# The Adverse Drug Reactions of Erythropoietin in Chronic Kidney Disease Patients

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**Abstract.** Anaemia is a severe problem for chronic kidney failure patients who want to maintain their quality of life. A decrease in erythropoietin production causes anaemia. Erythropoietin therapy is crucial in treating anaemia in chronic kidney failure patients. However, erythropoietin therapy can cause adverse drug reactions. This study aims to identify the case of adverse erythropoietin in chronic kidney failure patients in hospitals. This study implemented a cross-sectional observational design with prospective data collection on chronic kidney failure patients undergoing routine hemodialysis. The research subjects were patients who underwent routine hemodialysis and received erythropoietin therapy from October to December 2020 at the hemodialysis unit of Moewardi Hospital Surakarta and Universitas Negeri Surakarta Hospital. The data obtained from medical records and interviews with patients or families were then analyzed descriptively. The Naranjo algorithm was applied to determine whether the patients' adverse reactions or complaints were related to the use of erythropoietin. The study subjects were 117 patients, consisting of 64 male patients (54.70%) and 53 female patients (45.30%). The most age range category of patients was 55–64 years by 38 patients (32.48%), and the length of hemodialysis record was 12–24 months (51.28%). Identification of adverse drug cases showed that 21 patients (7.92%) experienced side effects after using erythropoietin. The most prevalent side effects of using erythropoietin therapy were on the cardiovascular system in increased blood pressure and oedema in 12 patients (10.25%). The pharmacists should concern about the side effects of using erythropoietin in chronic kidney failure patients undergoing hemodialysis to minimize the risk in the anaemia treatment.

**Keywords:** Hemodialysis · Erythropoietin · Side Effects · Chronic Kidney Failure

## 1 Introduction

Based on Basic Health Research (Riskesdas) data in 2018, the prevalence of chronic kidney disease in Indonesia has increased by 1.8% from 2013, with an average of 3.8% throughout Indonesia [1]. Data from the Indonesian Renal Registry (2018) showed that


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active patients undergoing hemodialysis were147,340, while new patients were 73,935 [2].

Based on data from the Indonesian Renal Registry in 2018, anaemia was one of the critical clinical conditions of dialysis patients, additionally, the procedures for the treatment of anaemia in Indonesia apply a Hb limit of <10 g/dL to obtain further therapy. From the 87,000-patient data, only 19,557 patients (22%) experienced Hb > 10 g/dL. The use of erythropoietin therapy in hemodialysis patients from 2010 to 2018 continued to increase; in 2018, 652,708 people [2].

Erythropoietin is the selective therapy for anaemia in chronic kidney disease patients with a target Hb level of 11–12 g/dL. Corrective phase erythropoietin therapy is conducted when Hb < 10 g/dL. The correction phase of erythropoietin therapy aims to correct anaemia until the Hb target is met. Erythropoietin is given subcutaneously twice weekly for four weeks at a 2000–5000 IU dose. The expected response target is that Hb increases by about 0.5–1.5 g/dL in four weeks [3].

Erythropoietin therapy is reported to have side effects that occur immediately after using epoetin. The side effect that has been conveyed is flu-like symptoms that will subside 24 h after taking erythropoietin. Other side effects are increased blood pressure, thrombosis, allergic reactions, seizures, hyperkalemia, and thrombocytosis [4] [5]. Side effects due to the use of erythropoietin are more frequently reported in patients undergoing dialysis [6]. Complications and the use of various drugs in chronic kidney failure patients cause a high possibility for erythropoietin side effects. Therefore, adverse drug reactions in the use of erythropoietin should be identified. Measurement of erythropoietin side effects can be utilized to minimize risk in treating anaemia in chronic kidney failure patients undergoing hemodialysis [7].

Ramadhela explained that the most common side effects when using epoetin were on the cardiovascular system by 20 patients (40%) in the form of oedema and an increase in blood pressure; the category of side effects was probable (high probability of side effects). Side effects with definite category (definite side effects) occurred in one patient with symptoms of dizziness after taking epoetin [8].

