



## Ferritin and Cardiac Electrophysiology in End-Stage Renal Disease: Evaluating the Impact of Index of Cardio-Electrophysiological Balance

Son Dönem Böbrek Yetersizliğinde Ferritin ve Kardiyak Elektrofizyoloji: Kardiyo-Elektrofizyolojik Denge İndeksinin Etkisinin Değerlendirilmesi

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# Ferritin and Cardiac Electrophysiology in End-Stage Renal Disease: Evaluating the Impact of Index of Cardio-Electrophysiological Balance

## ABSTRACT

**Objective:** Ferritin is a critical protein involved in iron storage and functions as an acute-phase reactant, playing a significant role in chronic inflammation and the pathogenesis of cardiovascular diseases. Elevated ferritin levels in end-stage renal disease patients undergoing hemodialysis may influence cardiac electrophysiological parameters, such as the corrected index of cardio-electrophysiological balance, a marker of proarrhythmic risk. This study aimed to investigate the association between ferritin levels and the corrected index of cardio-electrophysiological balance in patients with end-stage renal disease undergoing hemodialysis.

**Material and Method:** This retrospective cross-sectional study included 438 patients with end-stage renal disease undergoing hemodialysis, categorized into two groups according to their ferritin levels: Group 1 ( $\geq 1000$  ng/mL,  $n=254$ ) and Group 2 ( $\leq 200$  ng/mL,  $n=184$ ). Demographic, biochemical, and electrocardiographic data, including corrected index of cardio-electrophysiological balance, were analyzed. The correlation between ferritin levels and the corrected index of cardio-electrophysiological balance was assessed.

**Results:** The index of cardio-electrophysiological balance was significantly higher in Group 1 compared to Group 2 (5.1 vs. 4.9,  $p=0.003$ ). A moderate positive correlation between ferritin levels and the index of cardio-electrophysiological balance was identified ( $r=0.326$ ,  $p<0.005$ ). While significant differences were observed in heart rate, QRS duration, and PR intervals between the groups, other electrocardiographic parameters, such as Tp-e and QT intervals, did not show significant differences. The logistic regression analysis identified gender and ferritin levels as significant predictors of elevated iCEBc ( $\geq 4.5$ ) (Ferritin odds ratio of 1.08 (95% CI: 1.03-1.12,  $p<0.005$ ).

**Conclusion:** Elevated ferritin levels in end-stage renal disease patients undergoing hemodialysis are associated with an increased corrected index of cardio-electrophysiological balance, reflecting heightened proarrhythmic risk. These findings underscore the importance of ferritin as a potential marker for arrhythmia risk assessment in this population. Further research is warranted to explore strategies for mitigating cardiovascular risks associated with iron metabolism dysregulation.

**Keywords:** End-stage renal disease, ferritin, hemodialysis, Index of Cardio-Electrophysiological Balance.

## ÖZET

**Amaç:** Ferritin, demir depolanmasında anahtar bir protein olup, aynı zamanda kronik inflamasyon ve kardiyovasküler hastalıklarla ilişkili bir akut faz reaktanıdır. Hemodiyaliz uygulanan son dönem böbrek yetmezliği hastalarında artan ferritin seviyelerinin, proaritmik riski yansıtan kardiyoelektrofizyolojik denge indeksi gibi elektrokardiyografik parametreleri etkileyebileceği düşünülmektedir. Bu çalışma, hemodiyaliz alan son dönem böbrek yetersizliği hastalarında ferritin seviyeleri ile kardiyoelektrofizyolojik denge indeksi arasındaki ilişkiyi değerlendirmeyi amaçlamaktadır.

**Gereç ve Yöntem:** Bu retrospektif, kesitsel çalışmada, hemodiyaliz uygulanan 438 son dönem böbrek yetersizliği hastası yer almıştır. Hastalar ferritin seviyelerine göre iki gruba ayrılmıştır: Grup 1 ( $\geq 1000$  ng/mL,  $n=254$ ) ve Grup 2 ( $\leq 200$  ng/mL,  $n=184$ ). Demografik, biyokimyasal ve elektrokardiyografik veriler (kardiyoelektrofizyolojik denge indeksi dahil) analiz edilmiştir. Ferritin seviyeleri ile kardiyoelektrofizyolojik denge indeksi arasındaki ilişki değerlendirilmiştir.

