storage iron from macrophages and hepatocytes, favouring iron sequestration (and hence higher ferritin) even as iron available for erythropoiesis becomes scarce.[11] This concept, elaborated within the broader anemia-of-inflammation framework, explains why ferritin values in the 500–600 ng/mL range — as observed in this cohort — should not automatically be interpreted as iron overload or used in isolation to withhold iron therapy; rather, ferritin needs to be read alongside CRP and other inflammatory indicators to distinguish functional from absolute iron deficiency.[12] Although hepcidin itself was not measured in the present study, the combination of high ferritin, high CRP, and advanced CKD stage is strongly suggestive of this mechanism.

CRP showed weaker correlations with renal parameters than ferritin and did not remain an independent predictor of eGFR on multivariate analysis. This is broadly consistent with the more variable, comorbidity-dependent nature of CRP elevation compared with ferritin, which — responding to both systemic inflammation and CKD-associated iron-handling abnormalities — may more consistently track with declining renal function.

### Limitations

This study is limited by its single-centre, cross-sectional design, which precludes causal inference and does not permit determination of whether elevated ferritin/CRP precede or follow renal function decline. The convenience sample size (n = 70), the markedly unequal distribution of patients across CKD stages (very few in Stages 2–4), the absence of hepcidin, transferrin saturation, or direct oxidative stress markers such as malondialdehyde or total antioxidant capacity, and the lack of adjustment for comorbidities such as diabetes and cardiovascular disease are further limitations that should be addressed in future prospective, multi-centric studies with larger, stage-balanced cohorts.

## CONCLUSION

Serum ferritin and CRP were both markedly elevated in this cohort of CKD patients undergoing or approaching dialysis and rose progressively with advancing CKD stage, in parallel with declining eGFR. Serum ferritin, in particular, showed a strong, statistically significant association with renal function parameters and emerged as an independent predictor of eGFR alongside serum creatinine. These findings support the interpretation that hyperferritinemia in advanced CKD predominantly reflects an inflammation-driven, functional iron-handling abnormality rather than true iron overload, and reinforce the recommendation that ferritin be interpreted jointly with CRP and renal function parameters rather than as an isolated iron index. Combined assessment of these markers may assist in disease staging, guide anemia-management decisions, and help identify patients at higher risk of rapid progression.

## DECLARATIONS

### *Ethical approval*

This study was approved by the Institutional Ethics Committee of Hind Institute of Medical Science (Ehical no. IEC/2023/1563). Written informed consent was obtained from all participants.

### Conflict of interest

The authors declare no conflict of interest.

### Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

### Author contributions

[To be completed by authors as per journal requirements — concept, design, data acquisition, analysis, manuscript drafting, and critical review.]

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