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RESEARCH

MALNUTRITION-INFLAMMATION SCORE, ANTHROPOMETRIC INDICES, AND ERYTHROPOIETIN REQUIREMENT IN GERIATRIC HEMODIALYSIS PATIENTS

ABSTRACT

Introduction: Studies have demonstrated that there is a correlation between malnutrition, inflammation, and erythropoietin requirement in adult hemodialysis patients. However, in geriatric hemodialysis patients, no evident data has been found associated with this relationship. The purpose of this study is to investigate the relation between malnutrition-inflammation score, erythropoietin requirement, and erythropoietin resistance in geriatric hemodialysis patients.

Materials and Method: One hundred fifty-four adult hemodialysis patients were included in this cross-sectional study. Erythropoietin resistance index, weekly erythropoietin dose, weekly erythropoietin dose per weight, and malnutrition-inflammation score were calculated for all patients. Measurements of laboratory and anthropometric parameters associated with nutrition and inflammation were performed.

Results: Mean age of 154 patients included in the study was 59.5±14.5 years; 81 were male and 68 were geriatric (age ≥65 years). The median duration of dialysis was 36 months (interquartile range, 18–76). Mean malnutrition-inflammation score was found to be higher in geriatric patients than in adult patients (p=0.004). Malnutrition-inflammation score was determined in correlation with weekly erythropoietin dose per weight in both geriatric and adult patient groups (p<0.001, r=0.484; p=0.029, r=0.235, respectively). Malnutrition-inflammation score was determined in correlation with erythropoietin resistance index in both geriatric and adult patient groups (p<0.001, r=0.497; p=0.014, r=0.497, respectively).

Conclusions: In both geriatric and adult (<65 years) hemodialysis patients, malnutrition-inflammation score is correlated with weekly erythropoietin dose per weight and erythropoietin resistance index. Moreover, malnutrition and inflammation is more often observed among geriatric hemodialysis patients compared with adult (<65 years) hemodialysis patients.

Key Words: Erythropoietin; Geriatrics; Renal Dialysis; Malnutrition; Inflammation.

ARAŞTIRMA

GERİATRİK HEMODİYALİZ HASTALARINDA MALNÜTRİSYON İNFLAMASYON SKORU, ANTROPOMETRİK BELİRTEÇLER VE ERİTROPOİETİN İHTİYACI

ÖZ

Giriş: Çalışmalarda erişkin hemodiyaliz hastalarında malnütrisyon ve inflamasyon ile eritropoietin ihtiyacı arasında korelasyon olduğu gösterilmiştir. Fakat geriatrik hemodiyaliz hastalarında bu ilişki ile ilgili belirgin veriler bulunmamaktadır. Bu çalışmanın amacı geriatrik hemodiyaliz hastalarında malnutrisyon inflamasyon skoru, eritropoietin ihtiyacı ve eritropoietin direnci ilişkisinin araştırılmasıdır.

Gereç ve Yöntem: Bu kesitsel çalışmaya yüz elli dört erişkin hemodiyaliz hastası alındı. Hastaların eritropoietin direnç indeksi, haftalık eritropoietin dozu, haftalık kilo başına eritropoietin dozu ve malnutrisyon inflamasyon skoru hesaplandı. Hastaların nütrisyon ve inflamasyon ilişkili laboratuar ve antropometrik parametreleri ölçüldü.

Bulgular: Çalışmaya alınan 154 hastanın yaş ortalaması 59,5±14,5 yıl, 81'i erkek, 68'i geriatrik (yaş ≥65 yıl) idi. Ortalama diyaliz süresi 36 aydı (çeyreklikler arası, 18-76). Geriatrik hastalarda, malnutrisyon inflamasyon skoru ortalaması daha yüksek bulundu (p=0,004). Malnutrisyon inflamasyon skoru, geriatrik ve erişkin hasta gruplarının her ikisinde de haftalık kilo başına eritropoietin dozu ile korele bulundu (sırasıyla p<0,01, r=0,484; p=0,029, r=0,235). Malnutrisyon inflamasyon skoru, geriatrik ve erişkin hasta gruplarının her ikisinde de eritropoietin direnç indeksi ile korele bulundu (sırasıyla p<0,01, r=0,497; p=0,014, r=0,497).

