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# Impact of pharmacist-led medication review among hemodialysis patients: a systematic review

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**ABSTRACT**

**Background:** Medication-related problems (DRPs) are common among hemodialysis (HD) patients, and pharmacist-led medication reviews have been shown to address such issues. However, the impact of these interventions and the specific types of DRPs among this patient group remain unclear.

**Objectives:** This systematic review aimed to assess the impact of pharmacist-led medication reviews among HD patients, identify the most prevalent types of DRPs, and explore the factors associated with these problems.

**Methods:** A systematic search was conducted across databases such as *Medline via PubMed*, Science Direct, Google Scholar, and EBSCOHost, for studies published from January 2012 to July 2023. Studies included were those focusing on pharmacist interventions in HD patients. The Newcastle-Ottawa Scale (NOS) was used to evaluate the quality of selected studies.

**Results:** After screening 343 articles, 10 studies (involving 1342 HD patients) were included. Nine studies were rated as high quality, and one as fair quality. The studies predominantly used prospective designs. A total of 4511 DRPs were identified, with suboptimal drug treatment, non-adherence to medications, and drug use without indication being the most common issues. Pharmacist interventions led to the resolution or reduction of DRPs, shorter hospital stays, improvement in laboratory outcomes, better quality of life (QoL), and enhanced patient understanding. However, interventions had minimal or no significant impact on reducing unplanned admissions, mortality rates, or improving medication adherence. The reduction in healthcare utilisation costs was inconsistent across studies.

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**Conclusion:** Pharmacist-led medication reviews were effective in resolving DRPs and improving clinical outcomes in HD patients, such as quality of life and lab values. However, their impact on healthcare utilisation and mortality remains inconclusive. Further research with longer follow-up is needed to assess the long-term economic outcomes of these interventions.

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**KEYWORDS** Non-communicable disease; drug safety; disease burden; renal disease; hemodialysis; patient safety

## 1. Introduction

Chronic kidney disease (CKD) is a chronic condition that is characterised by progressive deterioration in kidney function over time. It is defined as kidney damage either by structural or functional abnormalities, with or without decreased glomerular filtration rate (GFR) for ≥3 months, or GFR <60 mL/min/1.73 $m^2$ with or without kidney damage for ≥3 months (Kasiske, 2014). HD is one of the renal replacement therapies (RRT) that is indicated in end stage renal disease (ESRD), which is the final stage or stage 5 of CKD that is identified when the GFR is <15 mL/min/1.73 $m^2$ (KDIGO, 2024). ESRD is irreversible and it has been a common health problem owing to the incremental prevalence and incidence over the years, as well as the significant expense of its treatment (CDC Surveillance System, 2021; Ismail, Abdul Manaf et al., 2019; Ismail, Al-Subhi et al., 2019; National Renal Registry, 2018a; Saminathan et al., 2020). Despite the availability of RRT, the reported mortality has still been high over the years (United States Renal Data System, 2019).

DRPs are common in HD patients because chronic comorbidities such as diabetes mellitus (DM), hypertension and dyslipidemia, and other complications such as CKD-mineral and bone disorder (CKD-MBD) and CKD-associated anemia are usually coexisted with CKD, thereby leading to polypharmacy in HD patients as they are required to be on many medications to manage different diseases concurrently. Polypharmacy is defined as regular use of ≥5 medications (Halli-Tierney et al., 2019). It is one of the contributing factors to DRPs and it may also cause HD patients to be reluctant to adhere to complex regimens. Hemodialysis patients are at high risk for drug related problems (DRPs) because of the polypharmacy and the impaired renal excretion (Wahid et al., 2017). Study done by Garedow et al. (2019) stated that each HD patient had at least one type of medication related problem with the number of issues per participant ranging between 2 and 4.

Nevertheless, DRPs are mostly preventable (Al-Ramahi et al., 2016; Faisal et al., 2024). Thus, medication reviews may be crucial as an intervention to reduce the prevalence of DRPs and improve various outcomes in HD patients

such as health status, quality of life and polypharmacy (Kim et al., 2021; Subeesh et al., 2020). Pharmacists' involvement to detect and resolve DRPs has been shown to improve the treatment outcomes by suggesting evidence-based clinical interventions to the prescribers (Susilawati et al., 2021; Atmaja et al., 2024). Despite pharmacists' expertise in pharmaceutical care, their involvement in medication reviews within dialysis centers is limited. While pharmacists possess specialised knowledge, they are not consistently integrated into all settings, including outpatient hemodialysis (HD) centers, as noted by Salgado et al. (2013)

However, there are limited studies to evaluate the impacts of pharmacist-led medication reviews in preventing and solving DRPs among HD patients. Hence, the aim of this systematic review is to summarise all the available articles to determine the type of DRPs and their associated factors, as well as the outcomes of pharmacist-led medication reviews among HD patients.

## 2. Methodology

### *2.1. Search strategy*

A comprehensive search strategy was developed to capture all relevant studies on pharmacist-led medication reviews and drug-related problems (DRPs) among hemodialysis (HD) patients. We conducted a detailed search across multiple databases, including *Medline via PubMed*, Science Direct, Google Scholar, and EBSCOHost. The search terms used included a combination of key concepts related to pharmacist interventions, medication reviews, DRPs, and hemodialysis patients. Terms included 'pharmacist-led interventions,' 'medication review,' 'drug-related problems,' 'chronic kidney disease,' 'hemodialysis,' and 'renal patients.' We consulted a professional librarian to ensure that our search strategy was comprehensive and captured the full range of terminology associated with the concepts of DRPs and pharmacy interventions.

### *2.2. Grey literature search*

In addition to the database searches, a grey literature search was conducted to capture any unpublished or ongoing research. This included searching relevant conference proceedings, institutional repositories, and contacting experts in the field for potential studies not available in mainstream academic databases.

### *2.3. Inclusion and exclusion criteria*

The literature search for this systematic review was conducted in 2023. To ensure comprehensive coverage, all relevant articles published within the 10

years preceding the search (2013–2023) were included. The free full-text articles of clinical trials randomised controlled trials, cohort studies, cross-sectional studies, case control studies and reviews written in English were deemed eligible for inclusion, whereas the articles of systematic reviews, case reports, case series and editorials, and articles that were not written in English or could not be viewed in full text for free were not included. Limiting the studies to 'free full-text' had an insignificant impact on the resultant selection of studies as the author came across few studies that required payment for access. The studies involving ≥18-year-old HD patients were included, whereas studies with CKD patients not receiving HD or receiving other types of RRT, or <18 years old, were excluded.

### 2.4. Study selection

We used predefined inclusion and exclusion criteria to select relevant studies. Studies were included if they assessed the impact of pharmacist-led medication reviews in HD patients, identified types of DRPs, and explored factors associated with DRPs. We excluded studies that were not published in English, did not focus on HD patients, or did not evaluate pharmacist interventions. Inter-rater agreement for study selection and data extraction was assessed using Cohen's kappa statistic. A kappa score of ≥0.80 was considered excellent, indicating strong agreement between the two reviewers. Disagreements were resolved by discussion and, if needed, consultation with a third reviewer to achieve consensus.

