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Current Situation of Anemia Management among Hemodialysis Patients in Mongolia

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Objectives: The purpose of our study was to determine the current practice of anemia management prevalent among hemodialysis patients in Mongolia. Furthermore, we assessed the appropriateness of anemia management by comparing the observed practice to evidence-based clinical guidelines. **Methods:** A survey was conducted on 132 patients undergoing hemodialysis in State First Hospital, State Third Hospital, ICU Dialysis Center, and Intermed Hospital. All patients who were over 18 years of age with ESRD undergoing hemodialysis were included. Patients were excluded if they had cancer, were receiving chemotherapy or radiotherapy, or undergoing dialysis less than three times per week. Data on anemia parameters, erythropoietin dosing, iron supplementation, in addition to demographic data, were collected. The data were collected over a one year retrospectively from January 1 to December 31, 2018. Patients were assessed according to a pre-specified protocol. **Results:** Data were collected from 132 patients. The mean Hgb value for those patients was 10.31 ± 1.59 g/dL. Seventy-four patients (56.1%) had mean Hgb values between 9.5 and 11.5 g/dL, the target range recommended by KDIGO guidelines. The mean weekly prescribed dose of erythropoietin was 3825 ± 5054 IU/week (57 ± 72 IU/kg/week). Information on ferritin concentrations was available for 32 (24.2%) patients. The median serum ferritin concentration for those patients was 95.41 ng/mL (IQR=40.83 - 259.27). None of the patients had transferrin saturation (TSAT) values recorded. **Conclusion:** There is an opportunity to improve anemia management in hemodialysis patients in Mongolia through the evaluation of secondary causes of low response to erythropoietin and better monitoring and management of iron status.

Keywords: Anemia, Chronic kidney disease, Dialysis, Erythropoietin, Iron status

Introduction

Diseases of the urinary system have been one of the five major causes of morbidity among the population of Mongolia within the last decade [1]. The prevalence and incidence of end-stage renal disease (ESRD) have been increasing steadily for the past several years. Renal replacement therapy offered to patients with ESRD in Mongolia began with the introduction of hemodialysis in 1975, kidney transplantation in 1996, and peritoneal dialysis in 2014. Hemodialysis is the primary mode of treatment offered for patients ESRD in the country. It is expected that more than 100–140 new ESRD patients per year will need hemodialysis in Mongolia [2]. The anemia of ESRD is a common complication that leads to poor patient outcomes and quality of life, and if left untreated, hematocrit values of 18 - 24% are typical [3-6]. The introduction of erythropoiesis-stimulating agents in the 1980s has dramatically changed the situation [7]. Studies assessing the appropriateness of anemia management among dialysis patients have revealed that one-third of the surveyed patients had suboptimal hemoglobin levels and iron stores [8]. Despite the improvement in anemia management among hemodialysis patients for the last decade, previous studies reported that 10 - 23% of patients were not meeting current targets for hemoglobin [9-12]. There is no systematic study at present to address this issue among the dialysis population in Mongolia. The purpose of our study was to determine the current practice of anemia management prevalent among hemodialysis patients in Mongolia. Furthermore, we assessed the appropriateness of anemia management by comparing the observed practice to the Kidney Disease Outcomes Quality Initiative (KDOQI) evidence-based clinical guidelines and practice recommendations [6].

Materials and Methods

Study population

A survey was conducted of 132 patients undergoing hemodialysis in State First Hospital, Third State Hospital, ICU Dialysis Center, and Intermed Dialysis Center in Ulaanbaatar, Mongolia. All patients who were over 18 years of age with ESRD undergoing hemodialysis were included. Patients were excluded if they had cancer or were receiving chemotherapy or radiotherapy or undergoing dialysis less than three times per week.

Data collection

Data on anemia parameters including iron levels (μmol/l), ferritin (μmol/l) and transferrin saturation (TSAT, %), erythropoietin dosing, iron supplementation, in addition to demographic data were collected. The data were collected over a 1-year period retrospectively from January 1, 2018, to December 31, 2018. Patients were assessed according to our pre-specified protocol.

