http://jmscr.igmpublication.org/home/
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: https://dx.doi.org/10.18535/jmscr/v8i8.36

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Is There a Difference in the Resistance to Erythropoietin Stimulating Agents in Dialysis Patients Depending on Whether or not they Received such Treatment Before Starting Hemodialysis?

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Abstract
Background: *The aim of the present study was to investigate a differences in the resistance to Erythropoietin Stimulating Agents (ESAs) in dialysis patients, depending on Whether or not they received such treatment before starting hemodialysis.*
Material and Methods: *This was a cross-sectional study from January 2009 to January 2020, 775 patients with end-stage kidney disease, on hemodialysis treatment (HDT). For a 12 years, the following categories were monitored by sex: age, hemoglobin levels, ESA dosage, Erythropoietin resistance index (ERI) in patients on periodic dialysis treatment in the Department of Dialysis Treatment /DDT/, UMHAT Sveta Anna Sofia. The following methods were used: Questionnaire; Hemoglobin test; ERI calculation by formula; Statistical methods–methods of prospective follow-up, Data analysis–t-Test: Two-Sample Assuming Unequal Variances, Descriptive and deductive statistics, Parametric analysis.*
Results: *1.A very large number of patients have initiated hemodialysis treatment in emergency, without knowing about their disease and were not monitored by a nephrologist and were not treated with ESAs before dialysis. 2.There is a statistically significant difference in the mean hemoglobin level in women who were ESA treatment-naïve before HD compared to men who were ESA treatment-naïve before HD (p=0.047006), 3.There is a difference in terms of resistance- Erythropoietin Resistance Index(ERI) in were ESA treatment-naïve before HD compared to men who were ESA treatment-naïve before HD (p=0.013).*
Conclusion: *It is necessary to expand the scope, follow-up and treatment in patients with nephrological diseases without waiting for the progression of the disease. When administering ESA, always take into account the sex of the patients and consider the specific characteristics of female patients.*
Keywords: *Hemoglobin, CKD, hemodialysis, anemia, Erythropoiesis-stimulating agents (ESAs), Erythropoietin resistance index (ERI).*

Background

Anemia is frequently experienced by patients with non–dialysis-dependent chronic kidney disease (NDDCKD)[1]. The prevalence varies with the definition of anemia, but increases to 50% in CKD stage 4/5. For many patients, anemia causes unpleasant symptoms, such as fatigue and shortness of breath. In recent years, the recognition of serious adverse risks associated with erythropoietin analogue treatment may have drawn attention away from the importance of anemia-related symptoms. Depending on severity

and duration, these symptoms can significantly degrade the richness and quality of a patient's life. In addition, anemia in NDD-CKD causes an increased likelihood for blood transfusions and is associated with (but may not be a cause of) a higher prevalence of left ventricular hypertrophy and greater risk for hospitalizations and death[2–4].

TREAT, CREATE, and CHOIR were studies of erythropoietin analogues. There are multiple published studies that have indicated concern about treatment with erythropoietin analogues to the high doses required to reach high hemoglobin levels[5–7]. The use of the high doses associates more closely with adverse outcomes in the large anemia Randomized controlled trials(RCTs) than achieved hemoglobin levels[7,8] It is clear from TREAT, CHOIR, and CREATE that high-dose erythropoietin analogues should not be used to increase the hemoglobin level to normal hemoglobin targets (>13 g/dL).

How high should the hemoglobin level be increased? Unfortunately, CREATE, CHOIR, and TREAT leave unanswered whether the hemoglobin range of risk extends to hemoglobin targets<13 g/dl. Without such knowledge, and in the absence of RCTs of intermediate hemoglobin targets (11, 11.5, and 12 g/dl), treatment of anemia inNDD-CKD must remain conservative. It would seem reasonable to avoid hemoglobin targets>11 g/dl in NDD-CKD to stay well clear of some of the risks uncovered by CREATE, CHOIR, and TREAT[7,8].