### 2.5. Data extraction

Two independent reviewers conducted the study selection process and data extraction. Disagreements were resolved through discussion and consultation with a third reviewer to reach a consensus. The quality of the included studies was assessed using the Newcastle-Ottawa Scale (NOS), which evaluates the methodological quality of observational studies.

### 2.6. Quality assessment

The Newcastle-Ottawa Scale (NOS) was used to assess the quality of the included articles. This scale is popularly used to assess the quality of non-randomised studies such as case–control and cohort studies, and it has also been customised for assessment of cross-sectional studies. These studies were rated by a 'star scoring system' based on three perspectives, constituting of the selection of study groups, comparability of the study groups and ascertainment of exposure (for case–control studies) or outcome (for cohort and cross-sectional studies) of interest. A maximum of 9 stars could be awarded for case–control and cohort studies whereas cross-sectional studies could be awarded up to a

maximum of 10 stars. Studies that were rated 7–10 stars were regarded as high quality, while those with 4–6 stars and 0–3 stars were considered as fair quality and poor quality, respectively (Modesti et al., 2016; Wells et al., 2011).

## 3. Results

### 3.1. Study selection

The initial electronic searches yielded 343 results and 31 potential articles were shortlisted based on initial title and abstract screening. Finally, only 10 articles were selected for inclusion into this study after deduplication and full-text screening for eligibility criteria. All 10 included studies fulfilled the eligibility criteria. The process of search strategy and selection of articles is illustrated in detail in the PRISMA flow diagram below (Figure 1).

### 3.2. Quality of included studies

Based on the NOS, the quality of the 10 selected papers was evaluated. All the selected articles had 3–4 stars in the selection domain, 0–2 stars in the

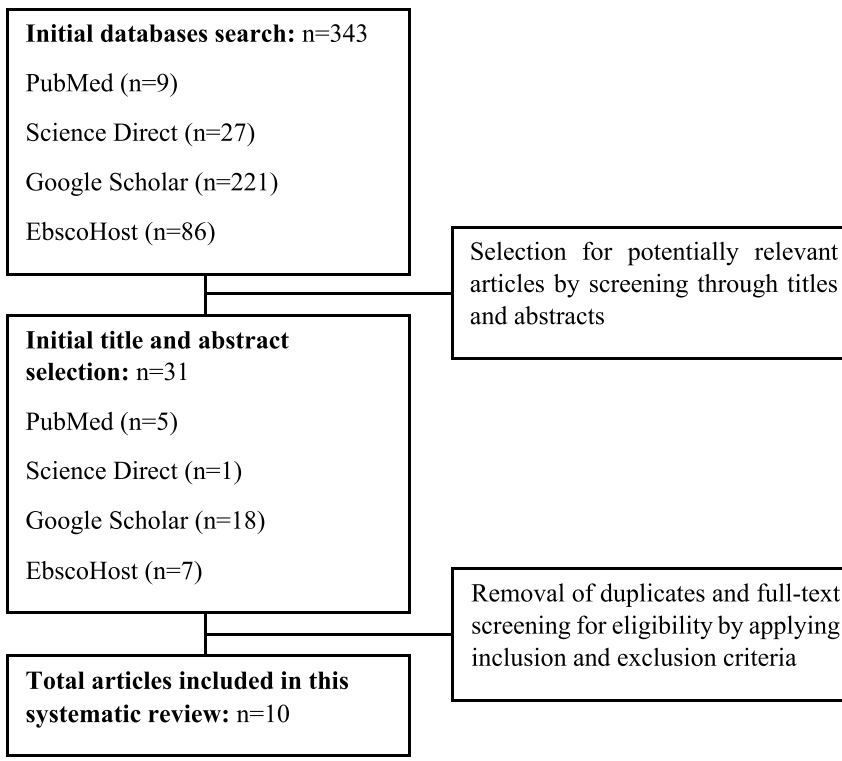


**Figure 1.** PRISMA flow diagram.

comparability domain and 2–3 stars in the exposure or outcome domain. Thus, it was determined that of the 10 included studies, nine studies were of high quality with a total score of 7–9 stars while one study was rated as fair quality with a total score of 6 stars. The summary of the papers' quality is tabulated in Table 1.

### 3.3. General study characteristics

All 10 included studies were conducted between 2014 and 2022, in various countries, and this allowed the relevant information from heterogeneous populations to be gathered in this study. Three studies were carried out in Indonesia, two in the US, two in Saudi Arabia, and one study each in Iraq, Singapore and Canada. The study design among most (seven) of the included studies was a prospective study, while two studies were performed retrospectively, and one study was carried out as a cross-sectional study.

The sample size of the study population among the 10 studies ranged from a minimum of 36 participants to a maximum of 324 participants. A total of 1342 participants were included in this study. Most of the recruited ESRD patients from the selected papers received their HD session as outpatients. The majority of the patients participating were between the ages of 41 and 69, and the majority in most ($n = 7$), of the studies were male, ranging from 51% to 65% male participants.

There were many types of pharmacist interventions to manage drug therapy of the HD patients looked at across the selected papers, including medication reviews, patient interviews and counseling, medication reconciliation, medication counseling, medication therapy management, motivational interviews, relative pharmaceutical care, and monitoring and evaluation of drug therapy outcomes. The characteristics of the included studies are summarised in Table 2.

**Table 1.** NOS scores of the included studies.

| No. | Author, year | Selection | Comparability | Exposure/ outcome | Total stars |
|---|---|---|---|---|---|
| 1 | Peri and Nasution (2022) | *** | * | *** | 7 |
| 2 | Daifi et al. (2021) | *** | * | *** | 7 |
| 3 | Talib and Mudhafar (2021) | **** | * | *** | 8 |
| 4 | Alshamrani et al. (2018) | **** | * | ** | 7 |
| 5 | Chia et al. (2017) | *** | – | *** | 6 |
| 6 | Lumbantobing et al. (2017) | **** | ** | *** | 9 |
| 7 | Chan et al. (2015) | **** | * | *** | 8 |
| 8 | Sulistyowati et al. (2014) | *** | * | *** | 7 |
| 9 | Ismail, Abdul Manaf et al. (2019), Ismail, Al-Subhi et al. (2019) | **** | – | *** | 7 |
| 10 | Patricia and Foote (2016) | **** | * | ** | 7 |

**Table 2.** Summary of characteristics of the included studies.

| No. | Author, year & country | Study Design & Population | Pharmacists' Management | Type of DRPs | Factors Associated with DRPs | Outcomes |
|---|---|---|---|---|---|---|
| 1 | Peri and Nasution (2022), Indonesia | Prospective analytical cohort study<br>HD inpatients with stage 5 CKD ($n$ = 83) | Medication review, Patient counseling | Using PCNE classification V9.00.<br>A total number of 470 DRP were identified and classified into 5 types: suboptimal drug effects ($n$ = 239), untreated symptoms/ indications ($n$ = 104), ADRs events ($n$ = 83), no drug effect ($n$ = 42), and others such as problems with cost-effectiveness ($n$ = 2).<br>Twelve causes of the DRPs were determined, including inappropriate combination of drugs, drug and herbal remedies, or drugs and herbal supplements ($n$ = 173),<br>No or incomplete drug treatment despite existing indication ($n$ = 106), other causes ($n$ = 90), under-administration of drugs by a health professional ($n$ = 37),dose too low ($n$ = 19), inappropriate timing of administration or dosing intervals by a health professional ($n$ = 17), patient uses drug incorrectly ($n$ = 14), dose too high ($n$ = 6), patient intentionally uses/take less drug than prescribed or does not take the drug at all for whatever reason ($n$ = 6), inappropriate duplication of therapeutic group or active ingredient ($n$ = 1), too long duration ($n$ = 1) and inappropriate timing/dosing interval ($n$ = 1). | Complexsocio-economic factors,<br>Level of education,<br>Medication adherence of patients | Reduced DRPs (significant; $p$ = 0.000),<br>Improved BP level (not significant; $p$ = 0.069),<br>Improved patients' QoL (significant; $p$ = 0.000) |

