

Association of Hepatitis C Virus Seropositivity with Iron Metabolism Biomarkers in Patients with Chronic Kidney Disease

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Abstract

Background: Iron dysregulation and anemia are common complications of chronic kidney disease (CKD). Hepatitis C virus (HCV) may further alter iron homeostasis, potentially complicating the interpretation of iron indices in patients receiving dialysis.

Objective: To compare serum iron, total iron-binding capacity (TIBC), and unsaturated iron-binding capacity (UIBC) between HCV-seropositive and HCV-seronegative patients with CKD and to explore the relationships and discriminatory performance of these biomarkers.

Methods: This cross-sectional study included 200 patients with CKD attending the dialysis center at Al-Imamain Al-Kadimain Medical City, Baghdad, Iraq: 100 HCV-seropositive and 100 HCV-seronegative patients. HCV serostatus was determined by enzyme-linked immunosorbent assay (ELISA). Serum iron, TIBC, and UIBC were evaluated. Between-group comparisons were performed using the independent-samples t-test, associations among biomarkers were assessed using Pearson correlation, and exploratory receiver operating characteristic (ROC) analysis was performed.

Results: TIBC was significantly higher in the HCV-seropositive group than in the HCV-seronegative group (302.26 ± 54.92 vs. 280.22 ± 63.71 $\mu\text{g/dL}$; $p = 0.009$). Serum iron did not differ significantly (89.16 ± 12.94 vs. 86.43 ± 22.32 $\mu\text{g/dL}$; $p = 0.291$), and neither did UIBC (203.16 ± 50.89 vs. 194.31 ± 79.67 $\mu\text{g/dL}$; $p = 0.350$). In the HCV-seronegative group, serum iron correlated negatively with TIBC ($r = -0.684$, $p < 0.001$) and UIBC ($r = -0.804$, $p < 0.001$), whereas TIBC correlated positively with UIBC ($r = 0.983$, $p < 0.001$). These relationships were attenuated in the HCV-seropositive group. ROC analysis showed limited standalone discrimination for serum iron (AUC = 0.631) and TIBC (AUC = 0.595), while UIBC was not discriminatory (AUC = 0.533, $p = 0.413$).

Conclusion: Among patients with CKD, HCV seropositivity was associated with higher TIBC and altered relationships among iron-related biomarkers, while serum iron and UIBC did not differ significantly between groups. Serum iron, TIBC, and UIBC alone have limited value for classifying HCV serostatus and should be interpreted within a broader clinical and laboratory assessment.

Keywords: hepatitis C virus; chronic kidney disease; iron metabolism; total iron-binding capacity; unsaturated iron-binding capacity; hemodialysis

Introduction

Chronic kidney disease (CKD) is defined by the presence of kidney damage or decreased kidney function for at least three months [1]. Anemia is a frequent complication of CKD and results from multiple mechanisms, including reduced erythropoietin production, iron dysregulation, chronic inflammation, nutritional deficiencies, impaired intestinal iron absorption, and blood loss [2]. These abnormalities are particularly relevant in patients receiving dialysis, in whom reliable assessment of iron status is essential for guiding anemia management.

Hepatitis C virus (HCV) infection is clinically important in patients with kidney disease and has been associated with several renal manifestations and adverse outcomes [3]. HCV can also disturb systemic and hepatic iron regulation. Proposed mechanisms include suppression of hepcidin signaling and altered iron export and storage, which may contribute to abnormal serum iron indices and hepatic iron accumulation [4]. Consistent with this interaction, successful HCV eradication with direct-acting antiviral therapy has been associated with improvement or normalization of abnormal iron studies in many patients [5].

Serum iron, TIBC, and UIBC are routinely used laboratory indices that provide complementary information about circulating iron and transferrin-binding capacity [6]. However, the behavior of these biomarkers in CKD patients with concomitant HCV seropositivity remains clinically relevant because both CKD-related inflammation and HCV-associated changes in iron handling may influence their interpretation.

The present study therefore compared serum iron, TIBC, and UIBC between HCV-seropositive and HCV-seronegative patients with CKD. It also evaluated correlations among these biomarkers and explored their ability to distinguish HCV serostatus.

Materials and Methods

Study design and setting

A cross-sectional study was conducted among patients with CKD attending the dialysis center at Al-Imamain Al-Kadimain Medical City in Baghdad, Iraq.