Sonuç: Malnutrisyon inflamasyon skoru, geriatrik ve erişkin (yaş<65) hemodiyaliz hastalarının her ikisinde de haftalık kilo başına eritropoietin dozu ve eritropoietin direnç indeksi ile koreledir. Ayrıca, malnütrisyon ve inflamasyon geriatrik hemodiyaliz hastalarında erişkin (yaş<65) hemodiyaliz hastalarından daha fazla görülmektedir.

Anahtar Sözcükler: Eritropoietin; Geriatri; Hemodiyaliz; Malnütrisyon; İnflamasyon.

Introduction

Recently, a significant increase in geriatric patient population undergoing hemodialysis due to end stage renal disease (ESRD) has been observed worldwide (1). Anemia in patients with chronic kidney disease (CKD) is a frequent occurrence as a result of relative deficiency of erythropoietin (EPO). Therefore, in treatment of renal anemia, the use of erythropoiesis-stimulating agents (ESA) is now standard of care (2). However, ESA might result in low response rates in some patients due to factors such as iron deficiency, protein-energy malnutrition (PEM), inflammation, infection, vitamin B_{12} or folate deficiency, serious hyperparathyroidism, and insufficient dialysis (3). In ESA resistance, the target hemoglobin (Hb) level cannot be achieved despite administration of ESA or, alternatively, high doses of ESA might be required (3). Some studies have reported a relationship between increase in mortality and usage of high-dose recombinant human erythropoietin (rHu-EPO) even though the level of Hb is in the expected range (4,5).

EPO resistance index (ERI) is calculated as the weekly dose of EPO per kilogram (kg) of body weight divided by Hb level (g/dL) (6). ERI is used in the analysis of rHu-EPO resistance and has shown to have a relationship with mortality and comorbidity in hemodialysis patients (6). In addition, as reasons for variance in patients' response to rHu-EPO is complex and multi-factorial, it could not be explained completely (3). The existence of anemia in hemodialysis patients reduces quality of life, worsens cardiovascular morbidity, and is an independent indicator for mortality (7).

Co-occurrence of malnutrition and inflammation is designated as malnutrition–inflammation complex syndrome (MICS) in maintenance hemodialysis patients. It has been shown that MICS is related to acceleration in atherosclerosis, mortality, and morbidity (8). Malnutrition-inflammation score (MIS) is a comprehensive and specific scoring system used for evaluation of MICS in hemodialysis patients (9). MIS is associated with endothelial dysfunction, coronary artery disease, quality of life, mortality, sleep disorders, depression, and decreased exercise capacity in maintenance dialysis patients (9-11).

In two studies, MIS was found to be associated with EPO hyporesponsiveness and rHu-EPO dose requirement (12,13). However, there has been no data regarding such an association in geriatric hemodialysis patients. Moreover, the relationship between MIS and ERI has not been identified precisely in geriatric hemodialysis patients. In geriatric patients, there are many unexplained aspects of anemia etiology and response to treatment (14). The objective of this study was to investigate the effect of malnutrition and inflammation defined as MIS on EPO requirement and EPO resistance in geriatric hemodialysis patients.

Materials and Method

Patients

One hundred fifty-four adult patients (age ≥18 years), who underwent conventional hemodialysis three times a week for at least six months were included in this cross-sectional study. The study received approval from our university hospital ethics committee and informed consent was obtained from all pateints before participation. Study data were collected from patients at three different hemodialysis centers in our city, from December 2013 to January 2014.

Duration of each dialysis session was 4–5 hours with blood flow rate of 300–400 mL/min, and standard bicarbonate dialysis solution was used. Patients with iron deficiency, folate deficiency, hemolysis, vitamin B_{12} deficiency, malignancy, specific infection/inflammation (C-reactive protein (CRP)>10 mg/L), hospitalization, or transfusion history within last three months, insufficient hemodialysis (Kt/V<1.2), serious hyperparathyroidism (parathormone (PTH) ≥800 pg/dl), or thyroid dysfunction were excluded. Also patients receiving parenteral nutrition, who were unable to answer the questions due to senility or dementia, who had not received any rHu-EPO treatment within last three months, or who had chronic gastrointestinal blood loss were excluded. All patients included were clinically euvolemic. Demographic characteristics of patients, such as age, gender, and dialysis duration, were recorded. Patients were divided into two groups as adult (age <65 years) and geriatric (age ≥65 years).

