Association Analysis of Complications, Number of Drugs, and Medication Adherence in End-Stage Renal Disease Patients Undergoing Hemodialysis

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Abstract: Hemodialysis (HD) in its implementation is reported to cause complications. Complications may cause the patients to receive >3 types of drugs and decrease their medication adherence. This study aimed to analyze the association between the number of complications and the number of drugs, and the association between the number of drugs with medication adherence in End-Stage Renal Disease (ESRD) patients. This research was conducted at the private hospital Denpasar in March-May 2021 with a cross-sectional design involving 93 respondents. The purposive sampling technique was used according to inclusion criteria (ESRD patients with complications, undergoing HD at least twice a week, signing informed consent) and exclusion criteria (having poor or unstable health, unable to communicate well). The research instrument used was a questionnaire (ESRD-AQ). The Mann-Whitney test and Kendall tau-b test were used to analyze the association in this study. The results showed that the majority of patients were <65 years old (83.9%), male (66.7%), 35.5% high school education, still working (51.6%), and long of diagnosed with ESRD <5 years (77%), respectively. The average patient had ≥2 complications (81.72%) and 80.64% received 1-6 types of drugs with high levels of medication adherence (67.74%). There was an association between the number of complications and the number of drugs (p= 0.026) and the association between the number of drugs and medication adherence (p= 0.023) with a weak correlation (r=-0,227). This indicates that complications can affect the number of drugs consumed and indirectly also affect the medication adherence of ESRD patients.

Keywords: *End-stage renal disease, hemodialysis, complications, number of drugs, medication adherence*

1. Introduction

End-stage renal disease (ESRD) is a non-communicable disease that globally affects 10% of the world's population (Forouzanfar et al., 2016). ESRD is characterized by a decrease in the Glomerular Filtration Rate (GFR) of <15 mL/minute/1.73 m^2 (Kadir *et al*., 2019; Kefale *et al*., 2018). The incidence of ESRD sufferers is in the top 20 in the world with high mortality and morbidity rates. United States Renal Data System (USRDS) data shows that the prevalence of ESRD has increased from 2014 (0.13%) to 2018 reaching 2.3% (USRDS, 2018). The same as in Indonesia, the incidence of CKD sufferers from 2007-2014 was recorded at 50,909 as active patients. Based on data from Riset Kesehatan Dasar (RISKESDAS) in 2018, Bali Province is in second place after Jakarta with a total of 12,092 ESRD patients (Kemenkes RI, 2018).

In the management of therapy, hemodialysis (HD) is the main choice for renal replacement therapy for ESRD patients, because kidney transplantation is still limited and

expensive. The HD process can help the kidneys maintain metabolism and balance fluids and electrolytes in the body (Kefale *et al*., 2018; Mehmood *et al*., 2019; *et al*., 2017). However, on the other hand, HD therapy cannot fully restore the patient's kidney function (Maqrifah *et al*., 2020). The findings of previous studies show that during or after HD causes complications, such as anemia, hypertension, fever, muscle cramps, vitamin depletion, nausea and vomiting, dry and itchy skin, abdominal cramps, chest, and back pain, shortness of breath, and thrombosis (Hasan *et al*., 2017b; Mehmood *et al*., 2019b). A study showed that an average of 96.25% of ESRD patients had one type of complication and around 3.75% had two types of complications (Hasan *et al*., 2017b). In addition, several studies have found hypertension (85.9%) and anemia (64.8%) to be the most common complications of ESRD patients (Kadir *et al*., 2019; Rajauria *et al*., 2020).

Complications due to HD have an impact on increasing the number of drugs consumed by ESRD patients (Kefale *et al*., 2018). Several previous studies stated that there was a significant relationship ($p<0.05$) between the number of complications and the number of drugs prescribed to patients undergoing HD (Kadir *et al*., 2019; Rajauria *et al*., 2020). A study showed that CKD patients who took >5 types of medication showed a decrease in medication adherence (Kefale *et al*., 2018). Medication adherence is essential to achieve good clinical outcomes because non-adherence can worsen the condition, and increase hospitalization, mortality, and morbidity (Ghimire *et al*., 2015; Okpechi *et al*., 2021; Siva *et al*., 2019; T *et al*., 2019). Research regarding the association between the number of complications with the number of drugs and the number of drugs with medication adherence in ESRD patients is still limited and has never used The End Stage Renal Disease-Adherence Questionnaire (ESRD-AQ) in Indonesia, especially in Bali, so that is the reason carried out this research.

