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The Impact of Polypharmacy on Medication Problems and Clinical Outcomes in Patients with Stage 5 Chronic Kidney Disease Undergoing Hemodialysis: A Narrative Review

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Abstract
Patients with stage 5 chronic kidney disease (CKD) who undergo routine hemodialysis (HD) often receive a complex treatment regimen (polypharmacy) to control comorbidities. This condition increases susceptibility to drug-related problems (DRPs) due to pharmacokinetic and pharmacodynamic changes after nephron damage. This narrative review aims to evaluate the impact of polypharmacy on the incidence of drug problems (DRPs) and its implications on various clinical outcomes, quality of life, and cost burden in stage 5 CKD patients with routine HD. This writing used a narrative review method through searching literature from various scientific data sources such as Google Scholar, PubMed, and Scince Direct, as well as national journals with a publication time span of the last 5-10 years. Literature analysis showed that polypharmacy was strongly correlated with a high incidence of moderate to major drug interaction potential (DDI) (49–89%) and drug side effect multiplication (ADRs). The use of drugs without proper dosage adjustment to the dialysis circuit triggers therapy failure. Monitoring of therapeutic outputs has been proven to integrate the dimensions of clinical data, laboratory biomarkers, economic aspects, and drug burden reduction through deregulation. Polypharmacy in ESRD-HD patients poses massive clinical and financial problems. The active involvement of clinical pharmacists through treatment reconciliation and selection of drug types with safe non-renal elimination is crucial to minimize the risk of toxicity, optimize clinical outcomes, and improve patients' quality of life.

INTRODUCTION

Chronic kidney disease (CKD) is a global problem with an increasing prevalence. In Indonesia, data released by Basic Health Research (Riskesdas) shows an increase in prevalence in 2018, the prevalence of CKD in Indonesia was 0.38% or around 713,783 people. Meanwhile, the latest modeling data (2023/2024) shows an increasing trend of cases, with prevalence reports reaching 2%-3.8%. As the body's (Febriyani & Padmasari, 2024) main elimination organ, the kidneys are responsible for excreting metabolic waste products as well as xenobiotics, including drugs. When the kidneys undergo structural damage and a permanent

decline in their filtration function for more than three months, the body will develop uremic syndrome. (Febriyani & Padmasari, 2024)

In *Terminal State* or *End-Stage Renal Disease (ESRD)* conditions where the Glomerular Filtration Rate (LFG) falls below 15ml/minute/1.73 m2, the patient requires Kidney Replacement Therapy (TPG) to sustain life, most commonly in the form of routine hemodialysis (HD). In this condition, the kidneys are no longer able to maintain the homeostatic fluid, electrolytes. Hemodialysis is the (Grasia Situmorang et al., n.d.) *most dominant renal replacement therapy* used to prolong patient survival. Although HD effectively replaces the function of mechanical filtration, it is intermittent (usually 2-3 times a week for 4-5 hours) and cannot replace the endocrine functions of the kidneys (such as erythropoetin secretion and vitamin D activity), so patients continue to experience a variety of chronic systemic complications (Pramitaningastuti, 2024)

Patients undergoing maintenance HD generally suffer from chronic and severe multiple comorbidities. The most commonly manifested comorbidities include hypertension, diabetes mellitus, renal anemia, dyslipidemia, coronary heart disease, *Congestive Heart Failure* (CHF), and *Chronic Kidney Disease-Mineral and Bone Disorder* (CKD-MBD). (Khusfiani et al., 2023; Oosting et al., 2024) This condition requires the patient to consume a large drug regimen or commonly referred to as polypharmacy, which is clinically often defined as the use of five or more types of drugs consumed. (Battistella & Ng, 2021) Polypharmacy in HD patients includes not only a massive number of oral drug items, but also a high pill *burden* that must be swallowed as well as a complicated dosage regimen, which often has to be modified between the day of dialysis and the day of non-dialysis (In Hijazeen et al., 2020). Polypharmacy also occurs due to the complexity of the management procedures to control the symptoms *of ESRD* as well as its comorbidities. The combination of the use of these drugs triggers therapeutic problems due to the interaction and alteration of the elimination organs. The negative clinical outcomes due to polypharmacy can be seen from the following parameters: (Pramitaningastuti, 2024)

a. Clinical data: the appearance of *Adverse Drug Reaction* (ADRs) symptoms such as orthostatistical hypotension, arrhythmias, gastrointestinal bleeding, and decreased consciousness.
b. Laboratory data: failure to achieve the therapeutic target can be monitored from electrolyte level instability (hyperkalemia, hypocalcemia), failure to achieve hemoglobin (Hb) target levels, fluctuations in blood glucose levels, and serum phosphate level accumulation (> 5.5 mg/dl) due to phosphate binding interactions
c. Complications: occurrence of vascular classification, secondary coronary heart disease, refractory metabolic acidosis, and toxic uremic encephalopathy due to the accumulation of drug metabolites.