Laboratory Evaluation

Before the dialysis session, blood samples for routine biochemical parameters including creatinine, total cholesterol, triglyceride, PTH, ferritin, albumin, calcium, phosphorus, Hb, hematocrit (Hct), total iron-binding capacity (TIBC), and CRP were drawn from an antecubital vein of all participants after overnight fasting. CRP was assayed by immunoturbidimetric method (normal range of CRP, 0–5 mg/L). Serum albumin levels were measured by the quantitative colorimetric method. All the other laboratory parameters were studied by using standard automated methods. The mean values of three months were examined for laboratory values. After the dialysis session, blood was taken to determine post- dialysis ure-

a and calculate Kt/V of urea. Laboratory results were evaluated by recording in patient cards.

Erythropoietin Resistance Index and Erythropoietin Requirement

Patients were administered EPO alpha, EPO beta, or darbepoetin alfa as ESA. Target Hb level was 11–12 g/dl. Medicine dose of those administered darbepoetin alfa was multiplied by 200 and converted into unit dose (15). Total dose of rHu-EPO administered for three months to all patients included in the study was divided by 12 to determine the weekly mean rHu-EPO dose (EPO dose/week; U/week). By dividing weekly rHu-EPO doses by the weight of each patient, EPO dose per body weight was calculated (U/week/kg). ERI was calculated by dividing weekly EPO dose (U/week/kg) into Hb (g/dl) (6).

Malnutrition-Inflammation Score

MIS is a scale in which 10 parameters are evaluated by giving scores between 0 (normal) and 3 (severely abnormal) (9). Seven out of ten parameters include following questions and examinations in subjective global assessment (SGA): weight loss within last six months, decrease in eating, existence of gastrointestinal symptoms such as nausea and diarrhea, comorbidity, functional capacity, loss of subcutaneous fatty tissue, and loss of muscle. The additional three parameters were body mass index (BMI), serum albumin level, and serum TIBC. The sum of all 10 MIS components ranges from 0 (normal) to 30 (severely malnourished and inflammation status). MIS of all patients was calculated accordingly.

Anthropometric Measurements

Mid-arm circumference (MAC), triceps skin-fold thickness (TSF), calf circumference, body weight, and height were measured as anthropometric measurements. Anthropometric parameters were measured 10–20 minutes after the completion of dialysis. MAC and calf circumference were measured using a metal tape measure. TSF was measured using a caliper. All measurements were repeated three times from the non-access arm and the mean was recorded. Mid-arm muscle circumference (MAMC) was calculated by the following formula: MAMC=MAC-(3.1415 x TSF) (16). The body mass index (BMI) was calculated as the ratio between body weight in kilograms and the square of height in meters (kg/m^2). Anthropometric parameters were measured by an experienced nutrition nurse.

Statistical Analysis

Normal distributed continuous variables were reported as mean ± SD whereas non-normally distributed variables were reported as medians (interquartile range, IQR). Differences in normal distributed continuous variables between groups were determined by using unpaired t-test whereas differences in non-normal distributed continuous variables were compared by using Mann-Whitney U-test. Categorical variables were analysed by Chi-square test. Pearson's correlation was used to assess the strength of association between MIS, EPO requirement, and anthropometric parameters. A p value of <0.05 was considered as statistically significant. SPSS software (Statistical Package for the Social Sciences, version 17.0, SSPS Inc., Chicago, Ill, USA) was used to conduct the statistical analysis.

RESULTS

The mean age of 154 patients included in the study was 59.5±14.5 years (range: 21–87); 81 were male (52.5%) and 68 were geriatric. The median duration of dialysis was 36 months (IQR, 18–76). Table 1 illustrates the demographic and clinical characteristics of geriatric and adult patients. Albumin and creatinine of geriatric patient group were lower than those of adult group ($p=0.001$, $p < 0.001$, respectively). Table 2 illustrates MIS, ERI, weekly EPO dose, and anthropometric parameters of geriatric and adult patients.