## 2 Method

### 2.1 Research Design

The study implemented a cross-sectional observational research design. Data were obtained prospectively from medical records and patient interviews at the hospital. This research has received Ethical Clearance approval from the Health Research Ethics Committee (KEPK), Faculty of Medicine, Universitas Muhammadiyah Surakarta, with letter number Ref. No. 2999/B.1/KEPK-FKUMS/VII/2020.

### 2.2 Place and Time of Research

The study was completed from October to December 2020 at the hemodialysis unit of Moewardi Hospital Surakarta and Universitas Negeri Surakarta Hospital.

### 2.3 Research Materials and Subjects

The research subjects were all outpatients diagnosed with chronic kidney failure undergoing hemodialysis at the hemodialysis unit at Moewardi Hospital Surakarta and Universitas Negeri Surakarta Hospital. Subject inclusion criteria included outpatients diagnosed with chronic kidney failure, patients who had received erythropoietin therapy for at least four weeks, and patients undergoing hemodialysis. Exclusion criteria were patients who had incomplete medical record data and passed away during data collection.

The sampling technique used was consecutive sampling. The sample was selected based on predetermined inclusion and exclusion criteria. The sampling process completes after the number of samples is sufficient or the specified research time limit has been met [9]. The minimum sample size used in this study was calculated using the sample size determination formula in health studies. It is by estimating a population proportion with specified absolute precision. The formula used in this research is:

$$n = \frac{\mathrm{Z}\,\alpha^2.\mathrm{P.Q}}{\mathrm{d}^2}$$

Information:
N: Number of samples
Zα: 95% confidence level (1.96)
P: Proportion (0.58)
Q: 1-P
d: Precision (10% = 0.1)
Calculation of the sample size is as follows:

$$n = \frac{1,96^2.0,58.(1-0,58)}{(0,1)^2}$$

$$n = 93,58$$

From these calculations, the minimum number of samples is 94 samples. In this study, the number of samples obtained was 117 patients.

### 2.4 Data Analysis

Descriptive analysis was used to determine patient characteristics (gender, age, comorbidities, and length of history of hemodialysis).

The side effects of using erythropoietin were evaluated from interviews, physical examinations, patient complaints recorded in medical records, and laboratory examinations. Evaluation of drug side effects was completed by asking whether the patient experienced side effects that might occur due to the use of erythropoietin based on the reference Drug Information Handbook, edition 17 of 2009.

The Probability determination of side effects using erythropoietin was based on the Naranjo algorithm. It consists of ten questions aiming at ascertaining the primary differences in the probability aspects of side effects occurring by answering Yes, NO, or do not know. The results were then summed and the values obtained were used to identify the probability of drug side effects. The range of values was used to determine the probability of side effects using erythropoietin in chronic kidney failure patients.

# 3 Results and Discussion

## 3.1 Characteristics of Research Subjects

Characteristics of the subjects in this study included gender, age, comorbidities, and duration of hemodialysis history obtained from medical record data and patient interviews. Then, descriptive statistical analysis was performed.

Table 1 displays the data on the characteristics of the subjects based on gender. The subjects were 117 patients consisting of 64 male patients (54.70%) and 53 female patients (45.30%). It is in line with several previous studies. One of them is Silbiger and Neugarten's (2008) study, which revealed that with polycystic, membranous nephropathy, and chronic kidney disease without an unknown cause, male patients developed terminal kidney failure faster than women [10].