(*Continued*)

**Table 2.** Continued.

| No. | Author, year & country | Study Design & Population | Pharmacists' Management | Type of DRPs | Factors Associated with DRPs | Outcomes |
|---|---|---|---|---|---|---|
| 2 | Daifi et al. (2021), US | Retrospective observational descriptive study<br>HD inpatients ($n$ = 157) | Medication reconciliation,<br>Medication review | Unknown classification was used.<br>A total number of 1407 DRPs were identified and classified into 10 types: adherence (31.3%), needs additional drug therapy (21.5%), dose too low (13.1%), cost, accessibility, need for refills (11.9%), unnecessary drug therapy (8.8%), dose too high (4.6%), wrong drug (4.5%), adverse drug reaction (2.6%), drug-drug interactions (1.1%) and additional/other (0.6%). | Comorbid conditions,<br>Multiple readmissions into hospital,<br>Frequent changes to medications,<br>Patient education,<br>Cultural view of medications,<br>Lack of interest in health care,<br>Financial concerns surrounding medications | Cost savings ($447,355),<br>Improved vitamin D level (13%; significant),<br>Improved BP level (12%; significant),<br>Improved parathyroid hormone (PTH) level (7%; significant),<br>Improved calcium level (3%),<br>Improved phosphorus level (2%),<br>Improved patients' understanding (94.7%; significant),<br>Improved adherence (77%) |
| 3 | Talib and Mudhafar (2021), Iraq | Prospective, intervention, clinical study<br>HD outpatients ($n$ = 180) | Medication review,<br>Patient counseling | Using PCNE classification V9.00.<br>A total number of 230 DRPs were identified and classified into 5 types: effect of drug treatment not optimal (58.7%), no effect of drug treatment (17.8%), unnecessary drug treatment (9.6%), adverse drug event (possibly) occurring (9.1%) and untreated symptoms or indication (4.8%).<br>15 causes of the DRPs were determined, including inappropriate combination of drugs, or drugs and herbal medications, or drugs and dietary supplements (17.4%), patient uses/takes less drug than prescribed or does not take the drug at all (17.4%), no or | Polypharmacy,<br>Complications of CKD,<br>Comorbidities | Intervention accepted, implementation unknown (51.3%),<br>Intervention accepted and fully implemented (34.3%),<br>Intervention not accepted: no agreement (7.8%),<br>Intervention accepted, partially implemented (4.3%),<br>Intervention accepted but not implemented (2.2%),<br>Improved patients' outcome,<br>Improved patients' adherence to therapy |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | incomplete drug treatment in spite of existing indication (12.2%), no indication for drug (10.4%), drug dose too low (9.6%), adverse drug event (possibly) occurring (9.1%), inappropriate timing or dosing intervals (9.1%), dose too high (5.2%), inappropriate drug according to guidelines/ formulary (3.0%), patient uses/takes more drug than prescribed (2.6%), duration of treatment too short (2.2%), inappropriate duplication of therapeutic group or active ingredient (0.4%), duration of treatment too long (0.4%), prescribed drug not available (0.4%) and inappropriate timing of administration or dosing intervals (0.4%). | | |
| 4 | Alshamrani et al. (2018), Saudi Arabia | Cross-sectional study<br>HD outpatients ($n$ = 83) | Medication review | Unknown classification was used.<br>A total number of 280 DRPs were identified and classified into 8 types: medication use without indications (36%), sub-therapeutic dosing (23%), overdosing (15%), indication without drug (10%), duplicate therapy (5%), laboratory test requested (5%), contraindications (4%) and alternative medication suggested (3%). | Polypharmacy | Polypharmacy reduced |
| 5 | Chia et al. (2017), Singapore | Retrospective observational study<br>HD patients<br>-Collaborative care ($n$ = 134) | Medication reconciliation,<br>Medication review,<br>Medication counseling | Classified under 8 categories as defined by Hepler & Strand.<br>A total number of 515 DRPs were identified and classified as: non-adherence (42.5%), no indication for use (15.1%), over | Frequent changes to medication regimen,<br>Multiple transitions of care between different healthcare providers,<br>High pill burden, | Lower risk of unplanned admission (not significant; $p = 0.047$),<br>Shorter length of hospital stay(significant; $p < 0.001$),<br>Lower healthcare utilisation cost (not significant; $p = 0.165$), |

(*Continued*)

**Table 2.** Continued.

| No. | Author, year & country | Study Design & Population | Pharmacists' Management | Type of DRPs | Factors Associated with DRPs | Outcomes |
|---|---|---|---|---|---|---|
| | | -Usual care ($n$ = 190) | | dosage (12.8%), untreated indication (12.0%), under dosage (5.8%), adverse reaction (5.7%), improper selection (3.7%), interactions (1.2%) and others (1.2%). | Complexity of medication regimen | Lower mortality risk (not significant; $p = 0.189$) |
| 6 | Lumbantobing et al. (2017), Indonesia | Prospective experimental study with pre-post design HD outpatients ($n = 86$) | Medication review | Using PCNE classification V6.20. A total number of 337 DRPs were identified and classified into 7 types: suboptimal therapeutic effect (52.23%), non-allergic adverse drug effect (26.71%), failed therapy (18.69%) and indication of non-administration of drug (2.37%), effect of wrong medication (0%), allergic adverse drug effect (0%) and toxic effect (0%). | Hemodialysis frequency, Number of comorbidities, Number of drugs prescribed | Decrease in type and number of DRPs |
| 7 | Chan et al. (2015), Canada | Prospective observational study HD patients ($n$ = 228) | Medication reconciliation, Medication review | Classified under 7 categories as defined by Cipolle et al. A total number of 512 DRPs were identified with drug discrepancies and classified as: patient not willing to take prescribed medication (28%), additional therapy required (25%), unnecessary drug (24%), dose too low (14%), dose too high (7%), ineffective drug (1.5%) and adverse event (0.5%). | Comorbidities, Followed by multiple specialists, Mostly no communication on changes to patients' medications, Polypharmacy | Most of the important/clinically significant DRPs were potentially solved |