MIS was higher in geriatric patients than adult patients ($p=0.004$),whereas MAC, TSF, and MAMC were lower in geriatic patients than in adult patients ($p=0.004$, $p=0.045$, and $p=0.009$, respectively) (Table 2). However, EPO dose per body weight and ERI were not different in geriatric patients compared with those in adult hemodialysis patients (Table 2). MIS was in positive correlation with hemodialysis duration ($p=0.039$, $r=0.224$) whereas it was in negative correlation with albumin and BMI ($p=0.003$, $r=-0.313$; $p=0.000$, $r=-0.387$, respectively) in adult patients. Similarly, in geriatric patient group, MIS was in positive correlation with hemodialysis duration ($p=0.006$, $r=0.329$) and in negative correlation with albumin and BMI ($p=0.000$, $r=-0.521$; $p=0.000$, $r=-0.425$, respectively). Moreover, while there was minimal negative correlation between MIS and total cholesterol in geriatric patients ($p=0.050$, $r=-0.239$), there was no significant correlation in adult patients.

MIS was correlated with EPO dose per body weight and ERI in both adult and geriatric patients (Table 3) (Figure 1). Albumin, which is a biochemical indicator of nutritional sta-

Table 1— Demographic, Clinical, and Biochemical Parameters of Patients in Geriatric and Adult Hemodialysis Patients.

Parameter	Age < 65 (n=86)	Age ≥ 65 (n=68)	p
Age (year)	49.3 ± 10.3	72.4 ± 6.6	<0.001*
Gender (female/male)	36/50	37/31	0.083
Dialysis duration (month)	35 (18–85)	36 (18–67.2)	0.610
Diabetes, n (%)	35 (40.7)	28 (41.2)	0.541
Ischemic heart disease, n (%)	13 (15.1)	18 (26.5)	0.062
Hematocrit (%)	32.2 ± 3.1	31.5 ± 3.8	0.206
Hemoglobulin (g/dL)	10.6 ± 1	10.3 ± 1.1	0.072
Serum ferritin (ng/mL)	453 ± 184	435 ± 191	0.602
TIBC (µg/dL)	183 ± 42	182 ± 44	0.754
Albumin (g/dL)	4 ± 0.4	3.8 ± 0.4	0.001*
Total cholesterol (mg/dL)	166 ± 45	179 ± 51	0.088
Triglyceride (mg/dL)	149 (110–215)	129 (104–184)	0.158
Creatinine (mg/dL)	8.2 ± 1.8	6.9 ± 1.7	<0.001*
CRP (mg/L)	4 (2–7.4)	4.4 (1.8–8.8)	0.494
Calcium (mg/dL)	8.5 ± 0.7	8.5 ± 0.8	0.820
Phosphorus (mg/dL)	5 (3.8–5.8)	5.3 (4.4–6.4)	0.105
PTH (pg/mL)	361 ± 210	356 ± 222	0.771
Kt/V	1.5 (1.3–1.6)	1.5 (1.3–1.6)	0.955

*p < 0.05. TIBC: total iron binding capacity, CRP: C-reactive protein, PTH: Parathyroid hormone. Data are expressed as mean ± standard deviation or median (interquartile range).

Table 2— Malnutrition Inflammation Score, Erythropoietin Resistance Index, Erythropoietin Requirement, and Anthropometric Parameters of Patients in Geriatric and Adult Hemodialysis Patients.

Parameter	Age < 65 (n=86)	Age ≥ 65 (n=68)	p
MIS	5 (4–7.2)	7 (5–11.7)	0.004*
EPO dose (U/week)	8000 (6000–9000)	8000 (5250–8000)	0.768
EPO dose per body weight (EPO dose/kg)	110 ± 40	116 ± 45	0.360
ERI (EPO dose per body weight / Hb)	10.5 ± 4.1	11.7 ± 4.5	0.093
BMI (kg/m2)	24.5 ± 4.7	24.3 ± 4.5	0.786
Weight (kg)	67.6 ± 15.4	63.2 ± 13.3	0.060
MAC (cm)	27.2 ± 3.5	25.6 ± 3.5	0.004*
TSF (mm)	12 (9.7–16)	10 (8–16)	0.045*
MAMC (cm)	22.9 (21.2–24.6)	21.5 (20.1–23.2)	0.009*
Calf circumference (cm)	32.3 ± 3.6	33.3 ± 3.8	0.148

*p < 0.05. MIS: Malnutrition inflammation score, EPO: Erythropoietin, ERI: Erythropoietin resistance index, Hb: Hemoglobin, BMI: Body mass index, MAC: Mid-arm circumference, TSF: Triceps skinfold thickness, MAMC: Mid arm muscle circumference. Data are expressed as mean ± standard deviation or median (interquartile range).

te, was in negative correlation with EPO dose per body weight and ERI in geriatric patients (Table 3). Furthermore, in geriatric patient group, BMI, which is an anthropometric parameter, was in negative correlation with EPO dose per body weight and ERI (Table 3).