**Table 1.** Characteristics of Research Subjects

| Patient Characteristics | Classification | Total | % |
|---|---|---|---|
| Age | 10–14 years old | 1 | 0.85 |
| | 15–24 years old | 5 | 4.27 |
| | 25–34 years old | 7 | 5.98 |
| | 35–44 years old | 21 | 17.95 |
| | 45–54 years old | 29 | 24.79 |
| | 55–64 years old | 38 | 32.48 |
| | ≥65 years old | 16 | 13.68 |
| Gender | Male | 64 | 54.70 |
| | Female | 53 | 45.30 |
| History of Hemodialysis | <12 months | 33 | 28.21 |
| | 12–24 months | 60 | 51.28 |
| | 25–36 months | 10 | 8.55 |
| | 37–48 months | 10 | 8.55 |
| | >48 months | 4 | 3.42 |
| Comorbidities | Hypertension | 53 | 45.30 |
| | Hypertension + CHF | 23 | 19.66 |
| | Hypertension + CHF + DM | 7 | 5.98 |
| | Hypertension + DM | 15 | 12.82 |
| | Hypertension + Gout | 7 | 5.98 |
| | Hypertension + Hypercholesterolemia | 7 | 5.98 |
| | DM | 5 | 4.27 |

In Wandilla's research (2014) at the UGM Academic Hospital in Yogyakarta, it was mentioned that the percentage of male patients undergoing hemodialysis was 62.5% [11]. Septiwi's research (2010) found that the percentage of male patients undergoing hemodialysis at the Margono Soekarjo Hospital, Purwokerto, was 58.4% [12].

Safarudin (2012) discovered that the number of male patients undergoing hemodialysis was more than female patients, 53.2% [13]. In females, the decrease in GFR occurs more slowly. It is because, in women, the systolic blood pressure is 10 mmHg lower than in men. Blood pressure is one of the primary determinants of atherosclerosis and the development of chronic kidney disease. Other aspects that can affect the decline in kidney function include differences in hormonal conditions and lifestyle, including protein intake, salt, smoking habit, alcohol, and supplement drinks [14].

The age in Table 1 is divided into several classifications according to the age category in the 2018 Indonesian Renal Registry. This study results revealed that the highest proportion was in the 55–64 year age group by 38 patients (32.48%) compared to other age groups.

Based on Ana et al. (2013), the average age of chronic kidney disease patients undergoing hemodialysis in Brazil was 51.90 years with an age range of 28–76 years [15]. Additionally, a study conducted by Cabral et al. (2005) uncovered that the average age of chronic kidney disease patients undergoing hemodialysis in Brazil was 50.4 years, with the largest age group being 58–62 years [16].

According to Junaidi (2009), the average age of chronic kidney disease patients undergoing hemodialysis in Jakarta was 50.48 years [17]. Research by Weiner et al. (2005) explained that chronic kidney disease could occur at any age. However, at the age of 30 years, there will be progressive physiological changes in the glomerulus due to glomerulosclerosis, resulting in a decrease in GFR reaching 8 ml/minute/1.73 $m^2$ from normal GFR. At the age of 40 years, there will be a decrease of approximately 10% in the number of functional nephrons after the patient is 40 years old due to nephrosclerosis and glomerulosclerosis, which will cause the patient to experience chronic kidney disease and must undergo hemodialysis [18].

The high prevalence of chronic kidney disease in old age is caused by various risk factors such as diabetes and hypertension. Older age is a risk factor for progression of chronic kidney disease to end-stage, low mean glomerular filtration rate and higher rates of kidney loss occur in elderly patients compared to younger patients [19]. The results of this study are consistent with research conducted by Badariah et al. (2017), which elucidated that the age proportion of patients with chronic kidney failure at the Kotabaru District Hospital is primarily in the age range of 41–50 years with 15 patients (30%) and at the age of 51–60 years with 14 patients (28%) [20].

The characteristics of patients in Table 1 based on the type of comorbidities is hypertension by 53 patients (45.30%). Hypertension is a disease complication often suffered by CKD patients undergoing hemodialysis. Other comorbidities frequently found in CKD include fluid and electrolyte abnormalities, anaemia, hyperphosphatemia, hyperparathyroidism, metabolic acidosis, cardiovascular disease, and poor patient nutritional status. Hypertension as the primary cause or complication of CKD can cause damage to the kidneys due to uncontrolled blood pressure, increasing systemic blood pressure in the glomeruli [21].

