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BMJ Open Clinical pharmacist-led medication reconciliation supplemented with medication review in admitted patients with chronic kidney disease: a costbenefit analysis

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ABSTRACT

Objective Chronic kidney disease (CKD) is associated with a high economic burden, which is exacerbated by the high susceptibility to drug-related problems (DRPs) in this patient population. This study aimed to evaluate the costbenefit ratio of medication reconciliation supplemented with medication review for inpatients with CKD, compared with the absence of this intervention.

Design This was a cost-benefit analysis conducted along with a prospective interventional study.

Setting The study was conducted at two hospitals in Jordan between February and May 2023.

Participants The prospective interventional study included 142 admitted patients with CKD.

Interventions Patients received medication reconciliation at admission and discharge as well as medication review throughout admission.

Primary and secondary outcome measures The primary outcome measures were the net benefit and the benefit-to-cost ratio of the intervention. A cost-benefit analysis was conducted from the healthcare system perspective by assessing the cost of the service (the pharmacist time required to complete the service per patient) and the economic benefit, including total and perpatient cost savings and cost avoidance.

Results The total estimated cost of all DRPs in the absence of interventions (cost avoidance) was \$83,052 (average of \$585±308 per patient); among which \$20623 was attributed to medication discrepancies. The cost savings were estimated at -\$467. The supplemented medication reconciliation service was estimated to cost \$714. As a result, the estimated net benefit totalled \$81 871, averaging \$577 per patient, with a benefit-to-cost ratio of 115.7:1 over the 4-month study period.

Conclusions Delivering a supplemented medication reconciliation service by a clinical pharmacist for patients with CKD is cost beneficial from the healthcare perspective in Jordan, an example of a low- and middleincome country. This finding further confirms the pivotal role of clinical pharmacists in multidisciplinary healthcare

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ The study was carried out alongside a prospective interventional study, allowing for a more accurate estimation of the time required to complete the medication reconciliation service and providing a closer examination of potential drug-related problems (DRPs).
- ⇒ Evaluation of the probability scores of DRPs was conducted by an expert panel composed of five independent evaluators.
- ⇒ The exact real cost of adverse events resulting from DRPs could not be measured.
- ⇒ The study relied on admission charges, medication prices and lab prices rather than actual costs.

INTRODUCTION

Chronic kidney disease (CKD) is associated with high financial burden globally, exceeding expenditures incurred by other highly burdened patients such as those with stroke and cancer. 12 CKD is a complex medical state accompanied by multiple concurrent illnesses, which inflate the cost of management. Around \$18 billion had been spent by the national US Department of Veterans Affairs for the care of patients with CKD without renal replacement therapy, with expenditures increased across the advanced stages of CKD.^{3 4} In Jordan, the Ministry of Health expended approximately \$17.7 million per year for haemodialysis patients management in 2010, with an average annual cost of \$9979 per patient.⁵ A study conducted in Lebanon reported the median cost for all CKD stages per year of \$4764.02 (IQR \$2475.24-23 455.61) in 2019 from a society perspective.⁶ Studies highly recommend implementing programmes and policies to reduce progression and complications of



CKD to mitigate the growing disease burden, especially in countries with limited resources. ⁷⁸

Patients with CKD are very vulnerable to medication discrepancies and other drug-related problems (DRPs). 9 10 Interestingly, many serious DRPs are preventable in patients with CKD. 11 Developing DRPs increased the exposure to rehospitalisation, extended length of hospital stays and early death, and therefore expanded the cost. 12-14 Clinical pharmacy services targeting DRPs have revealed a positive economic impact on healthcare organisations across the literature. 15 Medication reconciliation and medication review, primarily led by a clinical pharmacist, are vital services focused on preventing and resolving medication discrepancies and other DRPs. These processes play a key role in enhancing patient outcomes and reducing healthcare costs. 16 Medication reconciliation ensures that the patient's medication list is accurate and up to date during transitions of care, while medication review involves a thorough and structured assessment of the patient's medications to ensure they are receiving the most appropriate treatment regimen. 1