**Bulgular:** Kardiyoelektrofizyolojik denge indeksi Grup 1'de Grup 2'ye kıyasla anlamlı derecede yüksek saptandı (5.1'e karşı 4.9,  $p=0.003$ ). Ferritin düzeyleri ile kardiyoelektrofizyolojik denge indeksi arasında orta düzeyde pozitif bir korelasyon tespit edilmiştir ( $r=0.326$ ,  $p<0.005$ ). Gruplar arasında kalp hızı, QRS süresi ve PR aralıklarında anlamlı farklılıklar gözlenirken, Tp-e ve QT aralıkları gibi diğer elektrokardiyografik parametreler anlamlı farklılıklar göstermemiştir. Lojistik regresyon analizi, cinsiyet ve ferritin düzeylerini yüksek iCEBc ( $\geq 4,5$ ) için anlamlı öngörücüler olarak tanımlamıştır (Ferritin odds ratio 1,08 (%95 CI: 1,03-1,12,  $p<0.005$ ).

**Sonuç:** Hemodiyaliz uygulanan son dönem böbrek yetersizliği hastalarında yüksek ferritin seviyeleri, proaritmik riski yansıtan kardiyoelektrofizyolojik denge indeksi ile ilişkilendirilmiştir. Bu bulgular, ferritinin bu popülasyonda aritmi riski değerlendirmesinde potansiyel bir belirteç olarak önemini vurgulamaktadır. Çalışmamız ile demir metabolizmasının düzensizliği ile ilişkili kardiyovasküler riskleri azaltmaya yönelik stratejilerin araştırılması gerektiği sonucuna varılmıştır.

**Anahtar Sözcükler:** Ferritin, hemodiyaliz, Kardiyoelektrofizyolojik Denge İndeksi, Son dönem böbrek hastalığı.

## Introduction

Ferritin is a protein essential for the storage and regulation of iron homeostasis, functioning at both intracellular and extracellular levels (1). Additionally, as an acute-phase reactant, elevated ferritin levels have been associated with chronic inflammation, metabolic disorders, chronic kidney failure, and cardiovascular diseases (2-6).

Elevated ferritin levels are frequently observed in individuals with end-stage renal disease (ESRD). Hemodialysis, a primary treatment for these patients, can further complicate iron regulation, contributing to elevated ferritin levels (5).

Both elevated and reduced ferritin levels have been linked to a heightened risk of arrhythmias and mortality in diverse patient populations (6,7). Additionally, increased serum ferritin levels have been shown to cause changes in QTc dispersion, which is a well-recognized marker associated with a greater likelihood of ventricular arrhythmias and sudden cardiac death (8).

Electrocardiographic parameters, including the frontal QRS axis, QT interval, QRS duration, Tp-E interval, and the corrected index of cardio-electrophysiological balance (iCEBc), are considered valuable tools for assessing cardiac health and identifying arrhythmogenic conditions. Studies have identified the iCEBc, the Tp-E interval, and the frontal QRS axis as potential markers for ventricular arrhythmias, sudden cardiac death, and overall mortality in various patient populations. (9-12).

Given the high incidence of cardiovascular complications in patients with ESRD, understanding the role of ferritin levels and their effects on electrocardiographic parameters is critical for developing strategies aimed at improving clinical outcomes. In this context, this study aims to investigate the relationship between elevated ferritin levels and electrocardiographic parameters in patients with ESRD.

## Material and Methods

### Study Population

This cross-sectional, retrospective, single-center study included patients who presented to nephrology and cardiology outpatient clinics between January 1, 2023, and January 1, 2024, and were undergoing hemodialysis treatment due to ESRD. Patients were

stratified into two groups according to their ferritin levels: Group 1 comprised individuals with ferritin levels  $\geq 1000$  ng/mL, while Group 2 included those with ferritin levels  $\leq 200$  ng/mL.