Although the administration of many drugs aims to manage comorbidities, polypharmacy in the hemodialysis population is a challenge for health workers, especially clinical pharmacists. This is due to changes in pharmacokinetic and pharmacodynamic parameters in patients with very low renal function, which directly increases the risk of Drug-Related Problems (DRPs).

DRPs that include drug side effects, adverse drug interactions, dosage inaccuracies, unindicated, and untreated indications, are a real threat to patient safety. Various empirical

studies report that the incidence of unidentified DRPs is directly correlated with failure of medical therapy, increased frequency and duration of hospital stays, increased treatment costs, deterioration of clinical outcomes (mortality), and a dramatic decrease in the patient's quality of life ((Sayed Ali et al., 2025) *Health-Related Quality of Life*). (Kitamura et al., 2021a)

The quality of life of ESRD patients who underwent routine HD showed a significant decrease in almost all domains of life compared to the general population (da Trindade Valente et al., 2025) . Specifically, the most significant decreases occurred in physical health components such as chronic fatigue, muscle weakness due to uremic sarcopenia, sleep disturbances and mobility (Tannor et al., 2017) limitations. Psychological burdens also dominate the patient's clinical output, anxiety, and chronic depression arise due to prolonged dialysis, strict fluid restriction, as well as such loss of identity (Alhazmi et al., 2024) . The financial burden also affects the quality of life of dialysis patients. Chronic kidney disease is the disease with the highest treatment costs in the world. The duration of undergoing HD (the patient's survival undergoing dialysis therapy) is directly proportional to the accumulated costs that must be incurred, both direct costs (dialysis costs, laboratories, non-BPJS drugs) and (Masajtis-Zagajewska et al., 2025) *indirect costs* (the possibility of losing their jobs and routine income because the patient has to spend 8-10 hours per week in the hospital to undergo the dialysis process). (Jha et al., 2023)

The survival rate of ESRD on HD patients is greatly influenced by financial stability. Globally, the 5-year life expectancy of HD patients ranges up to 50%. However, in patients who experience financial toxicity due to inability to pay for secondary comorbidity medications, this figure increases dramatically in the first 1-2 years of HD treatment. Patients with long HD (> 3 years) tend to experience financial burnout (Tannor et al., 2017; Masajtis-Zagajewska et al., 2025), which means they miss a dialysis schedule or do not make up for routine medications that should be taken regularly, thereby lowering medication adherence and accelerating organ failure (Alhazmi et al., 2024). This narrative review aims to determine the prevalence of polypharmacy in hemodialysis patients, identify the most dominant types of DRPs arising from polypharmacy, and analyze their impact on patient clinical outcomes. Through this review, it is hoped that it can be a basis for clinical pharmacists in developing intervention strategies, such as drug deprescribing or reconciliation, to improve patient safety.

METHOD

The writing of narrative reviews is compiled through the development of literary sources on scientific data sources such as Google Scholar, PubMed, and ScientDirect, as well as national pharmaceutical journals accredited by Sinta. The keywords used, namely: "chronic kidney disease", "Hemodialysis", "Polypharmacy", "DRPs", "Clinical Outcome", "Polypharmacy in Hemodialysis", "Drug Related Problems CKD", "Clinical Outcomes", "Quality of life", "Cost Burden". The selected literature includes observational studies, cohorts, original research articles discussing polypharmaceuticals, DRPs, as well as clinical outcomes in CKD-HD patients published in the last 5-10 years to ensure data novelty.

The inclusion criteria set in this literature review are: (1) studies involving adult patients diagnosed with CKD/CKD (2) research focus examines polypharmaceutical aspects, potential drug interactions, DRP category analysis based on standard classification system and measurement of clinical outcomes and quality of life and (3) original research articles and

systematic review. Exclusion criteria include case reports, incomplete proceedings abstracts, and articles that do not have full-text access. Articles that meet the criteria are extracted from data to be analyzed qualitatively and quantitatively, then narrated thematically to draw valid and objective scientific conclusions.