The debate in search of optimal target hemoglobin level, achieved by treatment with an erythropoiesis-stimulating agent (ESA) has been going on for many years. This is a review a the history of ESA use in patients with CKD, discussing changing guidance, benefits, limitations and appropriate use of ESAs in these patients. See Table 1 for a chronological listing of the key guidelines consulted.

In Bulgaria there is a well developed system for the treatment of anemia in patients with CKD stage 3-5 and are constantly updated[9]. The criteria for the inclusion of certain groups of medicines are precisely defined. Costly drugs 100% are reimbursed by the health fund. At the same time, there are many uncertainties about patients' resistance to anti-anemic treatment.

Despite changes in guidance, the question of whether focus should be directed on avoiding high Hb levels or avoiding high ESA doses in ESA-resistant patients remained. A meta-regression analysis published in 2013 examined the association of ESA dose with adverse outcomes in CKD, independent of the target or Hb level achieved[10]. In 12,956 patients, all-cause mortality was associated with higher total-study-period mean ESA dose and higher first-3-month mean ESA dose. Total-study-period mean ESA dose and first-3-month ESA dose remained significant after adjusting for target Hb or first-3-month mean Hb, respectively. Hypertension, stroke, and thrombotic events, including dialysis vascular access-related thrombotic events, were increased with higher total-study-period mean ESA dose[10].

Erythropoiesis-stimulating agents have transformed the management of anemia in patients with CKD. Some studies suggesting they improve quality of life (QoL) in certain subsets of patients with anemia[11–15]. Although target Hb levels have been a key component of guidance, evolving data suggest that ESA dose and the speed at which Hb levels change in response to ESAs are also important considerations when treating anemic patients[16]. Indeed, the latest product labeling no longer specifies a target Hb level, but use of the lowest ESA dose sufficient to reduce the need for transfusions. Biosimilar ESA products have been used successfully for many years, with safety and efficacy comparable to originator products, bringing cost savings to patients and healthcare systems, and increased access to ESAs and other expensive drugs due to reallocation of resources. Further research will provide guidance on individualization of ESA therapy for different patients and indications so that the optimal benefit to risk ratio may be achieved[17].

Resistance to ESA is common in patients undergoing chronic hemodialysis (HD) treatment. In many HD patients, target hemoglobin levels are not reached due to a varying degree of ESA resistance. A diminished response to ESA has been associated with various factors, including (functional) iron deficiency andvitamin deficiency, an impaired nutritional state and the presence of (micro) inflammation[18 ´19] .

Furthermore, the microbiological purity of the dialysis fluid[2°], the presence of hyperparathyroidism[21] and low dialysis adequacy[22] have been associated with ESA resistance.

There are no publications in the medical literature comparing ESA resistance in dialysis patients depending on whether or not they received ESA before initiating hemodialysis treatment. Unclear whether patients treated with ESAs before hemodialysis, after initiating renal replacement therapy have different hemoglobin levels and/or different resistance than ESA-naïve patients prior to dialysis. The number of dialysis patients in Bulgaria is constantly growing and currently exceeds 3 700 people (3 763 in 2017). However, the number of CKD patients observed by a nephrologist who start periodic hemodialysis treatment as planned, as well as those who received ESA during the pre-dialysis period, remains small. The need for detailed studies related to the follow-up of this patient population is at the heart of this paper.

Objective

The aim of the present study was to investigate a differences in the resistance to Erythropoietin Stimulating Agents (ESAs) in dialysis patients, depending on whether or not they received such treatment before starting hemodialysis.

Material and Methods

Over a period of 12 years, the following categories were monitored by sex: age, hemoglobin levels, Erythropoietin Resistance Index ERI, ESA dosage in patients on periodic dialysis treatment in the Department of Dialysis Treatment /DDT/, UMHAT Sveta Anna AD Sofia, between 2009 and 2020. Patients were grouped into two groups: group A – patients who received ESA before the start of dialysis treatment, and group B – ESA treatment-naïve before starting dialysis treatment. 286 female and 489 male patients were followed. A total of 775 patients. A comparative analysis was performed between group A and group B by sex. The female patients in group A were compared to male patients in group A, and female patients in group B were compared to male patients in group B. The following categories were compared: age, mean hemoglobin level, ESA mean weekly dose, ESA mean weekly dose/kg body weight, and Erythropoietin Resistance Index (ERI).