The study excluded patients presenting with the following conditions: acute infections, severe coronary artery disease, moderate or severe valvular heart disease, atrial fibrillation, malignancy, chronic autoimmune diseases, abnormal serum electrolyte levels, ferritin levels between 200 and 1000 ng/mL, heart failure (EF  $< 40\%$ ), or the presence of complete or incomplete bundle branch blocks or pacemaker rhythm on the electrocardiogram (ECG). Additionally, patients receiving treatments that could influence ECG parameters such as antiarrhythmic drugs, selective serotonin reuptake inhibitors, antibiotics, antifungals, antipsychotics, and others were excluded from the study.

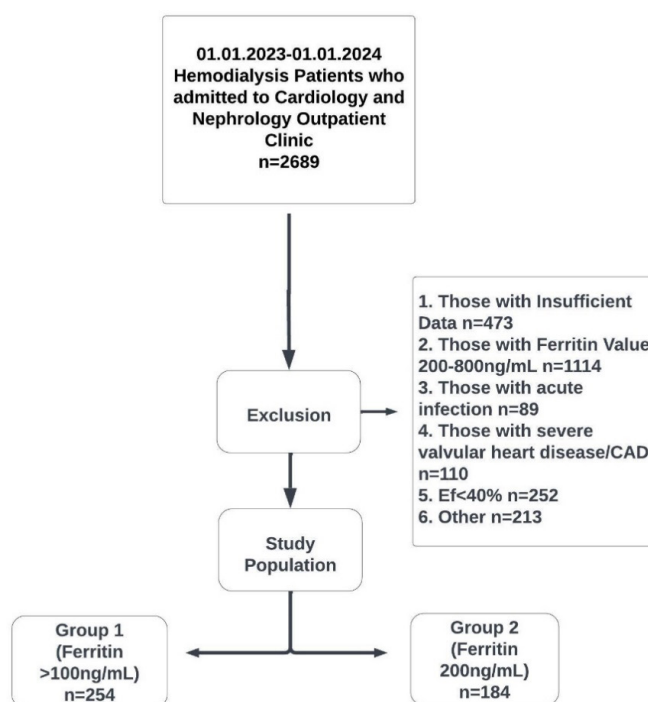
The study population consisted of 438 patients who met the inclusion criteria, with 254 participants in Group 1 (ferritin  $\geq 1000$  ng/mL) and 184 participants in Group 2 (ferritin  $\leq 200$  ng/mL).

Demographic data, as well as biochemical, hematological, and inflammatory parameters, were retrieved from the local database.

*A 12-lead ECG was obtained for all participants.*

The study design is illustrated in Figure I.

**Figure I.** Flow Chart of the Study Population



The research was conducted in accordance with the ethical principles outlined in the 1975 Declaration of Helsinki, and ethical approval was granted by the local ethics committee.

#### *Electrocardiogram Assessment*

Standard 12-lead ECGs were recorded using a device configured with a paper speed of 25 mm/s and an amplitude of 10 mm/mV. To reduce evaluation errors, a magnification tool was utilized. Measurements were conducted on leads V5 and DII. The ECG parameters analyzed included the T peak-to-end (Tp-e) interval, QRS duration, and QT interval.

The QT Interval: Measured from the onset of the QRS complex to the termination of the T wave.

The QTc Interval: QTc was calculated to account for heart rate variability using Bazett's formula:

$$QTc = \frac{QT}{\sqrt{R-R \text{ Interval}}}$$

Tp-e Interval: The T peak-to-end (Tp-e) interval was measured from the peak of the T wave, identified as its highest point, to the end of the T wave, defined as the intersection of its descending limb with the baseline. In cases where a U wave was present, the end of the T wave was identified as the notch between the T and U waves. The Tp-e/QT and Tp-e/QTc ratios were subsequently calculated based on these measurements.

ICEB and ICEBc: The index of cardio-electrophysiological balance (ICEB) was calculated as QT/QRS, and the corrected index (ICEBc) as QTc/QRS, as described in the literature.

The coefficients of variation for interobserver measurements were 3.3% and intraobserver measurements were 4.0%.

