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Association Between the Distributions of Mean Corpuscular Hemoglobin and Red Blood Cell, and Mortality in a 3-Year Retrospective Study of Hemodialysis Patients

Yoshihiro Tsuji[1, *], Yasumasa Hitomi[2], Naoki Suzuki[2], Yuko Mizuno-Matsumoto[3], Toshiko Tokoro[4], Masato Nishimura[5]

[1]Department of Medical Engineering, Faculty of Health Sciences, Morinomiya University of Medical Sciences, Osaka, Japan

[2]Department of Clinical Engineering, Tojinkai Hospital, Kyoto, Japan

[3]Graduate School of Applied Informatics, University of Hyogo, Kobe, Japan

[4]Department of Nephrology, Tojinkai Satellite Clinic, Kyoto, Japan

[5]Cardiovascular Division, Tojinkai Satellite Clinic, Kyoto, Japan

Email address:
yoshihiro_tsuji@morinomiya-u.ac.jp (Y. Tsuji)
*Corresponding author

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Abstract: Introduction: A red blood cell (RBC) concentration of 300 to $350\times10^4/\mu L$ and mean corpuscular hemoglobin (MCH) concentration of 30 to 35 pg have been proposed as management target values from the relationship of Hb=RBC×MCH to control anemia, wherein Hb levels should not exceed 12 g/dL. In contrast, even in patients whose Hb levels are maintained at 10 to 12 g/dL, Hb levels are widely distributed when divided into RBC and MCH. Objective: We examined the prognosis in the distribution of MCH and RBC. Methods: Patients were classified into two groups based on MCH and RBC values, wherein patients with MCH≥30 pg but<35 pg and RBC≤$350\times10^4/\mu L$ (Group I, n=177); and MCH<30 pg and RBC>$350\times10^4/\mu L$ (Group II, n=217). Associations between all-cause mortality and the distributions of MCH and RBC as well as the iron profiles of these two groups were assessed by Kaplan-Meier curves and Cox proportional hazards regression model, respectively. Results: Patients with MCH<30 pg and RBC>$350\times10^4/\mu L$ (Group II, n=217) had an increased long-term risk of death and a higher rate of iron deficiency than patients with MCH≥30 pg but<35 pg and RBC≤$350\times10^4/\mu L$ (Group I, n=177). Conclusions: The management goal for renal anemia would be to control MCH within the range of 30−35 pg and RBC within the range of 300−$350\times10^4/\mu L$, and to avoid absolute iron deficiency.

Keywords: Anemia Management, Hemodialysis, Hemoglobin, Mean Corpuscular Hemoglobin, Red Blood Cell

1. Introduction

Anemia is common in patients receiving hemodialysis (HD) and is associated with poor clinical outcomes [1]. Therefore, erythropoietin-stimulating agents (ESA) and intravenous iron administration (therapy) have a key role in the clinical practice of anemia management among patients undergoing HD. The Guidelines for Renal Anemia in Chronic Kidney Disease of 2015 Japanese Society for Dialysis Therapy recommend administration when hemoglobin (Hb) levels≥10 g/dL but<12 g/dL in dialysis patients [2]. However, it does not specifically describe how to use the ESA and the iron agent to achieve these Hb levels. The setting of red blood cell (RBC) 300 to $350\times10^4/\mu L$ and mean corpuscular hemoglobin (MCH) 30 to 35 pg as management target values from the relationship of Hb=RBC × MCH as anemia control has been proposed, wherein Hb levels do not exceed 12 g/dL.

