BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2024-087232
Article Type:	Original research
Date Submitted by the Author:	04-Apr-2024
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Keywords:	Medication Reconciliation, Health Services, Health economics < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Health & safety < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

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Research Article

Clinical pharmacist-led medication reconciliation supplemented with medication review in chronic kidney disease admitted patients: a cost-benefit analysis

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Running Title: Cost-benefit of medication reconciliation in CKD

Number of Tables: 2

Number of Figures: 3

Keywords: Medication reconciliation, clinical pharmacist, cost-benefit, chronic kidney disease, Jordan.

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 cost-benefit ratio of medication reconciliation supplemented with medication review among inpatients with CKD.

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.

Method: Patients received medication reconciliation at admission and discharge as well as medication review throughout admission. 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 in terms of cost savings and cost avoidance. The primary outcome measures were the net benefit and the benefit-to-cost ratio of the intervention.

Results: The total estimated cost of all DRPs in the absence of interventions (cost avoidance) was $83,052.4; among which $20,623.19 was attributed to medication discrepancies. The cost savings were estimated at -$467.5. The supplemented medication reconciliation service was estimated to cost $713.7. Accordingly, the estimated net benefit was $81,871.15 over the 4-month study period.

Conclusion: Delivering a supplemented medication reconciliation service by a clinical pharmacist for CKD patients is cost beneficial from the healthcare perspective in Jordan, an example of a low- and middle-income country (LMIC). This finding further confirms the pivotal role of clinical pharmacists in multidisciplinary healthcare teams.

Keywords: Medication reconciliation, clinical pharmacist, cost-benefit, chronic kidney disease, Jordan.

Strengths and limitations of this study

- The study was conducted along with a prospective interventional study.
- Evaluation of the probability scores of drug related problems (DRPs) was conducted by an expert panel composed of five independent evaluators.
- The exact real cost of adverse events resulting from drug 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.[1, 2] 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 (RRT), 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 hemodialysis patients management in 2010, with an average of annual cost of $9,979 per patient.[5] A study conducted in Lebanon reported the median cost for all CKD stages per year of $4,764.02 (IQR $2,475.24 - $23,455.61) in 2019 from a society perspective.[6] Studies highly recommend implementing programs and policies to reduce progression and complications of CKD to mitigate the growing disease burden especially in countries with limited resources.[7]

Interestingly, many serious Drug related problems (DRPs) are preventable in CKD patients.[8] Patients with CKD are very vulnerable to medication discrepancies and other DRPs.[9, 10] Developing DRPs increased the exposure to re-hospitalization, extended length of hospital stays, and early death, and therefore expanded the cost.[11-13] Clinical pharmacy services have revealed a positive economic impact on healthcare organizations across the literature.[14] Medication reconciliation is a healthcare service directed primarily by a clinical pharmacist and aimed at preventing and resolving DRPs and proposed to reduce health expenditures.[15] 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. Therefore, this study aimed to evaluate the cost-benefits of implementing a clinical pharmacist-led service for supplemented medication reconciliation among admitted patients with CKD in Jordan.

Methods

Study design

The cost-benefit analysis was developed along with a prospective interventional clinical study that involved patients with stages 2-5 CKD, who were admitted to two healthcare hospitals in Jordan: King Abdullah Hospital (KAUH) and Princess Basma Hospital (PBH). A clinical pharmacist was responsible for providing supplemented medication reconciliation to CKD-admitted patients over four months (from February to May 2023). The costs and benefits over the study period were calculated. The primary outcome measure was the net benefit generated by the supplemented medication reconciliation service provided to CKD patients 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 health care 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 summarized in the Supplementary Material (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 pre-admission medication list. The pre-admission 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 hospitalization 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 hospitalization, and new medications planned to be started upon 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 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

In the cost-saving analysis, the decreased medication costs due to interventions and the increased medication costs and costs attributed to requesting labs were estimated. 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.[16] Acute therapy duration was estimated based on the clinical scenario, while chronic medication use was calculated over three months' time horizon. Public per-unit prices of drugs were obtained from the Jordan Food and Drug Administration (JFDA).[17] 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 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.

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 [18] 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 Supplementary Material (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.[19] 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 CKD patients. 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 by the Pharmaceutical Care Network Europe (PCNE) Classification for Drug-Related Problems V9.1 based on the cause,[20] and the Medication Discrepancy Taxonomy (MedTax) system.[21] All financial data were extracted in Jordanian Dinar currency unit (JOD) and converted to United States Dollars (USD) at a rate of (1 JOD = 1.41 USD). 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 ± 20% of the base case cost. The average service time was varied over two SD of the mean, as calculated in this study. RCC was varied in the range (0.7 to 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.

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) minutes, ranging from 26 to 60.5 minutes. The total time spent by the clinical pharmacist on the supplemented medication reconciliation over the four-month intervention period was 6117.1 minutes (101.95 hours). The average duration to accomplish a primary medication reconciliation service at admission was 15.79 ± 1.74 minutes. Though, the average time for medication review during the admission was 21.6 ± 4.30 minutes (ranged from 11.6 to 35.5 minutes) per patient. Medication reconciliation time at discharge averaged 3.58 ± 1.55 minutes 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 4-month study period was $713.7 ($7 × 101.95 hours).

Benefits of supplemented medication reconciliation

Estimated cost saving

The total increased medication cost was estimated to be $9,349 and lab needed total cost was estimated at $5,248. The decrease in medication costs owing to the intervention was $14,012. Total cost saving (after being adjusted with RCC of 0.8) = $11,210[$14,012*0.8] - $7,479[$9,349 *0.8] - $4,198[$5,248*0.8] = -$467.5.

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 $340.20 (SD= $199.48). The assumed cost of a DRP was the estimated cost of two additional hospitalization days for patients with CKD in the current study [$680.4 multiplied by 0.8 RCC = $483.1]. 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 low-to 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 hospitalization days was $82.96 (SD=$57.7). The total estimated cost of all DRPs in the study was $83,052.4 (the cost avoidance). Patient transfer related DRPs (medications discrepancies) were found to be the third most expensive cause-based domain in the PCNE classification of DRPs (V9.1), contributing to around 25% of the total cost avoidance ($20,623.19). The greatest weight of discrepancies' cost avoidance was attributed to "drug omission" category ($12,693.54) followed by "discrepancy in frequency/strength/dose" ($4,612.56) and "drug addition" ($2,399.36), Table 1. A detailed summary of the cost avoidance per PCNE cause-based domains is presented in Table 1.

Cost benefit analysis

The net benefit was calculated by subtracting the total cost of intervention from total cost avoidance and saving [cost avoidance ($83,052.4) + cost saving (- 467.5) - cost of the intervention ($713.7) = $81,871.15]. 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).

Discussion

The major findings of the current study emphasize 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 to 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 with moderate to significant clinical impact. In a study conducted in Jordan among hospitalized 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).[22] In a study conducted in Canada, approximately half of the observed DRPs were moderate in severity in terms of causing harm to CKD patients.[23] The different scales used in severity assessment across the literature makes the comparison seems challenging. Overall, most

recognized 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 CKD patients in terms of the cost-benefits associated with this service. A recent review of 47 studies among CKD patients also supports this finding; 7 studies approved the significant cost savings and 15 studies reported improvement in clinical outcomes due to clinical pharmacy care, including blood pressure, anemia, length of hospital stay, readmissions, kidney function, and other laboratory tests (i.e., PTH, calcium, uric acid, cholesterol, and HbA1c).[14]

The average time needed for full supplemented medication reconciliation services provided for each CKD admission in the current study was 43.38 ± 6.65 minutes. This is comparable to other studies that measured the time needed for medication reconciliation services: 44.4 ± 21.8,[24] 40 ±17.2 minutes,[25] and 48 minutes.[26, 27] 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 minutes (IQR 20-30 minutes).[28] The specific time for medication reconciliation at admission was roughly similar to our finding (15 minutes (IQR 10–21)) in two previous studies.[29, 30] Moreover, medication reconciliation at discharge after conducting medication reconciliation at admission was previously estimated to need approximately 3.5 minutes,[31] 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 nine studies with an average of 34.5 (±39.4) minutes.[32] This variability could be 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, 33-35] DRPs have been associated with high costs that affect patient safety and healthcare expenditures.[36]. Our study estimated the

net benefit attributed to avoiding and resolving DRPs to be $81,871.15 over 4 months for a cumulative number of 142 CKD patients. Such remarkable benefit confirms the need of implementing supplemented medication reconciliation in CKD patients. Likewise, a recent retrospective cohort in the US among hemodialysis patients estimated cost saving from preventing DRPs to be $447,355 over a 6-month period of observation, attributing this benefit to performing medication reconciliation with medication review.[37] A Malaysian study measured the cost saving resulted from only dose adjustment in CKD inpatients to be $2,250 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.[38] This saved cost is considered much lower than the avoided cost resulting from renal dose adjustment in our study ($14,756 for 4 months, 94 dose adjustment interventions). An earlier prospective study conducted medication therapy evaluation by pharmacist found that the ratio of pharmaceutical care cost to healthcare system saving is $1 to $3.98 among end-stage renal disease patients in the USA.[39] This is much smaller compared to 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 $780,000 after implementing supplemented medication reconciliation with patient education in internal medicine wards in Kansas ascribed to reducing readmissions.[40] A Chinese trial found cost saving attributed to antimicrobial dose adjustment (number of adjusted doses= 183) by a clinical pharmacist of $3,525 per patient with sepsis undergoing continuous dialysis in the ICU.[41] Wage rates and the cost of health care may differ widely across regions and institutions which make the comparison in cost is not sufficiently clear/straightforward. This also highlights the need

to obtain relevant data from local or regional studies to better support the decisions of policy makers 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 $6,422.41.[42] In another study conducted in Jordan, clinical pharmacist intervention in the ICU reduced the total cost of drugs consumption by $211,574.90 over 10 months.[43] Still, the cost benefit of medication reconciliation among CKD patients 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.[44] 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.[18] 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 CKD admitted patients, with substantial cost avoidance compared to 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 toward evaluating the cost-benefit of such approaches.

Funding:

This work was supported by the Deanship of Scientific Research at the Jordan University of Science and Technology [grant number: 20220257]. The funding agency was not involved in the study design, conduct, writing, or decision to submit this article for publication.

Competing Interests:

The Authors declare that they have no conflicts of interest to disclose.

Ethical 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).

Author contributions

Altawalbeh S: Conceptualization, Methodology, Data curation, Formal analysis, Supervision, Project administration, Funding acquisition, Writing- Original draft preparation, Writing- Reviewing and Editing.

Nahlah M. Sallam: Conceptualization, Methodology, Data curation, Formal analysis, Writing- Original draft preparation, Writing- Reviewing and Editing.

Minas Al-Khatib, Osama Y. Alshogran: Conceptualization, Methodology, Data curation, and Writing- Reviewing and Editing.

Mohammad S. Bani Amer, MD: Data curation, and Writing- Reviewing and Editing.

Data availability statement

All data underlying this article are presented in the manuscript.

References

1. Small C, Kramer HJ, Griffin KA, et al. Non-dialysis dependent chronic kidney disease is associated with high total and out-of-pocket healthcare expenditures. *BMC Nephrol* 2017; 18: 3. 2017/01/07. DOI: 10.1186/s12882-016-0432-2.

2. Silva Junior GBD, Oliveira JGR, Oliveira MRB, et al. Global costs attributed to chronic kidney disease: a systematic review. *Rev Assoc Med Bras (1992)* 2018; 64: 1108-1116. 2018/12/21. DOI: 10.1590/1806-9282.64.12.1108.

3. Golestaneh L, Alvarez PJ, Reaven NL, et al. All-cause costs increase exponentially with increased chronic kidney disease stage. *Am J Manag Care* 2017; 23: S163-S172. 2017/10/06.

4. Saran R, Pearson A, Tilea A, et al. Burden and Cost of Caring for US Veterans With CKD: Initial Findings From the VA Renal Information System (VA-REINS). *Am J Kidney Dis* 2021; 77: 397-405. 2020/09/06. DOI: 10.1053/j.ajkd.2020.07.013.

5. Al-Shdaifat EA and Manaf MR. The economic burden of hemodialysis in Jordan. *Indian J Med Sci* 2013; 67: 103-116. 2013/12/12.