2. Materials and Methods

This type of research is analytic observational with a cross-sectional design. Subject observations and data collection were carried out in March-May 2021 at a private hospital in Denpasar, Bali. This research has obtained ethical review approval from STIKES Bina Usada Bali (Number:040/EA/KEPK-BUB-2021) and hospital permission. There were 93 respondents obtained in this research using a purposive sampling technique. Inclusion criteria included ESRD patients who with complications due to HD, HD at least twice a week, and signed an informed consent. Exclusion criteria were patients in unstable health conditions and unable to communicate properly.

The research instruments were data collection sheets (age, gender, education, diagnosis, and medication) and the Indonesian version of The End Stage Renal Disease-Adherence Questionnaire (ESRD-AQ). ESRD-AQ is a reliable and valid questionnaire for measuring the level of medication adherence in ESRD patients undergoing HD. Kim *et al*. (2010) were researchers who first tested the validity and reliability of the ESRD-AQ in Los Angeles, USA. The results obtained are that the ESRD-AQ is valid and reliable which is proven successively by the item-level content validity index (I-CVI) value of 0.99 and the intraclass correlation

coefficient (ICC) value obtained ranging from 0.83-1.00 (Kim *et al*., 2010; Naalweh *et al*., 2017).

In this study, repeated validity tests were carried out using face validity on 30 respondents in a private Hospital Denpasar. The face validity test aims to evaluate each question item regarding validity and minimize misinterpretation of the question sentence. The percentage value of the face validity test results in this study averaged >80% (CI 95%), which means that the ESRD-AQ questionnaire has clear sentences and is not confusing so that it can be understood by respondents (Privitera, 2022). This questionnaire has met the reliability test with a Cronbach's alpha value of 0.70. These results are also supported by previous research which used a similar questionnaire (Cronbach's alpha value of 0.75) (Yuliawati *et al*., 2022). Therefore, the ESRD-AQ questionnaire can be used to measure the level of treatment compliance of CKD patients in this study. The Mann-Whitney statistical test was used to analyze the association between the number of complications and the number of medications because the data normality test results were not normal so a non-parametric test was carried out. The Kendall Tau-b statistical test was used to analyze the association between the number of medications and medication adherence.

3. Results and Discussion

3.1 Patient demographic profile

Based on the data collected, it was found that the majority of ESRD patients were aged <65 years (83.9%), 66.7% were male, had high school education (35.5%), 51.6% were still working, and had been diagnosed ESRD <5 years (77%) (Table 1). Age is a risk factor for decreased kidney function. Previous study shows that in the 30-40 year age, there is a decrease in the number of nephrons of around 10% every 10 years, resulting in structural changes in the kidneys. Changes in lifestyle patterns can have an impact on the emergence of two chronic diseases that cause ESRD, namely hypertension and diabetes mellitus (Denic *et al*., 2016; Siagian and Damayanty, 2015). The incidence of ESRD in Indonesia in 2017 was dominated by males (56%) (PERNEFRI, 2018). When compared to women, men have worse lifestyles, such as smoking, consuming coffee, and alcohol, and also higher intake of protein and calories, which have an impact on the high incidence of damage to the endothelial vessels of the kidneys (Mahayundhari *et al*., 2018; Seong Kim *et al*., 2017; Widani dan Wisnu, 2020).

In this study, most of the patients had a high school education (35.5%). The level of education cannot be used as a benchmark for assessing the incidence of ESRD, because this disease can occur at all levels of education (Magacho *et al*., 2011; Suparti and Solikhah, 2021). On the other hand, a higher level of education has an impact on increasing knowledge of the disease they have, so that patients can maintain the health of their kidneys and the risk of getting ESRD will also be lower (Agussalim, 2020). Regarding employment status, several previous studies have shown that many CKD patients are no longer able to work because the patient's physical condition has declined and they easily feel tired. This is due to decreased hemoglobin levels due to disruption of the production of erythropoietin in the kidneys for the process of

forming red blood cells. The impact is that it can reduce the amount of oxygen and energy in the body which then affects a patient's ability to move (Putri *et al.*, 2019; Shroff *et al.*, 2022).