#### *Statistical analysis*

The study data were analyzed using SPSS software, version 21.0 (SPSS Inc., Chicago, IL). Descriptive statistics were reported as mean  $\pm$  standard deviation, median (interquartile range), median (minimum-maximum), frequencies, and percentages. For categorical variables, statistical analysis was performed using Pearson's Chi-Square Test, Fisher's Exact Test, and McNemar's Test. The distribution normality of continuous variables was evaluated using both visual tools, such as histograms and probability plots, and

statistical tests, including the Kolmogorov-Smirnov Test and the Shapiro-Wilk Test. For continuous variables with a normal distribution, comparisons between two independent groups were conducted using the Student's t-test. For variables that did not follow a normal distribution, the Mann-Whitney U Test was employed for comparisons between two groups. Correlations between variables were assessed using Spearman's Correlation Test. For the binary logistic regression analysis, an elevated iCEBc value was defined as  $\geq 4.5$  based on thresholds reported in the literature, and the analysis was conducted accordingly. A p-value of less than 0.05 was considered statistically significant.

## **Results**

### *Baseline Demographic, Laboratory, and Echocardiographic Characteristics*

The baseline demographic, laboratory, and echocardiographic characteristics of Group 1 (n = 254) and Group 2 (n = 184) are presented in Table I. Group 1 demonstrated distinct characteristics compared to Group 2. The median age was similar between the groups (59 years [48-68] in Group 1 vs. 60 years [48-70] in Group 2,  $p=0.294$ ), with nearly identical proportions of females (48.4% in Group 1 vs. 48.9% in Group 2,  $p=0.920$ ).

**Table I.** Baseline Demographic, Laboratory and Echocardiographic Findings of the Study Population

	<b>Group 1 (n=254)</b>	<b>Group 2 (n=184)</b>	<b>p</b>
Age, years	59 (48 - 68)	60 (48 - 70)	0.294
Female Sex, n (%)	123 (48.4%)	90 (48.9%)	0.920
HT, n (%)	192 (75.6%)	156 (84.8%)	<b>0.019</b>
DM, n (%)	84 (33.1%)	68 (37%)	0.399
HL, n (%)	55 (21.7%)	30 (16.3%)	0.162
CAD, n (%)	52 (20.5%)	38 (20.7%)	0.963
Rbc (million/nL)	3.6 (3.1 - 4.1)	3.7 (3.3 - 4.2)	<b>0.028</b>
Hb (g/dL)	10.6 (9.2 - 12)	10.8 (9.5 - 12.3)	0.169
Htc (%)	31.7 (27.7 - 36.6)	32.6 (29.2 - 36.9)	<b>0.032</b>
MCV (fL)	89.2 (85.1 - 94.4)	88.8 (84.5 - 93.8)	0.317
Na (mEq/L)	138.8 (136 - 141)	138.8 (136.8 - 140.5)	0.638
K (mEq/L)	4.8 (4.2 - 5.4)	4.8 (4.3 - 5.3)	0.666
Calcium (mg/dL)	9 (8.5 - 9.5)	9 (8.3 - 9.4)	0.194
Magnesium (mmol/L)	1 (0.8 - 1)	0.9 (0.8 - 0.9)	<b>0.006</b>
Fe ( $\mu$ g/dL)	75.4 (47.9 - 77.5)	56.5 (37.8 - 68.8)	<b>&lt;0.005</b>
TIBC ( $\mu$ g/dL)	213.6 (194 - 213.6)	264.9 (237.7 - 284.6)	<b>&lt;0.005</b>

Ferritin (ng/mL)	1465 (1211 - 2009.3)	116 (59 - 150)	<b>&lt;0.005</b>
Ejection Fraction	55 (55 - 60)	54 (54 - 60)	0.124

Quantitative variables were specified as medians (Q1-Q3). Categorical variables were shown as numbers and percentage values. Ht: Hypertension; DM: Diabetes Mellitus; HL: Hyperlipidaemia; CAD: Coronary artery disease; Rbc: Red blood cell ; Hb: haemoglobin; Htc: haematocrit; MCV: Mean Corpuscular Volume; Na:Sodyum; K: Potassium; Cl: Clorur; Fe: Iron; TIBC: Total iron binding capacity.

Laboratory values for Group 1 showed unique features. Iron levels (75.4 µg/dL [47.9-77.5]) were markedly higher in Group 1 compared to Group 2 (56.5 µg/dL [37.8-68.8],  $p < 0.005$ ), while total iron-binding capacity (TIBC) was significantly lower in Group 1 (213.6 µg/dL [194-213.6] vs. 264.9 µg/dL [237.7-284.6],  $p < 0.005$ ).