6. Aoun M, Helou E, Sleilaty G, et al. Cost of illness of chronic kidney disease in Lebanon: from the societal and third-party payer perspectives. *BMC Health Serv Res* 2022; 22: 586. 2022/05/04. DOI: 10.1186/s12913-022-07936-0.

7. Rizk R, Hiligsmann M, Karavetian M, et al. A societal cost-of-illness study of hemodialysis in Lebanon. *J Med Econ* 2016; 19: 1157-1166. 2016/06/29. DOI: 10.1080/13696998.2016.1207653.

8. Laville SM, Gras-Champel V, Moragny J, et al. Adverse Drug Reactions in Patients with CKD. *Clin J Am Soc Nephrol* 2020; 15: 1090-1102. 2020/07/03. DOI: 10.2215/CJN.01030120.

9. Chia BY, Cheen MHH, Gwee XY, et al. Outcomes of pharmacist-provided medication review in collaborative care for adult Singaporeans receiving hemodialysis. *Int J Clin Pharm* 2017; 39: 1031-1038. 20170821. DOI: 10.1007/s11096-017-0528-1.

10. Song YK, Jeong S, Han N, et al. Effectiveness of Clinical Pharmacist Service on Drug-Related Problems and Patient Outcomes for Hospitalized Patients with Chronic Kidney Disease: A Randomized Controlled Trial. *J Clin Med* 2021; 10 20210420. DOI: 10.3390/jcm10081788.

11. Bishop MA, Cohen BA, Billings LK, et al. Reducing errors through discharge medication reconciliation by pharmacy services. *Am J Health Syst Pharm* 2015; 72: S120-126. 2015/08/15. DOI: 10.2146/sp150021.

12. Ernst FR and Grizzle AJ. Drug-related morbidity and mortality: updating the cost-of-illness model. *J Am Pharm Assoc (Wash)* 2001; 41: 192-199. 2001/04/12. DOI: 10.1016/s1086-5802(16)31229-3.

13. Alruqayb WS, Price MJ, Paudyal V, et al. Drug-Related Problems in Hospitalised Patients with Chronic Kidney Disease: A Systematic Review. *Drug Saf* 2021; 44: 1041-1058. 2021/09/13. DOI: 10.1007/s40264-021-01099-3.

14. Al Raiisi F, Stewart D, Fernandez-Llimos F, et al. Clinical pharmacy practice in the care of Chronic Kidney Disease patients: a systematic review. *Int J Clin Pharm* 2019; 41: 630-666. 2019/04/10. DOI: 10.1007/s11096-019-00816-4.

15. Onatibia-Astibia A, Malet-Larrea A, Mendizabal A, et al. The medication discrepancy detection service: A cost-effective multidisciplinary clinical approach. *Aten Primaria* 2021; 53: 43-50. 2020/10/01. DOI: 10.1016/j.aprim.2020.04.008.

16. Houso A, Hamdan M and Falana H. Cost benefit analysis of clinical pharmacist interventions in medical intensive care unit in Palestine medical complex: Prospective interventional study. *Saudi Pharm J* 2022; 30: 1718-1724. 2023/01/06. DOI: 10.1016/j.jsps.2022.09.017.

17. Jordan Food and Drug Administration (JFDA) http://jfda.jo/Pages/viewpage.aspx?pageID=336 (accessed July 2023).

18. Nesbit TW, Shermock KM, Bobek MB, et al. Implementation and pharmacoeconomic analysis of a clinical staff pharmacist practice model. *Am J Health Syst Pharm* 2001; 58: 784-790. DOI: 10.1093/ajhp/58.9.784.
19. Chen CC, Hsiao FY, Shen LJ, et al. The cost-saving effect and prevention of medication errors by clinical pharmacist intervention in a nephrology unit. *Medicine (Baltimore)* 2017; 96: e7883. DOI: 10.1097/MD.0000000000007883.
20. *Pharmaceutical Care Network Europe, The PCNE CLassification V 9.1. Pharmaceutical Care Network Europe, p Classification for Drug related problems*. 2020.
21. Almanasreh E, Moles R and Chen TF. The medication discrepancy taxonomy (MedTax): The development and validation of a classification system for medication discrepancies identified through medication reconciliation. *Res Social Adm Pharm* 2020; 16: 142-148. 20190414. DOI: 10.1016/j.sapharm.2019.04.005.
22. AbuRuz SM, Alrashdan Y, Jarab A, et al. Evaluation of the impact of pharmaceutical care service on hospitalized patients with chronic kidney disease in Jordan. *Int J Clin Pharm* 2013; 35: 780-789. 20130725. DOI: 10.1007/s11096-013-9806-8.
23. Quintana-Barcena P, Lord A, Lizotte A, et al. Prevalence and Management of Drug-Related Problems in Chronic Kidney Disease Patients by Severity Level: A Subanalysis of a Cluster Randomized Controlled Trial in Community Pharmacies. *J Manag Care Spec Pharm* 2018; 24: 173-181. DOI: 10.18553/jmcp.2018.24.2.173.
24. Buckley MS, Harinstein LM, Clark KB, et al. Impact of a clinical pharmacy admission medication reconciliation program on medication errors in "high-risk" patients. *The Annals of pharmacotherapy* 2013; 47: 1599-1610. 20131015. DOI: 10.1177/1060028013507428.
25. Mendes AE, Lombardi NF, Andrzejevski VS, et al. Medication reconciliation at patient admission: a randomized controlled trial. *Pharm Pract (Granada)* 2016; 14: 656. 20160315. DOI: 10.18549/PharmPract.2016.01.656.
26. Cadman B, Wright D, Bale A, et al. Pharmacist provided medicines reconciliation within 24 hours of admission and on discharge: a randomised controlled pilot study. *BMJ Open* 2017; 7: e013647. 20170316. DOI: 10.1136/bmjopen-2016-013647.
27. Neeman M, Dobrinas M, Maurer S, et al. Transition of care: A set of pharmaceutical interventions improves hospital discharge prescriptions from an internal medicine ward. *Eur J Intern Med* 2017; 38: 30-37. 20161125. DOI: 10.1016/j.ejim.2016.11.004.
28. Cornu P, Steurbaut S, Leysen T, et al. Effect of medication reconciliation at hospital admission on medication discrepancies during hospitalization and at discharge for geriatric patients. *The Annals of pharmacotherapy* 2012; 46: 484-494. 20120313. DOI: 10.1345/aph.1Q594.
29. Sebaaly J, Parsons LB, Pilch NA, et al. Clinical and Financial Impact of Pharmacist Involvement in Discharge Medication Reconciliation at an Academic Medical Center: A Prospective Pilot Study. *Hospital pharmacy* 2015; 50: 505-513. DOI: 10.1310/hpj5006-505.
30. Vira T, Colquhoun M and Etchells E. Reconcilable differences: correcting medication errors at hospital admission and discharge. *Qual Saf Health Care* 2006; 15: 122-126. DOI: 10.1136/qshc.2005.015347.
31. Al-Jazairi AS, Al-Suhaibani LK, Al-Mehizia RA, et al. Impact of a medication reconciliation program on cardiac surgery patients. *Asian Cardiovasc Thorac Ann* 2017; 25: 579-585. 20171012. DOI: 10.1177/0218492317738382.
32. Fernandes BD, Almeida P, Foppa AA, et al. Pharmacist-led medication reconciliation at patient discharge: A scoping review. *Res Social Adm Pharm* 2020; 16: 605-613. 20190801. DOI: 10.1016/j.sapharm.2019.08.001.
33. Centers for Disease Control and Prevention. Chronic Kidney Disease

in the United States, 2023. Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention; 2023. Available at: https://www.cdc.gov/kidneydisease/publications-resources/ckd-national-facts.html.
34. prevention Cfdca. Chronic Kidney Disease in the United States, 2021. 2021.
35. Nguyen-Thi HY, Le-Phuoc TN, Tri Phat N, et al. The Economic Burden of Chronic Kidney Disease in Vietnam. *Health Serv Insights* 2021; 14: 11786329211036011. 20210728. DOI: 10.1177/11786329211036011.
36. Slawomirski L, Auraaen A and Klazinga NS. The economics of patient safety: strengthening a value-based approach to reducing patient harm at national level. 2017.
37. Daifi C, Feldpausch B, Roa PA, et al. Implementation of a Clinical Pharmacist in a Hemodialysis Facility: A Quality Improvement Report. *Kidney Med* 2021; 3: 241-247 e241. 20210210. DOI: 10.1016/j.xkme.2020.11.015.
38. Hassan Y, Al-Ramahi RJ, Aziz NA, et al. Impact of a renal drug dosing service on dose adjustment in hospitalized patients with chronic kidney disease. *The Annals of pharmacotherapy* 2009; 43: 1598-1605. 20090923. DOI: 10.1345/aph.1M187.
39. Manley HJ and Carroll CA. The clinical and economic impact of pharmaceutical care in end-stage renal disease patients. *Semin Dial* 2002; 15: 45-49. DOI: 10.1046/j.1525-139x.2002.00014.x.
40. Anderegg SV, Wilkinson ST, Couldry RJ, et al. Effects of a hospitalwide pharmacy practice model change on readmission and return to emergency department rates. *Am J Health Syst Pharm* 2014; 71: 1469-1479. DOI: 10.2146/ajhp130686.
41. Jiang SP, Zhu ZY, Ma KF, et al. Impact of pharmacist antimicrobial dosing adjustments in septic patients on continuous renal replacement therapy in an intensive care unit. *Scand J Infect Dis* 2013; 45: 891-899. 20130912. DOI: 10.3109/00365548.2013.827338.
42. Al-Qudah RA, Al-Badriyeh D, Al-Ali FM, et al. Cost-benefit analysis of clinical pharmacist intervention in preventing adverse drug events in the general chronic diseases outpatients. *J Eval Clin Pract* 2020; 26: 115-124. 20190624. DOI: 10.1111/jep.13209.
43. Aljbouri TM, Alkhawaldeh MS, Abu-Rumman AE, et al. Impact of clinical pharmacist on cost of drug therapy in the ICU. *Saudi Pharm J* 2013; 21: 371-374. DOI: 10.1016/j.jsps.2012.12.004.
44. Abushanab D, Gulied A, Hamad A, et al. Cost savings and cost avoidance with the inpatient clinical pharmacist interventions in a tertiary cancer care hospital. *J Oncol Pharm Pract* 2023: 10781552231160275. 20230322. DOI: 10.1177/10781552231160275.

Figure Legends:

Figure 1: The cost-benefit analysis model.

Figure 2: Tornado diagrams of one-way sensitivity analyses.

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

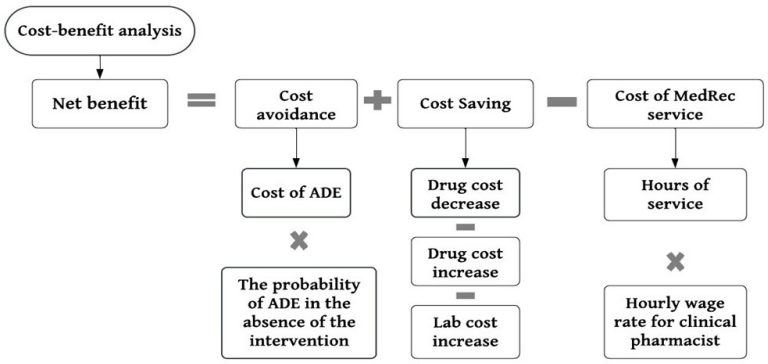
Primary domain	Cause	Cost avoidance ($)	Total ($)
Drug selection	Inappropriate drug according to guidelines/formulary	12,480.17	25,588.49
	No or incomplete drug treatment despite existing indication	8,645.98	
	No indication for drug	2,295.94	
	Inappropriate combination of drugs or drugs and dietary supplements	1,916.01	
	Too many different drugs/active ingredients prescribed for indication	250.39	
	Inappropriate duplication of therapeutic group or active ingredient	250.38	
Dose selection	Drug dose of a single active ingredient too high	13,710.33	21,141.39
	Dosage regimen too frequent	5,284.26	
	Drug dose too low	2,146.80	
Patient transfer related (discrepancies)	Drug omission	12,693.54	20,623.2
	Discrepancy in the strength and/or frequency and/or number of units of dosage form and/or total daily dose	4,612.57	
	Drug addition	2,399.36	
	Therapeutic class substitution	436.54	
	Drug duplication	337.48	
	Discrepancy in the dosage form/route of administration	143.70	
Drug use process	Inappropriate timing of administration or dosing intervals by a health professional	2,624.71	2,777.12
	Drug administered via wrong route by a health professional	152.41	
Treatment duration	Duration of treatment too long	273.25	469.21
	Duration of treatment too short	195.96	

Table 1: Cost avoidance per cause-based domains in the PCNE classification of DRPs (V9.1).