The Hb levels generally provide the value of RBC and iron status as MCH value is obtained by dividing the Hb by RBC

value. MCH depends on the size and concentration of erythrocytes. Thus, RBC and MCH values depend on dose of ESA and iron, respectively. Hb levels are represented by the product of the number of RBC and the average amount of MCH, which is one of the RBC constants. Specifically, since Hb=RBC × MCH, when Hb=10 or 12 g/dL, it is possible to draw a constant curve by applying this formula. Moreover, there is an upper limit on the number of hemoglobin that can be contained in a single RBC, and MCH does not exceed 35 pg in most patients. These results suggest that Hb levels can be stably maintained by controlling the RBC to 300 to $350 \times 10^4/\mu L$ by ESA and the MCH to 30 to 35 pg by iron supplementation. However, despite properly controlling Hb levels, the difference in prognosis, whether or not it falls within this range, remains unclear. Thus, even if Hb levels are adjusted in the range of 10-12 g/dL, RBC and MCH values are considered to vary. There are no reports on RBC values, MCH values, and prognosis; hence, recent reports on the prognostic impact of transferrin saturation (TSAT), which is thought to be related to MCH, were examined for possible effects of MCH on prognosis.

2. Methods

2.1. Ethical Considerations

The Ethics Committee for Human Research of Tojinkai Hospital approved this study. Informed consent was obtained from all individual participants included in the study. 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 NCT04227158) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

2.2. Patient and Study Measurements

We enrolled 437 patients (mean age, 71.0±12.2 years; women, 42%; mean duration of HD, 11.8±9.2 years) who were controlled with hemoglobin levels between≥10 g/dL and<12 g/dL and had undergone maintenance HD for>1 year at Tojinkai Hospital, Kyoto, Japan. We examined data from all individuals who underwent maintenance HD treatment three times weekly from 1 December 2015 to 31 December 2018. Patients were excluded if they had peritoneal dialysis combined with HD, did not have records of laboratory investigations during this period, or were transferred to another hospital or lost to follow-up.

We collected data regarding the demographic characteristics, patients' age, sex, dialysis duration, diabetes mellitus (DM) history, cardiovascular disease (CVD) history, height, dry weight (DW), body mass index (BMI), dialysis mode (HD of Online HDF), HD time, systolic and diastolic boiled pressure, HD dose (Kt/V$_{ure}$), erythropoietin resistance index (ERI) at baseline (1 December 2015), and geriatric nutritional risk index (GNRI). CVD included the presence of

ischemic heart disease, peripheral vascular disease, and cerebral vascular disease.

The DW was determined clinically and reflected the lowest weight that the patient could tolerate without intradialytic symptoms, hypotension, and overt fluid overload. The DW was continuously updated according to the medical doctors' changes in orders throughout the observation period. The BMI was calculated as the patient's DW divided by the square of the patient's height. The Kt/V$_{ure}$ was determined according to single-pool urea kinetics models [3]. ERI was calculated by dividing the total weekly erythropoietin dose by the patient's DW and patient's Hb level. The lower the result, the more sensitive is the response to recombinant human erythropoietin (rHuEPO). Conversely, a high ERI indicates relative resistance to rHuEPO erythropoietic effects [4]. The ideal body weight was calculated from the height and a BMI of 22 [5].

Biochemical parameters such as Hb levels, RBC, MCH, mean corpuscular volume (MCV), MCH concentration (MCHC), serum ferritin levels, TSAT, serum iron levels, total iron binding capacity (TIBC), unsaturated iron binding capacity (UIBC), serum albumin levels, blood urea nitrogen (BUN), serum creatinine levels (Cr), serum calcium levels, serum inorganic phosphorus levels, and high-sensitivity C-reactive protein (CRP) were obtained. Serum iron levels and CRP were measured using the Nitroso-PSAP method and the latex agglutination turbidimetry method, respectively. TSAT was calculated as serum iron divided by TIBC. Blood samples (4 mL) were obtained immediately before the HD session began for pre-HD measurements and at the end of the HD session for post-HD measurements on the first day of the week.