| | | | | | | |
|---|---|---|---|---|---|---|
| 8 | Sulistyowati et al. (2014), Indonesia | Prospective cohort observational analytic study<br>Terminal renal failure with hypertension (TRF-HT) patients undergoing HD ($n = 36$) | Pharmaceutical care involving medication review,<br>Monitoring and evaluation of drug therapy outcomes,<br>Patient interview | Classification according to the American Society of Health-System Pharmacist (ASHP) 1998 was used.<br>A total number of 275 DRPs related to the use of anti-hypertensive medications were identified and classified into 7 types: adverse drug reactions (37%), failure to receive medication (27%), drug interactions (24%), untreated indications (4%), over dosage (4%), improper drug selection (3%) and sub-therapeutic dosage (1%). | Antihypertensive drugs not received,<br>Additional antihypertensive drug required,<br>Drug combination, Risk of contradiction,<br>Dosage too low, Lack of understanding,<br>Less compliance/often forgotten,<br>Purposely not taking medication because of the belief that the drug is not suitable,<br>Inventory runs out/empty,<br>Cannot afford to buy drug,<br>Time to take medication less precise,<br>Different company (different formulation),<br>Dosage too high,<br>Addition of dosage by patient due to less effect,<br>Drug mechanism,<br>Allergic reaction,<br>ADR mechanism unknown certainly,<br>Pharmacokinetics, Pharmacodynamics,<br>Unknown | DRPs resolved or minimised,<br>Improved patients' understanding,<br>Improved patient compliance |

(*Continued*)

**Table 2.** Continued.

| No. | Author, year & country | Study Design & Population | Pharmacists' Management | Type of DRPs | Factors Associated with DRPs | Outcomes |
|---|---|---|---|---|---|---|
| 9 | Ismail, Abdul Manaf et al. (2019), Ismail, Al-Subhi et al. (2019), Saudi Arabia | Prospective quasi-experimental study<br>HD outpatients ($n = 72$) | Patient interview,<br>Medication review,<br>Medication therapy management,<br>Motivational interview,<br>Patient counseling | Unknown classification was used.<br>A total number of 421 DRPs were identified and classified into 11 types: drug use without indications (23.9%), failure to receive drugs (16.3%), indication without drug (13.1%), adverse drug events (11.8%), alternative drug (10.2%), overdosing (8.5%), underdosing (6%), laboratory monitoring (4.8%), monitoring required (2.6%), drug-drug interactions (2.4%) and improper drug selection (0.7%). | Not studied | Mean difference between self-reported medication use and electronic prescribing reduced (change in pharmacoadherenc e not significant; $p = 0.348$),<br>Mean pre-HD phosphate levels decreased (not significant; $p = 0.682$),<br>Mean systolic BP declined (not significant; $p = 0.083$),<br>Mean low-density lipoprotein (LDL) levels among patients receiving lipid-lowering agents decreased (not significant; $p = 0.096$),<br>Prevalence of DRPs decreased (44.9% reduced to 29.8%),<br>Median number of DRPs per prescribed medication declined (significant; $p = 0.002$) |
| 10 | Patricia and Foote (2016), US | Prospective study<br>HD patients ($n = 93$) | Medication reconciliation,<br>Medication review | Unknown classification was used.<br>A total number of 64 DRPs were identified and classified into 8 types: indication without drug (37.5%), dose too high (20.3%), drug without indication (18.8%), inappropriate adherence (7.8%), drug interaction (7.8%), dose too low (6.3%), wrong drug (1.6%) and adverse drug reaction (0%). | Not studied | 376 medication record discrepancies identified (3.1 per patient), 64 DRPs identified (0.5 per patient),<br>Reduced number of medication record discrepancies and DRPs after second medication review that was conducted12 months apart (not significant) |

### 3.4. Types of DRPs among HD patients

The types of DRPs among the recruited HD patients were identified and categorised by applying various classifications in the 10 included papers. Two of the studies used PCNE classification V9.00, one study used PCNE classification V6.20, one study each analyzed the types of DRPs using the classification defined by Hepler & Strand, classification defined by Cipolle et al. and classification according to the ASHP 1998, respectively, while unknown classification was applied by the remaining four studies. A total number of 4511 DRPs were identified in this study. The total number of DRPs among the selected studies varied from a minimum of 64 to a maximum of 1407, so on average 0.69 to 8.96 DRPs per patient.

A variety of DRP types were identified in the 10 included articles and several major types of DRPs were highlighted in this systematic review based on the included studies. 'Suboptimal drug treatment,' characterised by either under or overdosing, was concluded as the most prevalent and frequently occurring DRP among HD patients according to Peri et al. ($n = 239$; 50.9%), Talib & Mudhafar (58.7%) and Lumbantobing et al. (52.23%), as it accounted for more than half of the DRPs detected in these studies. It also appeared as the second and third most predominant DRP type in studies performed by Alshamrani et al. and Daifi et al., respectively (Alshamrani et al., 2018; Daifi et al., 2021; Lumbantobing et al., 2017; Peri & Nasution, 2022; Talib & Mudhafar, 2021). Besides that, three studies reported that patients' non- adherence to medications was the primary type of DRP among HD patients, constituting 31.3%, 42.5% and 28% of the DRPs identified by Daifi et al., Chia et al. and Chan et al., respectively (Chan et al., 2015; Chia et al., 2017; Daifi et al., 2021). As defined by PCNE classification V9.00, patients using/taking fewer drugs than prescribed or not taking the drugs at all is one of the causes of DRPs, and Chia et al. stated that it was one of the highest causes (17.4%) of DRPs in the study (Chia et al., 2017). Moreover, drug use without indications was determined as a major DRP by two studies carried out in Saudi Arabia, by Alshamrani et al. (36%) and Ismail et al. (23.9%) (Alshamrani et al., 2018; Ismail, Abdul Manaf et al., 2019; Ismail, Al-Subhi et al., 2019). Other than that, drug use without indication was also the second and third most frequently detected DRP in studies carried out by Chia et al. (15.1%) and Patricia & Foote (18.8%) (Chia et al., 2017; Patricia & Foote, 2016). Comparably, unnecessary drug treatment was revealed by Talib & Mudhafar (9.6%) and Chan et al. to be the third most common DRP in their studies (Chan et al., 2015; Talib & Mudhafar, 2021).

Nevertheless, Sulistyowati et al. and Patricia & Foote discovered different major types of DRPs compared to the above-mentioned studies, which were untreated indications (35%) and ADRs (37%), respectively (Patricia & Foote, 2016; Sulistyowati et al., 2014). Untreated indications were also reported as

the second most common cause of DRPs in studies by Peri et al. and Talib & Mudhafar, as well as being the third most frequently detected DRP in a study conducted by Ismail et al. (13.1%) (Ismail, Abdul Manaf et al., 2019; Ismail, Al-Subhi et al., 2019; Peri & Nasution, 2022; Talib & Mudhafar, 2021). Similarly, Daifi et al. and Chan et al. discovered that additional drug therapy required was the second major type of DRP based on their findings, at 21.5% and 25%, respectively (Chan et al., 2015; Daifi et al., 2021). Furthermore, ADRs were also found to be the third and second major DRP in studies, performed by Peri et al. ($n = 83$; 17.66%) and Lumbantobing et al. (26.71%), respectively (Lumbantobing et al., 2017; Peri & Nasution, 2022). The types of DRPs identified were consistent among the three studies conducted in Indonesia. This could be seen as suboptimal drug treatment was similarly found to be the majority of DRP types in two of the three aforementioned studies (Lumbantobing et al., 2017; Peri & Nasution, 2022). Additionally, ADRs were also detected as one of the major types of DRPs in three of the studies (Lumbantobing et al., 2017; Peri & Nasution, 2022; Sulistyowati et al., 2014).