The economic burden of medication discrepancies and other DRPs is understudied, particularly in developing countries, including Jordan. Moreover, there is a dearth of data regarding the efficiency of clinical pharmacy services implemented in patients with CKD, especially in low-income to middle-income countries. Although medication reconciliation has the potential to be beneficial in this population, it also incurs costs, highlighting the need for a health economic analysis to determine whether this service can deliver clinical benefits at a reasonable cost, providing a solid rationale for its clinical application. Efforts to evaluate the cost-benefit of medication reconciliation provide essential evidence for healthcare providers and policymakers regarding the value of implementing this clinical service, particularly in patients with CKD. Examining the costs associated with DRPs during CKD hospitalisations will further emphasise the burden of the disease and support efforts to reduce the significant healthcare expenses related to CKD. These insights will underscore the crucial role clinical pharmacists play as part of the multidisciplinary hospital team in alleviating the financial impact of CKD on the healthcare system. Therefore, this study aimed to evaluate the costbenefits of implementing a clinical pharmacist-led service for supplemented medication reconciliation for admitted patients with CKD in Jordan compared with the absence of this intervention.

METHODS Study design

The cost-benefit analysis was developed along with a prospective interventional clinical study that involved patients with stage 2–5 CKD, who were admitted to two healthcare hospitals in Jordan: King Abdullah Hospital (KAUH) and Princess Basma Hospital¹⁸. A clinical pharmacist was responsible for providing supplemented

medication reconciliation to CKD-admitted patients over 4 months (from February to May 2023). The costs and benefits during the study period were assessed in comparison to the absence of this intervention. The primary outcome measure was the net benefit generated by the supplemented medication reconciliation service provided to patients with CKD during the study period. The net benefit was estimated according to the following equation: [net benefit=total benefits (cost avoidance+cost saving) – service cost]. In addition, the benefit-to-cost ratio was estimated. The healthcare system perspective was adopted in the current study. Base case calculations were performed using Excel software. The cost-benefit analysis model is depicted in figure 1. The demographic and clinical characteristics of the study sample are summarised in online supplemental table S1.

Description of supplemented medication reconciliation

Patients received a supplemented medication reconciliation service across the transitions of care during their admission to the internal medicine ward, in addition to a medication review for possible DRPs. The procedure of supplemented medication reconciliation consisted of medication reconciliation at admission, medication review throughout admission and medication reconciliation at discharge. At admission, demographic, clinical and medical data for each enrolled patient were collected from the medical records, followed by interviews with the patients or their caregivers to verify the patients' demographics, medical history and preadmission medication list. The preadmission drug lists were also confirmed using all other available sources, such as bottles, prescriptions and previous medical records, to obtain the best possible medication history (BPMH). The BPMH was compared with the current hospital medication sheet (admission medication orders) to extract discrepancies at admission. Medication reviews and clinical case analyses were conducted regarding dose adjustments, drug interactions, missing medications, inappropriate medications, unnecessary medications and monitoring after admission and during the hospitalisation period to identify the DRPs. At discharge, the best possible discharge medication plan (BPMDP) was created from the BPMH, the last medication list during index hospitalisation, and new medications planned to be started on discharge. The BPMDP was compared with discharge prescription and summary. Patient education was provided to willing patients before discharge. All identified discrepancies and other DRPs were discussed with the resident responsible for the resolution as accessible.

Estimation of costs

Input costs in the current study include the resources used to provide the supplemented medication reconciliation, that is, the pharmacists' time. The time taken by the pharmacist to deliver the supplemented medication reconciliation per patient (in hours) was recorded for each admission. The cost of the medication reconciliation