Red blood cell (RBC) counts and hematocrit levels were slightly lower in Group 1 (RBC: 3.6 [3.1-4.1] vs. 3.7 [3.3-4.2],  $p = 0.028$ ; hematocrit: 31.7% [27.7-36.6] vs. 32.6% [29.2-36.9],  $p = 0.032$ ). Other hematological and electrolyte parameters, including hemoglobin, sodium, potassium, calcium, and magnesium, did not differ significantly between groups.

**Table II.** Electrocardiographic Features of The Study Population

	Group 1 (n=254)	Group 2 (n=184)	P
Heart Rate, bpm	81.5 (70.8 - 92)	78 (68.3 - 89)	<b>0.026</b>
PR Interval, ms	146 (130 - 166.5)	154 (138 - 172)	<b>0.012</b>
QRS Duration,ms	86 (80 - 96)	88 (82 - 95.8)	<b>0.028</b>
QT Interval,ms	382 (354 - 412)	386 (362.5 - 407.8)	0.247
cQT Interval, ms	442 (425.8 - 461)	436.5 (419 - 462.8)	0.123
Frontal QRS-T Angle (°)	40.5 (19.8 - 90.5)	36.5 (15.3 - 86)	0.252
Tp-e, ms	71 (60 - 80)	70 (60 - 80)	0.402
Tp-e/QT Ratio	0.2 (0.2 - 0.2)	0.2 (0.2 - 0.2)	0.257
Tp-e/QTc Ratio	0.2 (0.1 - 0.2)	0.2 (0.1 - 0.2)	0.727
iCEB (QT/QRS)	4.4 (4 - 4.8)	4.4 (4 - 4.7)	0.305
iCEBc (QTc/QRS)	5.1 (4.6 - 5.6)	4.9 (4.5 - 5.4)	<b>0.003</b>

Quantitative variables were specified as medians (Q1-Q3). QTc: Corrected QT interval; Tp-e:T wave peak-to-end; iCEB: index of cardioelectrophysiological balance; iCEBc: corrected iCEB

The logistic regression analysis identified gender and ferritin levels as significant predictors of elevated iCEBc ( $\geq 4.5$ ). Ferritin levels had an odds ratio (OR) of 1.08 (95% CI: 1.03-1.12,  $p < 0.005$ ), indicating that each unit increase in ferritin was associated with an 8% increase in the likelihood of having an iCEBc  $\geq 4.5$ . Other variables, including age, hemoglobin, diabetes, hypertension, hyperlipidemia, ejection fraction, magnesium, and iron levels, were not statistically

significant predictors in the model ( $p > 0.05$ ).

**Table III.** Binary Logistic Regression Analysis of Factors Influencing the iCEBc  $\geq 4.5$

	OR (%95CI)	P
Gender	0,519 (0,31 - 0,87)	<b>0.013</b>
Age	0,994 (0,976 - 1,013)	0.537
Hemoglobin	0,985 (0,875 - 1,108)	0.797
Diabetes Mellitus	0,786 (0,449 - 1,378)	0.401
Hypertension	1,43 (0,718 - 2,851)	0.309
Hyperlipidemia	1,031 (0,542 - 1,961)	0.927
Ejection Fraction	1,022 (0,981 - 1,064)	0.302
Ferritin	1,08 (1,03-1,12)	<b>0.000</b>
Magnesium	1,622 (0,415 - 6,341)	0.487
Iron Level	0,999 (0,992 - 1,006)	0.769

Cox & Snell R Square=0.079; Nagelkerke R Square= 0.124; Accuracy= 0,799. iCEBc:Corrected index of Cardio-Electrophysiological Balance

### Electrocardiographic Characteristics

The electrocardiographic features Group 1, presented in Table II, reveal some significant differences compared to Group 2. Group 1 had a higher median heart rate (81.5 bpm [70.8-92]) compared to Group 2 (78 bpm [68.3-89],  $p = 0.026$ ). The PR interval was shorter in Group 1 (146 ms [130-166.5] vs. 154 ms [138-172],  $p = 0.012$ ), and the QRS duration was also slightly shorter (86 ms [80-96] vs. 88 ms [82-95.8],  $p = 0.028$ ).