Other types of DRPs that were also identified in the 10 articles including no effect of drug treatment, failed therapy, overdosage, failure to receive drugs and drug interactions (Alshamrani et al., 2018; Chan et al., 2015; Chia et al., 2017; Daifi et al., 2021; Ismail, Abdul Manaf et al., 2019; Ismail, Al-Subhi et al., 2019; Lumbantobing et al., 2017; Patricia & Foote, 2016; Peri & Nasution, 2022; Talib & Mudhafar, 2021; Sulistyowati et al., 2014). Among the 10 included articles, only two articles showed the causes of DRPs and were in accordance with the PCNE classification V9.00. The causes of DRPs identified were comparable between these two studies as inappropriate combinations of drugs, drug and herbal remedies, or drugs and herbal supplements, appeared as the most common cause contributing to occurrence of DRPs, constituting 36.8% ($n = 173$) and 17.4% in studies conducted by Peri et al. and Talib & Mudhafar, respectively (Peri & Nasution, 2022; Talib & Mudhafar, 2021). Similar findings were made by Sulistyowati et al., who also identified improper drug combinations as one of the factors causing DRPs (Sulistyowati et al., 2014).

### 3.5. Factors associated with DRPs among HD patients

Factors associated with DRPs among HD patients were briefly studied in eight of the included articles. Polypharmacy was concluded as the major factor causing DRPs as it was reported in five out of the eight studies (Alshamrani et al., 2018; Chan et al., 2015; Chia et al., 2017; Lumbantobing et al., 2017; Talib & Mudhafar, 2021). Besides that, an increased number of comorbidities was also identified as one of the predictors associated with DRPs by Chan et al. (2015), Daifi et al. (2021), Lumbantobing et al. (2017), Talib and Mudhafar (2021). Moreover, multiple readmissions into hospital was determined to increase the risk of DRPs among HD patients by Daifi et al., and this factor

was correlated with frequent changes to medication regimens and multiple transitions of care between different healthcare providers, which were also the factors found by Chia et al. and Chan et al. (Chan et al., 2015; Chia et al., 2017; Daifi et al., 2021). Chan et al. also described that there was no communication on the changes to patients' medications most of the time (Chan et al., 2015). Comparably, Peri et al., Daifi et al. and Sulistyowati et al. uncovered complex socio-economic factors or HD patients having financial concerns surrounding medications. A lower level of education was also a determinant of the occurrence of DRPs among HD patients (Daifi et al., 2021; Peri & Nasution, 2022; Sulistyowati et al., 2014). As to the rest, the factors associated with DRPs revealed by the studies consisted of patients' medication adherence, cultural view of medications, lack of interest in healthcare, complications of CKD, complexity of medication regimens, and lower HD frequency (Chia et al., 2017; Daifi et al., 2021; Lumbantobing et al., 2017; Peri & Nasution, 2022; Sulistyowati et al., 2014; Talib & Mudhafar, 2021).

| Study | Classification used | Major DRPs identified | Prevalence of major DRPs (%) |
|---|---|---|---|
| Peri and Nasution (2022) | PCNE Classification V9.00 | Suboptimal drug treatment, Untreated indications, ADRs | Suboptimal drug treatment (50.9%) |
| Talib and Mudhafar (2021) | PCNE Classification V9.00 | Suboptimal drug treatment, Unnecessary drug treatment, ADRs | Suboptimal drug treatment (58.7%) |
| Lumbantobing et al. (2017) | PCNE Classification V9.00 | Suboptimal drug treatment, ADRs | Suboptimal drug treatment (52.23%) |
| Alshamrani et al. (2018) | Hepler & Strand Classification | Suboptimal drug treatment, Drug use without indication | Suboptimal drug treatment (reported as 36%) |
| Daifi et al. (2021) | Cipolle et al. Classification | Patients' non-adherence, Suboptimal drug treatment | Non-adherence to medications (31.3%) |
| Chia et al. (2017) | ASHP 1998 Classification | Patients' non-adherence, Drug use without indication | Non-adherence to medications (42.5%) |
| Chan et al. (2015) | Unknown Classification | Patients' non-adherence, Drug use without indication | Non-adherence to medications (28%) |
| Ismail, Abdul Manaf et al. (2019), Ismail, Al-Subhi et al. (2019) | Unknown Classification | Drug use without indication, ADRs | Drug use without indication (23.9%) |
| Sulistyowati et al. (2014) | Unknown Classification | Untreated indications, ADRs | Untreated indications (35%) |
| Patricia and Foote (2016) | Unknown Classification | ADRs, Drug use without indication | ADRs (37%) |

This table summarises the major DRPs identified across studies, categorised by the classification system used and the prevalence of each DRP type in the respective studies.

### 3.6. Outcomes of pharmacist-led medication reviews and other interventions

This systematic review pinpointed various outcomes of pharmacist-led medication reviews and other interventions in all 10 included articles as fulfilling the primary objective of this study. The most frequently reported outcome among the included studies was reduced or resolved DRPs and this result was found statistically significant by Peri et al. ($p = 0.000$) and Ismail et al. ($p = 0.002$) (Chan et al., 2015; Ismail, Abdul Manaf et al., 2019; Ismail, Al-Subhi et al., 2019; Lumbantobing et al., 2017; Peri & Nasution, 2022; Sulistyowati et al., 2014). Other significant impacts of pharmacists' involvement in drug therapy that were proved in the included studies consisted of improved patients' QoL ($p = 0.000$), improved patients' understanding (94.7%) and shorter length of hospital stay ($p < 0.001$) (Chia et al., 2017; Daifi et al., 2021; Peri & Nasution, 2022). Only two studies reported on economic outcomes. Interventions by pharmacists on HD patients' drug treatment could contribute to decreased healthcare utilisation costs, and this outcome was similarly revealed by Daifi et al. and Chia et al., but Chia et al. found this not significant ($p = 0.165$) (Chia et al., 2017; Daifi et al., 2021). Talib & Mudhafar found that patients' adherence to therapy could be enhanced with clinical interventions by pharmacists and this result concurred with the result demonstrated by Daifi et al. and Sulistyowati et al., but this was found to be insignificant by Ismail et al. ($p = 0.348$) (Daifi et al., 2021; Ismail, Abdul Manaf et al., 2019; Ismail, Al-Subhi et al., 2019; Sulistyowati et al., 2014; Talib & Mudhafar, 2021). Furthermore, it was evident that laboratory outcomes such as BP level ($p = 0.069$), pre-HD phosphate level ($p = 0.682$) and LDL level ($p = 0.096$) were also improved after pharmacists' management, although these outcomes were not statistically significant (Ismail, Abdul Manaf et al., 2019; Ismail, Al-Subhi et al., 2019; Peri & Nasution, 2022). Daifi et al. also revealed similar results with significant improvement of vitamin D level (13%), BP level (12%) and PTH level (7%) among the HD patients, but the improvements in calcium level (3%) and phosphorus level (2%) were not significant (Daifi et al., 2021).

