



# Association of Depressive Symptoms with Iron Management in Patients on Maintenance Hemodialysis: A Cross-sectional Study

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**Abstract:** Background: Iron status has a critical role in depressive symptoms, but evaluation of depressive symptoms associated with iron metabolism is not usually included as a clinical parameter in hemodialysis (HD) patients. We aimed to assess the correlations between depressive symptoms and clinical, demographic, and laboratory variables including iron metabolism. Methods: One hundred and thirty-eight HD patients were evaluated in this study. The Beck Depression Inventory Second Edition (BDI-II) was used to quantify levels of depressive symptoms. BDI-II scores  $\geq 14$  were defined as depressive symptoms. Mean age, duration of HD, haemoglobin levels, serum ferritin levels, serum iron levels, transferrin saturation (TSAT), total iron binding capacity, serum albumin levels, and C-reactive protein were included in the model. Patients were categorized into four groups according to serum ferritin levels and TSAT. Backward stepwise logistic regression analysis was performed and odds ratios (ORs) and 95% confidence intervals derived. Results: Depressive symptoms were significantly associated with increased serum ferritin levels (OR, 1.010;  $p=0.0008$ ). Compared with group 1 (ferritin  $<100$  ng/dL, TSAT  $\geq 20\%$ ) as reference, ORs for depressive symptoms were significantly increased in group 4 (ferritin  $\geq 100$  ng/dL, TSAT  $< 20\%$ ) (OR, 6.419;  $p=0.0073$ ). Conclusion: Higher serum ferritin levels and decreased iron utilization efficiency were found to be involved in depressive symptoms among patients undergoing HD. Understanding the pathophysiology of depressive symptoms could provide insights into the design of clinical iron management in HD patients.

**Keywords:** Depressive Symptoms, Hemodialysis, Iron Management

## 1. Introduction

Depressive symptoms represent the main psychological disorder in patients undergoing maintenance hemodialysis (HD) [1, 2] and are associated with increased mortality in patients undergoing HD [3, 4]. Moreover, depressive symptoms conventionally occur in patients who have just begun HD treatment; depression generally tends to resolve in

the maintenance phase. Despite the long-term survival benefit to patients resulting from advances in medical technology, depressive symptoms can still be present. In recent years, mental or psychological care has become a focus of dialysis therapy, to minimize systemic complications that appear together with the long-term reduction in quality of life.

Numerous studies have addressed that iron status has a critical role in brain function and cerebral mechanisms [5–7].

Previous studies have pointed out that depression is associated with decreased serum ferritin concentrations [8, 9]. Some studies have reported that there was no significant association between depression and serum ferritin concentration [10, 11]. Iron is an important component in the treatment of anaemia among HD patients. Serum ferritin levels and transferrin saturation (TSAT) are used to assess iron status, as a guide for anaemia therapy; both iron replacement and iron maintenance therapy are required to treat anaemia. However, not all previous studies have confirmed a relationship between depressive symptoms and iron status, and little is known about how to manage iron in HD patients from the standpoint of depressive symptoms. In this study, we aimed to assess the relationship among depressive symptoms and clinical, demographic, and laboratory variables including iron metabolism. Our present findings showed an association between depressive symptoms and iron status in HD patients.

## 2. Methods

### 2.1. Ethics Approval and Consent to Participate

This study was approved by The Ethics Committee for Human Research of Tojinkai Hospital. As collected data were obtained from routine clinical practice further consents were waived. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional, and national research committee at which the studies were conducted (IRB approval number NCT03096626) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