The corrected index of cardioelectrophysiological balance (iCEBc) was higher in Group 1 (5.1 [4.6-5.6]) compared to Group 2 (4.9 [4.5-5.4],  $p = 0.003$ ). No significant differences were noted in other electrocardiographic parameters, including QT interval, corrected QT (QTc) interval, Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio.

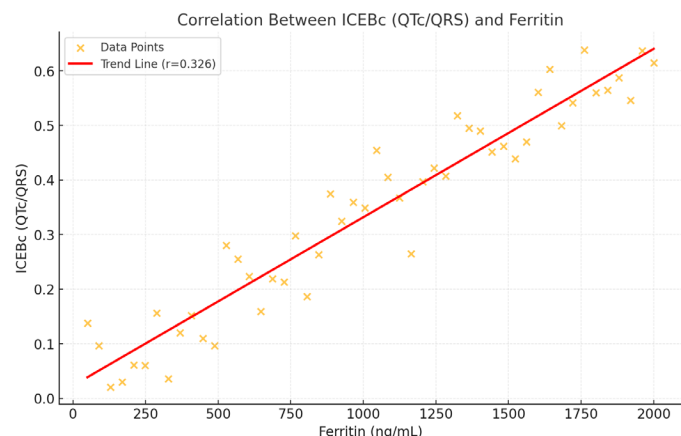
### Correlation Analysis of iCEBc and Ferritin

The correlation analysis, summarized in Table III, revealed a statistically significant moderate positive correlation between iCEBc and ferritin levels in Group 1 ( $r = 0.326$ ,  $p < 0.005$ ). This indicates that higher ferritin levels in Group 1 are associated with elevated iCEBc values. (Figure II).

In summary Group 1 exhibited unique characteristics compared to Group 2, including higher ferritin and iron levels, lower TIBC, and higher iCEBc. These findings suggest a distinct profile of iron metabolism and cardiac electrophysiological properties in Group 1. The significant moderate correlation between ferritin

and iCEBc further highlights the potential interplay between iron storage and cardiac function.

**Figure II.** Correlation Between iCEBc and Ferritin



## Discussion

To the best of our knowledge, this study is the first to provide evidence demonstrating an increase in the iCEBc in ESRD patients undergoing HD with ferritin levels >1000 ng/mL. A moderate correlation between iCEBc and ferritin levels was also identified. Serum iron levels significantly effect ECG parameters and are linked to proarrhythmic effects through various mechanisms (13). Iron overload has been shown to enhance the production of reactive oxygen species and depolarize mitochondrial membrane potential, thereby initiating calcium wave generation and promoting arrhythmogenesis (14). Conversely, low iron levels are also associated with arrhythmia risks, including prolonged QT and Tp-e intervals, which may increase the susceptibility to ventricular arrhythmias (15). These findings highlight the U-shaped relationship of serum iron levels with cardiac risk, where both low and high levels contribute to arrhythmic vulnerability (16). In our study, serum iron levels were observed to be significantly elevated in Group 1. Collectively, these findings underscore the importance of individualized iron management to mitigate cardiovascular and proarrhythmic risks associated with serum iron levels especially in patients with ESRD.

Serum ferritin is a key indicator of iron storage in the body (1). Furthermore, ferritin, in conjunction with transferrin and its' receptors, serves as an acute-phase reactant and is a component of the protein family involved in cellular defense against oxidative stress

and inflammation. The H-ferritin gene is activated through the antioxidant-responsive element in response to oxidative stress and proinflammatory cytokines, including interleukin (IL)-1, IL-6, and tumor necrosis factor-alpha (17). Consequently, inflammatory conditions such as chronic diseases and cancer can naturally influence serum iron and ferritin levels (1).