RESULTS AND DISCUSSION

Demographic, Comorbidity, and Polypharmacy Profiles of Hemodialysis Patients

From the data of various hospitals, the incidence rate of polypharmacy is very high in patients with chronic kidney disease undergoing hemodialysis, which ranges from 81.3% to 95.2%. In this prevalence, the majority of patients received more than 5 types of drugs, even in certain studies it was found that patients with extreme polypharmacy consumed up to 11 types of drugs daily (Febriyani & Padmasari, 2024; Pramitaningastuti, 2024) (Kitamura et al., 2021a)

This high incidence of polypharmaceuticals is influenced by the clinical characteristics of HD patients, most of whom have comorbidities. The most dominant comorbidities were hypertension at 19.62%, followed by diabetes mellitus at 9.18%, and coronary heart disease at 8.54%. A combination of routine medications such as antihypertensives, hypoglycemic age, phosphate binders (such as calcium carbonate), supplements, iron, calcium, and vitamins are the main reasons why most patients receive complex treatment regimens. (Pramitaningastuti, 2024)

Table 1. Data on the number of polypharmaceuticals, DRPs issues, clinical output impacts

Researcher and Researcher Year	Design and samples	Polypharmacy Profile	Key Findings of DRps and Drug Interactions	Impact on Clinical Outcomes and Quality of Life
(Kitamura et al., 2021a)	Retrospective cohort, 339 outpatient HD patients	Average 7-10 drugs/patient	Gastrointestinal drugs (PPIs, H2 blockers) dominate the category of non-essential drug use	Consumption of many non-essential medicines increases the risk of death by 2 times
(In Hijazeen et al., 2020)	Retrospective, cut the latitude of 300 ESRD patients with HD	Retang 4-12 drugs/patient	The prevalence of potential drug interactions (DDIs) reached 96.3%. As many as 60% of DDI are classified as serious interactions	High risk of toxicity due to serious interactions between calcium + nifedipine, as well as aspirin + enalapril
(Rawitri et al., 2024)	Cut the latitude, 72 HD patients at Dr Pirngadi Hospital	The majority of male patients (69.44%)	Cipolle's analysis detected DRPs of 88.8% occurring in patients. Drug interactions dominated by 35.13%	High incidence of DRPs affects the patient's quality of life

(Abrari & Susilo, 2025)	Retrospective, 60 HD patients at Hospital X	Female gender dominance (53.33%). All patients undergo pollipharmacy	The incidence of DRPs is 66.67%. The highest problem was therapy without clear medical indications (46.67%)	Overuse of PPI (omeprazole) to treat uremic nausea without a valid diagnosis of organic dyspepsia
(Sholihah et al., 2024)	Prospective, 27 CKD patients are hospitalized	A total of 51.85% of patients received a fairly high polypharmacy (> 10 types of drugs)	DRPs were identified in 66.7% of patients. The main case is the interaction of drugs at 36.67%	The incidence of drug side effects increases as prescriptions accumulate, triggering patient non-compliance
(Khusfiani et al., 2023)	Cut star, pre-dialysis patient stage 5	All patients were exposed to polypharmacy due to layered comorbidities	The micromedex assessment showed a strong correlation between the number of drugs and the total number of actual manifestations of DDIs	Increased risk of clinical side effects in the form of orthostatic hypotension and severe hyperkalemia due to external cardiovascular drug interactions
(Ulfa et al., 2025)	Cut Latitude, HD Patient at Cipto Mangunkusumo Hospital	Massive polypharmacy for the control of cardiovascular comorbidities	The majority of drug interactions are moderate to major which affects the clearance of other drugs during dialysis	The risk of bleeding is significantly increased due to the co-use of anticoagulants and double platelets
(Febriyani & Padmasari, 2024)	Observational retrospective analytics	The prevalence of polypharmacy reached 81.3% with the main comorbidity of hypertension	There is a significant increase in the potential for drug interactions as the number of drug items increases	Failure to control blood pressure due to antihypertensive drug interactions
(Septiani et al., 2024)	Descriptive retrospective, HD patients at Ponorogo Hospital	The gender distribution is dominated by men. All samples are at LFG stage 5	DRPs were detected in the majority of samples, dominated by inaccuracies in the dosage of antihypertensive drugs and renal vitamins	Insufficient dosage of the patient's clinical recovery period after hemodialysis session