Hypertension can be a leading cause of chronic kidney disease. High blood pressure can damage blood vessels gradually, which can reduce blood supply to vital organs such as the kidneys. High blood pressure can damage the tiny filtering units in the kidneys so that the kidneys can not dispose of waste and excess fluid in the blood. Excess fluid in the blood vessels can build up and increase blood pressure. Hypertension can also be a complication of chronic kidney disease. The kidneys play a crucial role in maintaining blood pressure. The abnormal kidney function causes impaired blood pressure regulation; as a result, blood pressure increases [22].

These study results are in line with research conducted by Sprague et al. (2018), which showed that most patients with chronic kidney failure suffered from comorbidities of hypertension, diabetes mellitus, and heart disease, where patients ad more than three comorbidities were 76.3% [23].

Hemodialysis is a kidney replacement therapy widely used to treat chronic kidney disease. The characteristics of the length of hemodialysis record in outpatients diagnosed with chronic kidney failure undergoing hemodialysis with erythropoietin administration at most were 12–24 months (51.28%). These results are consistent with Novitasari's (2015) research, which revealed that the proportion of characteristics based on the length of hemodialysis is mainly in the old category by 38 patients [24]. Research by Varelli and Aurora (2006) further elucidated that the mortality rate occurs in the first six months of dialysis, which will increase after six months of dialysis. At each age level, CKD patients on dialysis have a significantly increased mortality rate compared to non-dialysis and in person who does not suffer from kidney disease [25].

Folic acid deficiency can coexist with uremia, and if the patient is receiving hemodialysis therapy, water-soluble vitamins are lost through the dialysis membrane. An iron deficiency, one of the causes of anaemia in CKD, can be caused by blood loss during hemodialysis and poor gastrointestinal absorption. The hemodialysis process can cause a loss of 3–5 g of iron per year. Normally, individuals lose 1–2 mg of iron per day, so that in hemodialysis, patients lose 10–20 times more iron [17].

### 3.2 Adverse Drug Incidence Profile

Manifestations of drug side effects were obtained from interviews with patients in the form of complaints after using erythropoietin and complaints in the medical record of the patients' daily hemodialysis status during the study. The results indicated that of the 117 patients, 21 (7.92%) patients experienced side effects related to the use of erythropoietin. These data were obtained from the results of patient interviews after taking erythropoietin. Additionally, the patients' medical records also showed similar complaints during the study period. The Naranjo algorithm is used to estimate whether the side effects or complaints felt by the patients are side effects from erythropoietin.

Table 2 contains the recapitulation results of determining the side effects probability of erythropoietin used in the study, employing the Naranjo algorithm. Naranjo's algorithm classifies the probability of adverse drug reactions based on a list of questions. Those questions are factors related to drug administration and the occurrence of drug side effects, including other causes, dose-response relationship, and previous patient experience with drug administration. Drugs are evaluated individually for causality, and

**Table 2.** Probability of Side Effects Based on Naranjo Algorithm

| Side effects | Number of Cases (%) | Side Effects Category |
|---|---|---|
| **Cardiovascular** | | |
| Blood Pressure Increased | 9 (7,69) | *Probable* |
| Oedema | 3 (2,56) | *Probable* |
| **Gastrointestinal** | | |
| Nauseous | 6 (5,13) | *Probable* |
| **Central Nervous System** | | |
| Dizziness | 2 (1,71) | *Definite* |

Description:
Probable: High probability of side effect, Naranjo algorithm value 5-8
Definite: Definite side effects, Naranjo algorithm value 9

points are deducted if other factors contribute to the side effect, weakening the causal association [26].

Clinical evaluation of adverse drug use requires careful measurement. After obtaining a detailed description and severity of the cases, an explanation or other possible etiology that may have caused the case should be evaluated (non-medicated causes, worsening of pre-existing conditions, etc.). Likewise, the patients' age, gender, and medical condition and the factors that can cause, exacerbate, or even manifest these reactions should be considered [27].

Based on Table 2, the most common side effects of epoetin were the cardiovascular system by 12 patients (10.25%) in the form of increased blood pressure and oedema. Side effects such as an increase in blood pressure that occurred in this study can be stated to be true side effects due to the use of epoetin. However, based on Table 2, the probability of the side effects is probable (high). It is possible to have other factors besides erythropoietin that cause this complaint.

