RESEARCH ARTICLE

Association of the erythropoiesis-stimulating agent resistance index and the geriatric nutritional risk index with cardiovascular mortality in maintenance hemodialysis patients

Takahiro Yajima1*, Kumiko Yajima2, Hiroshi Takahashi3

1 Department of Nephrology, Matsunami General Hospital, Gifu, Japan, 2 Department of Internal Medicine, Matsunami General Hospital, Gifu, Japan, 3 Division of Medical Statistics, Fujita Health University School of Medicine, Aichi, Japan

* yajima5639@gmail.com

Abstract

Objective

Hyporesponsiveness to erythropoiesis-stimulating agent (ESA) may be associated with protein-energy wasting. We investigated the relationship of the ESA resistance index (ERI) and the geriatric nutritional risk index (GNRI) for cardiovascular mortality in hemodialysis (HD) patients.

Methods

A total of 180 maintenance HD patients were enrolled. The patients were stratified by the GNRI of 91.2, a previously reported cut-off value, and the ERI of 13.7 (IU/week/kg/g/dL), a cut-off value for predicting cardiovascular-specific mortality, and they were classified into four groups (group 1[G1]: higher GNRI and lower ERI, G2: higher GNRI and higher ERI, G3: lower GNRI and lower ERI, G4: lower GNRI and higher ERI).

Results

The ERI was independently associated with the GNRI (β = −0.271, p = 0.0005). During a median follow-up of 4.6 years, higher ERI and lower GNRI were independently associated with cardiovascular mortality, respectively (adjusted hazard ratio [aHR], 3.10; 95% confidence interval [CI], 1.31–7.34, and aHR, 6.64; 95%CI, 2.60–16.93, respectively). The 7-year survival rates were 96.1%, 70.3%, 77.3%, and 50.1% in G1, G2, G3, and G4, respectively. The aHR values for G4 versus G1 were 12.63 (95%CI, 3.58–44.59). With regards to model discrimination, adding the GNRI alone, the ERI alone, and both to the traditional risk model significantly improved the net reclassification improvement by 0.421, 0.662, and 0.671, respectively. Similar results were obtained for all-cause mortality.
**Conclusion**

The ERI was independently associated with the GNRI, and could predict cardiovascular mortality in HD patients. Moreover, the combination of GNRI and ERI could improve the predictability for cardiovascular mortality.

**Introduction**

Renal anemia, which is caused by decreased erythropoietin production due to kidney injury, is common among patients undergoing hemodialysis (HD), and is treated with erythropoiesis-stimulating agents (ESAs). It has been shown that HD patients who receive a high dose of ESAs relative to the hemoglobin (Hb) response experience poor outcomes, including increased risk of cardiovascular events or mortality[1–3]. It is not yet known whether these risks are caused by ESAs themselves, or underlying processes leading to increased ESA requirements. ESA hyporesponsiveness, or resistance, is generally defined as the requirement of higher than average doses of ESA to achieve an increase in Hb concentration[3–5]. The ESA resistance index (ERI) has been proposed as an indicator for ESA hyporesponsiveness, and some previous studies have shown that the ERI can predict all-cause mortality and/or cardiovascular events[6–8]. However, the associations between the ERI and cardiovascular mortality remain unclear.

The mechanisms of ESA hyporesponsiveness are not fully understood, but are likely to be multifactorial, relating to iron deficiency, inflammation, and malnutrition[9]. Recently, some studies have speculated that ESA hyporesponsiveness may be related to protein-energy wasting (PEW), a form of malnutrition characterized by loss of body protein and fuel reserves due to catabolic inflammation[10,11]. Okazaki et al. recently reported that high ERI and low geriatric nutritional risk index (GNRI) were associated with an increased risk of all-cause mortality in HD patients[12]. The GNRI can be used to classify patients according to a risk of complications in relation to conditions associated with PEW[13,14], and is also known to be an effective tool to identify those with malnutrition-related risks of all-cause and cardiovascular mortality in this population[15–17].

We investigated the associations of the ERI and the GNRI with cardiovascular and all-cause mortality in maintenance HD patients. In addition, we evaluated the combined predictability of the ERI and the GNRI for mortality in this population.