The data in table 1 shows that men often dominate the hemodialysis population as described by 69.44%. This is because pathophysiologically it is closely related to exposure to

higher lifestyle risk factors in men, such as smoking habits, alcohol consumption, and a high incidence of uncontrolled primary hypertension. In studies in other hospitals such as the one conducted by the Philippines, the prevalence of female sex was slightly higher, which was 53.33%. This shows that intrinsic risk factors such as recurrent urinary tract infections and autoimmune diseases (e.g. (Rawitri et al., 2024) (Grasia Situmorang et al., n.d.) (Abrari & Susilo, 2025) Systemic Lupus Erythematosus) also contribute significantly to the occurrence of end-stage kidney failure in women. In terms of age, the late adult age group and the elderly (45-65 years and above) dominated the entire study. Physiologically, kidney function experiences a natural structural decline in the form of glomerular sclerosis and tubule atrophy with age, where LFG decreases by about 1% annually after the age of 40 which makes the elderly age group very susceptible to ESRD. (Sholihah et al., 2024) (Zhang et al., 2023a)

The comorbidities that accompany HD patients prove to be very massive and complex. Hypertension, diabetes mellitus, renal anemia, coronary heart disease, and anasrka edema are constant clinical manifestations. The relationship between hypertension and CKD is (Septiani et al., 2024) bidirectional, chronic hypertension causes nephrosclerosis that triggers renal ischemia, while kidney dysfunction in excreting sodium and water and hyperactivity of the Renin-Angiotensin-Aldosterone (RAAS) system will aggravate the hypertensive condition. On the other hand, damage to the renal parenchyma causes a deficiency in the production of the hormone erythropoetin in absolute terms, resulting in severe anemia in almost all hemodialysis patients (Febriyani & Padmasari, 2024) (Septiani et al., 2024)

For the management of this entire disease, polypharmacy becomes an inevitable medical consequence. Patients routinely receive and consume antihypertensive drugs (such as amlodipine, candesartan, captopril, furosemide), erythropyesis stimulants, calcium carbonate supplements as phosphate binders (phosphate binder), folic acid, as well as stomach mucosal protective drugs (omeprazole or ranitidine). The level of polypharmacy ranges from the standard category (> 5 drugs) to the extreme polypharmacy, where a study by the study reported that 51.85% of patients consumed more than 10 kinds of drugs every day, even reaching an average of 14 drugs in inpatients. (Abrari and Susilo, 2025; Grasia Situmorang et al., n.d.) (Sholihah et al., 2024)

Profile of Polypharmaceutical Drugs and Classification of Problems

Based on data from the study of prescription data of HD patients, the drug profiles that are most often prescribed are cardiovascular and antihypertensive drugs (amlodipine, bisoprolol, candesartan), phosphate binders and mineral supplements (CaCo3, Calcium lactate, Vitamin D3), hematological agents (vitamin b complex, folic acid, erythropoetin injection), gastrointestinal drugs (lansoprazole, antacid). The specific problems found are outlined in the following table: (Battistella & Ng, 2021)

Table 2. Drug Data with Problem Classification

Drug Name	Key Problems Found	Clinic/Lab Manifestations
CaCo3	Drug Interactions (Pharmacokinetics of Absorption)	Iron binding. Anemia controlled, low Hb)
Amlodipin + Simvastatin	Drug Interactions (increased Simvastatin Levels)	Major ADRs: increased risk of rhabdomyolysis and myopathy

Antibiotics (beta lactam)	Dosage issues (not adjusted post-HD)	Subtherapeutic dosage because the drug is wasted through the HD machine)
Spironolactone	Dosage problems/side effects	Lab data: risk of extreme hyperkalemia (> 0.6 mEq/L)

Profile of Polypharmaceutical Drugs That Do Not Damage the Kidneys

In the *ESRD stage*, the main focus is no longer on preventing nephron damage (because the kidneys have undergone complete fibrosis), but rather on preventing toxic accumulations that worsen other organs. Some drugs that are categorized as safe because they have *a non-renal* metabolic pathway include: (Papotti et al., 2021)

1. Paracetamol: The analgesic of choice as it is metabolized in the liver (gluconidization).
2. Amlodipine: Not nephrotoxic and cleansing does not depend on kidney function.
3. Insulin: It is the safest option for glycemic control compared to OAD (Oral Anti-Diabetic Medication) such as Metformin which is totally contraindicated.
4. Lansoprazole: A PPI of safe choice to treat uremic dyspepsia without damaging the rest of the nephron's function.