Apart from that, Talib & Mudhafar also assessed the acceptance rate of pharmacists' interventions in detail. It was reported that the interventions by pharmacists were mostly accepted (92.2%), and there was 34.3% with full implementation and 4.3% with partial implementation, while the majority of the implementations were unknown (51.3%), and 2.2% was not implemented. In spite of that, 7.8% of the interventions were not accepted (Talib & Mudhafar, 2021). Comparatively, another six included articles also revealed the acceptance rate and implementation rate of pharmacists' interventions. 100% acceptance rate was reported by Peri et al. and Sulistyowati

et al., whereas 93% and 46.43% of the pharmacists' interventions were accepted in studies conducted by Ismail et al. and Alshamrani et al., respectively (Alshamrani et al., 2018; Ismail, Abdul Manaf et al., 2019; Ismail, Al-Subhi et al., 2019; Peri & Nasution, 2022; Sulistyowati et al., 2014). Furthermore, Patricia & Foote and Chia et al. reported 77% and 67.6% of the pharmacists' interventions were accepted and implemented, respectively, while Peri et al. identified that most of the interventions were just partially implemented (54.46%) (Chia et al., 2017; Patricia & Foote, 2016; Peri & Nasution, 2022). Patricia & Foote concluded that DRPs and medication record discrepancies could be identified through medication management with pharmacists' involvement as the outcomes. Additionally, they also found that the reduction in the number of DRPs and medication record discrepancies among 31 HD patients after the second medication review that was conducted twelve months apart were not significant (Patricia & Foote, 2016). Reduced polypharmacy was also determined as one of the impacts of pharmacists' interventions on drug treatment among HD patients (Alshamrani et al., 2018).

### *3.7. Evaluation of outcomes*

The included studies reported several outcomes of pharmacist-led medication reviews, including the reduction or resolution of drug-related problems (DRPs), improvements in patient understanding, healthcare utilisation, and costs. However, it is important to note that the majority of studies included in this review were observational in design, with no randomisation. The lack of randomisation means that evaluating the true impact of pharmacist-led interventions is challenging because DRP-related outcomes were identified and evaluated by pharmacists themselves. As a result, these outcomes should be interpreted cautiously, as there is a potential for bias in the identification of DRPs due to the self-assessment nature of these studies.

In most studies, DRPs were identified using a before-and-after comparison approach, where the pharmacist identified DRPs at baseline (before the intervention) and after the intervention. This method helps establish a change but does not provide a clear causal relationship between the intervention and the outcomes. Some studies did use independent criteria or standards to assess DRPs, such as clinical guidelines, while others relied on pharmacists' own judgment. In the cases where independent assessments were not conducted, it is important to interpret the findings with caution.

The studies varied in their use of control or comparison groups. Several studies employed historical controls (comparing outcomes before the intervention) or used a within-patient comparison (pre- and post-intervention comparisons). For outcomes such as improved patient understanding and

healthcare utilisation, many studies compared the intervention group to a baseline or standard care group. However, not all studies included a distinct control group, which limits the ability to draw definitive conclusions regarding the impact of pharmacist-led interventions.

## 4. Discussion

This systematic review synthesised evidence on the impact of pharmacist-led medication reviews among HD patients by summarising the results from ten recent studies conducted in different countries. Other pharmacists' interventions were also incorporated in the studies because they were interrelated with pharmaceutical care. The primary findings of this study indicated that pharmacists' interventions provided a variety of positive impacts on HD patients as well as the healthcare system. In addition, this systematic review also assessed the types of DRPs commonly encountered by HD patients and the factors associated with the occurrence of DRPs.

In this systematic review, with the participation of a total of 1342 patients, the importance of performing pharmacist-led medication reviews was indicated as a number of DRPs was able to be identified by the clinical pharmacists in the 10 included studies ranging from 64 DRPs up to 1407 DRPs, on average 0.69 to 8.96 DRPs per patient. Along with detection of DRPs, pharmacists were able to provide various pharmaceutical interventions significantly reduced the number of DRPs and resolved the DRPs effectively. This highlights the significant role of pharmacists in enhancing medication safety and reducing drug-related problems (Chan et al., 2015; Ismail, Abdul Manaf et al., 2019; Ismail, Al-Subhi et al., 2019; Lumbantobing et al., 2017; Peri & Nasution, 2022; Sulistyowati et al., 2014). Hence, medication reviews and other interventions carried out by pharmacists were critical to identify and resolve or reduce the incidences of DRPs as the results could be further extended to other positive impacts in terms of clinical, humanistic and economic outcomes. One of the included studies conducted the second medication review on 31 HD patients twelve months apart to evaluate the potency of the pharmacists' interventions, and it was stated that the reduction of number of DRPs (13 vs 11) and medication record discrepancies (95 vs 86) were not significant. Thus, medication reconciliations and medication reviews were suggested to be performed at a higher frequency by pharmacists in order to overcome the DRPs and medication record discrepancies effectively (Patricia & Foote, 2016).

As one of the clinical outcomes, the hospitalised HD patients who received multidisciplinary collaborative care, with an integrated pharmacist-led medication review, were found to have a shorter length of hospital stay compared to those who did not receive a medication review conducted by a pharmacist (Chia et al., 2017). This result was in accordance with the findings by Weinhandl

et al. who also identified fewer days of hospitalisation (6%) among the HD patients who received an integrated pharmacy program in intention-to-treat analyses (Weinhandl et al., 2013). A shorter hospital stay might provide other advantages such as lower costs and lower risk of hospital-acquired infections. Moreover, improved laboratory outcomes were also demonstrated by several included studies. Peri et al. revealed a significant association between the number of DRPs and BP level of the HD patients, which indicated that the higher the number of DRPs, the higher the BP level of the HD patients. Although the reduction of BP level was insignificant following interventions delivered by pharmacists, it still contributed to delaying the progression of the disease (Peri & Nasution, 2022). Nevertheless, improvement in BP level was significant according to Daifi et al., and there was also a significant increase in vitamin D level and PTH level (Daifi et al., 2021). Similarly, a randomised controlled study also found the reduction in BP level was significant ($p < 0.05$) in HD patients who were provided with pharmaceutical care (Mateti et al., 2018). Apart from that, clinical outcomes associated with pharmacist-led medication reviews were not significant, such as lower risk of unplanned admission and lower mortality risk, which was reported by Chia et al.. There was a 27%, insignificant, decline in unplanned admission risk among HD patients who received pharmacist-led medication reviews, according to Chia et al., and consistent results were found in a study conducted by Weinhandl et al. which showed 2%, insignificant, fewer hospital admissions with pharmacists' involvement (Chia et al., 2017; Weinhandl et al., 2013). The result of the insignificant lower mortality risk was supported by similar findings from Mateti et al. ($p > 0.05$) (Mateti et al., 2018).