Table 1. Patient demographic profile

Demographic profile	Total (%)
Age (years old)	
<65	78 (83.9%)
>65	15 (16.1%)
Gender	
Male	62 (66.7%)
Female	31 (33.3%)
Level of education	
No school	7 (7.5%)
Elementary school	20 (21.5%)
Junior high school	8 (8.6%)
Senior high school	33 (35.5%)
Higher education	25 (26.9%)
Job-status	
Yes	48 (51.6%)
No	45 (48.4%)
Duration of ESRD (years)	
<5	72 (77%)
5-10	19 (20.4%)
>10	2 (2.2%)

3.2 Complications in ESRD patient's

Overall, ESRD patients had ≥2 complications (81.72%). The highest types of complications were hypertension and mineral bone disorders (Table 2). In line with other studies, hypertension (85.18%) and bone mineral disorders (98.6%) were the most common complications experienced in ESRD patients with HD (Rajauria *et al.*, 2020; Seong Kim *et al.*, 2017). Hypertension and bone mineral abnormalities may occur due to inadequate ultrafiltration process during HD (Prajapati *et al.*, 2016; Raikou dan Kyriaki, 2018; Shroff *et al.*, 2022). First, the impact is an increase in the amount of fluid in the body and induces the formation of endothelin which increases blood pressure (Raikou and Kyriaki, 2018). Second, the HD process causes an imbalance in ion levels, such as increasing phosphate ion levels and decreasing calcium ion levels, which can disrupt the bone mineralization process (Shroff *et al.*, 2022).

Table 2. Number of complications

Category	Amount	Percentage (%)
<2 Complications	**17**	**18.28**
Hypertension	10	10.75
Mineral bone disorders	4	4.30
Anemia	1	1.08

174

Neuropathy	1	1.08
Nausea vomiting	1	1.08
≥2 Complications	**76**	**81.72**
Hypertension, mineral bone disorders	22	23.66
Anemia, hypertension, mineral bone disorders	8	8.60
Hypertension, anemia	7	7.53
Hypertension, nausea vomiting	3	3.23
Hypertension, coronary heart disease (CHD)	3	3.23
Hypertension, hyperuricemia, anemia	3	3.23
Hypertension, hyperuricemia, mineral bone disorders	3	3.23
Anemia, hypertension, CHD	2	2.15
Anemia, hyperuricemia, mineral bone disorders	2	2.15
Anemia, hypertension, hyperphosphatemia	2	2.15
Anemia, neuropathy, hypertension	2	2.15
Hypertension, heart failure, anemia	2	2.15
Hypertension, mineral bone disorders, neuropathy	2	2.15
Anemia, hyperuricemia	2	2.15
Hypertension, neuropathy	2	2.15
Anemia, mineral bone disorders	1	1.08
Anemia, hypertension, mineral bone disorders, neuropathy	1	1.08
Anemia, hyperphosphatemia, hypertension, CHD	1	1.08
Anemia, hypertension, mineral bone disorders, hyperuricemia	1	1.08
Anemia, hypertension, CHD	1	1.08
Hypertension, CHD, neuropathy	1	1.08
Hypertension, hyperuricemia, hyperphosphatemia	1	1.08
Hypertension, mineral bone disorders, neuropathy	1	1.08
Anemia, hypertension, PJK, hyperphosphatemia, hyperuricemia	1	1.08
Anemia, heart failure	1	1.08
Hypertension, hyperuricemia	1	1.08
Total	**93**	**100**

3.3 Number of drug use

The majority of patients received 1-6 types of drugs per day (80.64%) (Table 3). This is because HD patients are reported to experience a decrease in body physiology which has an impact on the occurrence of complications, that must be treated. One study said that the HD process causes ESRD patients to experience a faster process of protein catabolism due to the loss of amino acids as a result of the HD process which can then reduce the patient's physiology, such as feeling tired quickly and decrease the immune system (Khan *et al*., 2018; Tchape *et al*., 2018).

Table 3. Number of drug use

Category	Amount	Percentage (%)

175

1-6	75	80.64
7-12	17	18.28
13-18	1	1.08
Total	**93**	**100**

Some of the most widely prescribed classes of drugs, namely antihypertensives (irbesartan, candesartan, valsartan, amlodipine), hematopoietic agents (Erythropoiesis-Stimulating Agents, iron), phosphate binders (calcium acetate, calcium carbonate, sevelamer, lanthanum carbonate), anti-hyperuricemia (febuxostat, allopurinol), cardiovascular drugs (isosorbide dinitrate, carvedilol, bisoprolol, nebivolol, trimetazidine HCl, clonidine, nitroglycerin), antithrombosis (warfarin, enoxaparin), antiplatelet (aspirin, clopidogrel), vitamins (vitamin C, vitamin B6, vitamin B12), and supplements (folic acid). Drugs prescribed for patients with impaired renal function are reno-protective and do not worsen kidney function. This indicates that the use of drugs in patients with CKD requires rational planning and selection of drug therapy according to the patient's condition, to maintain the patient's quality of life (Pakingki *et al*., 2019; Veryanti and Meiliana, 2018).