Drug form	Inappropriate drug form/formulation	114.30	114.30
Other	Addition of a lab test	10,531.5	12,088.25
	No or inappropriate outcome monitoring	1,556.75	
Total			83,052.34

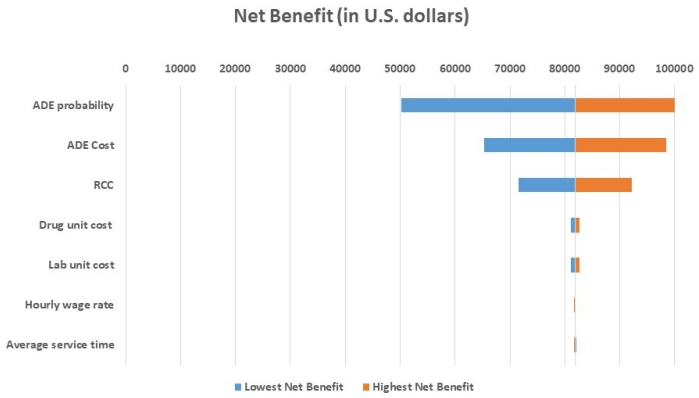
Table 2: Results of cost-benefit analysis

Outcome	**Value ($)**
Intervention cost over 4 months	713.70
Cost avoidance of all DRPs	83,052.4
Total cost saving	- 467.5
Net benefit over the study period (4 months)	81,871.15
Benefit to cost ratio	115.7:1



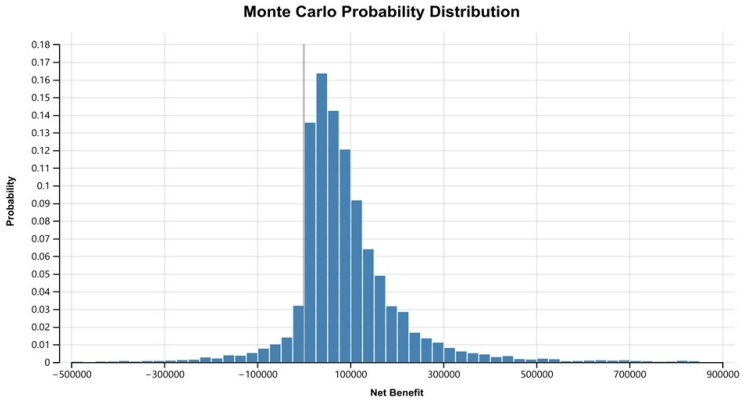
The cost-benefit analysis model.

338x190mm (96 x 96 DPI)



Tornado diagrams of one-way sensitivity analyses.

338x190mm (96 x 96 DPI)



Probabilistic sensitivity analysis for the net benefit of supplemented medication reconciliation service

338x190mm (96 x 96 DPI)

Research Article

Title: Clinical pharmacist-led medication reconciliation supplemented with medication review in chronic kidney disease admitted patients: a cost-benefit analysis

Journal: BMJ Open.

Table S1: Patient demographics and clinical characteristics of the study sample.

Variable	Study sample N(%) N = 142
Gender n (%)	
Female	53 (37.32)
Male	89 (62.68)
Age, years (M± SD)	57.16 ±15.96
BMI n (%)	
<18.5	6 (4.23)
18.5 -24.9	41 (28.87)
25-29.9	42 (29.58)
> 29.9	53 (37.32)
Marital status	
Married	109 (76.76)
Not married	33 (23.24)
Smoking status	
Yes	43 (30.28)
No	75 (52.82)
Ex-smoker	24 (16.90)
Educational level	
Not educated	20 (14.08)
School	93 (65.49)
University/higher education	29 (20.42)
Employment status	
Employed	26 (18.31)
Retired	32 (22.54)
Unemployed	84 (59.15)
Occupation	
Medical	3 (2.11)
Non-medical	64 (45.07)
No	75 (52.82)
Monthly income	
<500	110 (77.46)
500 -1000	29 (20.42)
>1000	3 (2.11)

Reason for admission	
AKI on Top of CKD related problems	42 (29.58)
CKD/dialysis related problems	71 (50.0)
Others	29 (20.42)
CKD stage	
Stage 2	2 (1.41)
Stage 3a	3 (2.11)
Stage 3b	12 (8.45)
Stage 4	32 (22.54)
Stage 5	93 (65.5)
Years of dialysis (M± SD)	2.33 ± 3.66
Years of CKD (M± SD)	5.02 ± 6.80
Number of comorbidities (M± SD)	6.36 ± 2.18
CCI (M ± SD)	6.08 ± 2.93
Number of medications at admission	9.58 (3.07)
Number of medications at discharge	9.24 (4.34)
Death at discharge	5 (3.52)
Length of stay	8.94 ± 8.59

Abbreviation: BMI: Body Mass Index, M± SD: Mean ± Standard deviation, CKD: Chronic Kidney Disease, AKI: Acute Kidney Disease. CCI: Charlson Comorbidity Index.

Table S2: Examples of the studied clinical cases with the probability score to cause ADEs.

A patient had a recent myocardial infarction (MI) and had previously undergone stent placement for the main coronary artery. She was taking febuxostat for gout. The clinical pharmacist recommended switching from febuxostat to allopurinol. (Black box warning)	High (0.6)
A female patient on hemodialysis, has a hemoglobin (Hb) level of 12 and a history of stroke. She was on alpha epoetin 4000 units prescribed every other day (EOD). (Black box warning)	High (0.6)
A 91-year-old female patient with CKD stage 5 (baseline serum creatinine is 500 mmol/l). Dialysis was delayed due to her age. The patient is experiencing uremia, including vomiting symptoms. She was prescribed metoclopramide 10 mg intravenously every 8 hours, which is a high dose considering her condition. Additionally, she is taking trimetazidine, which has a serious interaction with metoclopramide (category X). It is important to note that trimetazidine is contraindicated in patients with a GFR <30.	Medium (0.4)
A patient has osteoporosis and is undergoing hemodialysis. Initially, she was prescribed alendronate, but the clinical pharmacist recommended switching to denosumab. The physician stopped the alendronate as advised but could not provide denosumab due to economic issues. Subsequently, the patient visited the outpatient clinic (OPC) due to bone pain, and there she received denosumab treatment.	Medium (0.4), Low (0.1)
A patient has a CrCl (Creatinine Clearance) of 13, and he is currently taking fenofibrate. Additionally, the triglyceride level is less than 250 mg/dL.	Medium (0.4)
A patient underwent upper endoscopy, which revealed mild gastritis. There were no available tests for H. pylori, and the patient's serum creatinine level was 500 mmol/l (CrCl <15). Nevertheless, upon discharge, the patient was prescribed amoxicillin 1g twice daily and clarithromycin 500mg twice daily without renal adjustment and without confirming the diagnosis.	Medium (0.4)

A patient has AKI on top of CKD and has been experiencing severe vomiting for over a week. Upon admission, the patient's home medication included metoclopramide 10 mg three times daily taken orally. However, after admission, the route was changed to intravenous 10 mg TID (not renal dose) without improvement, the dose was changed to metoclopramide intravenously at 20 mg three times daily, which is considered too high. The clinical pharmacist recommended discontinuing metoclopramide and administering ondansetron as an alternative.	Medium (0.4)
A patient is undergoing hemodialysis and was diagnosed with deep vein thrombosis (DVT). Upon discharge, she was prescribed a therapeutic dose of Enoxaparin. The clinical pharmacist recommended switching to apixaban.	Medium (0.4)
A patient was admitted for liver cirrhosis, baseline CrCl 32, AKI, diabetes mellitus (DM), and recently diagnosed depression. He was initially admitted while taking metformin 500mg once daily. However, upon discharge, his medication regimen included metformin 850mg three times daily, mirtazapine, spironolactone, and hydrochlorothiazide. The clinical pharmacist was unable to reach the responsible physician to discuss the changes. Consequently, the patient was readmitted after 5 days due to diarrhea and hyponatremia.	Medium (0.4)
A patient has a UTI and is currently taking ciprofloxacin, calcium carbonate, and ferrous gluconate twice daily, both at 6 pm and 6 am, all by oral route.	Low (0.1)
A patient admitted with severe hypophosphatemia; the physician initially recorded that the patient was on calcium carbonate 500mg BID. With medication reconciliation we found that the actual home dose was calcium carbonate 1g TID, along with sevelamer TID, which was obtained from outside the hospital (and was not known by the physician). Resolving these discrepancies with the physician led to a change in the diagnosis.	Low (0.1)
A patient has been taking Combivent® every 8 hours for over than 2 weeks without any valid indication.	Low (0.1)

A 32-year-old patient has type 1 diabetes mellitus (DM1), end-stage renal disease (ESRD), partial retinopathy, and uncontrolled DM with recurrent hypoglycemia. Upon admission, she was using pre-mixed insulin. The clinical pharmacist suggested switching to a basal-bolus insulin regimen.	Low (0.1)
A patient was discharged without some of his hypoglycemic and antihypertensive agents unintentionally.	Low (0.1)
A patient on HD, was on famotidine 40mg once daily at home. Was not documented.	Very low (0.01)

BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2024-087232.R1
Article Type:	Original research
Date Submitted by the Author:	27-Sep-2024
Complete List of Authors:	Altawalbeh, Shoroq ; Jordan University of Science and Technology, Department of Clinical Pharmacy Sallam, Nahlah M.; Jordan University of Science and Technology, Department of Clinical Pharmacy Al-Khatib, Minas; Jordan University of Science and Technology, Department of Clinical Pharmacy Alshogran, Osama Y.; Jordan University of Science and Technology, Department of Clinical Pharmacy Bani Amer, Mohammad S.; Jordan University of Science and Technology, Department of Internal Medicine
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Medical management, Health services research, Health economics
Keywords:	Medication Reconciliation, Health Services, Health economics < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Health & safety < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

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Research Article

Clinical pharmacist-led medication reconciliation supplemented with medication review in chronic kidney disease admitted patients: a cost-benefit analysis

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Running Title: Cost-benefit of medication reconciliation in CKD

Number of Tables: 2

Number of Figures: 3

Keywords: Medication reconciliation, clinical pharmacist, cost-benefit, chronic kidney disease, Jordan.

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 cost-benefit ratio of medication reconciliation supplemented with medication review among inpatients with CKD.

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.

Method: Patients received medication reconciliation at admission and discharge as well as medication review throughout admission. 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 in terms of cost savings and cost avoidance. The primary outcome measures were the net benefit and the benefit-to-cost ratio of the intervention.

Results: The total estimated cost of all DRPs in the absence of interventions (cost avoidance) was $83,052.4; among which $20,623.19 was attributed to medication discrepancies. The cost savings were estimated at -$467.5. The supplemented medication reconciliation service was estimated to cost $713.7. As a result, the estimated net benefit amounted to $81,871.15, with a benefit-to-cost ratio of 115.7:1 over the 4-month study period.

Conclusion: Delivering a supplemented medication reconciliation service by a clinical pharmacist for CKD patients is cost beneficial from the healthcare perspective in Jordan, an example of a low- and middle-income country (LMIC). This finding further confirms the pivotal role of clinical pharmacists in multidisciplinary healthcare teams.

Keywords: Medication reconciliation, clinical pharmacist, cost-benefit, chronic kidney disease, Jordan.