Characteristic Analysis of Drug-Related Problems (DRPs)

The high incidence of polypharmacy in HD patients is directly proportional to the high incidence of DRPs. One of the articles stated that the prevalence of patients who experienced at least one incidence of DRP was in an alarming range, which was between 66.67% to 88.8%. Based on scientific classification, these clinical problems can be mapped into several main domains: (Abrari & Susilo, 2025; Rawitri et al., 2024)

Unnecessary Drug Therapy

One of the occurrences of DRPs that are widely found is the high rate of drug prescriptions without medical indications, reaching 46.67% in several health service centers. The most commonly detected cases are the prescription of (Abrari & Susilo, 2025) *Proton Pump Inhibitors* (PPIs) such as Omeprazole or Lansoprazole, as well as H2-blockers such as Ranitidine. Hemodialysis patients often complain of severe nausea and vomiting symptoms. However, PPI prescription writing is often not based on an objective diagnosis of organic dyspepsia or peptic ulcers, but rather on purely symptomatic therapy. Pathophysiologically, nausea-vomiting in patients with end-stage renal failure is generally triggered by (Kitamura et al., 2021a) *Chemoreceptor Trigger Zone* (CTZ) stimulation in the brain by a high accumulation of uremic toxin in the blood, not as a result of gastric hyperacidity. Long-term administration of PPIs without proper indications in kidney patients is very dangerous because it can trigger chronic hypomagnesemia, increase the risk (Abrari & Susilo, 2025) *of Clostridium difficile infection*, and accelerate the occurrence of vascular calcification through impaired calcium-phosphate homeostasis. (Kitamura et al., 2021a)

Dose *Selection & Overdose*

Extreme LFG reduction radically changes the parameters of drug clearance by the kidneys. Failure to adapt the dose to the remaining renal function (*residual renal function*) triggered DRPs in the *overdose* category by 29.59%. Many drugs whose elimination primarily depends on glomerular filtration remain prescribed in the usual doses of normal adults. The use of ACE-Inhibitor antihypertensive drugs (Zhang et al., 2023a) (such as Captopril) or ARB

(Candesartan) in high doses without close monitoring, which can trigger sudden hypotension after dialysis as well as worsen potassium retention. Furthermore, the clearance of hydrophilic antibiotics (such as the cephalosporin group) decreases dramatically in HD patients, so that standard dosing without prolonging the administration interval will lead to the accumulation of drugs in the serum, potentially triggering neurotoxicity (e.g. encephalopathy or seizures) and accelerating the deterioration of remaining kidney function. (Septiani et al., 2024) (Zhang et al., 2023a)

Drug dose *adjustment (dose adjusment)* should be made in *ESRD-HD patients* based on residual LFG values and drug properties by dialysis membranes. Medications that must be adjusted in dosage are antibiotics (cefotaxim, Ceftazdime, and aminoglycosides), gabapentin (anticonvulsant), metformin, and ranitidine. These drugs if not lowered in dose or extended interval will trigger systemic toxicity, such as encephalopathy or lactic acidosis. Meanwhile, drugs that do not require dose adjustment in CKD are drugs that are completely eliminated through hepatic metabolism or biliary excretion that do not require dose adjustment. Examples of antihypertensives (amlodipine, candesartan), analgesics (paracetamol), anticoagulants/anthoplatelets (clopidogrel), statin groups (atorvastatin) (Pramitaningastuti, 2024)

Potential Adverse Drug Interactions (Drug-Drug Interactions)

Drug interactions account for a large proportion of DRPs in hemodialysis patients, with the prevalence of potential interactions reaching 96.3%. Based on the analysis of clinical severity, drug interactions can be classified into: (In Hijazeen et al., 2020)

1. **Minor Interactions:** Mild pharmacokinetic interactions that generally involve absorption competition in the gastrointestinal tract. An example is the administration of calcium carbonate (CaCO3) along with folic acid or iron supplements, where the properties of calcium as an antacid raise the pH of the stomach and decrease the solubility and absorption of folic acid. (Grasia Situmorang et al., n.d.)
2. **Moderate Interactions:** Interactions that require strict clinical monitoring because they can alter the therapeutic effects of the drug. An example is a combination of *a beta-blocker* (Bisoprolol) with a Calcium Channel Blocker (CCB, such as Amlodipine) or ARB (Candesartan). This combination is highly effective in lowering blood pressure, but its pharmacodynamic synergies exponentially increase the risk of severe bracardia and extreme orthostatic hypotension, especially in the first hours after the patient completes a hemodialysis session. Another moderate interaction is the combination of ACE-Inhibitors with strong diuretics (Furosemide), which can trigger a sudden depletion of intravascular fluid volume. (Febriyani & Padmasari, 2024) (Khusfiani et al., 2023)
3. **Major Interactions:** Critical interactions that may threaten the patient's life safety and require immediate medical intervention. One of the major fatal interactions is the concomitant administration of intravenous Ceftriaxone and oral Calcium Carbonate. Chemically-pharmaceutically, absorbed calcium ions can bind to ceftriaxone in the bloodstream, forming an insoluble calcium-ceftriaxone salt precipitate complex. This precipitation can settle in vital organs such as the lungs and kidneys, triggering a vascular microembolism and fatal tissue damage; The administration of these two drugs