### 2.2. Study Population

The One hundred and fifty-two patients (mean age,  $65.9 \pm 11.4$  years; women, 50%; mean duration of HD,  $14.2 \pm 8.8$  years) undergoing maintenance HD three times weekly for over 1 year were included in this cross-sectional study. Data were obtained from the Tojinkai hospital. Subjects in the present study were sampled by a random process. Patients with chronic hepatitis B or C were excluded, as were 14 patients who refused to enrol in the present study and those who could not complete the questionnaire by themselves. Patients with low cognitive function and who declined to be enrolled in the study and those who could not complete the questionnaire themselves were excluded. As a result, 138 patients were enrolled as study participants (mean age,  $66.2 \pm 11.1$  years; women 51%; mean duration of HD,  $14.3 \pm 8.7$  years). We extracted the following clinical characteristics from patients' medical records: sex, mean age, height, dry weight (DW), body mass index (BMI), duration of HD, HD time, blood flow rate during HD, presence of underlying diabetes mellitus (DM), and  $Kt/V_{\text{urea}}$ . Calculations were made of erythropoiesis-stimulating agents (ESA) and intravenous iron preparations in average monthly doses for the past 3 months. The ESA was expressed as dosage of darbepoetin alfa ( $\mu\text{g}$ ). Blood samples (4 mL) were obtained just before

initiation of HD at the beginning of a regular HD session on the first day of the week. Laboratory data including haemoglobin levels, haematocrit, serum ferritin levels, serum iron levels, total iron binding capacity (TIBC), blood urea nitrogen (BUN), serum albumin levels, creatinine (Cr), and C-reactive protein (CRP) were obtained. Serum ferritin levels and CRP were measured using the latex agglutination turbidimetry method. Serum iron levels were measured with the Nitroso-PSAP method. TSAT was calculated as serum iron levels divided by TIBC. The geriatric nutritional risk index (GNRI) was calculated as follows:  $\text{GNRI} = [14.89 \times \text{serum albumin levels (g/dL)} + 41.7 \times (\text{body weight/ideal body weight})]$  [12]. Ideal body weight was calculated using the patients' height and a BMI of 22 [13, 14].

### 2.3. Assessment of Depressive Symptoms

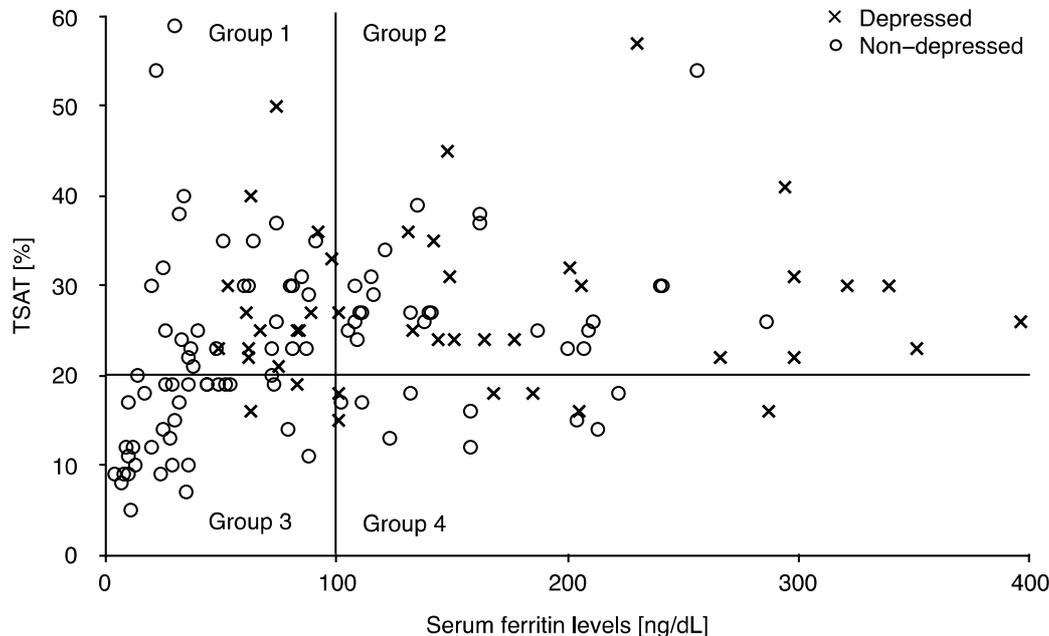
The Beck Depression Inventory Second Edition (BDI-II, Japanese version) was used to evaluate patients, so as to quantify depression levels [15]. The BDI-II has been the most widely used instrument for self-assessment of depression among patients undergoing dialysis [16, 17]. There are 21 items on the self-administered questionnaire assessing both the presence and severity of depression, with four possible responses to statements that are scored from 0 to 3 and total scores ranging from 0 to 63 [18]. A higher BDI-II score indicates a greater level of depression.