3.4 Level of medication adherence

The level of medication adherence of ESRD patients in this study was assessed based on four aspects namely HD care, medication, fluid restriction, and dietary recommendations. The final scoring range for patient compliance ranged from 0 to 1200. Based on the results of completing the ESRD-AQ questionnaire, 67.74% of patients had a high level of medication adherence (Table 4).

Medication adherence is very important to achieve therapeutic success, maintain a stable health condition, and improve the quality of life of ESRD patients. It was reported in a study that a patient's non-adherence to medication can be a major barrier to achieving an effective therapeutic outcome. In addition, the impact that can result from patient non-adherence can increase mortality, morbidity, and healthcare costs (Jain et al., 2018). Based on research by Jain et al. (2018), the average reason for patients not adhering to their medication was because of the high price of drugs (58%), the complexity of medication (49%), forgetting to take medication (45%), fear of drug side effects (43%), difficult to take a large number of drugs per day (32%), and patients do not understand the use of each drug that has been prescribed (15%) (Jain *et al*., 2018).

Table 4. Level of medication adherence

Category	Amount	Percentage (%)
Low (<80%)	18	19.35
Medium (80-89%)	12	12.90
High (90-100%)	63	67.74
Total	**93**	**100**

3.5 Association between the number of complications with the number of drugs

Statistical test results show that there is a significant association between the number of complications and the number of medications (p=0.026) (Table 5). The results of this study are in line with several previous studies, which obtained significant results related to the association between the number of complications and the number of drugs in ESRD patients. Complications that occur in patients undergoing HD have an impact on increasing the number of drug prescriptions (Kadir *et al.*, 2019; Sekti, 2020).

Table 5. Association between the number of complications with the number of drugs

Number of complications	Number of drugs (N (%))				p value
	1-6	**7-12**	**13-18**	**Total**	
<2	17 (18.28%)	0 (0%)	0 (0%)	17 (18.28%)	**0.026***
≥2	58 (62.37%)	17 (18.28%)	1 (1.08%)	76 (81.72%)	
Total	**75 (80.65%)**	**17 (18.28%)**	**1 (1.08%)**	**93 (100%)**	

Note: (*), significant <0.05, Mann-Whitney test

Overall, it appears that patients who had <2 complications received only 1-6 types of medication, whereas patients with ≥2 complications were prescribed 13-18 types of medication per day (Table 5). Previous studies showed similar results, ESRD patients with ≥2 complications received an average of up to 12 types of medication, while those with <2 complications received <7 types of medication per day (Gorriz *et al.*, 2013). This is also supported by other research which states that the increasing number of complications has an impact on increasing the number of drugs received by ESRD patients (Sekti, 2020).

Complications resulting from the HD process cause patients to be treated with several types of drugs (Kadir *et al.*, 2019). This was proven in patients with hypertension in this study who received a class of antihypertensive drugs that work on the renin-angiotensin-aldosterone system (RAAS), as well as a combination of ARBs and Calcium Channel Blockers (CCB), while patients who experienced complications of bone mineral disorders received 1 type of drug (phosphate binder). However, Gorriz *et al.* (2013) found different results in that HD patients with bone mineral disorders were given monotherapy with phosphate binders (34%) or combination therapy between phosphate binders and vitamin D (10.6%) (Gorriz *et al.*, 2013). According to research by Kefale *et al.* (2018), the average ESRD patient with hypertension was given antihypertensive medication alone (18%) and 52% of other patients received antihypertensive combination therapy (Kefale *et al.*, 2018).

Complications are a condition where pathological changes occur that can spread throughout the body and affect other organ systems, so they can cause the development of new diseases as a result of the disease (Ording and Sorensen, 2013). Complications that occur as a result of the HD process are said to increase the number of drugs prescribed to ESRD patients (Kefale *et al.*, 2018). The results of previous research explain that HD patients with complications are prescribed up to >10 types of medication per day (Schmidt *et al.*, 2019).