**Materials and methods**

**Study participants**

We conducted a retrospective cohort study of patients who had undergone maintenance hemodialysis therapy for at least 6 months. Patients who were treated with epoetin beta or darbepoetin alfa, but not with epoetin beta pegol for renal anemia were included. The study was performed using the medical records of the outpatient clinic of Matsunami General Hospital (Kasamatsu, Japan) between January 2008 and March 2020. Patients’ data were fully anonymized prior to access, and as such, the requirement for informed consent was waived. This study adhered to the principles of the Declaration of Helsinki, and the study protocol was approved by the Ethics Committee of Matsunami General Hospital (No. 459).

**Data collection**

The following patient data were collected from medical records: Age; sex; underlying kidney disease; duration of hemodialysis; history of alcohol, smoking, diabetes, hypertension, and
cardiovascular disease (CVD); dry weight; and height. CVD was defined as heart failure, angina pectoris, myocardial infarction, stroke, and peripheral artery disease. Diabetes was defined as a history or presence of diabetes, or prescription of glucose-lowering agents. Hypertension was defined as systolic blood pressure $\geq$ 140 mmHg and/or diastolic blood pressure $\geq$ 90 mmHg before hemodialysis, and/or prescription of anti-hypertensive drugs. Blood samples were collected in the supine position before hemodialysis sessions, which were conducted on either a Monday or a Tuesday. For the assessment of ESA responsiveness, the ERI was calculated by dividing the weekly weight-adjusted ESA dose (IU/week/kg) by the Hb concentration (g/dL)\[^6\]. The darbepoetin alfa dose was harmonized with erythropoietin data by multiplying by 200\[^18,19\]. The GNRI was calculated as follows: GNRI = (14.89 $\times$ albumin g/dL) + \([41.7 \times (\text{dry weight/ideal body weight})]^[13]\). When the dry weight exceeded the ideal body weight, the “(dry weight/ideal body weight)” element was set to 1.

**Follow-up study**

The primary endpoint was CVD mortality, and the secondary endpoint was all-cause mortality. Patients were divided by each cut-off point of ERI and GNRI; thereafter, patients were divided into four groups based on the combinations of each cut-off point of ERI and GNRI: Group 1 (G1), higher GNRI and lower ERI; G2, higher GNRI and higher ERI; G3, lower GNRI and lower ERI; and G4, lower GNRI and higher ERI. The patients were followed up until March 2020.

**Statistical analysis**

Normally distributed variables are expressed as means ± standard deviations, and non-normally distributed variables are expressed as medians and interquartile ranges. The differences among the four subgroups divided by the GNRI and the ERI were compared by one-way analysis of variance or the Kruskal-Wallis test for continuous variables, or by the chi-squared test for categorical variables. Univariate regression analysis was performed to determine factors correlated with the ERI. Multivariate regression analysis was performed with the factors that were significantly associated with the ERI in the univariate analysis.

A cut-off value of GNRI 91.2 was used; this value was defined from a previous study\[^13\]. Receiver operating characteristic (ROC) analysis was used to determine a cut-off value of the ERI to maximize the predictive value for cardiovascular-specific mortality. The Kaplan-Meier method was used to estimate the survival rate, and the difference was analyzed using the log-rank test. Hazard ratios (HRs) and 95% confidence intervals (CIs) for cardiovascular and all-cause mortality were calculated by Cox proportional hazard regression analysis. The multiple regression model included all covariates that were significant at p < 0.05 in the univariate analysis.

The C-index, net reclassification improvement (NRI), and integrated discrimination improvement (IDI) were calculated in order to assess whether the accuracy of predicting mortality improved after adding the GNRI and/or the ERI to the baseline model. The C-index was defined as the area under the receiver operating characteristic curve between individual predictive probabilities for mortality and the incidence of mortality. The C-index was compared between the baseline model, with all established risk factors, and the enriched model, including the GNRI and/or the ERI\[^20\]. The NRI was used as a relative indicator of the number of patients for whom the predicted mortality risk improved, and the IDI was used to show the average improvement in predicted mortality risk after adding the new variables to the baseline model\[^21\]. All statistical analyses were performed using IBM SPSS Version 21 (IBM Corp., Armonk, NY, USA). A p-value < 0.05 was considered statistically significant.
Results