### 2.4. Statistical Analysis

In the present study, we defined patients with BDI-II scores  $\geq 14$  as having depressive symptoms [19]. Patients were divided into two groups according to their BDI-II score, a non-depressed group (BDI-II score  $< 14$ ) and depressed group (BDI-II score  $\geq 14$ ). The clinical characteristics of the two groups were compared using the Mann-Whitney  $U$  test for mean age, height, DW, BMI, duration of HD, HD time, blood flow rate during HD, and laboratory variables. Because of nonnormality distribution of some clinical variables by using the Shapiro-Wilk normality test, nonparametric test was performed as a distribution-free test. The Fisher's exact probability test was used for sex and the presence of underlying DM. Logistic regression analysis was performed to select determinants between patients grouped by the presence or absence of depressive symptoms according to BDI-II score, the dependent variable. Mean age, duration of HD, haemoglobin levels, serum ferritin levels, serum iron levels, TSAT, TIBC, serum albumin levels, and CRP were included in the model. Data are presented as odds ratios (ORs) with 95% confidence intervals (CIs). Patients were categorized into four groups according to their serum ferritin levels and TSAT. Here, we used cut-off values for serum ferritin levels and TSAT of 100 ng/mL and 20%, respectively. Japanese guidelines for renal anaemia in chronic kidney disease recommend administration of iron to patients with serum ferritin levels  $< 100$  ng/mL and with TSAT  $< 20\%$  [20]. These are the values that the guidelines of 2008 Japanese Society for Dialysis Therapy for treating anemia in CKD recommend that iron be

administered to patients [20]. The four patient groups were as follows: Group 1, serum ferritin levels <100 ng/dL, TSAT  $\geq$ 20%; group 2, serum ferritin levels  $\geq$ 100 ng/dL, TSAT  $\geq$ 20%; group 3, serum ferritin levels <100 ng/dL, TSAT <20%; and group 4, serum ferritin levels  $\geq$ 100 ng/dL, TSAT <20%. For comparisons among the groups, a backward stepwise logistic

regression analysis test was performed to identify those risk factors that contribute to depressive symptoms. All statistical analyses were performed using of JMP 10 software (SAS Institute, Inc., Cary, NC, USA), with a *p*-value <0.05 considered statistically significant.



**Figure 1.** Distribution of depression symptoms according to serum ferritin levels and TSAT (transferrin saturation)  $\times$  and  $\circ$  indicate patients with depression and no depression symptoms, respectively. Patients were categorized into four groups according to serum ferritin levels and TSAT as follows: Group 1 ( $n=43$ ), TSAT  $\geq$ 20% and ferritin < 100 ng/dL; Group 2 ( $n=47$ ), TSAT  $\geq$ 20% and ferritin  $\geq$ 100 ng/dL; Group 3 ( $n=33$ ), TSAT <20% and ferritin <100 ng/dL; Group 4 ( $n=15$ ), TSAT <20% and ferritin  $\geq$ 100 ng/dL.