Study participants and laboratory assessment

The study included 200 patients with CKD. Of these, 100 were classified as HCV-seropositive and 100 as HCV-seronegative. HCV serostatus was determined by ELISA at the study center. Serum iron, TIBC, and UIBC were evaluated for all participants, and relevant information was obtained from medical records.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics version 26 (IBM Corp., Armonk, NY, USA). Continuous variables were assessed for normality using the Kolmogorov-Smirnov test and are presented as mean $\pm$ standard deviation (SD). Comparisons between the HCV-seropositive and HCV-seronegative groups were performed using the independent-samples t-test. Relationships among serum iron, TIBC, and UIBC were evaluated using Pearson's correlation coefficient (r). Exploratory receiver operating characteristic (ROC) analysis was used to evaluate the ability of the three biomarkers to distinguish HCV serostatus; area under the curve (AUC), cut-off values, and 95% confidence intervals (CIs) were reported. A two-sided p value < 0.05 was considered statistically significant.

Results

TIBC was significantly higher in HCV-seropositive patients than in HCV-seronegative patients (302.26 ± 54.92 vs. 280.22 ± 63.71 $\mu\text{g/dL}$; $t = 2.620$, $p = 0.009$). No significant between-group difference was observed for serum iron (89.16 ± 12.94 vs. 86.43 ± 22.32 $\mu\text{g/dL}$; $t = 1.058$, $p = 0.291$) or UIBC (203.16 ± 50.89 vs. 194.31 ± 79.67 $\mu\text{g/dL}$; $t = 0.936$, $p = 0.350$) (Table 1).

Table 1. Comparison of serum iron, TIBC, and UIBC between HCV-seropositive and HCV-seronegative groups.

Parameter	Group	n	Mean	SD	SE	t	p value
Serum iron	HCV-seropositive	100	89.16	12.937	1.294	1.058	0.291
	HCV-seronegative	100	86.43	22.321	2.232		
TIBC	HCV-seropositive	100	302.26	54.920	5.492	2.620	0.009
	HCV-seronegative	100	280.22	63.714	6.371		
UIBC	HCV-seropositive	100	203.16	50.891	5.089	0.936	0.350
	HCV-seronegative	100	194.31	79.669	7.967		

Abbreviations: HCV, hepatitis C virus; TIBC, total iron-binding capacity; UIBC, unsaturated iron-binding capacity; SD, standard deviation; SE, standard error.

Among HCV-seronegative patients, serum iron showed strong negative correlations with TIBC ($r = -0.684$, $p < 0.001$) and UIBC ($r = -0.804$, $p < 0.001$), while TIBC and UIBC were strongly positively correlated ($r = 0.983$, $p < 0.001$). In HCV-seropositive patients, the correlation between serum iron and TIBC was weak and not significant ($r = -0.163$, $p = 0.104$), the inverse correlation between serum iron and UIBC was weaker but remained significant ($r = -0.279$, $p = 0.005$), and the positive correlation between TIBC and UIBC remained strong ($r = 0.891$, $p < 0.001$) (Table 2).

Table 2. Pearson correlations among serum iron, TIBC, and UIBC by HCV serostatus.

Parameter pair	HCV-seronegative		HCV-seropositive	
	r	p value	r	p value
Serum iron vs. TIBC	-0.684	<0.001	-0.163	0.104
Serum iron vs. UIBC	-0.804	<0.001	-0.279	0.005
TIBC vs. UIBC	0.983	<0.001	0.891	<0.001

Abbreviations: HCV, hepatitis C virus; TIBC, total iron-binding capacity; UIBC, unsaturated iron-binding capacity.

Exploratory ROC analysis demonstrated limited discrimination of HCV serostatus by serum iron (AUC = 0.631, 95% CI 0.552-0.710, $p = 0.001$; cut-off 86.00 $\mu\text{g/dL}$) and TIBC (AUC = 0.595, 95% CI 0.516-0.675, $p = 0.020$; cut-off 264.50 $\mu\text{g/dL}$). UIBC showed no significant discriminatory ability (AUC = 0.533, 95% CI 0.452-0.615, $p = 0.413$; cut-off 169.00 $\mu\text{g/dL}$) (Table 3 and Figure 1).

Table 3. ROC analysis of serum iron, TIBC, and UIBC for classification of HCV serostatus.

Biomarker	Cut-off ($\mu\text{g/dL}$)	AUC	SE	p value	95% CI lower	95% CI upper
Serum iron	86.00	0.631	0.040	0.001	0.552	0.710
TIBC	264.50	0.595	0.041	0.020	0.516	0.675
UIBC	169.00	0.533	0.042	0.413	0.452	0.615

Abbreviations: ROC, receiver operating characteristic; AUC, area under the curve; SE, standard error; CI, confidence interval; HCV, hepatitis C virus.