Baseline characteristics

The baseline characteristics of the included patients are shown in Table 1. A total of 180 HD patients were included (age, 63.4 ± 13.9 years; male, 68.3%; HD duration, 0.6 [0.5–4.5] years; history of CVD, 67.8%). Hemoglobin, ferritin, transferrin saturation (TSAT), ESA dose, ERI, and GNRI levels were 10.7 ± 1.3 g/dL, 110 (49–201) ng/mL, 26.1 ± 12.7%, 4500 (4000–9000) IU/week, 8.7 (5.2–14.9) IU/week/kg/g/dL, and 94.5 ± 6.9, respectively. Univariate regression analysis showed that the ERI was significantly correlated with age ($\beta = 0.254$, $p = 0.0006$),
creatinine ($\beta = -0.174, p = 0.020$), TSAT ($\beta = -0.326, p < 0.0001$), and the GNRI ($\beta = -0.349, p < 0.0001$). Multivariate regression analysis, following adjustment for all significant founders in univariate analysis, revealed that the ERI was independently correlated with TSAT ($\beta = -0.289, p < 0.0001$) and the GNRI ($\beta = -0.271, p = 0.0005$) (Table 2).

**Associations of the GNRI and ERI with CVD mortality**

A total of 63 patients died during the follow-up period (4.6 [2.5–8.2] years), including 28 (44.4%) due to CVD-specific causes (14 heart failures, 7 sudden cardiac deaths or fatal arrhythmias, 4 strokes, and 3 myocardial infarctions), and 35 due to non-CVD-specific causes (25 infections, 7 malignancies, and 3 others).

In the multivariate Cox proportional hazards analysis adjusted by age, history of cardiovascular disease, creatinine, and C-reactive protein (CRP), which were significant in the univariate analysis, the GNRI (continuous) (HR = 0.87 [0.82–0.92], $p < 0.0001$) and ERI (continuous) (HR = 1.09 [1.05–1.13], $p < 0.0001$) were significantly associated with lower cardiovascular mortality. Lower GNRI (HR = 4.52 [2.10–9.73], $p < 0.0001$) and higher ERI (HR = 8.19 [3.58–18.74], $p < 0.0001$) were associated with higher cardiovascular mortality. Similar associations were observed for all-cause mortality (Table 3).

### Table 2. Univariate and multivariate regression analysis of the associations between the erythropoiesis-stimulating agent resistance index and baseline variables.

| Variables   | Univariate | Multivariate |
|-------------|------------|--------------|
|             | $\beta$    | $p$-value    | $\beta$    | $p$-value    |
| Age         | 0.254      | 0.0006       | 0.054      | 0.53         |
| Creatinine  | -0.174     | 0.020        | -0.069     | 0.38         |
| TSAT        | -0.326     | < 0.0001     | -0.289     | < 0.0001     |
| GNRI        | -0.349     | < 0.0001     | -0.271     | 0.0005       |

**Abbreviations:** TSAT: Transferrin saturation, GNRI: Geriatric nutritional risk index.

https://doi.org/10.1371/journal.pone.0245625.t002

### Table 3. Cox proportional hazards analysis of the erythropoiesis-stimulating agent resistance index and the geriatric nutritional risk index for mortality.

| Variables         | Non-adjusted | $p$-value | Adjusted | $p$-value |
|-------------------|--------------|-----------|----------|-----------|
| Cardiovascular    | HR (95%CI)   |           | HR (95%CI)|           |
| GNRI (continuous) | 0.87 (0.82–0.92) | < 0.0001 | 0.90 (0.84–0.96) | 0.0020 |
| ERI (continuous)  | 1.09 (1.05–1.13) | < 0.0001 | 1.07 (1.02–1.11) | 0.0050 |
| Lower GNRI        | 4.52 (2.10–9.73) | 0.0001 | 3.10 (1.31–7.34) | 0.0099 |
| Higher ERI        | 8.19 (3.58–18.74) | < 0.0001 | 6.64 (2.60–16.93) | < 0.0001 |
| Cross-classified (vs. G1) | < 0.0001 | < 0.0001 |< 0.0001 |
| G2                | 6.77 (1.85–24.76) | 0.0039 | 6.70 (1.60–28.16) | 0.0094 |
| G3                | 8.62 (2.94–25.30) | < 0.0001 | 9.58 (2.83–32.45) | 0.0003 |
| G4                | 13.75 (4.74–39.88) | < 0.0001 | 12.63 (3.58–44.59) | < 0.0001 |
| All-cause mortality |                      |           |          |           |
| GNRI (continuous) | 0.88 (0.85–0.91) | < 0.0001 | 0.92 (0.88–0.96) | 0.00012 |
| ERI (continuous)  | 1.08 (1.05–1.10) | < 0.0001 | 1.06 (1.03–1.08) | 0.00019 |
| Lower GNRI        | 5.14 (3.09–8.56) | < 0.0001 | 3.36 (1.92–5.87) | < 0.0001 |
| Higher ERI        | 3.38 (2.01–5.70) | < 0.0001 | 2.49 (1.42–4.37) | 0.0015 |
| Cross-classified (vs. G1) | < 0.0001 | < 0.0001 | < 0.0001 |
| G2                | 6.05 (2.85–12.86) | < 0.0001 | 4.33 (1.93–9.72) | 0.0004 |
| G3                | 3.55 (1.70–7.44) | 0.0008 | 2.91 (1.34–6.32) | 0.0071 |
| G4                | 9.18 (4.73–17.82) | < 0.0001 | 5.87 (2.81–12.24) | < 0.0001 |