Categorization of patients

Study patients were stratified into categories based on lab values to compare our patient's findings to guidelines and previous studies. Their hemoglobin levels were classified as below, within, or above the recommended hemoglobin range of 9.5 – 11.5 g/dL in the by KDIGO guideline [6]. Their serum ferritin concentration was grouped as below, or ≥200 ng/mL, and we attempted to categorize their TSAT values based on being either below or ≥20% using the same guidelines. They were also classified as being below or above the threshold PTH of ≥300 ng/ml and albumin threshold of ≥36 g/L for comparison with other published results.

Statistical analysis

Descriptive statistics and frequency distributions were computed for all the variables. The data were tested for normality using the Shapiro-Wilk test. For normally distributed data, the t-test was used. For non-parametric data, the Mann-Whitney and Kruskal-Wallis tests were used. Statistical significance was determined at a p-value lower than 0.05. The Chi-square test was used for categorical data. All statistical analysis was performed using SPSS (version 25).

Ethical statements

The study was approved by the Research Ethics Committee of the Mongolian National University of Medical Sciences) (№2017/3-08). All patients provided written informed consent before participating in the study.

Results

1. Demographic and clinical characteristics of the patient sample

Data were collected from 132 dialysis patients with a mean age of 49.0 ± 12.7 years. The most common primary cause of end-stage renal failure was chronic glomerulonephritis 92 (69.2%). Baseline characteristics of the study population, stratified by the type of center where they received their dialysis (private vs. public), are depicted in Table 1.

Comparing the different types of centers, patients undergoing hemodialysis in private centers were more likely to be newer to dialysis (p=0.000), and with the numbers available in our study, fell just short of having a statistically significantly higher proportion of males (p=0.054).

2. Hemoglobin level

The mean hemoglobin (Hgb) value was 10.31 ± 1.59 g/dL. Seventy-four patients (56.1%) had mean Hgb values between 9.5 and 11.5 g/dL, the target range recommended by KDIGO guideline [13]. Thirty-four patients (25.8%) had mean Hgb values of less than 9.5 g/dL. Twenty-four (18.2%) exceeded the recommended range (>11.5 g/dL). Figure 1 shows the distribution of patients based on Hgb values.

3. Erythropoietin dose

The mean weekly prescribed dose of erythropoietin was 3825 ± 5054 IU/week (56 ± 71 IU/kg/week) (Table 2).

Figure 3 illustrates that the erythropoietin dose for private and public centers stratified by hemoglobin levels was not different in groups with hemoglobin levels below, within, or above the recommended range of 9.5 - 11.5 g/dl (p=0.19).

When comparing the erythropoietin dose per kg of body weight between public and private centers, those receiving dialysis at private centers received higher doses of erythropoietin (p=0.001)(Table 2). Figure 3 also shows that the patients at the private dialysis centers received higher doses of erythropoietin.

4. Monitoring iron status

None of the study patients received iron replacement therapy. Information on ferritin concentrations was available for 32 (24.2%) patients. The median serum ferritin concentration for those patients was 95.41 ng/mL (IQR=40.83 - 259.27). None of

Table 1. Characteristics of the study participants.

Characteristic	Total (n = 132)	Public centers (n=89)	Private centers (n=43)	P-value
Age (years)				
Mean ± SD	49.0 ± 14.2	48.4 ± 11.2	50.3 ± 15.4	0.458[a]
Sex, n (%)				
Male	77 (58.3)	47(52.8)	30 (69.8)	0.054[b]
Female	55 (41.7)	42(47.2)	13 (30.2)	
Dry body weight (kg)				
Mean ± SD	67.9 ± 53.6	67.6 ± 13.1	68.6 ± 16.4	0.730[a]
Primary renal disease, n (%)				
Glomerulonephritis	92 (69.2)	68(76.4)	24 (55.8)	0.091[b]
T2DM	30 (22.6)	16 (18)	14 (32.6)	
Unknown and other	10(8.2)	5 (5.65)	5 (11.6)	
Duration of dialysis (year) n (%)				
0.5–1.9	67 (50.75)	34(38.2)	17 (39.6)	0.000 [b]
≥2	65 (49.24)	55 (61.8)	26 (60.5)	

Note: [a] Mann-Whitney [b] Chi-square test
Abbreviations: T2DM- Type 2 Diabetes Mellitus

Table 2. Erythropoietin dosing in public and private centers.