Methods: 1. Questionnaire. All study subjects were interviewed using a standardized questionnaire to provide the following data: gender, age, weight, monitoring during the pre-dialysis period, ESA administration during the pre-dialysis period. **2. Method of hemoglobin testing** (Colorimetric method at the University Hospital Sveta. Anna Sofia laboratory) **3. Erythropoietin Resistance Index (ERI) calculation by formula: ESA weekly dose/ body weight in kg/hemoglobin in g/dl. 4. Statistical methods.** The methods of prospective follow-up were used, Data analysis – t-Test: Two-Sample Assuming Unequal Variances, Descriptive and deductive statistics, Parametric analysis, Descriptive statistics: point estimates of parameters-finding averages.

Results and Discussion

Table 2, Chart 1 and Chart 2 show data of patients who were monitored by a nephrologist before initiating HD; ESA treatment before HD. Annually, at the beginning of January, patients were interviewed through a standardized questionnaire to provide the following data: gender, age, monitoring during the pre-dialysis period, ESA administration during the pre-dialysis period. Patients are examined for complete blood

counts and chemistry, the weekly dose per patient is monitored, as well as the weekly dose per kg/weight, and ERI is calculated for each patient.

Table 2 presents the data from the follow-up of patients in the years 2009-2020. It is important to note that the patients on periodic hemodialysis treatment who had started such treatment in emergency and patients with previously unknown CKD form much larger proportion.

It is obvious at first glance that there is a large number of patients who initiated emergency treatment. In all those 12 years, the percentage of monitored patients before the initiation of periodic hemodialysis treatment was not higher than 53.62%. The highest number of patients was observed in 2014 – 53.62%, and the lowest number of patients was observed in 2018 – 25.4%. The statistics are similar for patients who received ESA during the pre-dialysis period. The highest is the number of monitored patients who received ESA in 2010 – 34.78%, and the lowest in 2018 – 15.78%. The data for the USA for the period 1995-2012 were similar[23]. While in the USA this rate was around 15% by 2012, the rate at DDT, Sveta Anna Hospital Sofia was between 15.78% and 34.48% for the period 2009-2020.

Comparing the data from the results, it was found that there is no statistically significant difference in the mean hemoglobin levels of the two groups of female patients (group A compared to group B, i.e. patients who received ESA or were ESA treatment-naïve before the start of HD) (p=0.1373). No such difference was found in men (p=0.246)- Table 3. The results for the period 1995-2012 are similar for patients from the USA in terms of hemoglobin levels and comparison of the two groups of patients, i.e. with and without ESA treatment. There is no gender grouping in their follow-up[24] . However, in our patients, there was a statistically significant difference in the mean hemoglobin level of female patients who were ESA treatment-naïve (group B) before HD compared to male patients (group B) who were ESA treatment-naïve (p=0.047006). Female patients showed significantly lower hemoglobin level (9.345±0.25 g/l). In male patients, the mean value was 9.95±0.13 g/l. When comparing the mean hemoglobin levels in men and women receiving ESA (group A) there is no significant difference (p=0.833).

There is no data in the world literature to compare the results of the two groups of patients (with ESA treatment; ESA treatment-naïve before HD) in relation to ESA mean weekly dose, ESA mean weekly dose per kg/body weight, or ERI.

Table 4 shows the results of ERI calculation in both sexes and in both groups of patients. ERI calculation by formula: ESA weekly dose/ body weight in kg/hemoglobin in g/dl. No statistically significant difference was found in the data for the different groups of patients (with ESA treatment/ ESA treatment-naïve). P=0.573 for female patients. P=0.107 for male patients. There is no difference in ERI mean value between men and women who received ESA before HD (p=0.473). There was a statistically significant difference in terms of resistance (ERI) female patients who were ESA treatment-naïve (group B) before HD compared to men (group B) who were ESA treatment-naïve before HD (p=0.0098). Female patients show significantly higher resistance: mean ERI value 15.83±1.1862. In male patients, mean ERI value is 12.00369±0.55.