**Abbreviations:** ERI: Erythropoiesis-stimulating agent resistance index, GNRI: Geriatric nutritional risk index.

* Adjusted for age, history of cardiovascular disease, creatinine, and C-reactive protein, which were significant in the univariate analysis.

https://doi.org/10.1371/journal.pone.0245625.t003
univariate analysis, the GNRI and ERI were significant predictors for CVD mortality (HR, 0.87; 95%CI, 0.82–0.92, and HR, 1.09; 95%CI, 1.05–1.13, respectively) (Table 3). ROC analysis was performed to obtain the optimal cut-off values of the ERI for predicting the risk of CVD mortality. The cut-off value of the ERI was 13.7 IU/week/kg/g/dL (AUC = 0.655, p = 0.025). First, patients were divided by the GNRI of 91.2 into low and high groups, in which the 7-year CVD survival rates were 60.1% and 91.6%, respectively (p < 0.0001) (Fig 1A). Second, patients were then divided by the ERI of 13.7 IU/week/kg/g/dL into low and high groups, in which the 7-year CVD survival rates were 91.8% and 65.2%, respectively (p < 0.0001) (Fig 1B). Third, the patients were divided by each cut-off point of the GNRI and ERI into G1, G2, G3, and G4 groups, in which the 7-year CVD survival rates were 96.1%, 70.3%, 77.3%, and 50.1% (Fig 1C).

Multivariate Cox proportional hazards analysis was performed after adjusting for age, history of CVD, creatinine, and CRP, which were significant in the univariate analysis. The adjusted HR (aHR) values for CVD mortality were 3.10 (95%CI, 1.31–7.34, p = 0.0099) for lower GNRI, and 6.64 (95%CI, 2.60–16.93, p < 0.0001) for higher ERI. Moreover, the aHR values were 6.70 (95%CI, 1.60–28.16, p = 0.0094) for G2 vs G1, 9.58 (95%CI, 2.83–32.45, p = 0.0003) for G3 vs G1, and 12.63 (95%CI, 3.58–44.59, p < 0.0001) for G4 vs G1 (Table 3). Similar results were obtained for all-cause mortality (Table 3, Fig 1D–1F).

With regards to the model discrimination, the C-index for CVD mortality was greater in the model adding the GNRI alone (0.708, p = 0.83), the ERI alone (0.747, p = 0.28), and both variables (0.753, p = 0.26) compared to the traditional risk model (0.708), but did not reach
statistical significance. However, The NRI and IDI values for CVD mortality improved by adding the GNRI alone (0.421 [p = 0.020] and 0.011 [p = 0.093], respectively), the ERI alone (0.662 [p = 0.00065] and 0.041 [p = 0.025], respectively), and both variables (0.671 [p = 0.00055] and 0.041 [p = 0.0097], respectively) to the traditional risk model (Table 4). Similar results were obtained for all-cause mortality (Table 4).

Discussion

The results of the present study showed that the ERI was negatively and independently associated with the GNRI, and could predict CVD and all-cause mortality in patients undergoing maintenance HD. Moreover, the combination of the ERI and the GNRI could not only stratify the risk, but also improve the predictability for mortality. Therefore, both the ERI and the GNRI should be evaluated to more accurately predict CVD mortality in this population.

The most common causes of ESA hyporesponsiveness are iron deficiency, either absolute or functional, inflammation, and malnutrition[9]. Absolute iron deficiency may be due to external blood losses through the extracorporeal blood circuit or dialyzers, and/or exhaustion of iron stores due to an increase in erythropoiesis caused by ESA treatment. In this situation, iron administration to maintain adequate iron stores is required for reducing the ESA dose and for enhancing ESA efficacy. However, some clinical trials have shown that iron administration to ESRD patients is associated with increased risks of infection, CVD, hospitalization, and mortality[22–24]. Functional iron deficiency is a condition in which iron utilization is defective in the bone marrow due to chronic inflammation despite sufficient iron stores. Malnutrition is closely related to inflammation and atherosclerosis[25], and through common mediators such as IL-6 or TNF-α, it may play a relevant role in ESA hyporesponsiveness[26].