2.3. Statistical Analysis

All data are expressed as means and standard deviation (SD), or medians and interquartile range (IQR). Categorical variables were assessed with Fisher's exact probability test or Mann-Whitney's *U* test as appropriate. Firstly, the 394 patients were classified into two groups based on the values of MCH and RBC: patients with MCH≥30 pg but<35 pg and RBC≤350×10^4/μL (Group I, n=177); and MCH<30 pg and RBC>350×10^4/μL (Group II, n=217) to assess the mortality and the association between the distributions MCH and RBC. Secondly, among Groups I and II, patients were further divided into 4 subgroups based on TSAT and serum ferritin values to assess the iron status of patients. Here, we used cut-off values for serum ferritin levels and TSAT of 100 ng/mL and 20%, respectively. The four subgroups were as follows: Q1, serum ferritin levels ≥100 ng/dL, TSAT≥20%; Q2, serum ferritin levels<100 ng/dL, TSAT≥20%; Q3, serum ferritin levels<100 ng/dL, TSAT<20%; and Q4, serum ferritin levels≥100 ng/dL, TSAT<20%. Japanese guidelines for renal anemia in chronic kidney disease recommend administration of iron to patients with serum ferritin levels<100 ng/mL and with TSAT<20% [2]. These are the values that the guidelines of 2015 Japanese Society for Dialysis Therapy for treating anemia in CKD recommend that iron be administered to

patients [2]. Thirdly, patients were divided into two groups according to the presence or absence of iron deficiency, and MCH and RBC distribution were examined. Here, iron deficiency was defined as TSAT<20% with ferritin levels<100 ng/mL [2]. Finally, the correlation was investigated between TSAT and MCH, and TSAT and RBC in 384 patients. Pearson's product-moment correlation coefficient was used to study the relationship between TSAT and MCH, and TSAT and RBC.

Survival curves for 3-year survival, based on all available follow-up data, were constructed with the use of Kaplan–Meier estimates and compared between groups with use of the log-rank test, and used Holm's method as post hoc. Cox proportional hazards regression was used to examine predictors of the death in all patients, with patients' mean age, sex, dialysis duration, history of DM, history of CVD, BMI, serum albumin levels, CRP, and Kt/V_{ure}. The survival time for each patient was determined by the number of days from the start of this study to the end of the observation period or the date of the patient's death. The multicollinearity in the multivariable model was examined using regression diagnostic analysis. Furthermore, covariates were selected as those variables that might plausibly be associated with outcomes based on clinical precedent and evidence from the literature. p-values<0.05 indicated statistical significance. All statistical analyses were performed with R language (version 3.5.2).

3. Results

3.1. Baseline Characteristics in the Distribution According to MCH and RBC

Demographic, clinical, and biochemical characteristics categorized by the values of MCH and RBC of the study population are shown in Table 1. Among all patients, 177 with MCH≥30 pg but<35 pg and RBC≤350×10^4/μL (Group I); 217 patients with MCH<30 pg and RBC>350×10^4/μL (Group II). During the 3-year follow-up period, 25 patients (14%) in Group I and 58 patients (27%) in Group II died. Upon comparing Groups I and II, number of patients who survived, duration of survivals period, MCH, MCV, MCHC, serum ferritin levels, TSAT, and ERI were found to be significantly higher among participants in Group I than those among Group II (p=0.0028, p=0.0008, p<0.0001, p<0.0001, p<0.0001, p<0.0001, p=0.0023, p=0.0109, respectively). Hb levels, RBC, TIBC, and CRP were found to be significantly lower among participants in Group I than those among Group II (p<0.0001, p<0.0001, p=0.0263, p<0.0001, respectively). No differences were observed between Groups I and II regarding patients' age, sex, dialysis duration, with or without DM and CVD, mode (HD / On line HDF), HD time, systolic and diastolic blood pressure before HD, serum iron levels, UIBC, serum albumin levels, blood urea nitrogen, serum creatinine, serum calcium, serum inorganic phosphorus, Kt/V_{urea}, dose of ESAs IU/week, and GNRI (all, p>0.05).