### 3. Results

#### 3.1. Demographic Characteristics

Table 1 shows clinical characteristics categorized by the presence of depressive symptoms according to scores on the BDI-II. Among all patients, 43 with a BDI-II score  $\geq$  14 were considered depressed (31%); 95 patients with BDI-II score < 14 were considered non-depressed (69%). The median (interquartile range: IQR) values of BDI-II score were 20 (22.0–18.0) in the depressed group and 6.0 (8.5–3.0) in the non-depressed group. The demographic, clinical, and laboratory characteristics of all patients are summarized in Table 1. Upon comparing the depressed and non-depressed groups, BDI-II scores, serum ferritin levels, and TSAT were found to be significantly higher among participants in the depressed group than those among the non-depressed group ( $p < 0.0001$ ,  $p < 0.0001$ ,  $p = 0.0151$ , respectively). TIBC was significantly lower in the depressed group than in the non-depressed group ( $p = 0.0026$ ).

#### 3.2. Relationships Between Depressive Symptoms and Clinical Variables

Table 2 shows the results of logistic regression analysis of clinical variables. Relative to the non-depressed group, the

depressed group had increased ORs for serum ferritin levels (OR, 1.010; 95% CI: 1.004–1.016;  $p = 0.0008$ ). No significant differences were found between the depressed and non-depressed group for other clinical variable outcomes.

#### 3.3. Relationships Between Serum Ferritin Levels and TSAT

Figure 1 shows the distribution of patients with depressive symptoms and no depressive symptoms according to serum ferritin levels and TSAT. Table 3 shows the results of logistic regression analysis with ORs and 95% CIs for group 1 compared with the other three groups. When comparing group 1 (serum ferritin levels <100 ng/dL, TSAT  $\geq$ 20%) with group 2 (serum ferritin levels  $\geq$ 100 ng/dL, TSAT  $\geq$ 20%), group 3 (serum ferritin levels <100 ng/dL, TSAT <20%) and group 4 (serum ferritin levels  $\geq$ 100 ng/dL, TSAT <20%), ORs for depressive symptoms were significantly higher in group 4 (OR, 6.419; 95% CI, 1.583–43.523;  $p = 0.0073$ ). In a comparison of group 1 with groups 2 and 3, the differences were not statistically significant ( $p = 0.0868$ ,  $p = 0.5333$ , respectively).

### 4. Discussion

To identify the risk factors for depressive symptoms in HD patients, we focused on assessing those factors responsible for

depression including clinical, demographic, and laboratory variables that have been previously suggested. In our study, BDI-II score was used to assess the level of depressive symptoms, and the prevalence of depressive symptoms was 32.2% among our patients. In this study, the primary finding was that a higher serum ferritin level was an independent risk factor for depressive symptoms. Secondary findings were that higher serum ferritin levels and lower TSAT were associated with depressive symptoms. That is, ORs for patients with depressive symptoms were significantly higher among patients who had serum ferritin levels  $\geq 100$  ng/dL and TSAT  $< 20\%$  than in patients with serum ferritin levels  $< 100$  ng/dL and TSAT  $\geq 20\%$ .

Iron is an essential micronutrient for all living organisms as it is required for adequate erythropoietic function, oxidative metabolism, and cellular immune responses. However, excess iron causes various disorders. In general, iron promotes the production of free radical ions and damages cells or tissues, so iron is fundamentally a harmful substance to humans [21–23]. Most patients undergoing maintenance HD receive a combination of ESA and intravenous iron therapy for anaemia management. Japanese Guidelines for Renal Anemia in Chronic Kidney Disease recommend a target haemoglobin level in HD patients of 11–12 g/dL, and administration of iron therapy for patients with TSAT  $< 20\%$  and serum ferritin levels  $< 100$  ng/mL [20].

**Table 1.** Clinical characteristics and prevalence of depression according to the Beck Depression Inventory among HD patients.