In terms of humanistic outcomes, QoL was measured prospectively by Peri et al. using a WHO- QoL questionnaire, and it was found that the QoL of HD patients was significantly improved from the score of $40 \pm 9.87$ to $69 \pm 12.45$ following pharmacists' interventions. The range of scores indicated that the HD patients were enhanced from poor to good quality of life. This improvement could be explained by a reduction in DRPs after interventions by pharmacists because a significant association between the number of DRPs and patients' QoL was discovered. The higher the number of DRPs, the lower the QoL of the HD patients (Peri & Nasution, 2022). This result was consistent with a randomised controlled study which also found significant higher HRQoL scores ($p < 0.05$) among HD patients who received pharmaceutical care provided by pharmacists in comparison to those who did not (Mateti et al., 2017). Besides that, improved patient understanding was found in two studies, and Daifi et al. reported that this outcome was the most significant finding in the study (Daifi et al., 2021; Sulistyowati et al., 2014). Although patients' adherence was addressed as the most difficult obstacle to overcome owing to its multifactorial nature, four studies still mentioned about improved medication adherence among the HD patients (Daifi et al., 2021;

Ismail, Abdul Manaf et al., 2019; Ismail, Al-Subhi et al., 2019; Sulistyowati et al., 2014; Talib & Mudhafar, 2021). Daifi et al. disclosed that improved patients' compliance to medications (77%) after pharmacists' interventions led to significant optimisation of BP and vitamin D levels among the HD patients (Daifi et al., 2021). Based on the study conducted by Ismail et al., the level of the HD patients' adherence to medications after pharmacists' interventions was evaluated by measuring the mean difference between their self-report of medication use and their medication records as documented by electronic prescribing, but the result found was statistically insignificant (Ismail, Abdul Manaf et al., 2019; Ismail, Al-Subhi et al., 2019). None of these studies assessed the discrepancies in health literacy and other psychological factors such as depression, which could influence patients' compliance to the medications (Ossareh et al., 2014).

Economic outcomes were only reported by two studies. Daifi et al. analyzed and classified the pharmacists' interventions around managing DRPs to assess the estimated cost avoidance (ECA). The result was revealed with a total of 227 out of 1407 DRPs associated with the ECA: 121 incidences after interventions by pharmacists to avoid a visit to the emergency department, 82 incidences avoiding a physician visit and 24 incidences avoiding hospital admission. This led to ECAs of $149,193, $19,762 and $278,400, respectively, and the total cost savings were $447,355 following pharmacists' interventions during the 6-month study. However, no statistical analysis was done to assess whether the amount saved was statistically significant (Daifi et al., 2021). Apart from that, Chia et al. assessed the relationship between the integration of pharmacists into multidisciplinary teams and overall healthcare utilisation costs. It was evident that there were lower healthcare utilisation costs among HD patients receiving collaborative care involving pharmacists' management. The result was statistically insignificant despite the reduced costs of hospital admission, and the reduction was diminished by increased costs for medications and hospital visits. Increased medication costs could be attributed to pharmacists' recommendations of additional medication (17%) (Chia et al., 2017). The inconsistency in cost reduction upon pharmacists' involvement in medication management was similarly concluded by two systematic reviews that evaluated the outcomes among patients with chronic diseases in outpatient and community-dwelling settings, respectively. The reason for the increased costs was in line with the findings by Loh et al., while Viswanathan et al. claimed that healthcare utilisation varied as it would be increased or decreased depending on patients' conditions. Patients might increase healthcare utilisation when optimising pharmacotherapy, thus maximising other healthcare use (Loh et al., 2016; Viswanathan et al., 2015). Nonetheless, such increased spending was purely in the short term, and it would be plausible to eschew unnecessary spending in future with improved treatment outcomes, hence future studies could

design a longer follow-up duration to assess the long-term impact of pharmacists' interventions on economic outcomes among HD patients.

Other than the aforementioned outcomes, the acceptance rate of pharmacists' interventions was also assessed as one of the study outcomes. One study reported that most of the pharmacists' interventions were accepted, but more than half of the interventions were unknown owing to complications in following up with the patients after counseling them about the DRPs and the rejection of interventions due to no agreement (Talib & Mudhafar, 2021). Alshamrani et al. revealed that many physicians rejected pharmacists' interventions, as many interventions were recommendations for referral to other specialists to carry out a reevaluation of patients' needs (Alshamrani et al., 2018).

In addition, this systematic review also assessed the types of DRPs and the factors associated with DRPs as the secondary objective. The most prevalent type of DRP among HD patients discovered from the included studies was suboptimal drug treatment and the results were concordant among three studies that it was the most significant type of DRP, while it was found to be the second and third most common DRP by Alshamrani et al. and Daifi et al., respectively. The prevalence of this DRP was supported by high percentages, which were more than 50% among the three studies (Alshamrani et al., 2018; Daifi et al., 2021; Lumbantobing et al., 2017; Peri & Nasution, 2022; Talib & Mudhafar, 2021). Comparable results were demonstrated by Dlear et al. and Ramadaniati et al., who also reported that underdosage and suboptimal drug treatment were the most (29%) and the second most (28.7%) frequently occurring DRP in the studies, respectively (Dlear et al., 2015; Ramadaniati et al., 2016). Nonetheless, it was reported that there was a 63.59% reduction in this DRP after pharmacists' interventions (Peri & Nasution, 2022).

Patients' reluctance to adhere to medications could be the result of polypharmacy, as large quantity of medicines and the complexity of the medication regimen could be troublesome (Chan et al., 2015; Chia et al., 2017). Chan et al. established that patients' non-compliance, especially to anticoagulant and antihypertensive medications, could cause harm such as discomfort and/or clinical deterioration (Chan et al., 2015). However, this issue could be resolved with pharmacists' efforts by providing pharmaceutical care (Daifi et al., 2021; Ismail, Abdul Manaf et al., 2019; Ismail, Al-Subhi et al., 2019; Sulistyowati et al., 2014; Talib & Mudhafar, 2021).

Drug use without indication or unnecessary drug treatment was consistently reported as the primary type of DRP in two studies conducted in Saudi Arabia, and was also found in another four of the included studies (Alshamrani et al., 2018; Chan et al., 2015; Chia et al., 2017; Ismail, Abdul Manaf et al., 2019; Ismail, Al-Subhi et al., 2019; Patricia & Foote, 2016; Talib & Mudhafar, 2021). Such results highlighted the high frequency of polypharmacy among HD patients, especially in Saudi Arabia, and Alshamrani et al.

revealed that the prevalence of polypharmacy was up to 97.6% in their study (Alshamrani et al., 2018). Chan et al. also observed that taking narcotic medication without indication could have a harmful effect on patients (Chan et al., 2015). Therefore, pharmacist-led medication reviews were highly demanded and deprescribing was essential to resolve this DRP (Alshamrani et al., 2018; Ismail, Abdul Manaf et al., 2019; Ismail, Al-Subhi et al., 2019).