3.2. Survival Curves in the Distribution According to MCH

Table 2 shows the results of Cox proportional hazard regression analysis. Data were adjusted for CRP selected as covariates to adjust all-cause death to avoid multicollinearity in the statistical analyses as CRP was associated with increased mortality (HR, 1.40; 95% CI, 1.22–1.62, p<0.0001).

Figure 1 shows the survival curves adjusted for significant predictors at Cox proportional hazard regression analysis. During the follow-up period, 25 patients (14%) in Group I and 58 patients (27%) in Group II died, and the average survival periods (SD) were 1069 (174) and 975 (286) days, respectively. Survival curves were obtained using the Kaplan-Meier estimation method and compared using a log-rank test to determine the difference in survival rates between Groups I and II. The survival time for each patient was determined by the number of days from the start of this study to the end of the observation period or the date of the patient's death. With a follow-up of 3 years, a significantly greater patient mortality with MCH<30 pg and RBC>350×10^4/μL (Group II) was observed (p=0.0014).
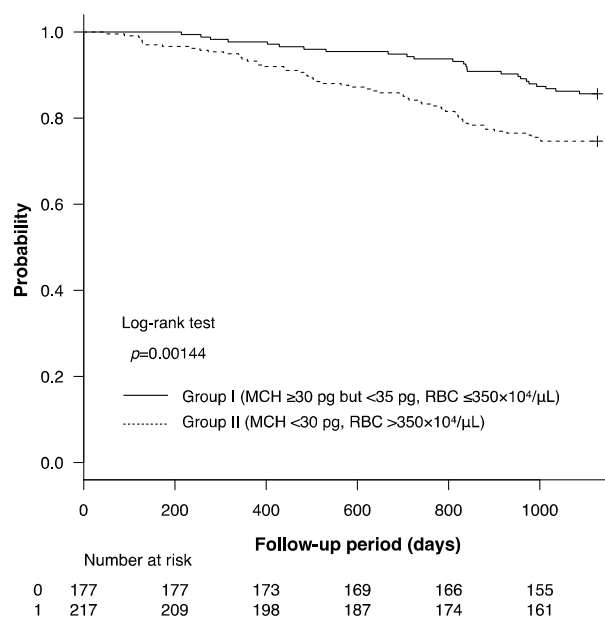

Figure 1. Survival curves according to the distribution of MCH and RBC during 3-year follow up periode.

Cox-adjusted survival during follow-up with regard to all-cause mortality in HD patients stratified by MCH and RBC values: Group I, MCH≥30 pg but<35 pg and RBC≤350×10^4/μ; Group II, MCH<30 pg and RBC>350×10^4/μL.

Table 3 shows the results of the distribution of group I (MCH≥30 pg but<35 pg and RBC≤350×10^4/μL) and II (MCH<30 pg and RBC>350×10^4/μL) according to serum ferritin levels and TSAT. Upon comparing both groups, the rate of TSAT≥20% and serum ferritin levels≥100 ng/mL were found to be significantly higher among participants in Group I than those among Group II (p<0.0001). The rate of

TSAT<20% and serum ferritin levels<100 ng/mL were significantly lower in Group I than in Group II ($p<0.0001$).
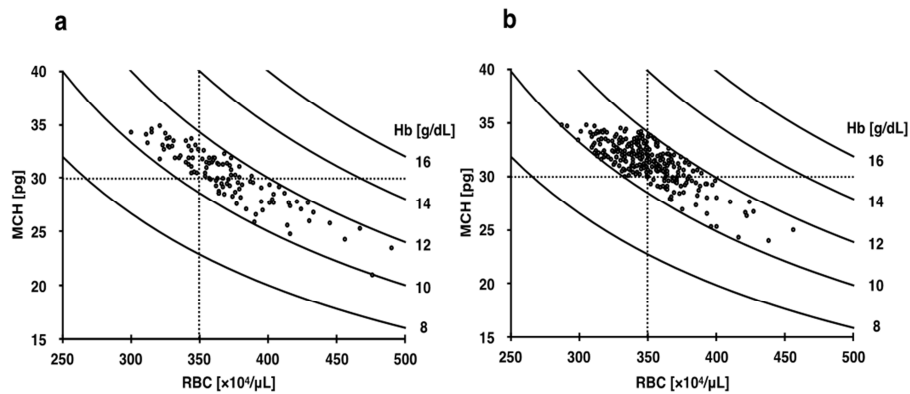