Discussion

In this study, MIS was found to be in significant correlation with EPO dose per body weight and ERI in both geriatric and adult patient groups. Moreover, in geriatric patients, EPO dose per body weight and ERI values were higher but

Table 3— Correlation Coefficients Between Erythropoietin Requirement, Erythropoietin Resistance Index and MIS Value, Anthropometric and Laboratory Parameters in Hemodialysis Patients.

	EPO Dose/Week		EPO Dose Per Body Weight		EPO Resistance Index	
	Age < 65	**Age ≥ 65**	**Age < 65**	**Age ≥ 65**	**Age < 65**	**Age ≥ 65**
MIS	0.006	0.223	0.235*	0.484*	0.264*	0.497*
	(p=0.959)	(p=0.068)	(p=0.029)	(p<0.01)	(p=0.014)	(p=0<0.01)
BMI (kg/m2)	0.265*	0.016	-0.319*	-0.401*	0.248*	-0.402*
	(p=0.014)	(p=0.899)	(p=0.003)	(p=0.001)	-(p=0.022)	(p=0.001)
TSF (mm)	0.051	-0.088	0.007	-0.155	0.037	-0.151
	(p=0.638)	(p=0.476)	(p=0.950)	(p=0.208)	(p=0.736)	(p=0.220)
MAC (cm)	0.106	0.076	0.038	0.016	0.024	0.010
	(p=0.330)	(p=0.539)	(p=0.730	(p=0.900)	(p=0.824)	(p=0.937)
Albumin (g/L)	-0.061	-0.216	-0.122	-0.307*	-0.148	-0.348*
	(p=0.574)	(p=0.077)	(p=0.265)	(p=0.011)	(p=0.172)	(p=0.004)
Hemoglobin (g/dL)	-0.280*	-0.325*	-0.241*	-0.366*	-0.490*	-0.584*
	(p=0.009)	(p=0.007)	(p=0.025)	(p=0.002)	(p<0.01)	(p<0.01)

Pearson's correlation test was used to determine correlation between parameters. P=values are shown in parentheses after each r value. *Statistically significant r values (p<0.05).
MIS: Malnutrition inflammation score, EPO: Erythropoietin, BMI: Body mass index, TSF: Triceps skinfold thickness, MAC: Mid-arm circumference.

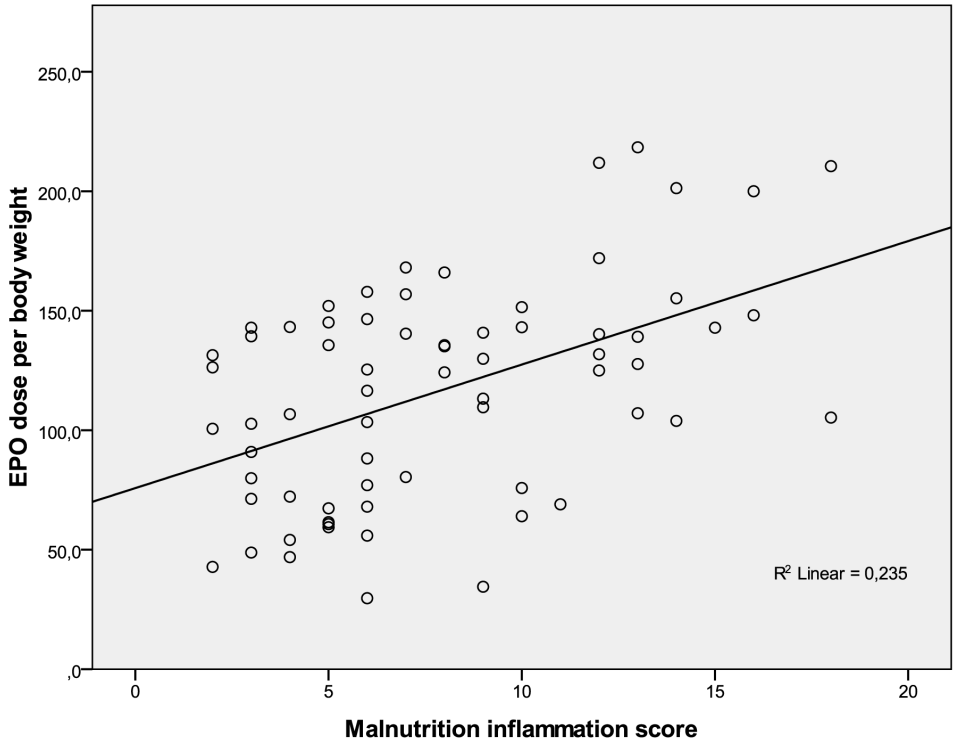

Figure 1— The scatter plot graph of correlation between malnutrition inflammation score and erythropoietin (EPO) dose per body weight per week in geriatric hemodialysis patients.