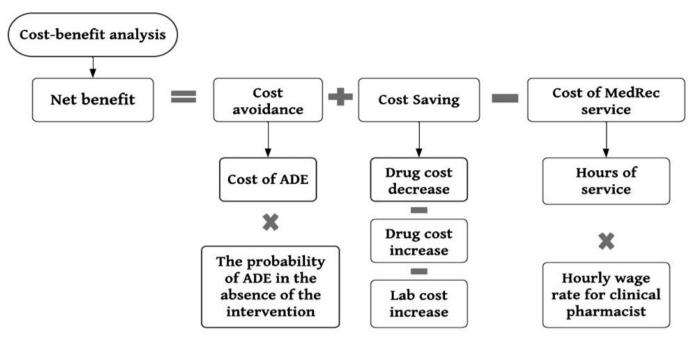


Figure 1 The cost-benefit analysis model. ADE, adverse drug event.

service was estimated by multiplying the service time by the average hourly wage rate for clinical pharmacists, as obtained from the financial department at KAUH. The average annual wage rate was converted to the hourly wage rate based on 240 working days per year and 8 working hours per day.

Estimation of benefits

The economic benefits associated with the potential prevention of DRPs through interventions recommended by clinical pharmacists were evaluated in terms of 'cost savings' and 'cost avoidance'.

Cost saving

The cost-saving analysis estimated the reduction in medication costs resulting from interventions, along with the additional medication costs and expenses associated with laboratory requests (cost savings=reduceddrug costs—(increased drug costs+increasedlab costs)).

The cost of any medication (increased or decreased) was estimated as the cost of medication per unit multiplied by the frequency per day and then by the duration of therapy.¹⁹ Acute therapy duration was estimated based on the clinical scenario, while chronic medication use was calculated over 3months' time horizon. Public per-unit prices of drugs were obtained from the Jordan Food and Drug Administration.²⁰ For interventions that included the addition of a laboratory test, the increased cost for each intervention was estimated using the prices of laboratory tests obtained from the KAUH laboratory department. Both drug and lab prices were converted to costs by multiplying them by an assumed ratio of cost to charge (RCC). The net cost saving was estimated by subtracting the total increased cost from the decreased cost resulting from the implementation of the supplemented

medication reconciliation services. Per-patient averages were calculated for total cost savings, drug cost reductions, drug cost increases and laboratory costs.

Cost avoidance

Cost avoidance was estimated for each intervention recommended by the clinical pharmacist in the current study as the cost avoided by potential prevention of DRPs. The probability of DRP in the absence of intervention was determined according to the Nesbit et al scale, 21 which has five levels of risk of causing DRPs: 0 (none), 0.01 (very low), 0.1 (low), 0.4 (medium) or 0.6 (high). The DRP probability in the absence of the intervention was estimated for all identified discrepancies and other DRPs by a team of experts, comprising four clinical pharmacists and one physician. Examples of the studied clinical cases with potential probabilities of DRPs are presented in online supplemental table S2. The cost avoidance attributed to each intervention was calculated by multiplying the corresponding DRP probability by the DRP cost. The cost of a DRP was assumed to be the cost of an additional 2 days of hospital stay. 22 Admission charges were retrieved from the billing system for all admissions included in the study, and the average charge per day was calculated for these patients with CKD. The average charge per day was adjusted using the assumed RCC to estimate the RCC cost of DRPs. Cost avoidance was estimated in total and as an average per patient. Cost avoidance was also estimated by the Pharmaceutical Care Network Europe (PCNE) Classification for Drug-Related Problems V9.1 based on the cause²³ and the Medication Discrepancy Taxonomy (MedTax) system.24 All financial data were extracted in Jordanian Dinar currency unit (JOD) and converted to US\$ at a rate of (1 JOD=US\$1.41). All cost data were



reported in 2023 values. The RCC value was assumed to be 0.8 throughout the base case analysis and varied in the sensitivity analysis.

Sensitivity analysis

One-way sensitivity analysis was conducted to account for the variability in the key model parameters. DRP probabilities were varied using the minimum and maximum probabilities assigned by the expert panel. All costs were varied over a range of $\pm 20\%$ of the base case cost. The average service time was varied over 2 SD of the mean, as calculated in this study. RCC was varied in the range (0.7--0.9). Probabilistic sensitivity analysis was conducted, in which the input variables were varied simultaneously over $10\,000$ Monte Carlo simulations. Beta distribution was used for DRP probabilities, uniform distribution for RCC and hourly wage rate, normal distribution for service time in minutes and gamma distribution for cost.