Figure 2. Distribution according to MCH and RBC in patients with or without iron deficiency.

Patients were categorized into two groups according to with or without iron deficiency as follows: (a), iron deficiency (+) group, n=109 (TSAT<20%, Ferritin<100 ng/mL); (b), iron deficiency (−) group, n=285 (TSAT≥20%, Ferritin≥100 ng/mL). Comparing the proportion of patients with RBC>$350×10^4$/μL and MCH<30 pg in the iron deficiency (+) group (n=48, [44%]) and iron deficiency (−) groups (n=61, [21%]), the proportion of patients with MCH<30 pg and RBC>$350×10^4$/μL in iron deficiency (+) group was significantly higher than in the iron deficiency (−) group
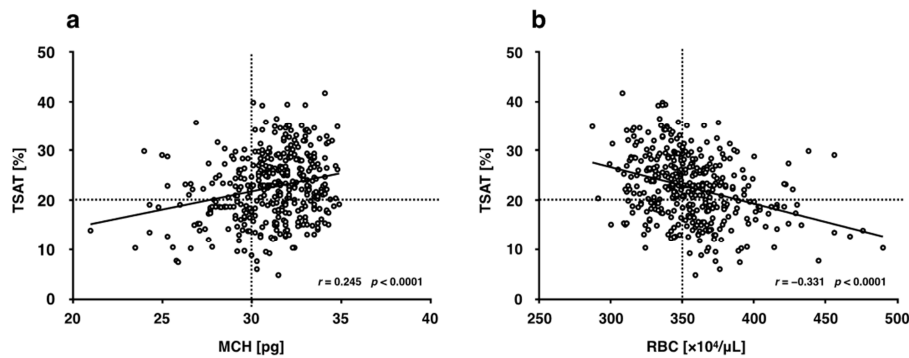

Figure 3. Correlation between TSAT and MCH (a), and between TSAT and RBC (b).

Pearson's product-moment correlation coefficient. A significant statistical positive correlation was observed between TSAT and MCH. Conversely, a significant statistical negative correlation was observed between TSAT and RBC. Pearson's correlation coefficient (r) and the corresponding *p* values for these correlation were r=0.245 and r=−0.331, and $p<0.0001$ in both cases.

Figure 2 shows the results of the distribution of MCH and RBC in two groups according to the presence or absence of iron deficiency. Of 394 patients, 109 (iron deficiency (+) group; TSAT<20% and serum ferritin levels<100 ng/mL) had iron deficiency, and 285 had no iron deficiency (iron deficiency (−); group; TSAT≥20% and serum ferritin levels≥100 ng/mL). Comparing the proportion of patients with RBC>$350×10^4$/μL and MCH<30 pg in the iron deficiency (+) group (n=48, [44%]) and iron deficiency (−) groups (n=61, [21%]), the proportion of patients with MCH<30 pg and RBC>$350×10^4$/μL in iron deficiency (+) group was significantly higher than in the iron deficiency (−) group ($p<0.0001$).

Table 1. Baseline and follow-up laboratory data of group according to the distribution of MCH and RBC.