The Result of the long-term 12-year follow-up of the patients in the Department of Dialysis Treatment, Sveta Anna Hospital AD Sofia shows:

1. A very large number of patients have initiated periodic hemodialysis treatment in emergency, without knowing about their disease and were not monitored by a nephrologist.
2. There is a high percentage of patients on periodic hemodialysis treatment who were not treated with ESA before dialysis.
3. There is a statistically significant difference in the mean hemoglobin level in women who were ESA treatment-naïve (group B) before HD compared to men (group B) who were ESA treatment-naïve before HD (p=0.047006). Female patients show a significantly lower hemoglobin level:

9.345±0.25 g/l. In male patients, the mean hemoglobin value is 9.95±0.13 g/l.

4. There is a statistically significant difference in terms of resistance (ERI) in were ESA treatment-naïve (group B) before HD compared to men (group B) who were ESA treatment-naïve before HD (p=0.013). Female patients show significantly higher resistance: mean ERI value 15.83±1.1862. In male patients, the mean value is 12.00369±0.55.
5. There is no difference in the age of the two groups of patients compared by sex and between the sexes, nor in ESA mean weekly dose.
6. There is no statistically significant difference between the sexes when comparing ERI levels in group A (those who received ESA treatment before HD), p=0.473.

Table 1 Guidelines and recommendations reviewed (1997–2018).

Guideline	Year	Key findings/Recommendations for ESA use
Nephrology:		
NKF-DOQI	1997	Target Hb level of 11–12 g/dL
FDA	2007	Black box warning recommending maintenance of Hb levels within the range of 10–12 g/dL for anemic patients with CKD
ERBP	2010	Target Hb level of 11–12 g/dL in CKD patients, do not intentionally exceed 13 g/dL
FDA	2011	Removed target Hb range of 10–12 g/dL; recommended use of the lowest ESA dose to reduce the need for transfusions
KDIGO	2012	For CKD patients with Hb concentration ≥ 10.0 g/dL, ESA therapy should not be initiated. Upper target limit of 11.5 g/dL. Individualization of therapy will be necessary because some patients may have improvements in QoL at Hb concentrations above 11.5 g/dL and will be prepared to accept the risks
NICE	2015	Target Hb range of 10–12 g/dL
Renal Association	2017	Target Hb range of 10–12 g/dL

ERBP, European Renal Best Practice;; FDA, United States Food and Drug Administration; KDIGO, Kidney Disease Improving Global Outcomes;; NICE, National Institute for Health and Care Excellence; NKF-DOQI, National Kidney Foundation Dialysis Outcomes Quality Initiative;

Table 2. The data from the follow-up of patients in the years 2009-2020

Year	2009 N (%)	2010 N (%)	2011 N (%)	2012 N (%)	2013 N (%)	2014 N (%)	2015 N (%)	2016 N (%)	2017 N (%)	2018 N (%)	2019 N (%)	2020 N (%)
Monitored by nephrologist before HD	23 (29,49%)	24 (52,17%)	22 (40%)	24 (35,29%)	32 (43,24%)	37 (53,62%)	24 (37,5%)	24 (31,58%)	20 (32,79%)	16 (25,4%)	21 (30,88%)	15 (29%)
Received ESA treatment before HD	17 29,49(%)	16 (34,78%)	12 (21,82%)	17 (25%)	21 (38,38%)	12 (17,39%)	17 (26,56%)	21 (27,63%)	15 (24,57%)	10 (15,87%)	12 (17,67%)	10 (17,67%)
Total patients on HD with ESA	78	46	55	68	74	69	64	76	61	63	68	53