not statistically significant. Around the world, the rate of geriatric patients who undergo renal replacement treatment is over 30% in most ESRD registries, and the rate continues to increase (1). In the elderly, pathophysiology of diseases follows a course different from that observed in young people due to changes such as functional, biochemical, and morphological (14). To our best knowledge, there has been no other study that investigates the relationship between MIS and EPO requirements in geriatric hemodialysis patients. In the study conducted by Kalantar Zadeh et al. (13), a significant correlation was reported between MIS and EPO hyporesponsiveness, and the mean age of patients was 54.7 ± 14.5. A study by Akgul et al. (12) found the same correlation in hemodialysis patients without inflammation, with the average age being 49.1 ± 11.4. Our study is important in terms of showing such a relationship in geriatric hemodialysis patient population, as well.

MIS was found in significant correlation with ERI in both geriatric and younger patients (<65 years) in this study. Moreover, ERI in geriatric patients was higher, but was not statistically significant. The ERI can be easily calculated in the clinic and is directly related to comorbidity and mortality in hemodialysis patients (6). The reasons for variance of responses to EPO in hemodialysis patients could not be explained precisely (3). EPO resistance and attainable Hb values are strong predictors for mortality risk (17). In hemodialysis patients, common reasons for EPO resistance include iron deficiency, infection/inflammation, chronic blood loss, folate or vitamin B12 deficiency, hemoglobinopathies, aluminum toxicity, and medicines (3,18). In the analysis of data of DOPPS III study, in which 8161 hemodialysis patients were evaluated, ERI was higher in Japanese geriatric patients compared to younger patients, but as in our study, no significant difference was found in Europe, Australia, New Zealand, and North America (1). Differences in clinical practices or characteristics of cases such as target Hb values could affect ESA administration.

In our study, we found BMI is in negative correlation with EPO dose per body weight and ERI in geriatric patient group. BMI is a conventional method used in the evaluation of nutritional state but it is not sensitive (19). Locatelli et al. (20) have shown that BMI and EPO hyporesponsiveness are independently related. Moreover, it has been reported that there is an inverse correlation between BMI and anemia control in hemodialysis patients (21).

In this study, we found that MICS was more common in geriatric patients than younger adults. Median MIS was 7 (IQR, 5–11.7) in geriatric hemodialysis patients whereas it was 5 (IQR, 4–7.2) in adult patients. In their study, Kalantar Zadeh et al. (13) determined mean MIS as 8.3 ± 4.2 in hemodialysis patients. In some studies, it has been shown that malnutrition is inversely proportional to age (22). However, other studies demonstrated that age does not affect malnutrition incidence (23). MIS is a comprehensive, quantitative, and easy method used to evaluate inflammation and nutrition states of hemodialysis patients (9). In recent studies, it has been demonstrated that MIS bears a relationship to long-term mortality in dialysis patients (11,24).

In this study, albumin of geriatric patients were significantly lower than that of adult patients. Furthermore, we have found MIS in significant negative correlation with albumin in both groups. Albumin is one of biochemical parameters that can show malnutrition and inflammation in patients but it is affected by the presence of edema, liver disease, and chronic inflammation (25). In this study, albumin demonstrated a significantly negative correlation with EPO dose per body weight and ERI in geriatric patients. Results of this study support the idea that malnutrition increases EPO resistance.

This study has some limitations. First, the number of patients is low and data were collected from a single region. Second, in this cross-sectional study, three months of patient data were analysed. Inflammation and malnutrition in hemodialysis patients is a dynamic process and may require longer follow-up.

In conclusion, MIS is in correlation with EPO dose per body weight and ERI in both adult (<65 years) and geriatric hemodialysis patient populations. Moreover, MICS is significantly more common among geriatric hemodialysis patients compared with adult hemodialysis patients (<65 years).

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