	Total (n = 132)	Public centers (n = 89)	Private centers (n = 43)	P-value
Mean dose (IU/week) ± SD	3825 ± 5054	2426 ± 3750	6720 ± 6123	0.000[a]
Mean dose (IU/kg/week) ± SD	56 ± 71	36 ± 58	90 ± 84	0.001[a]

Note: [a] Mann-Whitney test
The distribution of mean erythropoietin dose in hemodialysis patients is shown in Figure 2.

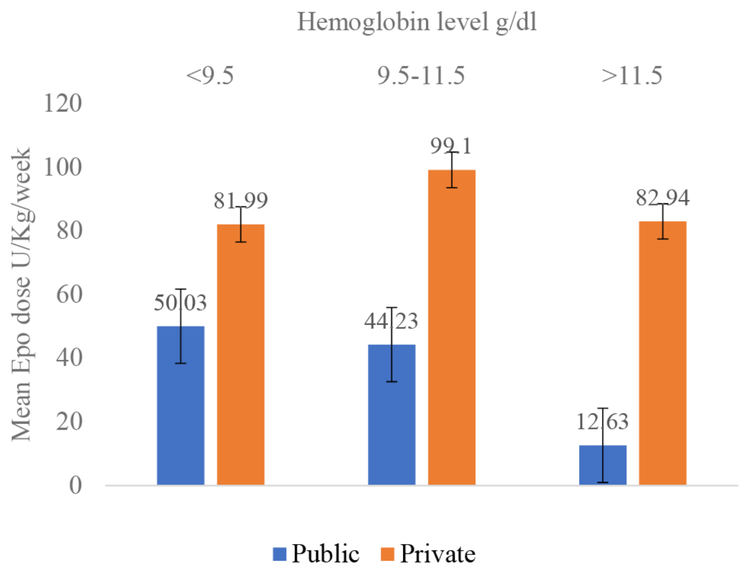

Figure 1. Distribution of patients based on hemoglobin value.

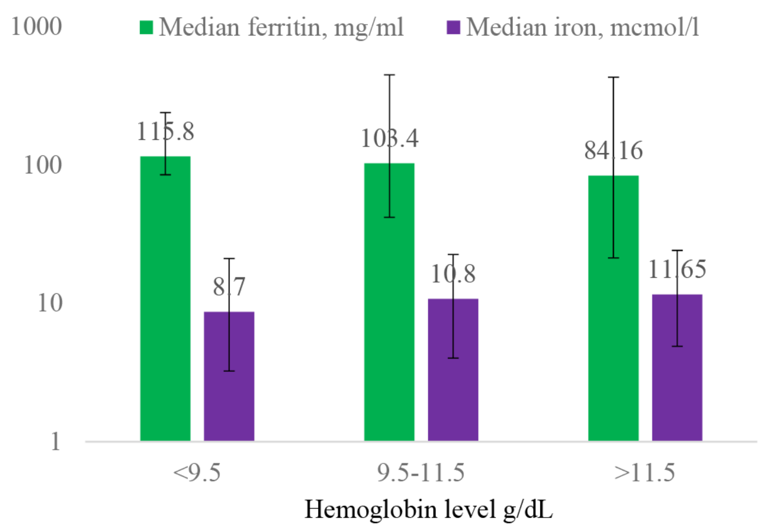

Figure 2. Distribution of weekly erythropoietin dose

those patients had transferrin saturation (TSAT) values recorded. Ten patients (31.25%) were assessed as having adequate iron status, as defined by the KDOQI guidelines as a serum ferritin concentration of ≥200 ng/mL. (Table 3). No TSAT values were documented, so those with a TSAT value of ≥20% could not be determined.

5. Patient characteristics associated with lower hemoglobin concentrations

The effect of factors such as gender, age, albumin level, parathyroid hormone (PTH), and duration of dialysis on the mean Hgb were investigated (Table 4). No significant differences were identified.

Figure 4 shows that the level of ferritin was not different between groups of patients with hemoglobin of less than 9.5, between 9.5 and 11.5, and more than 11.5 g/dl (p=0.82).