High ferritin levels in patients with chronic cardiovascular disease have been associated with worse outcomes and increased mortality (7). Kuragano et al. identified hyperferritinemia described as serum ferritin >100 ng/mL as a significant risk factor for cardiovascular disease, hospitalization, and mortality in their study which was published at 2014 included 1,086 Japanese HD patients (18). Similarly, in a 2020 study, HD patients with high ferritin levels and low transferrin saturation—suggesting inadequate iron utilization for erythropoiesis—were found to have a higher risk of death and cardiovascular disease (4). In another study, Ahmed et al. demonstrated the association between high serum ferritin levels ( $\geq 800$   $\mu\text{g/L}$ ) and left ventricular hypertrophy in HD patients (19). Based on these findings, we categorized our study population of ESRD patients receiving HD into a hyperferritinemia group (ferritin >1000 ng/mL) and a control group (ferritin <200 ng/mL). We believe that exploring the relationship between ferritin levels and electrocardiographically validated parameters can shed light on the evaluation of cardiovascular outcomes in HD patients.

In this context, iCEBc serves as a non-invasive parameter that offers insights into the depolarization and repolarization phases of the cardiac action potential, thereby reflecting the ventricular proarrhythmic risk (20). Although there are relatively fewer studies on iCEBc compared to other markers, it has been suggested to predict cardiac proarrhythmic risk more effectively than parameters such as Tp-e interval, Tp-e/QT ratio, and QT interval, which focus solely on repolarization (20,21).

iCEBc has emerged as a superior biomarker for identifying arrhythmogenic conditions compared to the QTc. Unlike QTc, which has limited sensitivity and specificity for arrhythmic risk, iCEBc provides a balanced measure of ventricular depolarization and repolarization, offering enhanced predictive value for

arrhythmias, including life-threatening ventricular fibrillation (22). Recent studies affirm that iCEBc correlates strongly with adverse cardiac outcomes and mortality, emphasizing its clinical significance in risk stratification and its potential application in diverse patient populations (23). These findings solidify iCEBc as a pivotal tool in cardiology for non-invasive arrhythmic risk assessment.

Yucetas et al. reported significantly higher iCEBc values in patients with subarachnoid hemorrhage, highlighting the proarrhythmic risk in this group (21). Similarly, Kaya et al. observed elevated iCEBc levels in patients with tinnitus, emphasizing its relevance to arrhythmogenic risk (24). Additionally, Nafakhi et al. found increased pericardial fat volume in patients with elevated iCEBc levels, suggesting a higher cardiovascular disease risk in these patients (25). Sivri et al. reported a rise in iCEBc levels in ESRD patients post-dialysis compared to pre-dialysis, underlining the proarrhythmic state in this population. In our study, we demonstrated that in ESRD patients undergoing HD, who are already at high cardiovascular risk, elevated ferritin levels are associated with a moderate increase in arrhythmic risk as reflected by higher iCEBc values. This highlights the potential importance of ferritin as a marker for assessing proarrhythmic risk in this vulnerable population.

This study has several limitations that should be acknowledged. First, its retrospective, single-center design restricts the generalizability of the findings to wider populations. Second, there is the potential influence of confounders. To address this, we conducted a binary logistic regression analysis to adjust for age, gender, and other cardiovascular disease risk factors. However, even after these adjustments, the model accounted for only a modest proportion of the variation (7.9% to 12.4%) and demonstrated moderate predictive accuracy (79.9%), suggesting that additional unmeasured factors might contribute to iCEBc variability. Third, although we utilized standard methodologies for ECG measurements, interobserver and intraobserver variability could introduce minor measurement errors. Fourth, significant limitation of our study, is the lack of direct assessment of cardiovascular mortality and major cardiovascular adverse events. This omission reflects the inherent

constraints of the retrospective design and limits our ability to explore the full clinical implications of iCEBc in predicting these outcomes. Lastly, this study focused only on ferritin and iCEBc without exploring other biomarkers or cardiac parameters that might provide additional insights into arrhythmic risks in ESRD patients. Future studies with a prospective design, larger sample sizes, and a broader scope of analysis are needed to validate and expand upon these findings.

## Conclusion

This study revealed a significant increase in the iCEBc among patients with ESRD undergoing HD who exhibited elevated ferritin levels (>1000 ng/mL). Additionally, a moderate correlation between ferritin levels and iCEBc was identified. These findings suggest that elevated ferritin levels, commonly observed in ESRD patients, may contribute to an increased arrhythmic risk, as reflected by higher iCEBc values. Given the high cardiovascular risk in this population, our results emphasize the potential role of ferritin as a marker for assessing proarrhythmic risks and underline the importance of further investigation into strategies to mitigate these risks.

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