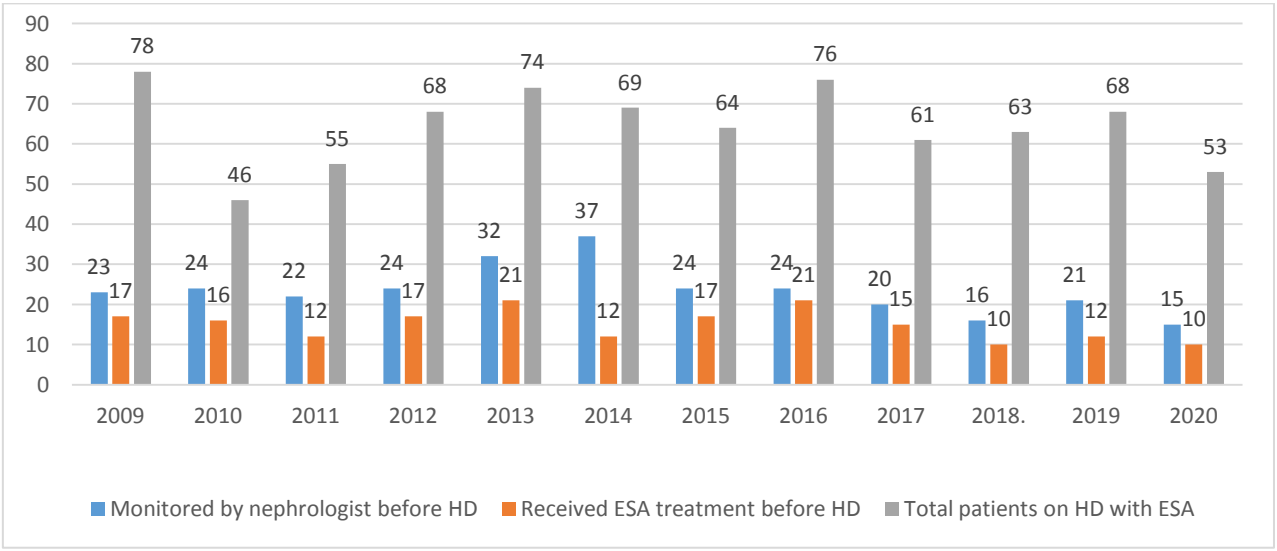

Chart 1 The data from the follow-up of patients in the years 2009-2020

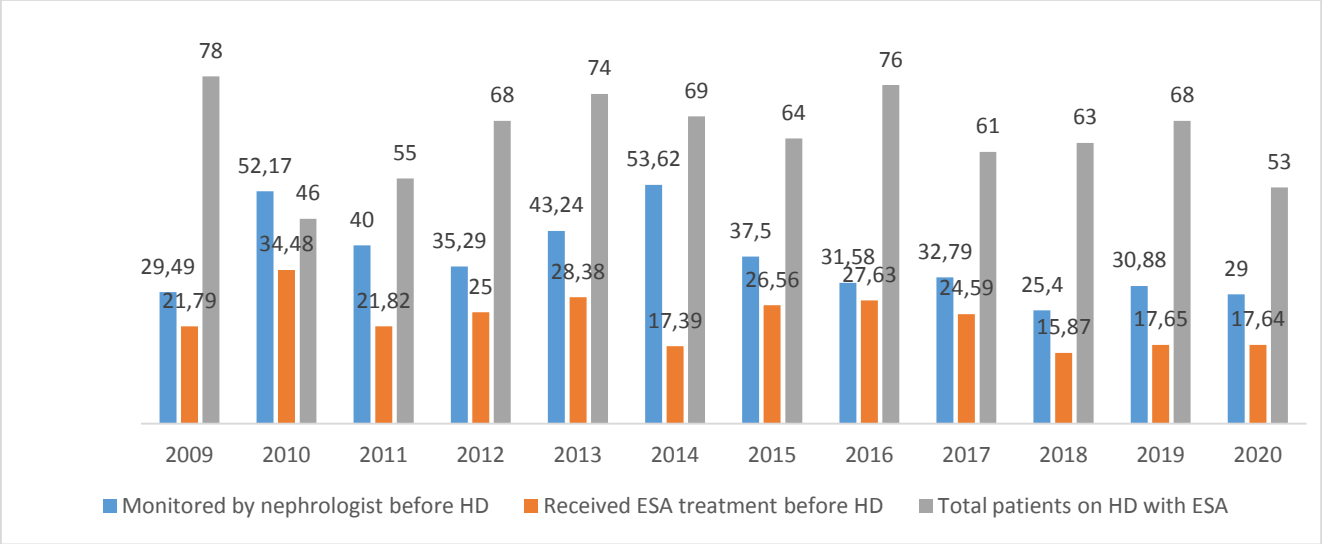

Chart 2 The data from the follow-up of patients in the years 2009-2020 in relative percentage

Table 3. Mean hemoglobin levels in male and female patients in both groups

Year	Total number female patients	Female patients receiving ESA before HD (group A)	Mean hemoglobin level in female patients receiving ESA before HD (group A)	Mean hemoglobin level in ESA treatment-naïve female patients before HD (group B)	Total number male patients	Male patients receiving ESA before HD (group A)	Mean hemoglobin level in male patients receiving ESA before HD (group A)	Mean hemoglobin level in ESA treatment-naïve female patients before HD (group B)
2009	30	9 = 42.85%	9.91±0.66 min.-6; max.-12.2	10.39±0.223 min.-8.1; max.-12.4	48	8 = 17% of all male patients	10.61±0.386 min.-8.9 max.-12.4	10.42±0.221 min.-6.7 max.-13.7
2010	19	9 = 47.36%	9,8±0,66 min.-6; max.-12.2	10.78±0.387 min.-19; max.-83	27	7 = 20.58%	10.71±0.43 min.-8.7 max.-12.4	10.38±0.33 min.-6.7 max.-13.7