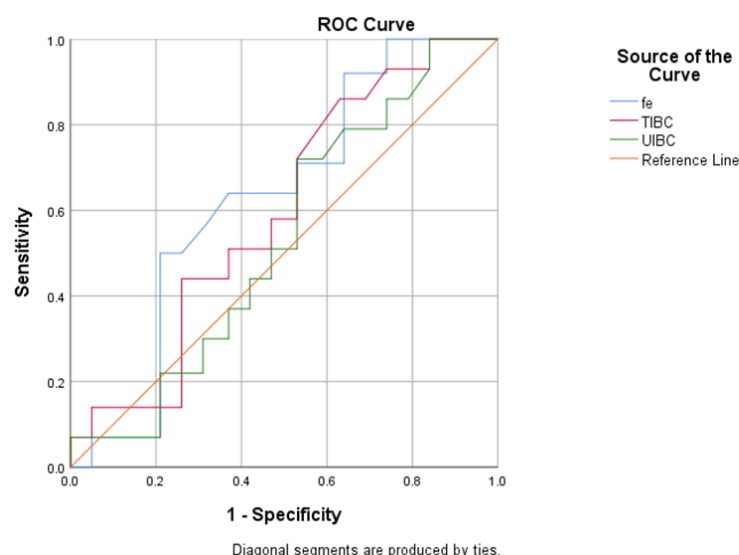


Figure 1. Receiver operating characteristic (ROC) curves for serum iron, TIBC, and UIBC in classification of HCV serostatus.

Discussion

The principal finding of this study was a significantly higher TIBC in HCV-seropositive patients with CKD compared with HCV-seronegative patients, whereas serum iron and UIBC did not differ significantly. The pattern of associations among the three iron-related biomarkers also differed by HCV serostatus, with attenuation of the inverse relationships involving serum iron in the HCV-seropositive group.

HCV-associated disturbances in iron regulation are biologically plausible. Chronic HCV infection has been linked to altered hepcidin regulation, changes in iron export and storage, and abnormal serum iron markers [4]. Studies in untreated chronic hepatitis C have also described abnormalities in serum iron indices in relation to hepatic injury and disease activity [7]. However, the higher TIBC observed in the present study should be interpreted cautiously. TIBC largely reflects transferrin availability, and the current dataset did not include

direct transferrin, ferritin, transferrin saturation, hepcidin, inflammatory markers, or liver-function measures that could clarify the mechanism responsible for this difference.

The correlation analysis further suggests altered relationships among iron indices in HCV-seropositive CKD patients. In the HCV-seronegative group, serum iron was strongly inversely associated with both TIBC and UIBC, while TIBC and UIBC were very strongly positively related. These relationships were weaker in the HCV-seropositive group, particularly for serum iron versus TIBC. Nevertheless, serum iron, TIBC, and UIBC are physiologically and analytically interdependent measures of transferrin-bound and unbound iron capacity; therefore, correlations among them should not be interpreted as independent mechanistic evidence.

The exploratory ROC results reinforce the limited role of these biomarkers for identifying HCV serostatus. AUC values for serum iron and TIBC were below 0.70, and UIBC did not significantly discriminate between groups. Accordingly, these iron indices should not be considered substitutes for established virological testing. Their value in this setting is more appropriately viewed as part of the broader evaluation of iron status and anemia in patients with CKD.

The findings are clinically relevant because iron abnormalities in CKD are already influenced by erythropoietin deficiency, inflammation, dialysis-related blood loss, and treatment exposures [2,6]. HCV may add further complexity to this background. Previous work has shown improvement in abnormal iron studies following successful HCV eradication with direct-acting antivirals [5], supporting the concept that HCV status may contribute to iron dysregulation in selected patients.

Study limitations

This study has several limitations. Its cross-sectional and single-center design limits causal inference and generalizability. HCV classification was based on ELISA, while confirmatory HCV RNA testing was not reported; therefore, seropositivity should not be assumed to represent active viremia in every participant. Important potential confounders were also not reported, including ferritin, transferrin saturation, hepcidin, hemoglobin, inflammatory markers, liver-function tests, dialysis duration, iron supplementation, erythropoiesis-stimulating agent use, and antiviral treatment. These factors should be incorporated into future prospective studies.

Conclusion

HCV seropositivity in patients with CKD was associated with significantly higher TIBC and altered relationships among serum iron, TIBC, and UIBC, while serum iron and UIBC did not differ significantly between HCV-seropositive and HCV-seronegative groups. The three biomarkers showed limited ability to classify HCV serostatus when used alone. Comprehensive assessment of iron status together with appropriate virological testing and relevant clinical variables is recommended when evaluating anemia and iron metabolism in CKD patients with HCV seropositivity.

References

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