Strengths and limitations of this study

- The study was conducted along with a prospective interventional study.
- Evaluation of the probability scores of drug related problems (DRPs) was conducted by an expert panel composed of five independent evaluators.
- The exact real cost of adverse events resulting fromDRPs 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.[1, 2] 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 (RRT), 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 hemodialysis patients management in 2010, with an average of annual cost of $9,979 per patient.[5] A study conducted in Lebanon reported the median cost for all CKD stages per year of $4,764.02 (IQR $2,475.24 - $23,455.61) in 2019 from a society perspective.[6] Studies highly recommend implementing programs and policies to reduce progression and complications of CKD to mitigate the growing disease burden especially in countries with limited resources.[7]

Patients with CKD are very vulnerable to medication discrepancies and other Drug related problems (DRPs).[8, 9] Interestingly, many serious DRPs are preventable in CKD patients.[10] Developing DRPs increased the exposure to re-hospitalization, extended length of hospital stays, and early death, and therefore expanded the cost.[11-13] Clinical pharmacy services targeting DRPs have revealed a positive economic impact on healthcare organizations across the literature.[14] Medication reconciliation and medication review, primarily led by a clinical pharmacist, are vital services focused on preventing and resolving medication discrepancies and other drug-related problems (DRPs). These processes play a key role in enhancing patient outcomes and reducing

healthcare costs. [15] 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. [16]

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 CKD patients. Examining the costs associated with drug-related problems (DRPs) during CKD hospitalizations will further emphasize 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 cost-benefits of implementing a clinical pharmacist-led service for supplemented medication reconciliation among admitted patients with CKD in Jordan.

Methods

Study design

The cost-benefit analysis was developed along with a prospective interventional clinical study that involved patients with stages 2-5 CKD, who were admitted to two healthcare hospitals in Jordan: King Abdullah Hospital (KAUH) and Princess Basma Hospital (PBH). A clinical pharmacist was responsible for providing supplemented medication reconciliation to CKD-admitted patients over four months (from February to May 2023). The costs and benefits over the study period were calculated relative to absence of this intervention. The primary outcome measure was the net benefit generated by the supplemented medication reconciliation service provided to CKD patients 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 health care 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 summarized in the Supplemental Material (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 pre-admission medication list. The pre-admission 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 hospitalization 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 hospitalization, and new medications planned to be started upon 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 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

In the cost-saving analysis, the decreased medication costs due to interventions and the increased medication costs and costs attributed to requesting labs were estimated. 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.[17] Acute therapy duration was estimated based on the clinical scenario, while chronic medication use was calculated over three months' time horizon. Public per-unit prices of drugs were obtained from the Jordan Food and Drug Administration (JFDA).[18] 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 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.

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 [19] 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 Supplemental Material (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.[20] 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 CKD patients. 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 by the Pharmaceutical Care Network Europe (PCNE) Classification for Drug-Related Problems V9.1 based on the cause,[21] and the Medication Discrepancy Taxonomy (MedTax) system.[22] All financial data were extracted in Jordanian Dinar currency unit (JOD) and converted to United States Dollars (USD) at a rate of (1 JOD = 1.41 USD). 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 ± 20% of the base case cost. The average service time was varied over two SD of the mean, as calculated in this study. RCC was varied in the range (0.7 to 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 the public were not actively involved in the design, conduct, reporting, or dissemination plans of this research.

Ethics approval and consent to participate

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.

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) minutes, ranging from 26 to 60.5 minutes. The total time spent by the clinical pharmacist on the supplemented medication reconciliation over the four-month intervention period was 6117.1 minutes (101.95 hours). The average duration to accomplish a primary medication reconciliation service at admission was 15.79 ± 1.74 minutes. Though, the average time for medication review during the admission was 21.6 ± 4.30 minutes (ranged from 11.6 to 35.5 minutes) per patient. Medication reconciliation time at discharge averaged 3.58 ± 1.55 minutes 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 4-month study period was $713.7 ($7 × 101.95 hours).

Benefits of supplemented medication reconciliation

Estimated cost saving

The total increased medication cost was estimated to be $9,349 and lab needed total cost was estimated at $5,248. The decrease in medication costs owing to the intervention was $14,012. Total

cost saving (after being adjusted with RCC of 0.8) = $11,210[$14,012*0.8] - $7,479[$9,349 *0.8] - $4,198[$5,248*0.8] = -$467.5. 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 $340.20 (SD= $199.48). The assumed cost of a DRP was the estimated cost of two additional hospitalization days for patients with CKD in the current study [$680.4 multiplied by 0.8 RCC = $483.1]. 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 low-to 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 hospitalization days was $82.96 (SD=$57.7). The total estimated cost of all DRPs in the study was $83,052.4 (the cost avoidance). Patient transfer related DRPs (medications discrepancies) were found to be the third most expensive cause-based domain in the PCNE classification of DRPs (V9.1), contributing to around 25% of the total cost avoidance ($20,623.19). The greatest weight of discrepancies' cost avoidance was attributed to "drug omission" category ($12,693.54) followed by "discrepancy in frequency/strength/dose" ($4,612.56) and "drug addition" ($2,399.36), 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 (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 ($83,052.4) + cost saving (- 467.5) - cost of the intervention ($713.7) = $81,871.15]. 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).

Discussion

The major findings of the current study emphasize 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 to 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 with moderate to significant clinical impact. In a study conducted in Jordan among hospitalized

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).[23] In a study conducted in Canada, approximately half of the observed DRPs were moderate in severity in terms of causing harm to CKD patients.[24] The different scales used in severity assessment across the literature makes the comparison seems challenging. Overall, most recognized 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 CKD patients in terms of the cost-benefits associated with this service. A recent review of 47 studies among CKD patients also supports this finding; 7 studies approved the significant cost savings and 15 studies reported improvement in clinical outcomes due to clinical pharmacy care, including blood pressure, anemia, length of hospital stay, readmissions, kidney function, and other laboratory tests (i.e., PTH, calcium, uric acid, cholesterol, and HbA1c).[14]

The average time needed for full supplemented medication reconciliation services provided for each CKD admission in the current study was 43.38 ± 6.65 minutes. This is comparable to other studies that measured the time needed for medication reconciliation services: 44.4 ± 21.8,[25] 40 ±17.2 minutes,[26] and 48 minutes.[27, 28] 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 minutes (IQR 20-30 minutes).[29] The specific time for medication reconciliation at admission was roughly similar to our finding (15 minutes (IQR 10–21)) in two previous studies.[30, 31] Moreover, medication reconciliation at discharge after conducting medication reconciliation at admission was previously estimated to need approximately 3.5 minutes,[32] 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 nine studies with an average of 34.5 (±39.4) minutes.[33] This variability could be 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, 34-36] DRPs have been associated with high costs that affect patient safety and healthcare expenditures.[37]. Our study estimated the net benefit attributed to avoiding and resolving DRPs to be $81,871.15 over 4 months for a cumulative number of 142 CKD patients. Such remarkable benefit confirms the need of implementing supplemented medication reconciliation in CKD patients. Likewise, a recent retrospective cohort in the US among hemodialysis patients estimated cost saving from preventing DRPs to be $447,355 over a 6-month period of observation, attributing this benefit to performing medication reconciliation with medication review.[38] A Malaysian study measured the cost saving resulted from only dose adjustment in CKD inpatients to be $2,250 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.[39] This saved cost is considered much lower than the avoided cost resulting from renal dose adjustment in our study ($14,756 for 4 months, 94 dose adjustment interventions). An earlier prospective study conducted medication therapy evaluation by pharmacist found that the ratio of pharmaceutical care cost to healthcare system saving is $1 to $3.98 among end-stage renal disease patients in the USA.[40] This is much smaller compared to 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 $780,000 after implementing supplemented medication reconciliation with patient education

in internal medicine wards in Kansas ascribed to reducing readmissions.[41] A Chinese trial found cost saving attributed to antimicrobial dose adjustment (number of adjusted doses= 183) by a clinical pharmacist of $3,525 per patient with sepsis undergoing continuous dialysis in the ICU.[42] Wage rates and the cost of health care may differ widely across regions and institutions which make the comparison in cost is not sufficiently clear/straightforward. This also highlights the need to obtain relevant data from local or regional studies to better support the decisions of policy makers 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 $6,422.41.[43] In another study conducted in Jordan, clinical pharmacist intervention in the ICU reduced the total cost of drugs consumption by $211,574.90 over 10 months.[44] Still, the cost benefit of medication reconciliation among CKD patients 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.[45] 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.[19] 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 CKD admitted patients, with substantial cost avoidance compared to 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 toward evaluating the cost-benefit of such approaches.

Funding:

This work was supported by the Deanship of Scientific Research at the Jordan University of Science and Technology [grant number: 20220257]. The funding agency was not involved in the study design, conduct, writing, or decision to submit this article for publication.

Competing Interests:

The Authors declare that they have no conflicts of interest to disclose.

Author contributions

SA contributed to conceptualization, methodology, data curation, formal analysis, supervision, project administration, funding acquisition, and writing original draft. NS contributed to conceptualization, methodology, data curation, formal analysis, and writing original draft. MA and OA contributed to conceptualization, methodology, data curation, and writing- reviewing and editing. MB contributed to data curation and writing- reviewing and editing. SA is the guarantor for the manuscript and accepts full responsibility for the overall content.

Data availability statement

All data underlying this article are presented in the manuscript.

References

1. Small C, Kramer HJ, Griffin KA, et al. Non-dialysis dependent chronic kidney disease is associated with high total and out-of-pocket healthcare expenditures. *BMC Nephrol* 2017; 18: 3. 2017/01/07. DOI: 10.1186/s12882-016-0432-2.
2. Silva Junior GBD, Oliveira JGR, Oliveira MRB, et al. Global costs attributed to chronic kidney disease: a systematic review. *Rev Assoc Med Bras (1992)* 2018; 64: 1108-1116. 2018/12/21. DOI: 10.1590/1806-9282.64.12.1108.
3. Golestaneh L, Alvarez PJ, Reaven NL, et al. All-cause costs increase exponentially with increased chronic kidney disease stage. *Am J Manag Care* 2017; 23: S163-S172. 2017/10/06.
4. Saran R, Pearson A, Tilea A, et al. Burden and Cost of Caring for US Veterans With CKD: Initial Findings From the VA Renal Information System (VA-REINS). *Am J Kidney Dis* 2021; 77: 397-405. 2020/09/06. DOI: 10.1053/j.ajkd.2020.07.013.
5. Al-Shdaifat EA and Manaf MR. The economic burden of hemodialysis in Jordan. *Indian J Med Sci* 2013; 67: 103-116. 2013/12/12.
6. Aoun M, Helou E, Sleilaty G, et al. Cost of illness of chronic kidney disease in Lebanon: from the societal and third-party payer perspectives. *BMC Health Serv Res* 2022; 22: 586. 2022/05/04. DOI: 10.1186/s12913-022-07936-0.
7. Rizk R, Hiligsmann M, Karavetian M, et al. A societal cost-of-illness study of hemodialysis in Lebanon. *J Med Econ* 2016; 19: 1157-1166. 2016/06/29. DOI: 10.1080/13696998.2016.1207653.
8. Chia BY, Cheen MHH, Gwee XY, et al. Outcomes of pharmacist-provided medication review in collaborative care for adult Singaporeans receiving hemodialysis. *Int J Clin Pharm* 2017; 39: 1031-1038. 20170821. DOI: 10.1007/s11096-017-0528-1.
9. Song YK, Jeong S, Han N, et al. Effectiveness of Clinical Pharmacist Service on Drug-Related Problems and Patient Outcomes for Hospitalized Patients with Chronic Kidney Disease: A Randomized Controlled Trial. *J Clin Med* 2021; 10 20210420. DOI: 10.3390/jcm10081788.
10. Laville SM, Gras-Champel V, Moragny J, et al. Adverse Drug Reactions in Patients with CKD. *Clin J Am Soc Nephrol* 2020; 15: 1090-1102. 2020/07/03. DOI: 10.2215/CJN.01030120.
11. Bishop MA, Cohen BA, Billings LK, et al. Reducing errors through discharge medication reconciliation by pharmacy services. *Am J Health Syst Pharm* 2015; 72: S120-126. 2015/08/15. DOI: 10.2146/sp150021.