Clinical variable	Group I (n=177)	Group II (n=217)	p-value
Age, years	71.9 (11.1)	70.5 (12.2)	0.246
Sex (man/woman)	100 / 77	134 / 83	0.304
Dialysis duration, years	11.1 (5.8−19.2)	9.8 (5.4−16.4)	0.213
Survival, n (%)	152 (86)	159 (73)	0.00275
Duration of survival period, day	1069 (174)	975 (286)	0.000871
Diabetes mellitus, n (%)	68 (38)	85 (39)	0.917
History of cardiovascular disease, n (%)	40 (22)	49 (23)	0.999
Dry weight, kg	54.2 (12.6)	53.2 (12.8)	0.989
Body mass index, kg/m²	21.3 (3.7)	21.5 (4.1)	0.493
Mode (HD/Online HDF)	162 / 15	203 / 14	0.447
Heamodialysis time, hr	4.4 (0.6)	4.3 (0.6)	0.378

Clinical variable	Group I (n=177)	Group II (n=217)	p-value
Systolic blood pressure before HD, mm Hg	140.2 (25.1)	147.3 (22.2)	0.0611
Diastolic blood pressure before HD, mm Hg	72.1 (15.8)	74.1 (15.1)	0.149
Hemoglobin levels, g/dl	10.8 (0.4)	11.1 (0.5)	<0.0001
Red blood cells, 104/μL	331.6 (13.3)	375.1 (25.1)	<0.0001
Mean corpuscular hemoglobin, pg	32.6 (1.2)	29.8 (2.1)	<0.0001
Mean corpuscular volume, fL	99.1 (92.2)	92.3 (5.3)	<0.0001
Mean corpuscular hemoglobin concentration,%	32.9 (0.9)	32.3 (1.0)	<0.0001
Serum ferritin levels, ng/dL	105.5 (66.3−164.3)	75.0 (32.2−121.0)	<0.0001
Serum iron levels, μg/dL	58.2 (23.2)	57.6 (25.1)	0.459
Transferrin saturation,%	25.6 (10.0)	22.8 (9.4)	0.0023
Total iron binding capacity, μg/dL	236.0 (49.2)	248.8 (51.3)	0.0263
Unsaturated iron binding capacity, μg/dL	177.9 (51.6)	191.2 (54.4)	0.0556
Serum albumin levels, g/dL	3.5 (0.4)	3.6 (0.4)	0.0707
Blood urea nitrogen, mg/dL	59.0 (15.3)	59.9 (14.3)	0.454
Serum creatinine, g/dL	9.5 (2.5)	9.6 (2.4)	0.421
Serum calcium, mg/dL	8.9 (0.7)	8.7 (0.6)	0.867
Serum inorganic phosphorus, mg/dL	4.8 (1.0)	4.8 (1.1)	0.555
Serum hs-CRP, mg/dl	0.32 (0.69)	0.54 (0.95)	<0.0001
Kt/Vurea	1.84 (0.36)	1.80 (0.33)	0.292
ESA, IU/week	1872 (450)	1933 (466)	0.187
Erythropoietin resistance index	4.9 (0.3−7.6)	4.1 (2.5−6.5)	0.0109
Geriatric nutritional risk index	91.1 (8.2)	92.2 (7.6)	0.18

Abbreviations: HD, hemodialysis; HDF, hemodiafiltration; hs-CRP, high-sensitivity C-reactive protein; ESA, erythropoiesis stimulating agent. Patients were divided into two groups: Group I, MCH≥30 pg and RBC≤350×10^4/μL; Group II, MCH<30 pg and RBC>350×10^4/μL.

Table 2. Cox hazard analysis for all-cause mortality.

Clinical variable	Hazard ratio (95% CI)	*p*–value
Mean age, yr	0.99 (0.98−1.02)	0.9873
Sex	1.01 (0.64−1.58)	0.9748
Dialysis duration, years	0.98 (0.95−1.01)	0.2657
Diabetes mellitus	0.79 (0.48−1.33)	0.3803
History of cardiovascular disease	0.77 (0.43−1.36)	0.3658
Body mass index, kg/m^2	0.92 (0.81−1.04)	0.1767
Serum albumin concentration, g/dL	0.21 (0.04−1.16)	0.0729
Serum hs-CRP, mg/dL	1.40 (1.21−1.62)	<0.0001
Kt/V$_{ure}$	1.24 (0.62−2.45)	0.5449

Abbreviations: hs-CRP, high-sensitivity C-reactive protein; CI, confidence interval.