2011	22	7 = 31.8%	9.81±0.26 min.-8.8; max.-10.8	10.48±0.12 min.-9.8; max.-11.6	33	5 = 15.15%	9.28±0.361 min.-8.1 max.-10.1	10.48±0.091 min.-9.7 max.-11.7
2012	19	7 = 31.84%	9.82±0.158 min.-9.3; max.-10.4	9.716±0.313 min.-7.8; max.-11.6	49	10 = 20.48%	9,86±0,2569 min.-8,1 max.-11,4	10.37±0.12 min.-7.8 max.-11.9
2013	30	12 = 40%	9.933±0.3875 min.-8.5 ; max.-13.2	9.7166±0.4339 min.-6.8; max.-13.9	44	8 = 18.18%	9.35±0.54 min.-6.3 max.-11.4	10.263±0.2628 min.-6.2 max.-13.7
2014	27	5 = 18.51%	9.75±0.5129 min.-8.2 ; max.-11.4	9.0545±0.362 min.-6; max.-133	42	7 = 16.66%	9.5±0.5761 min.-6,3 max.-11,2	9.3771±0.2824 min.-5.2 max.-12,2
2015	24	7 =29.16%	10.142±0.4275 min.-8.8; max.-12.4	8.8117±0.4548 min.-5,1; max.-12,1	40	10=25%	9.36±0.6155 min.-4.9 max.-11.6	9.566±0.2895 6.7 12.6
2016	28	9 = 21.14%	9.922±0.4342 min.-7.7; max.-12	9.4842±0.2527 min.-6.9; max.-11.4	48	12 = 25%	9.7916±0.3462 8.2 11.7	9.8556±0.3113 5.7 13.5
2017	27	8 = 29.62%	9.93±0.486 min.-8.4; max.-11.7	8.3±0.468 min.-6; max.-12.6	44	7 = 15.9%	8.857±0.6252 7.1 11.8	9.4918±0.2935 7.1 13.3