On the other hand, PEW is a state of malnutrition, which is frequently complicated with chronic kidney disease, and is associated with an increased risk of mortality[27–29]. Some previous studies have reported that a loss of muscle mass and fat mass in the presence of inflammation leads to an increased risk of CVD mortality by promoting vascular endothelial damage[28–32]. As an indicator of PEW, the GNRI, a simple and objective method for evaluating nutritional status, is well-known in HD patients. Bouillanne et al. firstly reported that the GNRI was a prognostic indicator of morbidity and mortality in elderly hospitalized patients at nutritional risk[33]. Yamada et al. reported that the GNRI was the most reliable screening tool

### Table 4. Predictive accuracy of the erythropoiesis-stimulating agent resistance index and the geriatric nutritional risk index for mortality.

| Variables            | C-index                        | p-value | NRI            | p-value | IDI            | p-value |
|----------------------|--------------------------------|---------|----------------|---------|----------------|---------|
| Cardiovascular mortality | 0.704 (0.589–0.820) | Ref. | 0.421 (0.020) | 0.011 (0.093) | 0.041 (0.025) | 0.0097 |
| Traditional risk factors* | 0.722 (0.645–0.799) | Ref. | 0.574 (0.0012) | 0.051 (0.0016) | 0.021 (0.043) | 0.0001 |
| + GNRI | 0.744 (0.667–0.820) | 0.37 | 0.0084 | 0.021 | 0.043 | 0.0001 |
| + ERI | 0.729 (0.653–0.805) | 0.70 | 0.0084 | 0.021 | 0.043 | 0.0001 |
| + GNRI and ERI | 0.767 (0.693–0.841) | 0.11 | 0.713 | <0.0001 | 0.072 | 0.0001 |
| All-cause mortality | 0.722 (0.645–0.799) | Ref. | 0.574 (0.0012) | 0.051 (0.0016) | 0.021 (0.043) | 0.0001 |
| Traditional risk factors* | 0.722 (0.645–0.799) | Ref. | 0.574 (0.0012) | 0.051 (0.0016) | 0.021 (0.043) | 0.0001 |
| + GNRI | 0.744 (0.667–0.820) | 0.37 | 0.0084 | 0.021 | 0.043 | 0.0001 |
| + ERI | 0.729 (0.653–0.805) | 0.70 | 0.0084 | 0.021 | 0.043 | 0.0001 |
| + GNRI and ERI | 0.767 (0.693–0.841) | 0.11 | 0.713 | <0.0001 | 0.072 | 0.0001 |

**Abbreviations**: ERI: Erythropoiesis-stimulating agent resistance index, GNRI: Geriatric nutritional risk index.

* Traditional risk factors include age, history of cardiovascular disease, creatinine, and C-reactive protein.

https://doi.org/10.1371/journal.pone.0245625.t004
for predicting malnutrition compared with other simple nutritional screening tools in maintenance hemodialysis patients[13]. They also determined the cutoff value of 91.2 for GNRI with the use of MIS as the standard reference, in this population[13]. Thereafter, many studies showed that the GNRI is a useful tool for stratifying malnourishment risks[14] and identifying nutrition-related risks of CVD events and all-cause or CVD mortality in HD patients [15,16,34]. A meta-analysis conducted by Xiong et al. also concluded that the GNRI is a significant indicator for predicting both all-cause and CVD mortality in patients undergoing HD [17]. Furthermore, we have recently reported that the ratio of extracellular fluid to intracellular fluid measured by bio-impedance analysis, a new marker of PEW, predicted not only all-cause, but also CVD mortality in patients undergoing HD[35]. Moreover, we have also revealed that the combining the ratio of extracellular fluid to intracellular fluid with the GNRI could improve predictability for mortality[35].

Several recent studies have reported the possible association between ESA hyporesponsiveness and PEW. Rattanasompattikul et al. have reported that the ERI was independently correlated with malnutritional-inflammation score, a comprehensive scoring system of nutrition in maintenance HD patients, and that the score was worse in the 4th quartile of ERI compared to the 1st quartile[10]. Furthermore, González-Ortiz et al. recently reported that HD patients with PEW, which was classified by malnutritional-inflammation score, have increased risks for the poorer response to ESA therapy than those without PEW[11]. In this study, the ERI was negatively, independently associated with GNRI, a marker of PEW; therefore, our findings supported that the ERI may be a plausible indicator of PEW.