Clinical variable	Depressed (n=43)	No-Depressed (n=95)	p-value
BDI score (IQR)	20 (22.0–18.0)	6.0 (8.5–3.0)	<0.0001 **
Men / Women	20 / 23	48 / 47	0.7152
Mean age, yr (SD)	65.7 (11.3)	66.4 (11.1)	0.6640
Height, cm (SD)	161.3 (9.9)	161.2 (9.1)	0.7077
Dry weight, kg (SD)	56.3 (11.5)	57.3 (12.7)	0.9519
Body mass index, kg/m <sup>2</sup> (SD)	21.5 (3.6)	21.7 (4.3)	0.7250
Duration of HD, yr (SD)	14.3 (9.4)	14.3 (8.4)	0.7130
HD time, hr (SD)	4.5 (0.5)	4.7 (0.6)	0.0716
Blood flow during dialysis, ml/min (SD)	287.2 (23.8)	289.1 (27.2)	0.6450
DM / non-DM	14 / 29	19 / 76	0.0722
Hemoglobin levels, g/dL (IQR)	10.9 (11.5–10.4)	11.0 (11.7–10.3)	0.5098
Hematocrit, % (IQR)	33.0 (34.3–31.7)	34.1 (36.0–31.7)	0.1252
Serum ferritin levels, ng/dL (IQR)	142.0 (205.5–83.0)	72.0 (119.8–30.0)	<0.0001 **
Serum iron levels, $\mu$ g/dL (IQR)	65.0 (80.5–53.0)	58.0 (75.0–42.0)	0.0820
TSAT, % (IQR)	25.0 (31.0–22.0)	23.0 (29.8–16.3)	0.0151 *
TIBC, $\mu$ g/dL (IQR)	243.0 (265.5–228.0)	270.0 (305.8–236.3)	0.0026 **
Serum albumin levels, g/dL (IQR)	3.9 (4.1–3.7)	3.9 (4.1–3.7)	0.7453
CRP, mg/dL (IQR)	0.084 (0.308–0.036)	0.092 (0.200–0.048)	0.7560
Serum creatinine levels, g/dL (IQR)	10.2 (11.9–9.4)	11.0 (12.0–9.9)	0.3476
Blood urea nitrogen, mg/dL (IQR)	59.0 (68.5–49.5)	60.0 (69.0–52.3)	0.5792
ESAs, $\mu$ g/week (SD)	12.1 (10.4)	13.0 (17.9)	0.8428
Intravenous iron preparation, mg (SD)	8.4 (9.7)	7.6 (9.7)	0.6873
GNRI (SD)	96.1 (5.3)	96.9 (5.0)	0.4663
Kt/V <sub>urea</sub> (SD)	1.95 (0.32)	1.96 (0.30)	0.7458

Abbreviations: BDI, Beck Depression Inventory; HD, hemodialysis; DM, diabetes mellitus; TAST, transferrin saturation; TIBC, total iron binding capacity; CRP, C-reactive protein; ESA, erythropoiesis-stimulating agent; GNRI, geriatric nutritional risk index.

Notes: Results reported as mean with standard deviation (SD) or median changes with interquartile range (IQR). Patients were divided into two groups according to BDI scores: non-depressed group (BDI score  $< 14$ ), and depressed group (BDI score  $\geq 14$ ). Differences between the two groups were assessed by Mann-Whitney *U*-test or Fisher's exact probability tests.

\*\*  $p < 0.01$ , \*  $p < 0.05$  for comparisons between the groups.

**Table 2.** Logistic regression analysis of the relationship between depression symptoms and clinical variable.

Clinical variable	Odds ratio (95% CI)	p-value
Mean age, yr	0.984 (0.941–1.029)	0.4758
Duration of HD, yr	0.992 (0.942–1.043)	0.7428
Hemoglobin levels, g/dL	1.034 (0.616–1.712)	0.8971
Serum ferritin levels, ng/dL	1.010 (1.004–1.016)	0.0008 **
TSAT, %	1.031 (0.983–1.083)	0.2055
TIBC, $\mu$ g/dL	0.988 (0.974–1.001)	0.0846
Serum albumin levels, g/dL	1.867 (0.257–13.805)	0.5349
CRP, mg/dL	0.741 (0.218–1.989)	0.5797

Abbreviations: HD, hemodialysis; TAST, transferrin saturation; TIBC, total iron binding capacity; CRP, C-reactive protein; CI, confidence interval. \*\*  $p < 0.01$ .