Ramadhela (2018) found that the most common side effects of using epoetin were on the cardiovascular system with 20 patients (40%) in the form of oedema and increased blood pressure. The category of side effects was probable (high probability of side effects). Side effects with definite category occurred in one patient with symptoms of dizziness after epoetin injection [8].

This study also evaluated the patients' blood pressure before and after hemodialysis by looking at the patients' blood pressure records in the patients' daily hemodialysis status to see the side effect. The records of the patients' blood pressure measurements indicated that there was a tendency for the patients' blood pressure to increase after hemodialysis constantly. Nevertheless, there were also results of the patients' blood pressure being unstable (sometimes increasing or decreasing) during erythropoietin therapy. Thus, it cannot be stated that the administration of erythropoietin therapy caused the increase in blood pressure because the possibility of an increase in blood pressure can be caused by the patients' non-compliance in fluid intake. Therefore, it increases blood pressure or the presence of other factors.

**Table 3.** Side Effects of Using Erythropoietin in Chronic Kidney Failure Patients in Hospitals

| Patient Number | Patient Complaint | | Patient Reactions and Complaints | Naranjo score | Side Effects Category |
|---|---|---|---|---|---|
| | Interview result | Written on Patient HD Status | | | |
| 10 | The patient's blood pressure was high after taking erythropoietin | The patient's blood pressure was high with oedema | Increase in blood pressure | 6 | Probable (high probability) |
| 11 | The patient claimed that the side effects of injecting erythropoietin had never been felt with certain clinical symptoms | Oedema was characterized by the patient's weight gain and swelling in the legs | Oedema | 6 | Probable (high probability) |
| 15 | Nausea, the side effects felt by the patient after hemodialysis was intermittent, the patient was difficult to determine whether the side effects are from erythropoietin or not | The patient felt nauseous about 15 min after taking erythropoietin | Nauseous | 5 | Probable (high probability) |
| 18 | The patients complained the nauseous about ten minutes after the epoetin injection | There was a complaint of nausea after epoetin injection and it was gone by itself about 24 h after epoetin injection | Nauseous | 5 | Probable (high probability) |

(*continued*)

**Table 3.** (*continued*)

| Patient Number | Patient Complaint | | Patient Reactions and Complaints | Naranjo score | Side Effects Category |
|---|---|---|---|---|---|
| | Interview result | Written on Patient HD Status | | | |
| 19 | High blood pressure after taking erythropoietin followed by dizziness about ten minutes after the epoetin injection | There was an increase in blood pressure after epoetin injection | Increase in blood pressure | 6 | Probable (high probability) |
| 21 | The patient's blood pressure was high after the use of erythropoietin | The patient's blood pressure increased after epoetin injection | Increase in blood pressure | 6 | Probable (high probability) |
| 24 | The patient said that the side effects of using erythropoietin had never been felt with certain clinical symptoms | Oedema was characterized by the patient's weight gain and swelling in the legs | Oedema | 6 | Probable (high probability) |
| 30 | The patient said he was frequently nauseous after the epoetin injection | The patient felt nauseous after epoetin injection | Nauseous | 5 | Probable (high probability) |
| 32 | The patient's blood pressure was high after the use of erythropoietin | The patient's blood pressure increased | Increase in blood pressure | 6 | Probable (high probability) |

(*continued*)

**Table 3.** (*continued*)

| Patient Number | Patient Complaint | | Patient Reactions and Complaints | Naranjo score | Side Effects Category |
|---|---|---|---|---|---|
| | Interview result | Written on Patient HD Status | | | |
| 34 | The patient said that the side effects of using erythropoietin had never been felt with specific clinical symptoms | Oedema was characterized by the patient's weight gain and swelling in the legs | Oedema | 6 | Probable (high probability) |
| 35 | The patient said he felt nauseous after the epoetin injection | The patient complained about nausea after epoetin injection | Nauseous | 5 | Probable (high probability) |
| 38 | The patient felt dizzy after epoetin injection | The patient complained about dizziness after epoetin injection | Dizziness | 9 | Definite (definite side effect) |
| 40 | The patient's blood pressure was high after taking erythropoietin | Blood pressure increased after epoetin injection | Increase in blood pressure | 6 | Probable (high probability) |
| 54 | The patient's blood pressure was high after taking erythropoietin | Blood pressure increased after epoetin injection | Increase in blood pressure | 6 | Probable (high probability) |
| 63 | The patient's blood pressure was high after using erythropoietin | Blood pressure increased after epoetin injection | Increase in blood pressure | 6 | Probable (high probability) |