In this study, higher ERI and lower GNRI were independently associated with CVD and all-cause mortality, respectively. Many observational studies have shown that the GNRI predicts all-cause and CVD mortality[15–17]. Although the associations between the ERI and all-cause mortality and CVD events has been already reported[6–8], the relationship between the ERI and CVD mortality remains unknown. Therefore, for the first time, we show that the ERI was a significant predictor for CVD mortality in HD patients. In the present study, the proportion of patients with a history of previous CVD was relatively high, and the study follow-up period was relatively long; thus, it was possible to determine the association between the ERI and CVD mortality. More interestingly, combining the ERI with the GNRI could stratify the risk of CVD mortality and improve the predictability. Therefore, both the ERI and the GNRI should be simultaneously evaluated in HD patients.

There were several limitations to this study. First, the present study was a single-center retrospective study with a relatively small number of participants. Second, patients with renal anemia who were treated with epoetin beta or darbepoetin alfa, but not with epoetin beta pegol were included. Since darbepoetin alfa but not epoetin beta pegol can be converted to the ESA dose of epoetin beta, our results might not be applicable to all patients in whom renal anemia is treated with ESAs. Third, the use of only baseline ERI and GNRI for data analysis was not allowed to consider any changes of these indicators during the follow-up periods. In addition, the changes of dialysis dose, nutritional status, and iron status markers might help to clarify the potential causes of a linked change of ERI, therefore future study may be needed to reveal these associations. Fourth, this study only included Japanese patients, and as such, our findings might not be representative of maintenance HD patients in other countries. Therefore, a further large-scale multicenter study may be needed to validate our results.

In conclusion, the ERI was independently associated with the GNRI and could predict CVD, as well as all-cause mortality in patients undergoing HD. Moreover, combining the ERI and the GNRI could not only stratify the risk of CVD and all-cause mortality, but could also improve the predictability for mortality. Therefore, both the ERI and the GNRI should be evaluated to more accurately predict CVD and all-cause mortality in this population.
Supporting information

S1 Data.
(XLSX)

Author Contributions

Conceptualization: Takahiro Yajima, Kumiko Yajima, Hiroshi Takahashi.

Data curation: Takahiro Yajima, Hiroshi Takahashi.

Formal analysis: Takahiro Yajima.

Investigation: Takahiro Yajima, Kumiko Yajima, Hiroshi Takahashi.

Methodology: Takahiro Yajima, Kumiko Yajima.

Project administration: Takahiro Yajima, Kumiko Yajima, Hiroshi Takahashi.

Supervision: Hiroshi Takahashi.

Validation: Takahiro Yajima, Hiroshi Takahashi.

Writing – original draft: Takahiro Yajima.

Writing – review & editing: Takahiro Yajima.

References

1. Kilpatrick R.D, Critchlow C.W, Fishbane S, et al. Greater epoetin alfa responsiveness is associated with improved survival in hemodialysis patients. *Clin. J. Am. Soc. Nephrol.* 2008; 3:1077–1083. https://doi.org/10.1053/j.ajkd.2004.08.042 PMID: 15696453

2. Kausz A.T, Solid C, Pereira B.J, Collins A.J, St Peter W. Intractable anemia among hemodialysis patients: a sign of suboptimal management or a marker of disease? *Am. J. Kidney Dis.* 2005; 45:136–147. https://doi.org/10.1053/j.ajkd.2004.08.042 PMID: 15696453

3. Zhang Y, Thamer M, Stefanik K, Kaufman J, Cotter D.J. Epoetin requirements predict mortality in hemodialysis patients. *Am. J. Kidney Dis.* 2004; 44:866–876. PMID: 15492953

4. Kalantar-Za deh K, Lee G.H, Miller J.E, et al. Predictors of hyporesponsiveness to erythropoiesis-stimulating agents in patients with maintained hemodialysis: a risk factor analysis. *Am. J. Kidney Dis.* 2009; 53:823–834. https://doi.org/10.1053/j.ajkd.2008.12.040 PMID: 19339087

5. Sibbel S.P, Koro C.E, Brunelli S.M, Cobitz A.R. Characterization of chronic and acute ESA hyporesponsiveness: a retrospective cohort study of hemodialysis patients. *B.M.C. Nephrol.* 2015; 16:144. https://doi.org/10.1186/s12882-015-0138-x PMID: 26283069