**Table 3.** Odds ratios for the presence of depression among haemodialysis patients in group 1 (ferritin < 100 ng/dL, TSAT  $\geq$  20%) compared with the other groups, by serum ferritin levels and TSAT.

	Number of patients (depressed)	Adjusted odds ratio (95% CI)	p-value
Group 1 Serum ferritin levels < 100 ng/dL TSAT $\geq$ 20%	43 (14)	Reference	–
Group 2 Serum ferritin levels $\geq$ 100 ng/dL TSAT $\geq$ 20%	47 (21)	0.460 (0.087–0.184)	0.0868
Group 3 Serum ferritin levels < 100 ng/dL TSAT < 20%	33 (2)	0.670 (0.191–2.421)	0.5333
Group 4 Serum ferritin levels $\geq$ 100 ng/dL TSAT < 20%	15 (6)	6.419 (1.583–43.523)	0.0073 *

Abbreviations: CI, confidence interval; TAST, transferrin saturation. Note: Group 1 is the reference. \*  $p < 0.051$ .

Haemodialysis patients are reported to have a high prevalence of inflammation that is associated with survival [24]. Patients with inflammation often develop anaemia that is associated with iron metabolism abnormalities caused by the expression of divalent metal transporter and transferrin receptors, which are iron uptake proteins, or a decrease in the expression of ferroportin 1, which is an iron export protein. As a result, iron localization, in which iron is enclosed within cells, causes the use of iron effective for haematopoiesis to decrease. That is, reticuloendothelial iron release disorder occurs, and iron is released from the mesenchymal system into the blood [25].

In this study, patients without depressive symptoms had serum ferritin levels <100 and TSAT  $\geq$ 20%, indicating that iron was used effectively to treat anaemia. That is, iron release from iron metabolic cells, including in the mesenchymal system, is thought to have occurred in a proper manner. On the other hand, in patients with depressive symptoms, TSAT was more than 25% but ferritin was higher and TIBC was lower than in patients with no depressive symptoms. These results suggest that patients with depressive symptoms might be in a state of functional iron deficiency. Functional iron deficiency is defined as a state in which there is insufficient incorporation of iron into erythroid precursors in the face of adequate body iron stores [26]. Additionally, higher serum ferritin levels and lower TSAT were associated with depressive symptoms. That is, ORs for patients with depressive symptoms were significantly higher in patients with serum ferritin levels  $\geq$ 100 ng/dL and TSAT <20% than those with serum ferritin levels <100 ng/dL and TSAT  $\geq$ 20%. Classification by serum ferritin levels and TSAT values could be thought of as follows. Group 1 (serum ferritin levels <100 ng/dL and TSAT  $\geq$ 20%) represents a state in which there is sufficient iron incorporation into erythroid precursors during iron absorption and recycling; group 2 (serum ferritin levels  $\geq$ 100 ng/dL, TSAT  $\geq$ 20%), a state of iron overload; group 3 (serum ferritin levels <100 ng/dL, TSAT <20%), a state of iron deficiency; and group 4 (serum ferritin levels  $\geq$ 100 ng/dL, TSAT <20%), a state of functional iron deficiency.