(*continued*)

**Table 3.** (*continued*)

| Patient Number | Patient Complaint | | Patient Reactions and Complaints | Naranjo score | Side Effects Category |
|---|---|---|---|---|---|
| | Interview result | Written on Patient HD Status | | | |
| 84 | The patient's blood pressure was high after using erythropoietin | Blood pressure increased after epoetin injection | Increase in blood pressure | 6 | Probable (high probability) |
| 85 | The patient claimed he was often nauseous after the epoetin injection | The patient felt nauseous after epoetin injection, and it would heal by itself | Nauseous | 5 | Probable (high probability |
| 88 | The patient's blood pressure was high after using erythropoietin | There was an increase in blood pressure after epoetin injection | Increase in blood pressure | 6 | Probable (high probability) |
| 93 | The patient felt dizzy after epoetin injection | The patient felt dizzy about ten minutes after the epoetin injection | Oedema | 9 | Definite (definite side effect) |
| 97 | The patient claimed he was often nauseous after the epoetin injection | The patient felt nauseous after the epoetin injection and healed by itself after resting | Nauseous | 5 | Probable (high probability) |
| 101 | The patient's blood pressure was high after taking erythropoietin | There was an increase in blood pressure after epoetin injection | Increase in blood pressure | 6 | Probable (high probability) |

The increase in the patients' blood pressure due to the use of erythropoietin usually appears 2–16 weeks. This increase in blood pressure is caused by an increase in the number of red blood cells. Thus, it can increase blood viscosity, decrease the hypoxic vasodilation response, or increase endothelial cell binding, causing a decrease in the release of Nitric Oxide (NO), which plays a role in maintaining blood vessel tone, especially for the relaxation process of blood vessels due to an increase in hemoglobin.

In addition, correction of anaemia causes an increase in peripheral resistance through direct arteriolar vasoconstriction [28] [29] [30].

Based on Table 3, patient number 19 from the interview reported that blood pressure increased after using erythropoietin, followed by dizziness about ten minutes after the epoetin injection. Blood pressure increased from the normal value of the patient's blood pressure after using erythropoietin about 4–5 times of use. From the records of the patient's blood pressure measurements for three months, it was proven that there was a tendency for blood pressure to increase quite sharply after using erythropoietin for two weeks. The results of measuring blood pressure using erythropoietin for three months in inpatient number 19 were random. Hence, it is difficult to determine the patient's blood pressure increase. In addition to complaining about an increase in blood pressure, patient number 19 also reported that the patient felt dizzy about ten minutes after the epoetin was injected. Based on the Naranjo algorithm, this symptom was a definite side effect.

In this study, side effects in the form of oedema were identified from medical records, marked by an increase in the patient's weight due to the accumulation of body fluids. The category of side effects in the form of oedema is probable. Hence, other factors besides erythropoietin side effects affect oedema, including the patient's non-adherence to the patient's diet to fluid intake resulting in fluid accumulation.

The limitation of this study is that researchers cannot monitor patients for an extensive period to examine the cause of adverse reactions in minimizing the risk of anaemia treatment in chronic kidney failure patients undergoing hemodialysis.

## 4 Conclusion

1. The most common side effect of using epoetin was on the cardiovascular system by 12 patients (10.25%) in increased blood pressure and oedema.
2. The role of pharmacists is needed to undergo clinical pharmacies in hospitals so that identification and treatment of drug side effects can be performed, especially in treating anaemia in hemodialysis patients.

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