must be separated for at least 48 hours. Another case of major interaction that is very often found is the combination of anticoagulants ((Grasia Situmorang et al., n.d.) *Heparin*) used during the dialysis process with double antiplatelets (Aspirin and Clopidogrel) for coronary heart comorbidities. These interactions multiply the risk of massive internal bleeding, such as gastrointestinal bleeding and hemorrhagic stroke. In addition, the joint use of two or more RAAS inhibitory agents (e.g. Captopril plus Valsartan) is strictly prohibited because it triggers refractory hyperkalemia which can lead to fatal cardiac arrhythmias. (Ulfa et al., 2025) (Khusfiani et al., 2023)

Multiply Drug Side Effects (ADRs) due to polypharmacy

Decreased renal clearance causes drugs with high protein bonds or those secreted through urine to accumulate in the blood. Polypharmacy exacerbates this condition through prescribing casade. For example, the use of antihypertensive polypharmaceuticals (amlodipine, bisoprolol, clonidin) often triggers side effects in the form of severe hypotension post-HD and bradycardia. The combination of antiplatelet drugs (aspirin) with other comorbidities increases the risk of mycorrovascular hemorrhage. Side effects in the form of nausea, vomiting, and dyspepsia due to the consumption of many drugs often overlap with uremia symptoms, resulting in worsening patient clinical outcomes and decreased medication adherence. (Lefebvre et al., 2020)

Impact of Polypharmacy and DRPs on Clinical Outcomes and Quality of Life (HRQoL)

The impact of the unsuccessful management of polypharmaceuticals and DRPs on hemodialysis patients manifests directly in the deterioration of the patient's physical condition and the decrease in their life expectancy.

Impact on Quality of Life (HRQoL)

Patients who undergo routine hemodialysis have experienced a significant decrease in quality of life due to physical limitations, chronic post-dialysis fatigue, strict fluid intake restrictions, and psychological disorders in the form of anxiety and depression. A quality-of-life evaluation using the EQ-5D-5L questionnaire instrument showed that the average index score of HD patients was in the low range (0.645 to 0.657), reflecting a marked impairment in the domains of mobility and daily activity. (Colombijn et al., 2024) (Rawitri et al., 2024)

Whenever a patient accumulates new DRPs such as the appearance of a new drug side effect or a failure to control blood pressure due to drug interactions the patient's quality of life decreases. In patients undergoing extreme polypharmacy with an accumulation of more than 5 DRP events per individual, the quality-of-life score fell to a very low number (0.160), where the patient experienced total physical disability, chronic unbearable pain, as well as severe mental distress. Too much pill (Colombijn et al., 2024) burden also triggers psychological saturation, which directly decreases the patient's medication non-adherence, thus creating a vicious cycle that further worsens the patient's health status. (Pramitaningastuti, 2024)

Impact on Clinical Prognosis and Mortality

In addition to reducing the quality of life, irrational polypharmacy has been proven to be an independent predictor of patient mortality. In a 10-year, long-term cohort study, an in-depth analysis was conducted by separating the types of medications patients were taking into two categories: essential medications (such as proper antihypertensives, antidiabetics, and statins) and non-essential medications (such as PPI/H2-blocker gastrointestinal medications, (Kitamura et al., 2021a) non-renal vitamin supplements, and oral vasopressors).

Hemodialysis patients who took more than 10 types of non-essential drugs had a double

risk of all-cause mortality compared to patients who took less than 5 non-essential drugs. This empirically proves that the addition of clinically unnecessary drugs in HD patients does not provide therapeutic benefits, but rather accelerates death due to the accumulation of toxic effects of drugs, secondary organ injury, and unmonitored fatal interactions.