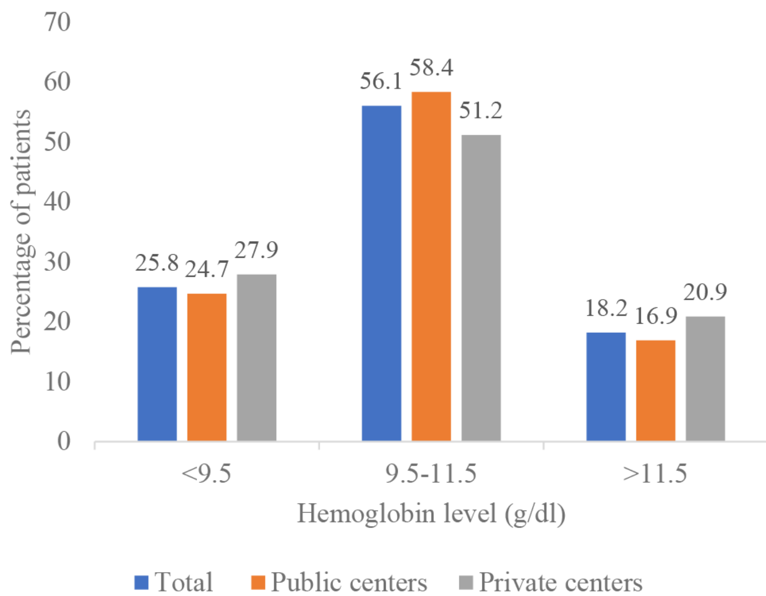

Figure 3. Weekly prescribed erythropoietin dose (mean ± SE) by hemoglobin level.

Table 3. Iron status assessment in different dialysis centers.

Iron status	Public centers	Private centers	P-value
Patients with recorded ferritin n (%)	23 (25.84)	9 (20.93)	
Mean ferritin level (ng/ml) ± SD	235.8 ± 351.6	241.63 ± 272.50	0.433[a]
Patients with ferritin >200 ng/ml (n)	6	4	

Note: [a] Mann-Whitney test

Table 4. Comparison of mean Hgb level by selected patient characteristics.

Characteristics	Mean Hgb g/dl ± SD	P-value
Age		
18–44 (n = 47)	**10.03 ± 1.69**	**0.310[a]**
45–65 (n = 74)	10.54 ± 1.56	
≥65 (n = 11)	10.00 ± 0.96	
Gender		
Female (n = 55)	10.19 ± 1.57	0.450[b]
Male (n = 77)	10.39 ± 1.60	
Albumin		
≥36 g/L (n = 77)	10.48 ± 1.6	0.062[b]
<36 g/L (n = 13)	9.56 ± 1.57	
PTH		
≥300 ng/ml (n = 32)	10.62 ± 1.7	0.971[b]
<300 (n = 15)	10.6 ± 1.58	
Duration of dialysis (year)		
0.5–0.99 (n = 7)	10.16 ± 1.28	0.666[a]
1–1.99 (n = 44)	10.09 ± 1.51	
>2 (n = 81)	10.45 ± 1.65	

Note: [a] Kruskal Wallis test [b] Mann-Whitney
Abbreviation: PTH – parathyroid hormone

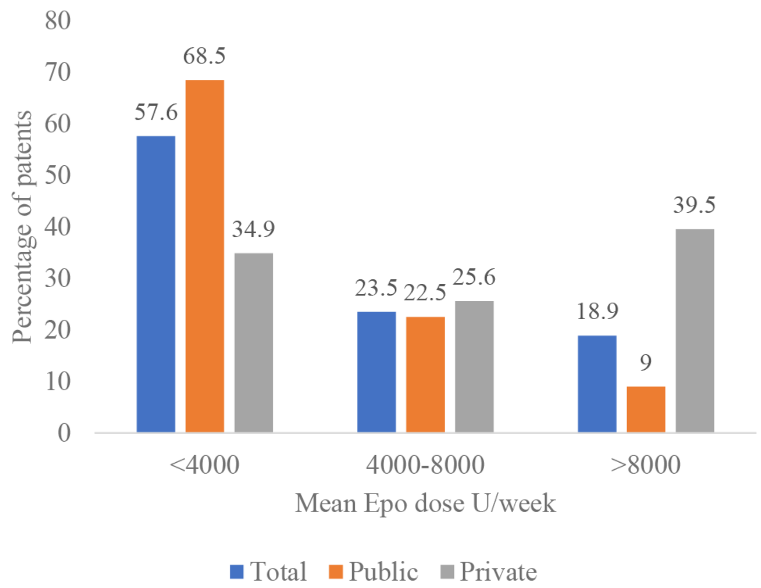

Figure 4. Iron status (median, IQR) by hemoglobin level.