2018	22	96 = 27.27%	8.62±1.50 min.-7.6; max.-11.2	8.33±0.540 min.-4.4; max.-10.9	41	4 = 8.8%	10.55±0.3095 9.7 11.1	9.587805±0.2751 5.7 13.3
2019	19	97 = 36.84%	9.78±0.456 min.-8.4; max.-11.3	8.55±0.44 min.-5.2; max.-10.8	39	6 = 15.38%	9.3±0.6865 6.8 11.5	10.3±0.28 7.3 14.4
2020	19	5(30%)	9.89±0.517 min.-8.4; max.-11.3	8.64±0.41 min.-4.9; max.-10.4	34	5(4.7%)	9.62±0.3813 8.2 10.3	9.3482±0.3050 6.7 13.8
		Mean	9.731666667	9.345			9.731666667	9.952608333
		Standard Error	0.172674301	0.251424728			0.172674301	0.131463361
		Minimum	8.85	8.3			8.85	9.34
		Maximum	10.71	10.78			10.71	10.48

Table 4. The results of ERI calculation in both sexes and in both groups of patients

Year	ERI in female patients receiving ESA before HD (group A)	ERI in female patients who were ESA treatment-naïve before HD (group B)	ERI in male patients receiving ESA before HD (group A)	ERI in female patients who were ESA treatment-naïve before HD (group B)
2009	19.6±6.751 min.-0,42; max.-55.05	13.89±1.99 min.-2.64; max.-38.98	12.67±3.10 min.-1.4 max.-27.36	9.7345±1.130 min.-0 max.-33.58
2010	19.80±6.64 min.-1.52; max.-55.059	8.718±0.985 min.-4.1; max.-14.6	12.166±3.5436 min.-1.4 max.-27.36	12.8995±2.43 min.-1.7 max.-41.8
2011	12.76±4.18 min.-0 max.-28.4	9.1420±1.51 min.-2.608 max.-22.6142	15.0745±5.644 min.-2.349 max.-35.4822	10.7949±1.0437 min.-2.62123 max.-22.404
2012	11.10389±1.8102 min.-4.5955 max.-18.61042	13.658±2.7470 min.-0 max.-28.05	9.6384±2.0752 min.-0 max.-23.894	8.9887±0.7289 min.-0 max.-18.987
2013	13.99903±2.3650 min.-0 max.-24,8139	15.38976±2.1783 min.-0 max.-32.08556	14.5867±2.7950 min.-0 max.-23894	9.917502±1.3143 min.-0 max.-35.27337
2014	12.784±3.516 min.-0 max.-21.7037	17.4817±1.7307 min.-0 max.-33.05785	13.13563±2.5487 min.-2.1258 max.-22.9489	12.90811±1.32504 0 28.14259
2015	10.0658±2.1560 min.-0 max.-17.04545	17.50755±2.282566 min.-0 max.-32.9912	13.44±3.0231 0 30.2343	11.1937±1.4334 0 30.12048
2016	11.44928±2.149045 0 1948052	15.02234±1.6210 2.7502 26.5252	9.8729±1.9644 1.0175 20.7039	11.7762±1.4079 0 26.86968
2017	11.7434±2.9603 0 22,7272	19.1943±2.6057 0 35.7142	16.9653±2.9135 5.2966 29.97003	12.9284±1.4629 0 30.2419

2018	11.78096±2.7276 4,6904 2160216	22.54±3.505033 4.80769 56.81818	10.97358±3.505033 6.8027 18.46438	13.60247±1.134344 6.8027 18.46438
2019	23.66±2.3193 13.0662 30.30303	19.79488±2.6887 5.102 37.0027	18.80719±2.5281 10.23018 27.57353	14.2744±1.3514 0 30.4414
2020	19.30099±5.1788 6.41256 30.30303	17.70515±2.48445 6.1274 35.46099	17.1362±5.6105 6.5821 38.8664	15.0261±1.9095 0 45.3429
	Mean-14.83 Standard Error-1.294 Minimum-10.06 Maximum-23.66	15.83625833 1.186223189 8.718 22.54	13.7039925 0.8421756 9.63 18.8	12.0036975 0.551053466 8.9887 15.0261

Conclusion

It is necessary to expand the scope, follow-up and treatment in patients with nephrological diseases without waiting for the progression of the chronic kidney disease. When administering ESA, always take into account the sex of the patients and consider the specific characteristics of female patients.

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