3.6 Association between the number of drugs with medication adherence

There was a significant association between the number of medications and medication adherence in ESRD patients (p=0.023) with a negative correlation found, meaning that increasing the number of medications would reduce patient medication adherence (r=-0.227) (Table 6). These results were shown in ESRD patients in this study who on average had a high level of medication adherence consuming 1-6 types of medication per day, while patients who were prescribed >6 types of medication showed lower medication adherence. Supported by research by Kadir *et al.* (2019) ESRD patients who receive ≤6 types of medication have a higher level of medication adherence compared to prescribers who receive >7 types of medication every day (Kadir *et al.*, 2019).

Table 6. Association between the number of drugs with medication adherence

Number of drugs	Level of medication adherence (N (%))				p value	r value
	Low	**Medium**	**High**	**Total**		
1-6	10 (10.75%)	11 (11.83%)	54 (58.06%)	75 (80.65%)	**0.023***	**-0.227**
7-12	7 (7.53%)	1 (1.08%)	9 (9.68%)	17 (18.28%)		
13-18	1 (1.08%)	0 (0%)	0 (0%)	1 (1.08%)		
Total	**18 (19.35%)**	**12 (12.90%)**	**63 (67.74%)**	**93 (100%)**		

Note: (*), significant <0.05, Kendall Tau-b test

Medication adherence is one aspect that supports patients to achieve the desired therapeutic outcomes (Naalweh *et al.*, 2017; Nielsen *et al.,* 2018). In retrospect, the majority of patients in this study had high medication adherence (67.74%). This is possible because the duration of ESRD is mostly (77%) <5 years. In one study, it was found that duration of illness affects patient medication adherence. For a short duration, patients tend to be more adherence with the medication given by health workers, because the longer they undergo treatment, the patient can feel bored and fed up (Ihwatun *et al.*, 2020; Liberty *et al.,* 2018). Apart from that, a study found that the longer a patient undergoes HD, the more impact it has on decreasing patient adherence in limiting fluid intake because the patient has reached the stage of acceptance of the disease he is experiencing (Mailani and Bakri, 2020).

However, previous studies have yielded different results, as many as 80% of patients undergoing HD have low levels of medication adherence (Nielsen *et al*., 2018). One previous study also supports that the majority of ESRD patients do not take medication as prescribed by the doctor (50-80%). Research by Sontakke *et al.,* (2015) has found that around 68% of HD patients are not aware of the importance of being adherence in taking medication which can then increase the incidence of ESRD patients' non-adherence to their medication (Sontakke *et al*., 2015).

Patient non-adherence to medication will be a major obstacle in achieving therapeutic outcomes which can then have an impact on increasing the risk of morbidity, mortality, hospitalization, and health care costs. (Jain *et al.*, 2018). Based on research conducted by Farisi (2020), it is explained that patients who are not adhering to their medication can reduce the effectiveness of the treatment they are undergoing. As a result, this can have implications for poor disease development, a decrease in the patient's clinical outcome achievement rate, and the risk of patients undergoing hospitalization will increase (Farisi, 2020). Reporting from one of the previous studies, it was stated that the condition of patients with or without comorbidities and complications can affect patient adherence to medication (Seng *et al.*, 2020). Other research also states that the average reason for ESRD patients not adhering to treatment is because of the high price of drugs (58%), forgetting to take medication (45%), patients are afraid of drug side effects (43%), and 15% of patients do not understand the use of each drug that has been prescribed (Jain *et al*., 2018).

The limitations of this study are that researchers only focus on analyzing the effect of the number of drugs and do not observe other factors that can also affect medication adherence in ESRD patients. Another limitation is that the number of samples used was relatively small and the researchers only carried out one measurement of patient treatment compliance, which could give different results if measurements were taken from time to time following the patient's disease prognosis and condition. This is because this research was conducted during the COVID-19 pandemic, so access and data collection time were limited.

Conclusion

Complications that occur as a result of the HD process have a significant association with number of the drugs (p=0.026). In addition, the number of drugs also has an association with medication adherence in ESRD patients (p=0.023). Increasing the number of drugs that must be consumed by ESRD patients can reduce the medication adherence of ESRD patients (r=-0.227). Therefore, health workers are expected to be able to provide information and education to patients, so that non-adherence to medications can be minimized.

Acknowledgments

Conflict of Interest

All authors declare no conflict of interest and agree with the content of the manuscript.

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