Discussion

We are not aware of a systematic, multi-center study addressing anemia management among the dialysis population in Mongolia. The purpose of our study was to determine the current practice of anemia management among prevalent hemodialysis patients. The most common primary cause of end-stage renal failure was chronic glomerulonephritis, followed by diabetes mellitus. The majority of the study population were male (58.3%). The mean hemoglobin in our study was 10.31 ± 1.59 g/dL, which is lower than in most hemodialysis studies reported previously [8,9,14]. Twenty-six percent of patients had a hemoglobin level lower than 9.5 g/dl. The recommended level is 9.5-11.5 g/dl [13], and this shows that there is an area for improvement in the practice of anemia management. The European Survey of Anemia Management (ESAM) [14] was a single day randomized survey conducted to assess anemia management in 8100 dialysis patients from 12 countries and demonstrated that only 66% of patients achieved Hgb level >11.0 g/dL. The Dialysis Outcomes and Practice Patterns Study (DOPPS) [9], a prospective observational study based on the data collected from 4591 hemodialysis patients from five European countries, found that only 53% of the patients achieved Hgb level >11.0 g/dL.

It is recommended that before the initiation of erythropoiesis-stimulating agents, iron status with serum ferritin and TSAT levels should be assessed in order to achieve adequate response [15].

The KDIGO guidelines recommend assessing iron stores in dialysis patients at least every three months, moreover in patients not on erythropoiesis-stimulating agents, a trial of initial IV iron has been suggested [13].

These tests may be altered by factors that are unrelated to iron metabolism. A common example is the chronic inflammatory state associated with malnutrition and clinical or subclinical infections, which may increase serum ferritin levels that falsely suggest a state of iron repletion [16]. Therefore, if ferritin levels suggest replete iron stores and TSAT level suggests insufficient iron availability, investigations should be done to exclude these other potential causes. However, mostly due to insurance issues, most of these tests are not done routinely in Mongolia. Some centers preferred to check serum iron levels, some ferritin levels, and none measure TSAT routinely. In our study, ferritin values were available for only 32 patients, and of them, 10 have an optimal ferritin level. An important observation is that regardless of the hemoglobin level, the ferritin values were not significantly different. In the patients with the highest hemoglobin, the ferritin values were still comparably low (Figure 4). This issue was addressed in a study conducted in the three largest cities in China (Beijing, Guangzhou, and Shanghai) [12].

As shown in Figure 3, the erythropoietin dosage administered did not differ between those people whose hemoglobin was below 9.5 and those meeting the target values between 9.5 - 11.5 g/dL, suggesting the dose was not being adjusted based on lab results. One explanation is that erythropoietin is not covered by insurance in Mongolia, unlike in many developed countries [17,18]. Hypo responsiveness to erythropoietin is another probable cause of the low hemoglobin level observed in some of our patients. KDOQI guidelines [6] defined the hypo responsiveness to erythropoietin as the presence of at least one of the following: a significant increase in the erythropoietin dose requirement is needed to maintain a certain Hgb level, a significant decrease in Hgb level despite a constant erythropoietin dose, or failure to increase the Hgb level to greater than 11 g/dL despite an erythropoietin dose equivalent to erythropoietin greater than 500 IU/kg/week. Several factors are associated with hypo responsiveness to erythropoietin, including iron deficiency, chronic blood loss, inflammation/infection, vitamin deficiencies, inadequate dialysis, hyperparathyroidism, and malignancy [19, 20]. Patients with an inadequate response to erythropoietin should undergo an evaluation to identify possible causes of the low response to erythropoietin and iron therapy. However, this may not always be the case in practice. A survey (SCOT) on physicians' attitudes towards strategies for the treatment of anemia in patients with CKD found that 86% (115/134) would investigate the cause of the low response to erythropoietin; however, a significant number of physicians would increase the dose without further investigation of the causes of inadequate response [21]. In our study, the groups of patients with low hemoglobin and optimal hemoglobin levels were prescribed similar doses of erythropoietin, even when doses were adjusted to per kg of body weight (Figure 3). When compared, erythropoietin dose per kg of body weight at private centers were prescribed higher doses of erythropoietin (p=0.001). Because erythropoietin is not covered by insurance in both of these settings, there should be other reasons for the difference in practice, such as the requirement for a patient copayment for treatment, the number of patients per physician, or patient education.