12. Ernst FR and Grizzle AJ. Drug-related morbidity and mortality: updating the cost-of-illness model. *J Am Pharm Assoc (Wash)* 2001; 41: 192-199. 2001/04/12. DOI: 10.1016/s1086-5802(16)31229-3.
13. Alruqayb WS, Price MJ, Paudyal V, et al. Drug-Related Problems in Hospitalised Patients with Chronic Kidney Disease: A Systematic Review. *Drug Saf* 2021; 44: 1041-1058. 2021/09/13. DOI: 10.1007/s40264-021-01099-3.
14. Al Raiisi F, Stewart D, Fernandez-Llimos F, et al. Clinical pharmacy practice in the care of Chronic Kidney Disease patients: a systematic review. *Int J Clin Pharm* 2019; 41: 630-666. 2019/04/10. DOI: 10.1007/s11096-019-00816-4.
15. Onatibia-Astibia A, Malet-Larrea A, Mendizabal A, et al. The medication discrepancy detection service: A cost-effective multidisciplinary clinical approach. *Aten Primaria* 2021; 53: 43-50. 2020/10/01. DOI: 10.1016/j.aprim.2020.04.008.
16. *World Health Organization, Medication safety in transitions of care: technical report, 2019*.
17. Houso A, Hamdan M and Falana H. Cost benefit analysis of clinical pharmacist interventions in medical intensive care unit in Palestine medical complex: Prospective interventional study. *Saudi Pharm J* 2022; 30: 1718-1724. 2023/01/06. DOI: 10.1016/j.jsps.2022.09.017.
18. Jordan Food and Drug Administration (JFDA) http://jfda.jo/Pages/viewpage.aspx?pageID=336 (accessed July 2023).
19. Nesbit TW, Shermock KM, Bobek MB, et al. Implementation and pharmacoeconomic analysis of a clinical staff pharmacist practice model. *Am J Health Syst Pharm* 2001; 58: 784-790. DOI: 10.1093/ajhp/58.9.784.
20. Chen CC, Hsiao FY, Shen LJ, et al. The cost-saving effect and prevention of medication errors by clinical pharmacist intervention in a nephrology unit. *Medicine (Baltimore)* 2017; 96: e7883. DOI: 10.1097/MD.0000000000007883.
21. *Pharmaceutical Care Network Europe, The PCNE CLassification V 9.1. Pharmaceutical Care Network Europe, p Classification for Drug related problems*. 2020.
22. Almanasreh E, Moles R and Chen TF. The medication discrepancy taxonomy (MedTax): The development and validation of a classification system for medication discrepancies identified through medication reconciliation. *Res Social Adm Pharm* 2020; 16: 142-148. 20190414. DOI: 10.1016/j.sapharm.2019.04.005.
23. AbuRuz SM, Alrashdan Y, Jarab A, et al. Evaluation of the impact of pharmaceutical care service on hospitalized patients with chronic kidney disease in Jordan. *Int J Clin Pharm* 2013; 35: 780-789. 20130725. DOI: 10.1007/s11096-013-9806-8.
24. Quintana-Barcena P, Lord A, Lizotte A, et al. Prevalence and Management of Drug-Related Problems in Chronic Kidney Disease Patients by Severity Level: A Subanalysis of a Cluster Randomized Controlled Trial in Community Pharmacies. *J Manag Care Spec Pharm* 2018; 24: 173-181. DOI: 10.18553/jmcp.2018.24.2.173.
25. Buckley MS, Harinstein LM, Clark KB, et al. Impact of a clinical pharmacy admission medication reconciliation program on medication errors in "high-risk" patients. *The Annals of pharmacotherapy* 2013; 47: 1599-1610. 20131015. DOI: 10.1177/1060028013507428.
26. Mendes AE, Lombardi NF, Andrzejevski VS, et al. Medication reconciliation at patient admission: a randomized controlled trial. *Pharm Pract (Granada)* 2016; 14: 656. 20160315. DOI: 10.18549/PharmPract.2016.01.656.
27. Cadman B, Wright D, Bale A, et al. Pharmacist provided medicines reconciliation within 24 hours of admission and on discharge: a randomised controlled pilot study. *BMJ Open* 2017; 7: e013647. 20170316. DOI: 10.1136/bmjopen-2016-013647.
28. Neeman M, Dobrinas M, Maurer S, et al. Transition of care: A set of pharmaceutical interventions improves hospital discharge prescriptions from an internal medicine ward. *Eur J Intern Med* 2017; 38: 30-37. 20161125. DOI: 10.1016/j.ejim.2016.11.004.

29. Cornu P, Steurbaut S, Leysen T, et al. Effect of medication reconciliation at hospital admission on medication discrepancies during hospitalization and at discharge for geriatric patients. *The Annals of pharmacotherapy* 2012; 46: 484-494. 20120313. DOI: 10.1345/aph.1Q594.

30. Sebaaly J, Parsons LB, Pilch NA, et al. Clinical and Financial Impact of Pharmacist Involvement in Discharge Medication Reconciliation at an Academic Medical Center: A Prospective Pilot Study. *Hospital pharmacy* 2015; 50: 505-513. DOI: 10.1310/hpj5006-505.

31. Vira T, Colquhoun M and Etchells E. Reconcilable differences: correcting medication errors at hospital admission and discharge. *Qual Saf Health Care* 2006; 15: 122-126. DOI: 10.1136/qshc.2005.015347.

32. Al-Jazairi AS, Al-Suhaibani LK, Al-Mehizia RA, et al. Impact of a medication reconciliation program on cardiac surgery patients. *Asian Cardiovasc Thorac Ann* 2017; 25: 579-585. 20171012. DOI: 10.1177/0218492317738382.

33. Fernandes BD, Almeida P, Foppa AA, et al. Pharmacist-led medication reconciliation at patient discharge: A scoping review. *Res Social Adm Pharm* 2020; 16: 605-613. 20190801. DOI: 10.1016/j.sapharm.2019.08.001.

34. Centers for Disease Control and Prevention. Chronic Kidney Disease

in the United States, 2023. Atlanta, GA: US Department of Health and Human

Services, Centers for Disease Control and Prevention; 2023. Available at: https://www.cdc.gov/kidneydisease/publications-resources/ckd-national-facts.html.

35. prevention Cfdca. Chronic Kidney Disease in the United States, 2021. 2021.

36. Nguyen-Thi HY, Le-Phuoc TN, Tri Phat N, et al. The Economic Burden of Chronic Kidney Disease in Vietnam. *Health Serv Insights* 2021; 14: 11786329211036011. 20210728. DOI: 10.1177/11786329211036011.

37. Slawomirski L, Auraaen A and Klazinga NS. The economics of patient safety: strengthening a value-based approach to reducing patient harm at national level. 2017.

38. Daifi C, Feldpausch B, Roa PA, et al. Implementation of a Clinical Pharmacist in a Hemodialysis Facility: A Quality Improvement Report. *Kidney Med* 2021; 3: 241-247 e241. 20210210. DOI: 10.1016/j.xkme.2020.11.015.

39. Hassan Y, Al-Ramahi RJ, Aziz NA, et al. Impact of a renal drug dosing service on dose adjustment in hospitalized patients with chronic kidney disease. *The Annals of pharmacotherapy* 2009; 43: 1598-1605. 20090923. DOI: 10.1345/aph.1M187.

40. Manley HJ and Carroll CA. The clinical and economic impact of pharmaceutical care in end-stage renal disease patients. *Semin Dial* 2002; 15: 45-49. DOI: 10.1046/j.1525-139x.2002.00014.x.

41. Anderegg SV, Wilkinson ST, Couldry RJ, et al. Effects of a hospitalwide pharmacy practice model change on readmission and return to emergency department rates. *Am J Health Syst Pharm* 2014; 71: 1469-1479. DOI: 10.2146/ajhp130686.

42. Jiang SP, Zhu ZY, Ma KF, et al. Impact of pharmacist antimicrobial dosing adjustments in septic patients on continuous renal replacement therapy in an intensive care unit. *Scand J Infect Dis* 2013; 45: 891-899. 20130912. DOI: 10.3109/00365548.2013.827338.

43. Al-Qudah RA, Al-Badriyeh D, Al-Ali FM, et al. Cost-benefit analysis of clinical pharmacist intervention in preventing adverse drug events in the general chronic diseases outpatients. *J Eval Clin Pract* 2020; 26: 115-124. 20190624. DOI: 10.1111/jep.13209.

44. Aljbouri TM, Alkhawaldeh MS, Abu-Rumman AE, et al. Impact of clinical pharmacist on cost of drug therapy in the ICU. *Saudi Pharm J* 2013; 21: 371-374. DOI: 10.1016/j.jsps.2012.12.004.

45. Abushanab D, Gulied A, Hamad A, et al. Cost savings and cost avoidance with the inpatient clinical pharmacist interventions in a tertiary cancer care hospital. *J Oncol Pharm Pract* 2023: 10781552231160275. 20230322. DOI: 10.1177/10781552231160275.

Figure Legends:

Figure 1: The cost-benefit analysis model.

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

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

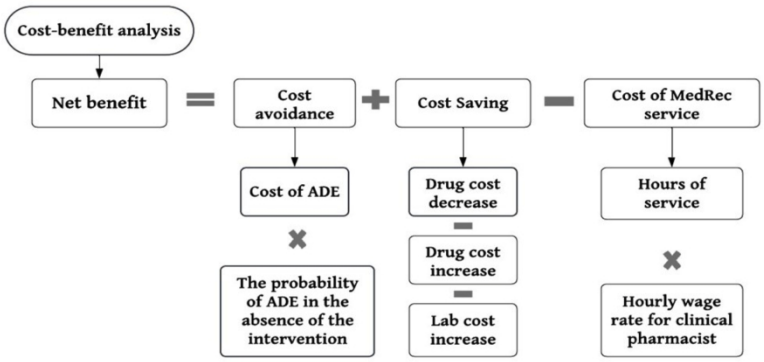
Table 1: Cost avoidance per cause-based domains in the PCNE classification of DRPs (V9.1).

Primary domain	Cause	Cost avoidance ($)	Total ($)
Drug selection	Inappropriate drug according to guidelines/formulary	12,480.17	25,588.49
	No or incomplete drug treatment despite existing indication	8,645.98	
	No indication for drug	2,295.94	
	Inappropriate combination of drugs or drugs and dietary supplements	1,916.01	
	Too many different drugs/active ingredients prescribed for indication	250.39	
	Inappropriate duplication of therapeutic group or active ingredient	250.38	
Dose selection	Drug dose of a single active ingredient too high	13,710.33	21,141.39
	Dosage regimen too frequent	5,284.26	
	Drug dose too low	2,146.80	
Patient transfer related (discrepancies)	Drug omission	12,693.54	20,623.2
	Discrepancy in the strength and/or frequency and/or number of units of dosage form and/or total daily dose	4,612.57	
	Drug addition	2,399.36	
	Therapeutic class substitution	436.54	
	Drug duplication	337.48	
	Discrepancy in the dosage form/route of administration	143.70	
Drug use process	Inappropriate timing of administration or dosing intervals by a health professional	2,624.71	2,777.12
	Drug administered via wrong route by a health professional	152.41	
Treatment duration	Duration of treatment too long	273.25	469.21
	Duration of treatment too short	195.96	
Drug form	Inappropriate drug form/formulation	114.30	114.30
Other	Addition of a lab test	10,531.5	12,088.25
	No or inappropriate outcome monitoring	1,556.75	
Total			83,052.34

Table 2: Results of cost-benefit analysis

Outcome	Total ($)	Average per patient $ (M± SD)	Number of patients
Intervention cost over 4 months	713.7	5.03± 0.77	142
Cost avoidance of all DRPs	83,052.40	584.88± 307.5	142
Total cost saving	-467.5		
Drug cost decrease	14012.85	98.68± 105.7	142
Drug cost increase	9349.08	65.84± 83.3	142
Lab cost increase	5248.02	50.95± 32.7	103
Net benefit over the study period (4 months)	81,871.15		
Benefit to cost ratio	115.7:1		