Public and patient involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

RESULTS

Cost of supplemented medication reconciliation

The average time required to perform a supplemented medication reconciliation service (medication reconciliation plus medication review during admission) was 43.38 (SD=6.65) min, ranging from 26 to 60.5 min. The total time spent by the clinical pharmacist on the supplemented medication reconciliation over the 4-month intervention period was 6117.1 min (101.95 hours). The average duration to accomplish a primary medication reconciliation service at admission was 15.79±1.74min. Though, the average time for medication review during the admission was 21.6±4.30 min (ranged from 11.6 to 35.5 min) per patient. Medication reconciliation time at discharge averaged 3.58±1.55min per patient. Based on the reported average monthly salary of the clinical pharmacist at KAUH, the wage per hour was \$7, assuming 8 hours per day. Taking this into account, the total intervention cost over the 4-month study period was \$713.7 $(\$7 \times 101.95 \text{ hours}).$

Benefits of supplemented medication reconciliation

Estimated cost saving

The average increase in medication costs was \$53±67 per patient, while the total cost of required lab work averaged \$30±29 per patient. Conversely, the intervention led to an average reduction in medication costs of \$79±85 per patient.

The total increased medication cost was estimated to be \$7479, and lab-needed total cost was estimated at \$4198. The decrease in medication costs owing to the intervention was \$11210. Total cost saving=\$11210 - \$7479 - \$4198 = -\$467 (\$3 negative cost saving per patient). Table

2 presents cost-saving values in total and at the patient level.

Estimated cost avoidance

The average admission charge for patients with CKD enrolled in the study was \$2811 (SD=\$2172), and the average admission charge per day was \$340 (SD=\$199). The assumed cost of a DRP was the estimated cost of two additional hospitalisation days for patients with CKD in the current study (\$680×0.8 RCC=\$483). The estimated probabilities of DRPs in the absence of intervention were averaged using a panel of five expert evaluators. The majority of DRPs (73.4%; n=735) were in the lowto-medium-risk category (0.1–0.4), while 21.2% (n=212) were in the low-risk category (<0.1) and 5.4% (n=54) were in the moderate-to-high-risk category (>0.4). The average cost of a potential DRP, estimated by multiplying the average DRP probability by the estimated RCC cost for two additional hospitalisation days, was \$83 (SD=\$58). The total estimated cost of all DRPs in the absence of interventions (cost avoidance) was \$83 052, averaging \$585±\$308 per patient. Patient transfer-related DRPs (medication discrepancies) were found to be the third most expensive cause-based domain in the PCNE classification of DRPs (V.9.1), contributing to around 25% of the total cost avoidance (\$20 623; \$145 per patient). The greatest weight of discrepancies' cost avoidance was attributed to the 'drug omission' category (\$12 694), followed by 'discrepancy in frequency/strength/dose' (\$4613) and 'drug addition' (\$2399), table 1. A detailed summary of the cost avoidance per PCNE cause-based domains is presented in table 1. Average cost avoidance per patient across the cause-based domains of DRPs (at the patient level) is detailed in the Supplemental Material (online supplemental table S3).

Cost-benefit analysis

The net benefit was calculated by subtracting the total cost of intervention from total cost avoidance and saving [cost avoidance (\$83 052)+cost saving (-\$467)-cost of the intervention (\$714)=\$81871]. The net benefit was estimated as \$577 per patient. The benefit-to-cost ratio estimated in this study was (115.7:1). Table 2.

Sensitivity analyses

The study conclusion was insensitive to uncertainty in any of the input variables, including DRP probabilities, DRP cost, RCC, per-unit cost of drugs and labs, hourly wage rate and average service time. The main driver of the outcome was the DRP probability, followed by the DRP cost, as depicted in figure 2. However, the net benefit was positive over all plausible ranges of the input variables. The minimum estimated net benefit was \$50 203 based on varying DRP probability. In probabilistic sensitivity analysis, the average expected value of the net benefit was \$90 451 (SD=\$126 294). Only 866 out of 100 000 iterations (8.7%) showed a negative net benefit (figure 3).