6. Panichi V, Rosati A, Bigazzi R, et al. RISCAVID Study Group. Anaemia and resistance to erythropoiesis-stimulating agents as prognostic factors in haemodialysis patients: results From the RISCAVID study. *Nephrol. Dial. Transplant.* 2011; 26:2641–2648. https://doi.org/10.1093/ndt/gfr282 PMID: 21325348

7. Okazaki M, Komatsu M, Kawaguchi H, Tsuchiya K, Nitta K. Erythropoietin resistance index and the all-cause mortality of chronic hemodialysis patients. *Blood Purif.* 2014; 37:106–112. https://doi.org/10.1159/000358215 PMID: 24603656

8. Eriguchi R, Taniguchi M, Ninomiya T, et al. Hyporesponsiveness to erythropoiesis-stimulating agent as a prognostic factor in Japanese hemodialysis patients: the Q-Cohort study. *J. Nephrol.* 2015; 28:217–225. https://doi.org/10.1007/s12245-014-0121-8 PMID: 25980399

9. Kanbay M, Perazella M.A, Kasapoglu B, Koroglu M, Covic A. Erythropoiesis stimulatory agent-resistant anemia in dialysis patients: review of causes and management. *Blood Purif.* 2010; 29:1–12. https://doi.org/10.1159/000245041 PMID: 19816014

10. Rattanasompatthkul M, Molnar M.Z, Zaritsky J.J, et al. Association of malnutrition-inflammation complex and responsiveness to erythropoiesis-stimulating agents in long-term hemodialysis patients. *Nephrol. Dial. Transplant.* 2013; 28:1936–1945. https://doi.org/10.1093/ndt/gst568 PMID: 23045341

11. González-Ortiz A, Correa-Rotter R, Vázquez-Rangel A, Vega-Vega O, Espinosa-Cuevas Á. Relationship between protein-energy wasting in adults with chronic hemodialysis and the response to treatment.
with erythropoietin. *B.M.C. Nephrol*. 2019; 20:316. https://doi.org/10.1186/s12882-019-1457-0 PMID: 31412807

12. Okazaki M, Komatsu M, Shiohira S, et al. Associations between the erythropoiesis-stimulating agent resistance index and the geriatric nutritional risk index of maintenance hemodialysis patients and increased mortality. *Ren. Replace. Ther*. 2015; 1:7.

13. Yamada K, Furuya R, Takita T, et al. Simplified nutritional screening tools for patients on maintenance hemodialysis. *Am. J. Clin. Nutr*. 2008; 87:106–113. https://doi.org/10.1093/ajcn/87.1.106 PMID: 18175743

14. Takahashi H, Inoue K, Shimizu K, et al. Comparison of nutritional risk scores for predicting mortality in Japanese chronic hemodialysis patients. *J. Ren. Nutr*. 2017; 27:201–206. https://doi.org/10.1053/j.jrn.2016.12.005 PMID: 28215493

15. Kobayashi I, Ishimura E, Kato Y, et al. Geriatric nutritional risk index, a simplified nutritional screening index, is a significant predictor of mortality in chronic dialysis patients. *Nephrol. Dial. Transplant*. 2010; 25:3361–3365. https://doi.org/10.1093/ndt/gfq211 PMID: 20400447

16. Takahashi H, Ito Y, Ishii H, et al. Geriatric nutritional risk index accurately predicts cardiovascular mortality in incident hemodialysis patients. *J. Cardiol*. 2014; 64:32–36. https://doi.org/10.1016/j.jjcc.2013.10.018 PMID: 24365385

17. Xiong J, Wang M, Zhang Y, et al. Association of geriatric nutritional risk index with mortality in hemodialysis patients: A meta-analysis of cohort studies. *Kidney Blood Press. Res*. 2018; 43:1878–1889. https://doi.org/10.1159/000495999 PMID: 30566933

18. Cremieux P.Y, Van Audenrode M, Lefebvre P. The relative dosing of epoetin alfa and darbepoetin alfa in chronic kidney disease. *Curr. Med. Res. Opin*. 2006; 22:2329–2336. https://doi.org/10.1185/030079906X154024 PMID: 17257447

19. Bonafont X, Bock A, Carter D, et al. A meta-analysis of the relative doses of erythropoiesis-stimulating agents in patients undergoing dialysis. *N.D.T. Plus* 2009; 2:347–353. https://doi.org/10.1093/ndtplus/sfp097 PMID: 25949339