M± SD: Mean ± Standard deviation



The cost-benefit analysis model

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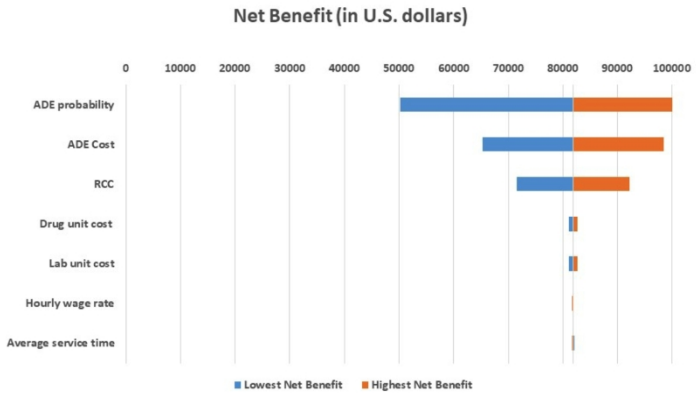
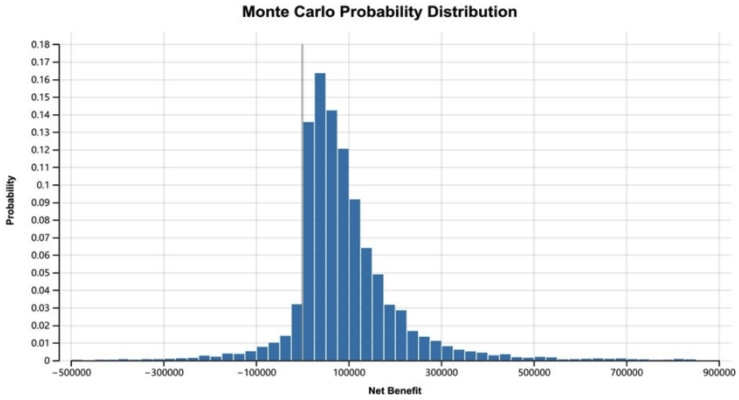


Tornado diagram illustrating the impact of various parameters on the net benefit of supplemented medication reconciliation service (one-way sensitivity analysis)

298x168mm (300 x 300 DPI)



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

298x168mm (300 x 300 DPI)

Research Article

Title: Clinical pharmacist-led medication reconciliation supplemented with medication review in chronic kidney disease admitted patients: a cost-benefit analysis

Journal: BMJ Open.

Table S1: Patient demographics and clinical characteristics of the study sample.

Variable	Study sample N(%) N = 142
Gender n (%)	
Female	53 (37.32)
Male	89 (62.68)
Age, years (M± SD)	57.16 ±15.96
BMI n (%)	
<18.5	6 (4.23)
18.5 -24.9	41 (28.87)
25-29.9	42 (29.58)
> 29.9	53 (37.32)
Marital status	
Married	109 (76.76)
Not married	33 (23.24)
Smoking status	
Yes	43 (30.28)
No	75 (52.82)
Ex-smoker	24 (16.90)
Educational level	
Not educated	20 (14.08)
School	93 (65.49)
University/higher education	29 (20.42)
Employment status	
Employed	26 (18.31)
Retired	32 (22.54)
Unemployed	84 (59.15)
Occupation	
Medical	3 (2.11)
Non-medical	64 (45.07)
No	75 (52.82)
Monthly income (JOD)	
<500	110 (77.46)
500 -1000	29 (20.42)
>1000	3 (2.11)

Reason for admission	
AKI on Top of CKD related problems	42 (29.58)
CKD/dialysis related problems	71 (50.0)
Others	29 (20.42)
CKD stage	
Stage 2	2 (1.41)
Stage 3a	3 (2.11)
Stage 3b	12 (8.45)
Stage 4	32 (22.54)
Stage 5	93 (65.5)
Years of dialysis (M± SD)	2.33 ± 3.66
Years of CKD (M± SD)	5.02 ± 6.80
Number of comorbidities (M± SD)	6.36 ± 2.18
CCI (M ± SD)	6.08 ± 2.93
Number of medications at admission (M± SD)	9.58 ± 3.07
Number of medications at discharge (M± SD)	9.24 ± 4.34
Death at discharge	5 (3.52)
Length of stay	8.94 ± 8.59

Abbreviation: BMI: Body Mass Index, M± SD: Mean ± Standard deviation, JOD: Jordanian Dinar , CKD: Chronic Kidney Disease, AKI: Acute Kidney Disease, CCI: Charlson Comorbidity Index.

One JOD is equivalent to 1.41 US Dollars (USD).

Table S2: Examples of the studied clinical cases with the probability score to cause ADEs.

A patient had a recent myocardial infarction (MI) and had previously undergone stent placement for the main coronary artery. She was taking febuxostat for gout. The clinical pharmacist recommended switching from febuxostat to allopurinol. (Black box warning)	High (0.6)
A female patient on hemodialysis, has a hemoglobin (Hb) level of 12 and a history of stroke. She was on alpha epoetin 4000 units prescribed every other day (EOD). (Black box warning)	High (0.6)
A 91-year-old female patient with CKD stage 5 (baseline serum creatinine is 500 mmol/l). Dialysis was delayed due to her age. The patient is experiencing uremia, including vomiting symptoms. She was prescribed metoclopramide 10 mg intravenously every 8 hours, which is a high dose considering her condition. Additionally, she is taking trimetazidine, which has a serious interaction with metoclopramide (category X). It is important to note that trimetazidine is contraindicated in patients with a GFR <30.	Medium (0.4)
A patient has osteoporosis and is undergoing hemodialysis. Initially, she was prescribed alendronate, but the clinical pharmacist recommended switching to denosumab. The physician stopped the alendronate as advised but could not provide denosumab due to economic issues. Subsequently, the patient visited the outpatient clinic (OPC) due to bone pain, and there she received denosumab treatment.	Medium (0.4), Low (0.1)
A patient has a CrCl (Creatinine Clearance) of 13, and he is currently taking fenofibrate. Additionally, the triglyceride level is less than 250 mg/dL.	Medium (0.4)
A patient underwent upper endoscopy, which revealed mild gastritis. There were no available tests for H. pylori, and the patient's serum creatinine level was 500 mmol/l (CrCl <15). Nevertheless, upon discharge, the patient was	Medium (0.4)

prescribed amoxicillin 1g twice daily and clarithromycin 500mg twice daily without renal adjustment and without confirming the diagnosis.	
A patient has AKI on top of CKD and has been experiencing severe vomiting for over a week. Upon admission, the patient's home medication included metoclopramide 10 mg three times daily taken orally. However, after admission, the route was changed to intravenous 10 mg TID (not renal dose) without improvement, the dose was changed to metoclopramide intravenously at 20 mg three times daily, which is considered too high. The clinical pharmacist recommended discontinuing metoclopramide and administering ondansetron as an alternative.	Medium (0.4)
A patient is undergoing hemodialysis and was diagnosed with deep vein thrombosis (DVT). Upon discharge, she was prescribed a therapeutic dose of Enoxaparin. The clinical pharmacist recommended switching to apixaban.	Medium (0.4)
A patient was admitted for liver cirrhosis, baseline CrCl 32, AKI, diabetes mellitus (DM), and recently diagnosed depression. He was initially admitted while taking metformin 500mg once daily. However, upon discharge, his medication regimen included metformin 850mg three times daily, mirtazapine, spironolactone, and hydrochlorothiazide. The clinical pharmacist was unable to reach the responsible physician to discuss the changes. Consequently, the patient was readmitted after 5 days due to diarrhea and hyponatremia.	Medium (0.4)
A patient has a UTI and is currently taking ciprofloxacin, calcium carbonate, and ferrous gluconate twice daily, both at 6 pm and 6 am, all by oral route.	Low (0.1)
A patient admitted with severe hypophosphatemia; the physician initially recorded that the patient was on calcium carbonate 500mg BID. With medication reconciliation we found that the actual home dose was calcium carbonate 1g TID, along with sevelamer TID, which was obtained from outside the hospital (and was not known by the physician). Resolving these discrepancies with the physician led to a change in the diagnosis.	Low (0.1)

A patient has been taking Combivent® every 8 hours for over than 2 weeks without any valid indication.	Low (0.1)
A 32-year-old patient has type 1 diabetes mellitus (DM1), end-stage renal disease (ESRD), partial retinopathy, and uncontrolled DM with recurrent hypoglycemia. Upon admission, she was using pre-mixed insulin. The clinical pharmacist suggested switching to a basal-bolus insulin regimen.	Low (0.1)
A patient was discharged without some of his hypoglycemic and antihypertensive agents unintentionally.	Low (0.1)
A patient on HD, was on famotidine 40mg once daily at home. Was not documented.	Very low (0.01)

Table S3: Average cost avoidance per patient across cause-based domains in the PCNE classification of DRPs (Version 9.1).

Primary domain	Cause	Cost avoidance ($) Average per patient	Number of patients
Drug selection	Inappropriate drug according to guidelines/formulary	195.0	64
	No or incomplete drug treatment despite existing indication	139.5	62
	No indication for drug	71.7	32
	Inappropriate combination of drugs or drugs and dietary supplements	174.2	11
	Too many different drugs/active ingredients prescribed for indication	83.5	3
	Inappropriate duplication of therapeutic group or active ingredient	83.5	3
Dose selection	Drug dose of a single active ingredient too high	207.7	66
	Dosage regimen too frequent	83.9	63
	Drug dose too low	89.4	24
Patient transfer related (discrepancies)	Drug omission	133.6	95
	Discrepancy in the strength and/or frequency and/or number of units of dosage form and/or total daily dose	118.3	39
	Drug addition	150.0	16
	Therapeutic class substitution	24.3	18

	Drug duplication	84.4	4
	Discrepancy in the dosage form/route of administration	71.9	2
Drug use process	Inappropriate timing of administration or dosing intervals by a health professional	77.2	34
	Drug administered via wrong route by a health professional	152.4	1
Treatment duration	Duration of treatment too long	91.1	3
	Duration of treatment too short	65.3	3
Drug form	Inappropriate drug form/formulation	38.1	3
Others	Addition of a lab test	118.3	89
	No or inappropriate outcome monitoring	91.6	17

BMJ Open

Clinical pharmacist-led medication reconciliation supplemented with medication review in chronic kidney disease admitted patients: a cost-benefit analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2024-087232.R2
Article Type:	Original research
Date Submitted by the Author:	07-Dec-2024
Complete List of Authors:	Altawalbeh, Shoroq ; Jordan University of Science and Technology, Department of Clinical Pharmacy Sallam, Nahlah M.; Jordan University of Science and Technology, Department of Clinical Pharmacy Al-Khatib, Minas; Jordan University of Science and Technology, Department of Clinical Pharmacy Alshogran, Osama Y.; Jordan University of Science and Technology, Department of Clinical Pharmacy Bani Amer, Mohammad S.; Jordan University of Science and Technology, Department of Internal Medicine
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Medical management, Health services research, Health economics
Keywords:	Medication Reconciliation, Health Services, Health economics < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Health & safety < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

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Research Article

Clinical pharmacist-led medication reconciliation supplemented with medication review in chronic kidney disease admitted patients: a cost-benefit analysis

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Running Title: Cost-benefit of medication reconciliation in CKD

Number of Tables: 2

Number of Figures: 3

Keywords: Medication reconciliation, clinical pharmacist, cost-benefit, chronic kidney disease, Jordan.

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 cost-benefit ratio of medication reconciliation supplemented with medication review for inpatients with CKD, compared to 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 per-patient cost savings and cost avoidance.

Results: The total estimated cost of all DRPs in the absence of interventions (cost avoidance) was \$83,052.4 (average of \$584.88± 307.5 per patient); among which \$20,623.19 was attributed to medication discrepancies. The cost savings were estimated at -\$467.5. The supplemented medication reconciliation service was estimated to cost \$713.7. As a result, the estimated net benefit totaled \$81,871.15, averaging \$576.56 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 CKD patients is cost beneficial from the healthcare perspective in Jordan, an example of a low- and middle-income country (LMIC). This finding further confirms the pivotal role of clinical pharmacists in multidisciplinary healthcare teams.

Keywords: Medication reconciliation, clinical pharmacist, cost-benefit, chronic kidney disease, Jordan.