Table 1 Cost avoidance per cause-based domains in the Pharmaceutical Care Network Europe classification of drug-related problems (V.9.1)

Primary domain	Cause	Cost avoidance (\$)	Total (\$)
Drug selection	Inappropriate drug according to guidelines/formulary	12480	25 588
	No or incomplete drug treatment despite existing indication	8646	
	No indication for drug	2296	
	Inappropriate combination of drugs or drugs and dietary supplements	1916	
	Too many different drugs/active ingredients prescribed for indication	250	
	Inappropriate duplication of therapeutic group or active ingredient	250	
Dose selection	Drug dose of a single active ingredient too high	13710	21 141
	Dosage regimen too frequent	5284	
	Drug dose too low	2147	
Patient transfer related (discrepancies)	Drug omission	12694	20 623
	Discrepancy in the strength and/or frequency and/ or number of units of dosage form and/or total daily dose	4613	
	Drug addition	2399	
	Therapeutic class substitution	437	
	Drug duplication	337	
	Discrepancy in the dosage form/route of administration	144	
Drug use process	Inappropriate timing of administration or dosing intervals by a health professional	2625	2777
	Drug administered via wrong route by a health professional	152	
Treatment duration	Duration of treatment too long	273	469
	Duration of treatment too short	196	
Drug form	Inappropriate drug form/formulation	114	114
Other	Addition of a lab test	10532	12088
	No or inappropriate outcome monitoring	1557	
Total			83 052

DISCUSSION

The major findings of the current study emphasise the substantial economic burden of medication discrepancies and other DRPs in patients with CKD. In addition, the results showed that the estimated economic benefit was remarkable compared with the estimated cost of the medication reconciliation service. Overall, the results indicate that supplemented medication reconciliation services mediated by clinical pharmacists are cost beneficial.

The majority of DRPs in the current study were classified as having a medium risk of DRPs. Despite the different scales used to evaluate the clinical significance of DRPs in patients with CKD, most studies have found that the majority of DRPs in this high-risk population were of moderate to significant clinical impact. In a study conducted in Jordan among hospitalised patients with CKD, the majority of DRPs (62%) were classified

among the significant category; however, the study used a different scale (extremely significant, much significant, significant and slightly significant). ²⁵ In a study conducted in Canada, approximately half of the observed DRPs were moderate in severity in terms of causing harm to patients with CKD. ²⁶ The different scales used in severity assessment across the literature make the comparison seem challenging. Overall, most recognised DRPs were considered clinically important in the current study and potentially preventable.

This study revealed the beneficial effect of clinical pharmacist medication reconciliation intervention on patients with CKD in terms of the cost-benefits associated with this service. A recent review of 47 studies among patients with CKD also supports this finding; 7 studies approved the significant cost savings and 15 studies reported improvement in clinical outcomes due to clinical pharmacy care,



Table 2 Results of cost-benefit analysis

		Average per patient \$
Outcome	Total (\$)	(M±SD)
Intervention cost over 4 months	714	5±1
Impact on the cost of drug-related problems	-83 052	-585±308
Impact on medication costs		
Reduced drug costs	-11 210	-79±85
Increased drug costs	7479	53±67
Increased lab costs	4198	30±29
Net benefit over the study period (4 months)*	81 871	577
Benefit-to-cost ratio†	115.7:1	

The total number of patients is 142.

including blood pressure, anaemia, length of hospital stay, readmissions, kidney function and other laboratory tests (ie, parathyroid hormone (PTH), calcium, uric acid, cholesterol and HbA1c). ¹⁵