4. Discussion

We assessed the association between the distributions of MCH and RBC in a 3-year mortality period among hemodialysis patients retrospectively. We divided the patients into two groups based on the MCH and RBC values; patients with MCH≥30 pg but<35 pg and RBC≤350×10^4/μL (Group I, n=177), and patients with MCH<30 pg and RBC>350×10^4/μL (Group II, n=217). In this study, the primary finding from this study is that MCH<30 pg and RBC >350×10^4/μL in patients on regular thrice weekly HD treatment is associated with an increased long-term risk of the death (Figure 1). The secondary findings were that as a result of comparing the iron profiles of these two groups, the percentage of patients with high iron-deficiency in group II was significantly higher than that in group I. These results suggested that iron was deficient in group II (Figure 2). The proportion of patients with MCH<30 pg and RBC >350×10^4/μL was significantly higher in patients with absolute iron deficiency than in patients without absolute iron deficiency. This result suggests that absolute iron deficiency is more common in patients with high RBCs.

Table 3. Distribution of Group I and II according to serum ferritin levels and TSAT.

Category	Group I (n=177)	Group II (n=217)	*p*-value
Q1 (TSAT≥20% and Ferritin≥100 ng/mL)	50 (28%)	25 (11%)	*p*<0.0001
Q2 (TSAT≥20% and Ferritin<100 ng/mL)	32 (18%)	56 (26%)	0.3721
Q3 (TSAT<20% and Ferritin<100 ng/mL)	9 (5%)	46 (21%)	*p*<0.0001
Q4 (TSAT<20% and Ferritin≥100 ng/mL)	86 (49%)	90 (42%)	0.01899

Abbreviations: hs-CRP, high-sensitivity C-reactive protein; CI, confidence interval.

Regarding the relationship between TSAT, which is one of   the iron metabolism markers, and mortality, it has been

reported that the prognosis is good in the case of TSAT is 20-40%, and the prognosis is poor in the case of TSAT is 20% or less. Hayashi et al. reported that patients with low TSAT had high cardiothoracic ratio (CTR) [6. Hayashi T,]. That high CTR was poor prognosis has been reported in the MBD-5D study and the Q-cohort study [7, 8]. Regarding TSAT, it is reported that the prognosis is the best when the TSAT value is 20 to 40%, and the prognosis is poor in case of TSAT≤20%. [9. Koo HM]. Although there is no report on the prognosis of MCH, it is speculated that setting MCH to 30 pg or more is not wrong from the viewpoint of prognosis, considering that MCH correlates with TSAT.

According to the report of Hatamizadeh et al., the prognosis with TSAT 30-40% was best regardless of the presence or absence of polycystic kidney disease (PKD), and the prognosis with TSAT≤20% was poor. Moreover, they reported that the hazard ratio was lower for serum ferritin levels 100-800 ng/mL than for less than 100 ng/mL with U-curve. [10]. Although it is based on US data, iron deficiency should not be neglected. For RBC>350×10^4/μL or higher, MCH is low, and because there are many patients with absolute iron deficiency, RBC is 350×10^4/μL or less, MCH is 30 pg or more, TSAT is at least 20% or more, and ferritin is 100 ng/mL or less. Instead, the management goal is to avoid absolute iron deficiency. [11]. Assuming that the width of TSAT is 20-40%, it can be seen from Figure 3 that quite a few patients with MCH of 30 pg or more and TSAT 20-40%. If TSAT is 20 to 40%, the regression equation of MCH and TSAT is within this range, and it seems that the fit of MCH 30 pg or more is better. Meanwhile, hyperferritinemia is reportedly a risk factor for poor prognosis and generally has the best prognosis in patients with ferritin levels<100 ng / mL [12].