20. DeLong E.R, DeLong D.M, Clarke-Pearson D.L. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics* 1988; 44:837–845. PMID: 3203132

21. Pencina M.J, D’Agostino R.B. Sr, D’Agostino R.B. Jr, Vasan R.S. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat. Med*. 2008; 27:157–172. https://doi.org/10.1002/sim.2929 PMID: 17569110

22. Brookhart M.A, Freburger J.K, Ellis A.R, Wang L, Winkelmayer W.C, Kshirsagar A.V. Infection risk with erythropoietin. *B.M.C. Nephrol*. 2019; 20:316. https://doi.org/10.1186/s12882-019-1457-0 PMID: 31412807

23. Pencina M.J, D’Agostino R.B. Sr, D’Agostino R.B. Jr, Vasan R.S. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat. Med*. 2008; 27:157–172. https://doi.org/10.1002/sim.2929 PMID: 17569110

24. BAILIE G.R, LARKINA M, GOODKIN D.A, et al. Data from the Dialysis Outcomes and Practice Patterns Study validate an association between high intravenous iron doses and mortality. *Kidney Int*. 2014; 86:845–854. https://doi.org/10.1038/ki.2014.114 PMID: 24759150

25. STENVINKEL P, ALVESTRAND A. Inflammation in end-stage renal disease: sources, consequences, and therapy. *Semin. Dial*. 2002; 15:329–337. https://doi.org/10.1046/j.1525-139x.2002.00083.x PMID: 12358637

26. Pecois-Filho R, Lindholm B, Axelsson J, Stenvinkel P. Update on interleukin-6 and its role in chronic renal failure. *Nephrol. Dial. Transplant*. 2003; 18:1042–1045. https://doi.org/10.1093/ndt/fgf111 PMID: 12748331

27. Fouque D, Kalantar-Zadeh K, Kopple J, et al. A proposed nomenclature and diagnostic criteria for protein-energy wasting in acute and chronic kidney disease. *Kidney Int*. 2008; 73:391–398. https://doi.org/10.1038/sj.ki.5002585 PMID: 18094682

28. Yajima T, Yajima K, Takahashi H, Yasuda K. The impact of abdominal fat levels on all-cause mortality in patients undergoing hemodialysis. *Nutrients* 2018; 10:480. https://doi.org/10.3390/nu10040480 PMID: 29649164

29. Yajima T, Arao M, Yajima K, Takahashi H, Yasuda K. The associations of fat tissue and muscle mass indices with all-cause mortality in patients undergoing hemodialysis. *PLOS ONE* 2019; 14:e0211988. https://doi.org/10.1371/journal.pone.0211988 PMID: 30759133

30. Zimmermann J, Herrlinger S, Pruy A, Metzger T, Wanner C. Inflammation enhances cardiovascular risk and mortality in hemodialysis patients. *Kidney Int*. 1999; 55:648–658. https://doi.org/10.1046/j.1523-1755.1999.00273.x PMID: 9987089
31. Qureshi A.R, Alvestrand A, Divino-Filho J.C, et al. Inflammation, malnutrition, and cardiac disease as predictors of mortality in hemodialysis patients. J. Am. Soc. Nephrol. 2002; 13 (Suppl. 1):S28–36.

32. Kalantar-Zadeh K, Kopple J.D, Humphreys M.H, Block G. Block comparing outcome predictability of markers of malnutrition-inflammation complex syndrome in haemodialysis patients. Nephrol. Dial. Transplant. 2004; 19:1507–1519. https://doi.org/10.1093/ndt/gfh143 PMID: 15069177

33. Bouillanne O, Morineau G, Dupont C, et al. Geriatric Nutritional Risk Index: a new index for evaluating at-risk elderly medical patients. Am J Clin Nutr 2005; 82:777–783. https://doi.org/10.1093/ajcn/82.4.777 PMID: 16210706

34. Yajima T, Yajima K, Takahashi H. Impact of Annual Change in Geriatric Nutritional Risk Index on Mortality in Patients Undergoing Hemodialysis. Nutrients. 2020; 12:3333. https://doi.org/10.3390/nu12113333 PMID: 33138201

35. Yajima T, Yajima K, Takahashi H, Yasuda K. Combined predictive value of extracellular fluid/intracellular fluid ratio and the geriatric nutritional risk index for mortality in patients undergoing hemodialysis. Nutrients 2019; 11:2659. https://doi.org/10.3390/nu11112659 PMID: 31690024