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.[1, 2] 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 (RRT), 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 hemodialysis patients management in 2010, with an average of annual cost of $9,979 per patient.[5] A study conducted in Lebanon reported the median cost for all CKD stages per year of $4,764.02 (IQR $2,475.24 - $23,455.61) in 2019 from a society perspective.[6] Studies highly recommend implementing programs and policies to reduce progression and complications of CKD to mitigate the growing disease burden especially in countries with limited resources. [7, 8]

Patients with CKD are very vulnerable to medication discrepancies and other Drug related problems (DRPs).[9, 10] Interestingly, many serious DRPs are preventable in CKD patients.[11] Developing DRPs increased the exposure to re-hospitalization, 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 organizations 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 drug-related problems (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. [17]

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 CKD patients. Examining the costs associated with drug-related problems (DRPs) during CKD hospitalizations will further emphasize 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 cost-benefits of implementing a clinical pharmacist-led service for supplemented medication reconciliation for admitted patients with CKD in Jordan, compared to 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 stages 2-5 CKD, who were admitted to two healthcare hospitals in Jordan: King Abdullah Hospital (KAUH) and Princess Basma Hospital (PBH). A clinical

pharmacist was responsible for providing supplemented medication reconciliation to CKD-admitted patients over four months (from February to May 2023). The costs and benefits during the study period were assessed in comparison to absence of this intervention. The primary outcome measure was the net benefit generated by the supplemented medication reconciliation service provided to CKD patients 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 health care 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 summarized in the Supplemental Material (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 pre-admission medication list. The pre-admission 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 hospitalization 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 hospitalization, and new medications planned to be started upon 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 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

In the cost-saving analysis, the decreased medication costs due to interventions and the increased medication costs and costs attributed to requesting labs were estimated. 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.[18] Acute therapy duration was estimated based on the clinical scenario, while chronic medication use was calculated over three months' time horizon. Public per-unit prices of drugs were obtained from the Jordan Food and Drug Administration (JFDA).[19] 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 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 [20] 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 Supplemental Material (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.[21] 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 CKD patients. 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 cause,[22] and the Medication Discrepancy Taxonomy (MedTax) system.[23] All financial data were extracted in Jordanian Dinar currency unit (JOD) and converted to United States Dollars (USD) at a rate of (1 JOD = 1.41 USD). 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 ± 20% of the base case cost. The average service time was varied over two SD of the mean, as calculated in this study. RCC was varied in the range (0.7 to 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 the public were not actively involved in the design, conduct, reporting, or dissemination plans of this research.

Ethics approval and consent to participate

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.

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) minutes, ranging from 26 to 60.5 minutes. The total time spent by the clinical pharmacist on the supplemented medication reconciliation over the four-month intervention period was 6117.1 minutes (101.95 hours). The average duration to accomplish a primary medication reconciliation service at admission was 15.79 ± 1.74 minutes. Though, the average time for medication review during the admission was 21.6 ± 4.30 minutes (ranged from 11.6 to 35.5 minutes) per patient. Medication reconciliation time at discharge averaged 3.58 ± 1.55 minutes 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 4-month study period was $713.7 ($7 × 101.95 hours).

Benefits of supplemented medication reconciliation

Estimated cost saving

The total increased medication cost was estimated to be $7479.26 (average of $52.67± 66.7 per patient) and lab needed total cost was estimated at $4198.42 (average of $29.57± 28.8 per patient). The decrease in medication costs owing to the intervention was $11,210.28(average of $78.95± 84.6 per patient). Total cost saving (after being adjusted with RCC of 0.8) = $11,210.28 - $7,479.26 - $4,198.42 = -$467.4 ($3.29 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 $340.20 (SD= $199.48). The assumed cost of a DRP was the estimated cost of two additional hospitalization days for patients with CKD in the current study [$680.4 multiplied by 0.8 RCC = $483.1]. 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 low-to 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 hospitalization days was $82.96 (SD=$57.7). The total estimated cost of all DRPs in the absence of interventions (cost avoidance) was $83,052.4, averaging $584.88 ± $307.5 per patient. Patient transfer related DRPs (medications discrepancies) were found to be the third most expensive cause-based domain in the PCNE classification of DRPs (V9.1), contributing to around 25% of the total cost avoidance ($20,623.19; $145.2 per patient). The greatest weight of discrepancies' cost avoidance was attributed to "drug omission" category ($12,693.54) followed by "discrepancy in frequency/strength/dose" ($4,612.56) and "drug addition" ($2,399.36), 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 (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 ($83,052.4) + cost saving (- $467.5) - cost of the intervention ($713.7) = $81,871.15]. 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).

Discussion

The major findings of the current study emphasize 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 to 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 with moderate to significant clinical impact. In a study conducted in Jordan among hospitalized

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).[24] In a study conducted in Canada, approximately half of the observed DRPs were moderate in severity in terms of causing harm to CKD patients.[25] The different scales used in severity assessment across the literature makes the comparison seems challenging. Overall, most recognized 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 CKD patients in terms of the cost-benefits associated with this service. A recent review of 47 studies among CKD patients also supports this finding; 7 studies approved the significant cost savings and 15 studies reported improvement in clinical outcomes due to clinical pharmacy care, including blood pressure, anemia, length of hospital stay, readmissions, kidney function, and other laboratory tests (i.e., 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 minutes. This is comparable to other studies that measured the time needed for medication reconciliation services: 44.4 ± 21.8,[26] 40 ±17.2 minutes,[27] and 48 minutes.[28, 29] 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 minutes (IQR 20-30 minutes).[30] The specific time for medication reconciliation at admission was roughly similar to our finding (15 minutes (IQR 10–21)) in two previous studies.[31, 32] Moreover, medication reconciliation at discharge after conducting medication reconciliation at admission was previously estimated to need approximately 3.5 minutes,[33] 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 nine studies with an average of 34.5 (±39.4) minutes.[34] This variability could be 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, 35-37] DRPs have been associated with high costs that affect patient safety and healthcare expenditures.[38]. Our study estimated the net benefit attributed to avoiding and resolving DRPs to be $81,871.15 over 4 months for a cumulative number of 142 CKD patients, averaging $576.56 per patient. Such remarkable benefit confirms the need of implementing supplemented medication reconciliation in CKD patients. Likewise, a recent retrospective cohort in the US among hemodialysis patients estimated cost saving from preventing DRPs to be $447,355 over a 6-month period of observation, attributing this benefit to performing medication reconciliation with medication review.[39] A Malaysian study measured the cost saving resulted from only dose adjustment in CKD inpatients to be $2,250 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.[40] This saved cost is considered much lower than the avoided cost resulting from renal dose adjustment in our study ($14,756 for 4 months, 94 dose adjustment interventions). An earlier prospective study conducted medication therapy evaluation by pharmacist found that the ratio of pharmaceutical care cost to healthcare system saving is $1 to $3.98 among end-stage renal disease patients in the USA.[41] This is much smaller compared to 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 $780,000 after implementing supplemented medication reconciliation with

patient education in internal medicine wards in Kansas ascribed to reducing readmissions.[42] A Chinese trial found cost saving attributed to antimicrobial dose adjustment (number of adjusted doses= 183) by a clinical pharmacist of $3,525 per patient with sepsis undergoing continuous dialysis in the ICU.[43] Wage rates and the cost of health care may differ widely across regions and institutions which make the comparison in cost is not sufficiently clear/straightforward. This also highlights the need to obtain relevant data from local or regional studies to better support the decisions of policy makers 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 $6,422.41.[44] In another study conducted in Jordan, clinical pharmacist intervention in the ICU reduced the total cost of drugs consumption by $211,574.90 over 10 months.[45] Still, the cost benefit of medication reconciliation among CKD patients 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.[46] 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.[20] 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 CKD admitted patients, with substantial cost avoidance compared to 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 toward evaluating the cost-benefit of such approaches.

Funding:

This work was supported by the Deanship of Scientific Research at the Jordan University of Science and Technology [grant number: 20220257]. The funding agency was not involved in the study design, conduct, writing, or decision to submit this article for publication.

Competing Interests:

The Authors declare that they have no conflicts of interest to disclose.

Author contributions

SA contributed to conceptualization, methodology, data curation, formal analysis, supervision, project administration, funding acquisition, and writing original draft. NS contributed to conceptualization, methodology, data curation, formal analysis, and writing original draft. MA and OA contributed to conceptualization, methodology, data curation, and writing- reviewing and editing. MB contributed to data curation and writing- reviewing and editing. SA is the guarantor for the manuscript and accepts full responsibility for the overall content.

Data availability statement

All data underlying this article are presented in the manuscript.

References

1. Small C, Kramer HJ, Griffin KA, et al. Non-dialysis dependent chronic kidney disease is associated with high total and out-of-pocket healthcare expenditures. *BMC Nephrol* 2017; 18: 3. 2017/01/07. DOI: 10.1186/s12882-016-0432-2.
2. Silva Junior GBD, Oliveira JGR, Oliveira MRB, et al. Global costs attributed to chronic kidney disease: a systematic review. *Rev Assoc Med Bras (1992)* 2018; 64: 1108-1116. 2018/12/21. DOI: 10.1590/1806-9282.64.12.1108.
3. Golestaneh L, Alvarez PJ, Reaven NL, et al. All-cause costs increase exponentially with increased chronic kidney disease stage. *Am J Manag Care* 2017; 23: S163-S172. 2017/10/06.
4. Saran R, Pearson A, Tilea A, et al. Burden and Cost of Caring for US Veterans With CKD: Initial Findings From the VA Renal Information System (VA-REINS). *Am J Kidney Dis* 2021; 77: 397-405. 2020/09/06. DOI: 10.1053/j.ajkd.2020.07.013.
5. Al-Shdaifat EA and Manaf MR. The economic burden of hemodialysis in Jordan. *Indian J Med Sci* 2013; 67: 103-116. 2013/12/12.
6. Aoun M, Helou E, Sleilaty G, et al. Cost of illness of chronic kidney disease in Lebanon: from the societal and third-party payer perspectives. *BMC Health Serv Res* 2022; 22: 586. 2022/05/04. DOI: 10.1186/s12913-022-07936-0.
7. Alshogran OY, Hajjar MH, Muflih SM, et al. The role of clinical pharmacist in enhancing hemodialysis patients' adherence and clinical outcomes: a randomized-controlled study. *Int J Clin Pharm* 2022; 44: 1169-1178. 2022/07/14. DOI: 10.1007/s11096-022-01453-0.
8. Rizk R, Hiligsmann M, Karavetian M, et al. A societal cost-of-illness study of hemodialysis in Lebanon. *J Med Econ* 2016; 19: 1157-1166. 2016/06/29. DOI: 10.1080/13696998.2016.1207653.
9. Chia BY, Cheen MHH, Gwee XY, et al. Outcomes of pharmacist-provided medication review in collaborative care for adult Singaporeans receiving hemodialysis. *Int J Clin Pharm* 2017; 39: 1031-1038. 20170821. DOI: 10.1007/s11096-017-0528-1.
10. Song YK, Jeong S, Han N, et al. Effectiveness of Clinical Pharmacist Service on Drug-Related Problems and Patient Outcomes for Hospitalized Patients with Chronic Kidney Disease: A Randomized Controlled Trial. *J Clin Med* 2021; 10 20210420. DOI: 10.3390/jcm10081788.
11. Laville SM, Gras-Champel V, Moragny J, et al. Adverse Drug Reactions in Patients with CKD. *Clin J Am Soc Nephrol* 2020; 15: 1090-1102. 2020/07/03. DOI: 10.2215/CJN.01030120.
12. Bishop MA, Cohen BA, Billings LK, et al. Reducing errors through discharge medication reconciliation by pharmacy services. *Am J Health Syst Pharm* 2015; 72: S120-126. 2015/08/15. DOI: 10.2146/sp150021.
13. Ernst FR and Grizzle AJ. Drug-related morbidity and mortality: updating the cost-of-illness model. *J Am Pharm Assoc (Wash)* 2001; 41: 192-199. 2001/04/12. DOI: 10.1016/s1086-5802(16)31229-3.
14. Alruqayb WS, Price MJ, Paudyal V, et al. Drug-Related Problems in Hospitalised Patients with Chronic Kidney Disease: A Systematic Review. *Drug Saf* 2021; 44: 1041-1058. 2021/09/13. DOI: 10.1007/s40264-021-01099-3.
15. Al Raiisi F, Stewart D, Fernandez-Llimos F, et al. Clinical pharmacy practice in the care of Chronic Kidney Disease patients: a systematic review. *Int J Clin Pharm* 2019; 41: 630-666. 2019/04/10. DOI: 10.1007/s11096-019-00816-4.
16. Onatibia-Astibia A, Malet-Larrea A, Mendizabal A, et al. The medication discrepancy detection service: A cost-effective multidisciplinary clinical approach. *Aten Primaria* 2021; 53: 43-50. 2020/10/01. DOI: 10.1016/j.aprim.2020.04.008.
17. *World Health Organization, Medication safety in transitions of care: technical report, 2019*.