In HD patients, iron is often supplemented intravenously because intravenous iron administration is effective in correcting anaemia. Excessive accumulation of iron is thought to cause tissue damage and to possibly contribute to arteriosclerosis [27–28]. Excessive accumulation of iron in regions of the brain that undergo degeneration is a cause of neurological diseases such as Alzheimer disease, Parkinson disease, and other disorders [29–34]. Furthermore, it has been reported that hippocampus volume and function are decreased

in depressed patients. Although the precise role of iron in the cause of many neurodegenerative diseases is unclear, a previous study reported that neurodegeneration accompanied by iron accumulation disrupts the neural network in the associative field of hippocampus and cortex and gradually causes neurologic symptoms, such as dementia, to manifest [35]. The results of the present study suggest the appearance of depressive symptoms may be associated with neurodegeneration as a result of brain iron accumulation by an overload of iron that is not effectively used for haematopoiesis. Iron excretion disorder among HD patients occurs when excess free iron within cell causes cellular injury. Therefore, serum ferritin levels and TSAT must be simultaneously controlled and kept at levels <100 ng/dL and  $\geq$ 20%, respectively. The involvement of iron in depressive symptoms needs further elucidation but understanding the pathophysiology of depressive symptoms could provide insight into the role of iron and help in the design of clinical iron management for HD patients.

There are some limitations in our study. The observed associations were obtained by using a cross-sectional design, which does not permit us to draw casual conclusions with confidence. Therefore, more prospective studies to determine whether depressive symptoms among HD patients are associated with iron status are needed. Depressive symptoms were estimated from using only the BDI-II; therefore, we could not eliminate the possibility of a multifaceted psychological impact on the score results. Using two or more different kinds of questionnaire for psychological testing is required to more thoroughly assess depressive symptoms. In addition, there is a need to conduct the psychiatric interviewer or depressive symptoms by a screening test or screening low cognitive function for the presence of clinical depression by a trained psychiatric interviewer. In this study, we did not consider the association between iron status and dietary habits; therefore, we cannot exclude the possibility that the observed associations had to do with dietary intake of iron. Iron status and dietary iron intake (e.g., iron-based phosphorus binders) should be considered in future investigation of associations between iron status and depressive symptoms among HD patients. Serum albumin levels and CRP, which are important indexes of biomarkers in HD patients, were not found to be associated with depressive symptoms in the present study. Several other studies have shown that lower serum albumin levels and higher CRP caused depressive symptoms [36–38]. However, further prospective trials may be required to examine the impact of nutritional and inflammation status upon depressive symptoms in HD patients and to determine whether serum albumin levels

and higher CRP are associated with depressive symptoms. This observational retrospective study allowed only limited conclusions. We could not prove cause-and-effect relationship between iron metabolism and the presence of depressive symptoms. Since serum ferritin is both an iron storage protein and an acute phase reactant, further prospective studies are needed for the comparisons of the clinical presentation of anemia and depressive symptoms. The several covariates used in multivariate analysis are not only directly influenced by response variables but are also affected by other covariates which often hinders analysis. In this study, we did not take into the consideration the patients' BMI, psychosocial dimensions, including economic status, family support, gender differences, reproductive age and menopausal, and some other emotional stresses related to depressive symptoms. Previous study reported that there was a significant difference in the levels of serum ferritin concentrations between genders in a Japanese population [39]. In future research, we need to consider and remove the effect of confounding the patient background factors such as diseases associated with depression such as history of stroke and other neurological conditions, bed bound patients, and even social conditions such as monthly income, family support.

## 5. Conclusion

In summary, we found higher serum ferritin levels were associated with the presence of depressive symptoms among patients undergoing HD. Because iron metabolism in HD patients may be associated with depressive symptoms, we believe that careful iron management is necessary in HD treatment. Our findings will be useful when considering adjustment of serum ferritin levels and TSAT for HD patients. In the clinical assessment of iron status, it must be kept in mind that inappropriate iron management of HD patients may be involved in the appearance of depressive symptoms.

## Disclosure Statement

All authors declare no competing financial interests.

## Statement of Ethics

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committees at which the studies were conducted (IRB approval number NCT03096626) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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## Author Contributions

YT designed the study. NS and YH analyzed and

interpreted the data. TN, TT, and YMM drafted the article and revised it. All authors participated in drafting the article or revising it critically for important intellectual content. All authors read and approved the final manuscript.

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