Iron plays an important role in energy metabolism, and iron deficiency has been reported to increase FGF-23 and cause left ventricular hypertrophy [8]. Red cell distribution width (RDW) increase was found to be an independent risk factor for prognosis [13, 14]. Furthermore, RDW increased in iron deficiency and RDW decreased after oral administration of ferric citrate [15]. These results suggest that the poor prognosis in the high RBC group may be due to iron deficiency.

TSAT is a value obtained by dividing the serum iron levels by TIBC, and the TSAT decreases when the serum iron levels are low. MCH reflects the amount of iron used during the period corresponding to RBC life, and MCH is reduced if iron is not fully utilized due to iron deficiency. Therefore, TSAT and MCH are considered to show a positive correlation; in fact, our results showed a significant positive correlation (Figure 3). TSAT 20-40%, which has a good prognosis in the literature, generally matched MCH 30-35 pg. The Hb levels generally provide the value of RBC and iron status because MCH is derived from the Hb divided by RBC. MCH depends on the size and concentration of erythrocytes. Thus, RBC and MCH values depend on ESA and iron doses, respectively. Hb is expressed as the product of RBC and MCH, and the upper limit of MCH is approximately 35 pg. Therefore, if RBC is reduced to approximately 350×10^4/μL or less, even if MCH

increases to 35 pg by iron administration, theoretically, Hb levels do not exceed 12 g/dL. To prevent Hb levels from falling below 10 g/dL, at least RBC must be 300×10^4/μL or more, or MCH must be 30 pg or more. When MCH rises to a maximum of 35 pg due to iron supplementation, Hb levels theoretically does not exceed 12 g/dL at RBC less than 350×10^4/μL; however, when RBC exceeds 350×10^4/μL, the more RBC, the more Hb levels tends to exceed 12 g/dL. If RBC and MCH are adjusted with ESAs and iron, respectively, the management target values are RBC $300-350\times10^4$/μL for ESA and MCH 30 to 35 pg for iron. If RBC is less than 300×10^4/μL, increase ESA, and if RBC is more than 350×10^4/μL, decrease ESA. When MCH is low, it becomes an index of iron deficiency anemia, and when MCH is less than 30 pg, supplementation with iron can be used to maintain Hb levels 10-12 g/dL recommended by the Japanese guidelines for renal anemia in chronic kidney disease. As there have been no reports on the prognosis of MCH and RBC distribution, the study therefore significantly contributes to the lack in the literature. Further, it would be of great interest to the readership as the novel findings provide valuable guiding information for clinical practice and even basis for future researches.

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 the mortality among HD patients are associated with MCH and RBC status are needed. 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 and anemia status among HD patients. This observational retrospective study allowed only limited conclusions. Hence, we could not establish a cause-and-effect relationship between iron metabolism and anemia. 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 serum ferritin. The several covariates used in multivariate analysis are not only directly influenced by response variables but are also affected by other covariates which often hinder analysis. In this study, we did not take into the consideration the patients' BMI, psychosocial dimensions, such as economic status, family support, gender differences, reproductive age and menopause, 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 [16]. In future research, the effect of confounding the patient background factors such as diseases associated with depression, history of stroke and other neurological conditions, bed bound patients, and even social conditions such as monthly income and family support should be disregarded.

5. Conclusion

The condition to satisfy Hb levels 12 g/dL could be fulfilled by a variety of combinations of MCH and RBC. This study indicates that maintaining RBC 300-350×10^4/μL and MCH 30 to 35 pg may not only achieve Hb level management not exceeding 12 g/dL, but also have a positive impact on prognosis.

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 NCT04227158) 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 YM 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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