The Impact of Cost Burden on Patients' Financial and Psychological Outcomes

The cost burden in ESRD patients with polypharmacy affects clinical stability. Although the basic hemodialysis procedure in Indonesia is generally covered by the national health insurance (BPJS), the cost component of non-dialysis is often not fully covered or has a monthly quota limit. Costs for supporting essential drugs, such as recombinant erythropoetin alpha injections for severe anemia, an active vitamin D analogue (calcitriol), and a new, safer generation of non-calcium phosphate-binding drugs, require enormous (Ulfa et al., 2025) out-of-pocket expenditure. (Jha et al., 2023)

This economic impact extends to the caregiver burden, as one family member may have to stop working to become a permanent companion to the patient during the dialysis process. When patients experience drug-related problems (DRPs) such as severe drug side effects (ADRs) due to accumulated drug toxicity that is not dosage adjustment, the risk of emergency (Tannor et al., 2017) hospitalization (re-hospitalization) increases. This hospitalization triggers an unexpected surge in costs that exacerbates the patient's mental stress, triggers clinical depression, and manifests itself in the patient's unwillingness to continue routine drug therapy ((Altaf et al., 2026) intentional non adherence). (Zhang et al., 2023)

The description of Clinical External Components in the Journal

In evaluating the success of therapy in ESRD-HD patients with polypharmacy, the scientific journal of pharmacy classifies clinical outcomes into multidimensional, undisintegrated indicators:

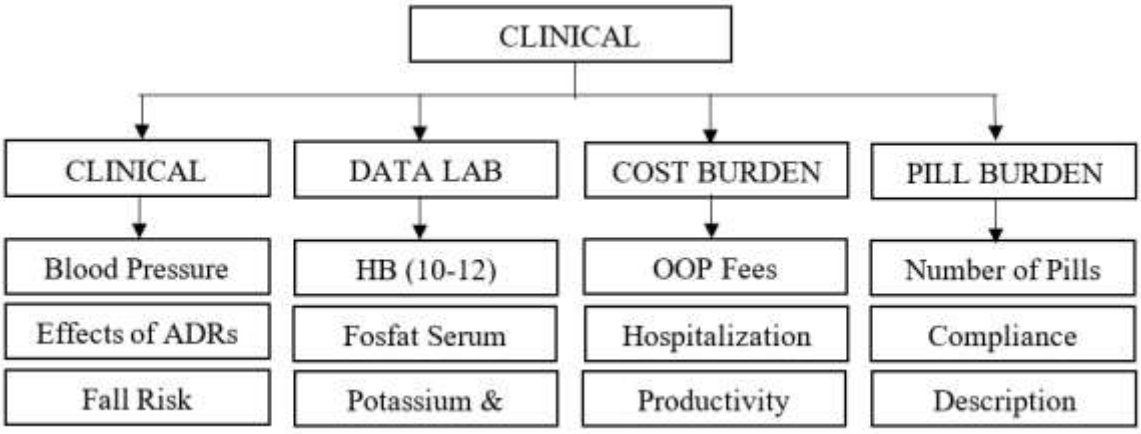

Figure 1 Multidimensional Framework for Evaluating Clinical Outcomes in Stage 5 Chronic Kidney Disease Patients Undergoing Hemodialysis with Polypharmacy

Clinical Data

Clinical data is a direct physical indicator that can be observed in patients during the treatment monitoring period. The main components include systemic blood pressure stability (controlled hypertension without triggering orthostatic hypotension or intradialytic hypotension due to antihypertensive drug interactions). Good clinical outcomes are characterized by a minimum of subjective complaints in the form of nausea, dizziness,

gastrointestinal disorders, and arrhythmias that are clinical manifestations of drug side effects. In addition, the reduction in physical fragility score ((Febriyani & Padmasari, 2024) (Khusfiani et al., 2023) *frailty*) and the incidence of falling risk due to the reduction of extreme polypharmacy burden are also crucial clinical achievements for patients, especially in geriatric patients. (Kitamura et al., 2021b)

Data Laboratory (*Biomarker*)

Laboratory data provide objective quantitative evidence regarding the biological effectiveness of drug therapy management. Key indicators monitored include:

1. **Hemoglobin (Hb) Levels:** The external target is in the range of 10 - 12 g/dL as a sign of successful anemia therapy using erythropoetin and iron supplements without being disturbed by calcium interactions. (Pereira-Céspedes et al., 2023)
2. **Serum Phosphate and Calcium Levels:** The serum phosphate target < 5.5 mg/dL to prevent vascular calcification, which is regulated through the appropriateness of phosphate-binding drug consumption. (Ulfa et al., 2025)
3. **Electrolyte Balance and Dialysis Adequacy:** Strict monitoring of serum potassium levels (3.5 - 5.1 mEq/L) to prevent cardiac toxicity, as well as the achievement of a Kt/V value of > 1.2 indicating the efficiency of uremic toxin clearance by an artificial dialysis machine. (Sholihah et al., 2024)