The average time needed for full supplemented medication reconciliation services provided for each CKD admission in the current study was 43.38±6.65 min. This is comparable to other studies that measured the time needed for medication reconciliation services: 44.4±21.8, ²⁷ 40±17.2 min²⁸ and 48 min. ^{29 30} In addition, the total time to deliver a primary medication reconciliation

service at all transitions of care per patient was estimated with a median of 24 min (IQR 20–30 min).³¹ The specific time for medication reconciliation at admission was roughly similar to our finding (15 min (IQR 10–21)) in two previous studies.^{32 33} Moreover, medication reconciliation at discharge after conducting medication reconciliation at admission was previously estimated to need approximately 3.5 min,³⁴ which is also comparable to the estimated time in the current study. However, a recent systematic review reported a wider range of the mean time for medication reconciliation implementation across

Net Benefit (in U.S. dollars)

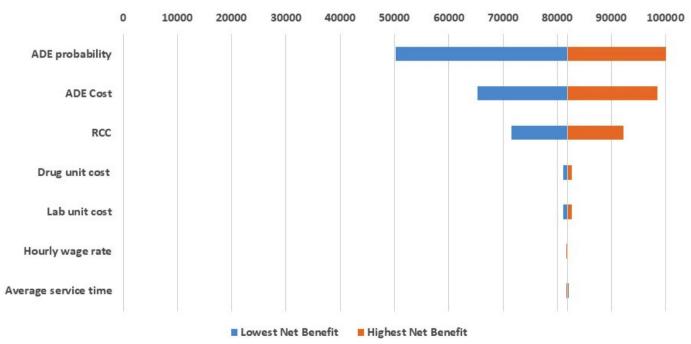


Figure 2 Tornado diagram illustrating the impact of various parameters on the net benefit of supplemented medication reconciliation service (one-way sensitivity analysis). ADE, adverse drug event.

^{*}The benefits of the intervention include cost avoidance (reduced cost of drug-related problems) + cost savings (reduced drug costs – (increased drug costs + increased lab costs). Net benefit = the benefit of the intervention – Intervention cost over 4 months.

[†] Benefit-to-cost ratio = the benefits of the intervention/intervention cost over 4 months.

M±SD, mean±SD.

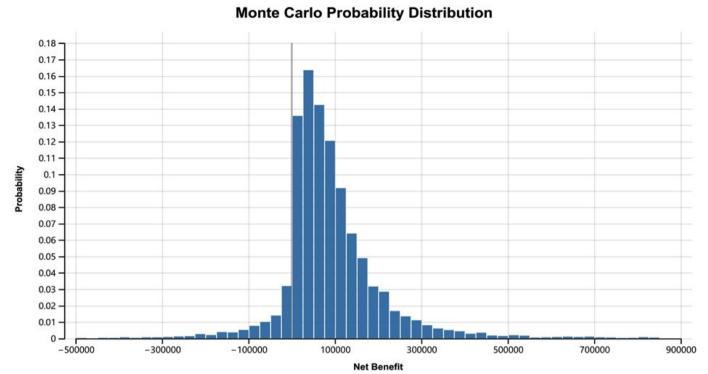


Figure 3 Probabilistic sensitivity analysis evaluating the net benefit of supplemented medication reconciliation service.

nine studies with an average of $34.5~(\pm 39.4)~\text{min.}^{35}$ This variability could have originated from the diverse models and services involved across the pooled studies and variations in study population.

CKD has been associated with a high economic burden.^{3 36–38} DRPs have been associated with high costs that affect patient safety and healthcare expenditures.³⁹ Our study estimated the net benefit attributed to avoiding and resolving DRPs to be \$81871.15 over 4 months for a cumulative number of 142 patients with CKD, averaging \$576.56 per patient. Such remarkable benefit confirms the need for implementing supplemented medication reconciliation in patients with CKD. Likewise, a recent retrospective cohort in the USA among haemodialysis patients estimated cost saving from preventing DRPs to be \$447355 over a 6-month period of observation, attributing this benefit to performing medication reconciliation with medication review. 40 A Malaysian study measured the cost saving resulting from only dose adjustment in CKD inpatients to be \$2250 for 212 dose-related recommendations over 4 months, in which the clinical pharmacist worked within a multidisciplinary rounds with the nephrology team to adjust the doses as needed. 41 This saved cost is considered much lower than the avoided cost resulting from renal dose adjustment in our study (\$14756 for 4 months, 94 dose adjustment interventions). An earlier prospective study conducted medication therapy evaluation by pharmacists found that the ratio of pharmaceutical care cost to healthcare system saving is \$1 to \$3.98 among patients with end-stage renal disease in the USA. 42 This is much smaller compared with the benefit-to-cost ratio estimated in the current study (115:1). This variability might