Untreated indication or additional drug therapy required was also found as one of the DRP types among HD patients and this was concordant with the findings by George et al. in which untreated indication was reported as the third most frequently occurred DRP (3.98%). The study discovered that depression was a prominent indication among HD patients, yet no prescribed drugs were identified for its treatment (Chan et al., 2015; Daifi et al., 2021; George et al., 2017; Ismail, Abdul Manaf et al., 2019; Ismail, Al-Subhi et al., 2019; Patricia & Foote, 2016; Peri & Nasution, 2022; Talib & Mudhafar, 2021). Peri et al. found a reduction of 47.11% in this DRP after pharmacists' interventions (Peri & Nasution, 2022). ADRs were also commonly seen among HD patients and comparable results were discovered by Ramadaniati et al. and George et al. as ADRs was the most (38.9%) and the second most common (4.98%) DRPs in the studies, respectively (George et al., 2017; Lumbantobing et al., 2017; Peri & Nasution, 2022; Ramadaniati et al., 2016; Sulistyowati et al., 2014). Ramadaniati et al. revealed that the majority of the ADRs were gastrointestinal bleeding or upset, potassium imbalance and diarrhea, caused by antiplatelets, phosphate binders and laxatives (Ramadaniati et al., 2016). Peri et al. also showed that ADRs were greatly reduced, by up to 90.36%, after pharmacists' interventions (Peri & Nasution, 2022).

Generally, the major DRPs identified in the included studies were mostly comparable. A pooled analysis of seven studies showed that the most prevalent type of DRP was inappropriate laboratory monitoring (23.5%), followed by dosing errors (20.4%) including both overdosage and underdosage, untreated indication (16.9%) and drug without indication (14.9%), whereas the least frequently identified DRP was drug interactions (4.5%) (Manley et al., 2005). The diversity of types of DRPs found in these studies could be attributed to different populations and healthcare settings, multiple prescribing patterns and individual patients' medical insurance status (Ismail, Abdul Manaf et al., 2019; Ismail, Al-Subhi et al., 2019).

Inappropriate combination of drugs, drug and herbal remedies, or drugs and herbal supplements, was the most predominant cause of DRPs (Peri & Nasution, 2022; Talib & Mudhafar, 2021). Consistent results were found by Ramadaniati et al., as inappropriate drug combinations were determined to be the main cause of DRPs (41.8%) (Ramadaniati et al., 2016). Inappropriate drug combination was also identified by Sulistyowati et al. as one of the factors causing DRPs and it was mentioned that adverse effects could be rendered because of the mechanism of pharmacokinetic and

pharmacodynamics interactions, which could lead to increased drug toxicity or reduced drug effectiveness (Sulistyowati et al., 2014). Drug interactions could arise from inappropriate drug combinations, as shown by the studies conducted by George et al. (86.38%) and Sulistyowati et al. (24%), which proved that drug interactions were prevalent among HD patients (George et al., 2017; Sulistyowati et al., 2014). Polypharmacy could complicate the conditions of patients with these DRPs and it was reported in five of the included studies as one of the predictors of the occurrence of DRPs (Alshamrani et al., 2018; Chan et al., 2015; Chia et al., 2017; Lumbantobing et al., 2017; Talib & Mudhafar, 2021). It was proved that regular pharmacist-led medication reviews could reduce polypharmacy among HD patients (Alshamrani et al., 2018). Additionally, HD patients with a higher number of comorbidities were susceptible to multiple hospitalisations and there were frequent changes to medication regimens as they were managed by different healthcare providers during the transitions of care, thus causing DRPs to occur (Chan et al., 2015; Chia et al., 2017; Daifi et al., 2021; Lumbantobing et al., 2017; Talib & Mudhafar, 2021). In order to reduce the risk of DRP occurrence, communication was of utmost importance to avoid the undocumented intentional medication discrepancies (Chan et al., 2015). Complex socio-economic factors or HD patients having financial concerns surrounding medications as well as lower level of education were also the factors associated with DRPs among HD patients. It was evident that patients with lower level of education had poorer adherence to their medications due to lack of knowledge about their diseases and the relative treatments that were needed (Aggarwal et al., 2018; Daifi et al., 2021; Jain et al., 2018; Peri & Nasution, 2022; Sulistyowati et al., 2014).

The primary strength of this systematic review was compiling comprehensive information concerning the types of DRPs among HD patients with the associated factors, as well as the impacts of pharmacist-led medication reviews, to provide an overview of the DRP-associated issues in HD patient care, and the crucial role of pharmacists to be integrated into patients' medication management. In addition, the selected studies in this systematic review included findings across different healthcare settings and countries in order to gather the desired information available from diverse populations to produce findings for this study that were more robust. Moreover, this study only included studies that had been conducted recently to ensure the latest information was compiled.

While this systematic review identified several positive outcomes related to pharmacist-led medication reviews in HD patients, it is important to highlight the methodological limitations of the included studies. Most studies were observational in nature and lacked randomisation, which is a significant limitation when evaluating causal effects. Randomised controlled trials (RCTs) are considered the gold standard for assessing intervention effectiveness, but

due to the nature of the intervention and patient population, such studies are often difficult to conduct. The lack of randomisation means that the observed outcomes may be influenced by confounding factors, such as baseline differences between the intervention and control groups or the effectiveness of other interventions being provided simultaneously.

In many studies, DRPs were identified by the pharmacists themselves, and as such, the detection of DRPs may have been influenced by the intervention itself. Without independent assessment of DRPs, it is difficult to determine whether the observed reductions in DRPs were genuinely due to the pharmacist-led intervention or if they reflect inherent biases in the identification process. Furthermore, the use of before-and-after comparisons does not account for potential temporal biases, such as improvements that may have occurred naturally over time.

For outcomes like patient understanding, healthcare utilisation, and costs, many studies did not include distinct control groups, which further complicates the ability to draw firm conclusions. The use of historical or within-patient comparisons is valuable but does not provide the same level of evidence as a properly randomised controlled trial.

The role of pharmacist in detecting, managing and preventing DRPs has been evident in this study. However, whether pharmacist can consistently integrate this role in the patient care and work collaboratively with other health professionals to sort out this issue remains a question. Apart from positive findings which was mainly gathered from trials in this study, it is interesting to observe the implementation of integrated patient care in the real world evidence. Given the limitations of the included studies, it is difficult to definitively attribute improvements in patient outcomes to pharmacist-led medication reviews. The evidence from this review suggests that such interventions can have positive effects on DRPs, patient understanding, and healthcare outcomes, but the impact of these interventions must be interpreted with caution due to the methodological flaws in the studies. Future research with rigorous study designs, including RCTs, is needed to better assess the effectiveness of pharmacist-led interventions in this population.

## 5. Conclusion

This systematic review synthesises and summarises evidence from several countries and different healthcare settings to identify the outcomes of clinical pharmacists' roles in medication review, types of DRPs and the associated factors among HD patients. Suboptimal drug treatment was the most prevalent DRP and polypharmacy was the main factor contributing to DRPs. The findings emphasize that pharmacist-led medication reviews are crucial in detecting and resolving DRPs among HD patients and subsequently bring positive impacts to the HD patients. Therefore, it is recommended to

integrate pharmacists into multidisciplinary teams to perform medication reviews and relative pharmaceutical care on HD patients. Nevertheless, the impact of pharmacists' interventions on economic outcomes among HD patients is debated and requires future studies to have a study design with longer follow-up duration in order to assess this impact in the long term.

In summary, while pharmacist-led medication reviews show promise in improving outcomes for HD patients, the lack of randomised controlled trials and the reliance on self-reported outcomes highlight the need for more robust studies to establish definitive evidence. Future research should aim to address these limitations and explore the long-term economic impact and effectiveness of these interventions in reducing DRPs and improving patient outcomes in hemodialysis patients.

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## Data sharing statement

All data have been included in the manuscript.

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