***Cost* Burden**

Outputs from the economic aspect of health measure the efficiency of the real costs borne by the patient and the healthcare provider system. This component is measured from the decrease in the value *of out-of-pocket costs* to redeem drugs outside the guarantee scheme, as well as the decrease in total annual healthcare costs through a reduction in the frequency and duration of hospital stays due to preventable complications of DRPs. This reduction (Masajtis-Zagajewska et al., 2025) *in cost burden* is an important indicator in the *cost-effectiveness* analysis of pharmaceutical care in hospitals. (Diongolé et al., 2026)

Pill Burden

Burden consumption measures the level of psychological and physical burden a patient has in adhering to their daily treatment regimen. These output parameters are evaluated based on the quantity *of pill count* that the patient must swallow per day. This reduction in consumption burden improves patient (Theofilou & Bilali, 2026) *adherence* and improves quality of life scores in the domain of mental function (. (Paneerselvam et al., 2023)

Clinical Solutions: Reconciliation, Deprescribing, and the Role of Clinical Pharmacists

In the face of the high threat to patient safety due to polypharmacy, the conventional healthcare model must be changed by integrating the active role of clinical pharmacists directly within the nephrology medical team. One of the scientific strategies that has proven effective in tackling polypharmacy and DRPs is a structured deprescribing program (Sayed Ali et al., 2025). Deprescribing is defined as the process of planning to stop, reduce doses, or replace medications that no longer have clear medical indications, medications whose risks outweigh their benefits, or medications that are not aligned with the patient's goals of care. (Paneerselvam et al., 2025) (Bortolussi-Courval et al., 2024)

Prospective studies conducted by prove that the presence of clinical pharmacists who conduct comprehensive (Zhang et al., 2023a) medication reviews, drug reconciliation when patients are admitted to treatment, and provide direct clinical recommendations to nephrology

specialists can drastically reduce the proportion of patients who experience DRPs, from 45.95% to only 7.77%. The acceptance rate of physicians to the recommendations submitted by pharmacists reached a very high figure of 85.53%, which indicates that evidence-based pharmaceutical interventions are highly valued in interprofessional collaborative interactions.

To support the success of deprescribing in the hemodialysis unit, the use of evidence-based deprescribing algorithms (such as the nine Canadian deprescribing algorithms for HD patients validated by as well as the application of clinical decision support software such as (Lefebvre et al., 2020) MedSafer) has proven to be crucial. The device automatically matches the patient's electronic medical record data with a list of (Bortolussi-Courval et al., 2024) Potentially Inappropriate Medications (PIMs) for the renal disorder population. Through this approach, pharmacists can safely stop unnecessary use of PPIs, lower excessive antihypertensive doses, and cut back on non-essential supplements, thereby successfully lowering pill loads, preventing potential harmful drug interactions, improving patient adherence, and ultimately significantly improving the quality of life and clinical prognosis of hemodialysis patients (Bortolussi-Courval et al., 2024; Lefebvre et al., 2020; Pereira-Céspedes et al., 2023)

CONCLUSION

Polypharmacy is one of the clinical problems that often occur in CKD patients undergoing hemodialysis, as a result of the complexity of the disease and the many comorbidities that accompany it. Polypharmaceutical complex combinations of cardiovascular/antihypertensive drugs (Amlodipine, Bisoprolol), vascular phosphate binders (CaCO3), hematological essential supplements (folic acid, iron, erythropoetin). Unmonitored polypharmaceuticals have been proven to trigger a high incidence of DRPs. DRPs that occur are the potential for drug interactions with moderate-major severity (up to 89%), overdose, and prescription of gastrointestinal drugs (PPIs) without valid clinical indications. and the accumulation of drug side effects (ADRs) due to failure to adjust doses to the clearance of the hemodialysis circuit. The use of drugs that damage the kidneys (such as NSAIDs, Aminoglycosides) should be avoided completely or strictly adjusted because they can eliminate residual renal function. In contrast, the use of drugs with safe non-renal elimination such as Paracetamol, Amlodipine, Atorvastatin, and Insulin is a key pillar to maintain the stability of clinical outcomes and minimize toxicity without aggravating the body's metabolic clearance. Increased consumption of non-essential drugs has been shown to increase the risk of mortality by up to twofold. Interprofessional collaboration involving routine reviews, drug reconciliation and regular treatment monitoring is a mandatory service standard in every hemodialysis unit to ensure therapeutic safety and optimize the quality of life of patients

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