be related in part to the relatively lower wage rates of clinical pharmacists in Jordan than in the USA. However, the estimated cost of a DRP is also expected to be higher in terms of admission-day costs in the USA. Another study found annual direct cost savings of more than \$780000 after implementing supplemented medication reconciliation with patient education in internal medicine wards in Kansas ascribed to reducing readmissions. 43 A Chinese trial found cost saving attributed to antimicrobial dose adjustment (number of adjusted doses=183) by a clinical pharmacist of \$3525 per patient with sepsis undergoing continuous dialysis in the intensive care unit (ICU). Wage rates and the cost of healthcare may differ widely across regions and institutions, which makes the comparison in cost not sufficiently clear/straightforward. This also highlights the need to obtain relevant data from local or regional studies to better support the decisions of policymakers based on information from relevant settings.

In Jordan, the role of clinical pharmacists appears to be economically effective for other populations. Among outpatients with chronic diseases, the estimated cost avoidance per month due to pharmacist interventions (number of interventions=79 among 48 patients) was \$6422.41. In another study conducted in Jordan, clinical pharmacist intervention in the ICU reduced the total cost of drug consumption by \$211574.90 over 10 months. Still, the cost-benefit of medication reconciliation among patients with CKD has not been well addressed in Jordan and other developing countries. The results of the current study strongly support the need to implement medication reconciliation supplemented with continuous medication review during hospital admission in patients with CKD.



The current study has some limitations. We did not evaluate the actual adverse events resulting from DRPs or the actual role of interventions in decreasing these events. Furthermore, the exact real cost of adverse events resulting from DRPs could not be measured; however, the method of calculating cost avoidance in the current study has considered uncertainty and was implemented in previous studies.⁴⁷ In addition, the evaluation of the probability score of each DRP was conducted by an expert panel composed of five independent evaluators. Besides, the assessment of DRP probability scores was conducted independently by the study panel using a validated scale.²¹ Another limitation is that we relied on admission charges, medication prices and lab prices rather than actual costs. However, charges are widely used as a proxy for costs in the literature because of accessibility issues. Furthermore, we used an assumed RCC ratio to approach the actual costs, and this RCC was varied in the sensitivity analysis.

CONCLUSIONS

Pharmacist-led medication reconciliation supplemented with contentious medication review is very cost beneficial in admitted patients with CKD, with substantial cost avoidance compared with the cost of implementing this service. The results clearly showed that activating the role of clinical pharmacists in providing medication reconciliation with a comprehensive medication review contributed positively to the safety of admitted patients with CKD and had a remarkable economic impact in clinical settings. The net benefit of this intervention could be enhanced by designing an efficient collaborative approach with physicians in hospital settings, and future studies should be directed towards evaluating the cost-benefit of such approaches.

Contributors SA contributed to conceptualisation, methodology, data curation, formal analysis, supervision, project administration, funding acquisition and writing original draft. NMS contributed to conceptualisation, methodology, data curation, formal analysis and writing original draft. MA-K and OYA contributed to conceptualisation, methodology, data curation and writing—reviewing and editing. MSBA contributed to data curation and writing—reviewing and editing. SA is the guarantor for the manuscript and accepts full responsibility for the overall content.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Consent obtained directly from patient(s)

Ethics approval This study was approved by the Institutional Review Board (IRB) Committee at KAUH (ref number: 123/147/2022) and the Ministry of Health (ref number: 13902). Written informed consent was obtained from the participants after they were given comprehensive information about the study's purpose and details.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information. All data underlying this article are presented in the manuscript.

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