The percentage of patients with elevated Hgb concentrations (>11.5 g/dL) was 18.2. Many studies also reported a high proportion of hemodialysis patients with Hgb level >12 g/dL [9,10,22,23]. Number of studies questioned the beneficial effects of targeting Hgb levels in excess of 12.0 g/dL [24-27]. A meta-analysis of nine randomized controlled trials that enrolled 5143 chronic kidney disease patients found a significantly higher risk of all-cause mortality (risk ratio 1.17, 95% CI 1.01–1.35; p = 0.031) arteriovenous access thrombosis (risk ratio 1.34, 95% CI 1.16–1.54; p = 0.0001), and poorly controlled blood pressure (risk ratio 1.27, 95% CI 1.08–1.50; p = 0.004) in the higher Hgb target group (12–16 g/dL) than in the lower hemoglobin target group (9–12 g/dL) [23]. One possible explanation could be that dialysis patients are able to tolerate anemia at a higher degree than what would be expected, and many dialysis-related factors make the delivery of oxygen to the tissues easier [28]. Other evidence also suggests that targeting hemoglobin levels in excess of 12.0 g/dL leads to small and not clinically meaningful improvements in the health-related quality of life of the dialysis.

In a study conducted among the US dialysis population [23], they concluded that females, patients of African descent, patients 18–11 years old, and patients receiving hemodialysis for less than six months exhibit significantly lower hemoglobin values despite being prescribed on average, significantly higher erythropoietin doses than males, whites, older patients, and patients receiving hemodialysis for six months or more. The same study found an association between serum albumin values and administration of IV iron and Hg values >11 g/dL. In the multi-center study conducted in China of patients who were female, younger, or recently hospitalized patients had higher odds of having a Hgb < 9 [12]. Our results showed that having low serum albumin concentration appears to be associated with suboptimal serum hemoglobin concentrations (Table 3). Malnutrition, chronic inflammatory state, and low socio-economic status could be contributing factors among hemodialysis patients [29-31]. In a study by Al-Ageel et al., they found that female gender and low albumin level was associated with lower hemoglobin levels[11]. Our study did not reveal similar differences in hemoglobin based on gender or albumin levels.

Compared to the study by Al-Ageel et al. where the mean weekly prescribed dose of erythropoietin was 8099 ± 5946 IU/week (135 ± 99 IU/kg/week), in our study the mean weekly prescribed dose of erythropoietin was significantly lower at 3826 ± 5055 IU/week (56 ± 71 IU/kg/week), which is not far from the starting dose. Information on ferritin concentrations was available for 55% of their patients, whereas, in our study, 24.2% had recorded ferritin levels. Fifty-two patients had transferrin saturation (TSAT) values recorded in the study conducted in Saudi Arabia, while it was clearly not routinely recorded in

Mongolia [11]. As previously reported, the lack of coverage for laboratory tests could be one of the reasons for such a difference in our study. Zuo et al. reported that data on ferritin and TSAT levels were available in 66.5% and 60.1%, respectively [12].

There are some limitations to this study. We collected our data manually from the patients' medical records, and some information was missing. Several factors influencing hemoglobin values such as the presence of infection, inflammatory states, blood loss, and parathyroid hormone values were not evaluated. Due to the retrospective nature of our study, major outcomes due to poor anemia management such as hospitalization rate and mortality were not studied. We need larger studies addressing suboptimal anemia management such as social and economic factors, physician attitude, and patient compliance.

In conclusion, there is an opportunity to improve anemia management in hemodialysis patients in Mongolia through the evaluation of secondary causes of low response rate and better monitoring and management of iron status.

Conflict of Interest

The authors state no conflict of interest.

Acknowledgments

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