18. Houso A, Hamdan M and Falana H. Cost benefit analysis of clinical pharmacist interventions in medical intensive care unit in Palestine medical complex: Prospective interventional study. *Saudi Pharm J* 2022; 30: 1718-1724. 2023/01/06. DOI: 10.1016/j.jsps.2022.09.017.

19. Jordan Food and Drug Administration (JFDA) http://jfda.jo/Pages/viewpage.aspx?pageID=336 (accessed July 2023).

20. Nesbit TW, Shermock KM, Bobek MB, et al. Implementation and pharmacoeconomic analysis of a clinical staff pharmacist practice model. *Am J Health Syst Pharm* 2001; 58: 784-790. DOI: 10.1093/ajhp/58.9.784.

21. Chen CC, Hsiao FY, Shen LJ, et al. The cost-saving effect and prevention of medication errors by clinical pharmacist intervention in a nephrology unit. *Medicine (Baltimore)* 2017; 96: e7883. DOI: 10.1097/MD.0000000000007883.

22. *Pharmaceutical Care Network Europe, The PCNE CLassification V 9.1. Pharmaceutical Care Network Europe, p Classification for Drug related problems*. 2020.

23. Almanasreh E, Moles R and Chen TF. The medication discrepancy taxonomy (MedTax): The development and validation of a classification system for medication discrepancies identified through medication reconciliation. *Res Social Adm Pharm* 2020; 16: 142-148. 20190414. DOI: 10.1016/j.sapharm.2019.04.005.

24. AbuRuz SM, Alrashdan Y, Jarab A, et al. Evaluation of the impact of pharmaceutical care service on hospitalized patients with chronic kidney disease in Jordan. *Int J Clin Pharm* 2013; 35: 780-789. 20130725. DOI: 10.1007/s11096-013-9806-8.

25. Quintana-Barcena P, Lord A, Lizotte A, et al. Prevalence and Management of Drug-Related Problems in Chronic Kidney Disease Patients by Severity Level: A Subanalysis of a Cluster Randomized Controlled Trial in Community Pharmacies. *J Manag Care Spec Pharm* 2018; 24: 173-181. DOI: 10.18553/jmcp.2018.24.2.173.

26. Buckley MS, Harinstein LM, Clark KB, et al. Impact of a clinical pharmacy admission medication reconciliation program on medication errors in "high-risk" patients. *The Annals of pharmacotherapy* 2013; 47: 1599-1610. 20131015. DOI: 10.1177/1060028013507428.

27. Mendes AE, Lombardi NF, Andrzejevski VS, et al. Medication reconciliation at patient admission: a randomized controlled trial. *Pharm Pract (Granada)* 2016; 14: 656. 20160315. DOI: 10.18549/PharmPract.2016.01.656.

28. Cadman B, Wright D, Bale A, et al. Pharmacist provided medicines reconciliation within 24 hours of admission and on discharge: a randomised controlled pilot study. *BMJ Open* 2017; 7: e013647. 20170316. DOI: 10.1136/bmjopen-2016-013647.

29. Neeman M, Dobrinas M, Maurer S, et al. Transition of care: A set of pharmaceutical interventions improves hospital discharge prescriptions from an internal medicine ward. *Eur J Intern Med* 2017; 38: 30-37. 20161125. DOI: 10.1016/j.ejim.2016.11.004.

30. Cornu P, Steurbaut S, Leysen T, et al. Effect of medication reconciliation at hospital admission on medication discrepancies during hospitalization and at discharge for geriatric patients. *The Annals of pharmacotherapy* 2012; 46: 484-494. 20120313. DOI: 10.1345/aph.1Q594.

31. Sebaaly J, Parsons LB, Pilch NA, et al. Clinical and Financial Impact of Pharmacist Involvement in Discharge Medication Reconciliation at an Academic Medical Center: A Prospective Pilot Study. *Hospital pharmacy* 2015; 50: 505-513. DOI: 10.1310/hpj5006-505.

32. Vira T, Colquhoun M and Etchells E. Reconcilable differences: correcting medication errors at hospital admission and discharge. *Qual Saf Health Care* 2006; 15: 122-126. DOI: 10.1136/qshc.2005.015347.

33. Al-Jazairi AS, Al-Suhaibani LK, Al-Mehizia RA, et al. Impact of a medication reconciliation program on cardiac surgery patients. *Asian Cardiovasc Thorac Ann* 2017; 25: 579-585. 20171012. DOI: 10.1177/0218492317738382.

34. Fernandes BD, Almeida P, Foppa AA, et al. Pharmacist-led medication reconciliation at patient discharge: A scoping review. *Res Social Adm Pharm* 2020; 16: 605-613. 20190801. DOI: 10.1016/j.sapharm.2019.08.001.
35. Centers for Disease Control and Prevention. Chronic Kidney Disease in the United States, 2023. Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention; 2023. Available at: https://www.cdc.gov/kidneydisease/publications-resources/ckd-national-facts.html.
36. prevention Cfdca. Chronic Kidney Disease in the United States, 2021. 2021.
37. Nguyen-Thi HY, Le-Phuoc TN, Tri Phat N, et al. The Economic Burden of Chronic Kidney Disease in Vietnam. *Health Serv Insights* 2021; 14: 11786329211036011. 20210728. DOI: 10.1177/11786329211036011.
38. Slawomirski L, Auraaen A and Klazinga NS. The economics of patient safety: strengthening a value-based approach to reducing patient harm at national level. 2017.
39. Daifi C, Feldpausch B, Roa PA, et al. Implementation of a Clinical Pharmacist in a Hemodialysis Facility: A Quality Improvement Report. *Kidney Med* 2021; 3: 241-247 e241. 20210210. DOI: 10.1016/j.xkme.2020.11.015.
40. Hassan Y, Al-Ramahi RJ, Aziz NA, et al. Impact of a renal drug dosing service on dose adjustment in hospitalized patients with chronic kidney disease. *The Annals of pharmacotherapy* 2009; 43: 1598-1605. 20090923. DOI: 10.1345/aph.1M187.
41. Manley HJ and Carroll CA. The clinical and economic impact of pharmaceutical care in end-stage renal disease patients. *Semin Dial* 2002; 15: 45-49. DOI: 10.1046/j.1525-139x.2002.00014.x.
42. Anderegg SV, Wilkinson ST, Couldry RJ, et al. Effects of a hospitalwide pharmacy practice model change on readmission and return to emergency department rates. *Am J Health Syst Pharm* 2014; 71: 1469-1479. DOI: 10.2146/ajhp130686.
43. Jiang SP, Zhu ZY, Ma KF, et al. Impact of pharmacist antimicrobial dosing adjustments in septic patients on continuous renal replacement therapy in an intensive care unit. *Scand J Infect Dis* 2013; 45: 891-899. 20130912. DOI: 10.3109/00365548.2013.827338.
44. Al-Qudah RA, Al-Badriyeh D, Al-Ali FM, et al. Cost-benefit analysis of clinical pharmacist intervention in preventing adverse drug events in the general chronic diseases outpatients. *J Eval Clin Pract* 2020; 26: 115-124. 20190624. DOI: 10.1111/jep.13209.
45. Aljbouri TM, Alkhawaldeh MS, Abu-Rumman AE, et al. Impact of clinical pharmacist on cost of drug therapy in the ICU. *Saudi Pharm J* 2013; 21: 371-374. DOI: 10.1016/j.jsps.2012.12.004.
46. Abushanab D, Gulied A, Hamad A, et al. Cost savings and cost avoidance with the inpatient clinical pharmacist interventions in a tertiary cancer care hospital. *J Oncol Pharm Pract* 2023: 10781552231160275. 20230322. DOI: 10.1177/10781552231160275.

Figure Legends:

Figure 1: The cost-benefit analysis model.

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

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

Table 1: Cost avoidance per cause-based domains in the PCNE classification of DRPs (V9.1).

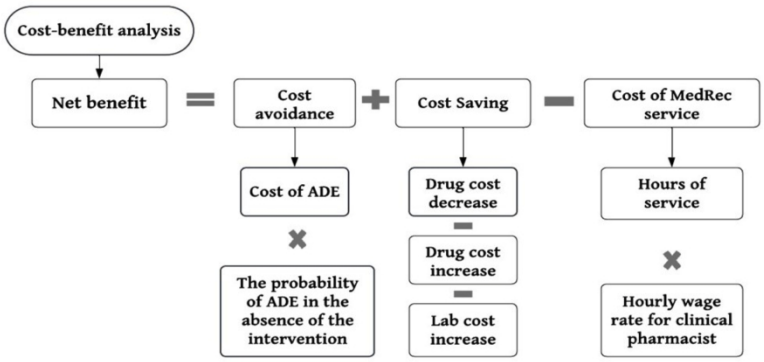
Primary domain	Cause	Cost avoidance ($)	Total ($)
Drug selection	Inappropriate drug according to guidelines/formulary	12,480.17	25,588.49
	No or incomplete drug treatment despite existing indication	8,645.98	
	No indication for drug	2,295.94	
	Inappropriate combination of drugs or drugs and dietary supplements	1,916.01	
	Too many different drugs/active ingredients prescribed for indication	250.39	
	Inappropriate duplication of therapeutic group or active ingredient	250.38	
Dose selection	Drug dose of a single active ingredient too high	13,710.33	21,141.39
	Dosage regimen too frequent	5,284.26	
	Drug dose too low	2,146.80	
Patient transfer related (discrepancies)	Drug omission	12,693.54	20,623.2
	Discrepancy in the strength and/or frequency and/or number of units of dosage form and/or total daily dose	4,612.57	
	Drug addition	2,399.36	
	Therapeutic class substitution	436.54	
	Drug duplication	337.48	
	Discrepancy in the dosage form/route of administration	143.70	
Drug use process	Inappropriate timing of administration or dosing intervals by a health professional	2,624.71	2,777.12
	Drug administered via wrong route by a health professional	152.41	
Treatment duration	Duration of treatment too long	273.25	469.21
	Duration of treatment too short	195.96	
Drug form	Inappropriate drug form/formulation	114.30	114.30
Other	Addition of a lab test	10,531.5	12,088.25
	No or inappropriate outcome monitoring	1,556.75	
Total			83,052.34

Table 2: Results of cost-benefit analysis

Outcome	Total ($)	Average per patient $ (M± SD)
Intervention cost over 4 months	713.7	5.03± 0.77
Cost avoidance of all DRPs	83,052.40	584.88± 307.5
Total cost saving	-467.4 (Negative net saving)	3.29
Drug cost decrease	11210.28	78.95± 84.6
Drug cost increase	7479.26	52.67± 66.7
Lab cost increase	4198.42	29.57± 28.8
Net benefit over the study period (4 months)	81,871.25	576.56
Benefit to cost ratio	115.7:1	

M± SD: Mean ± Standard deviation

The total number of patients is 142.



The cost-benefit analysis model

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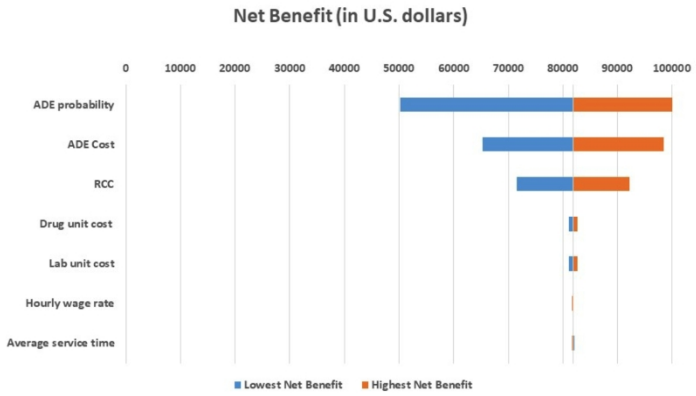
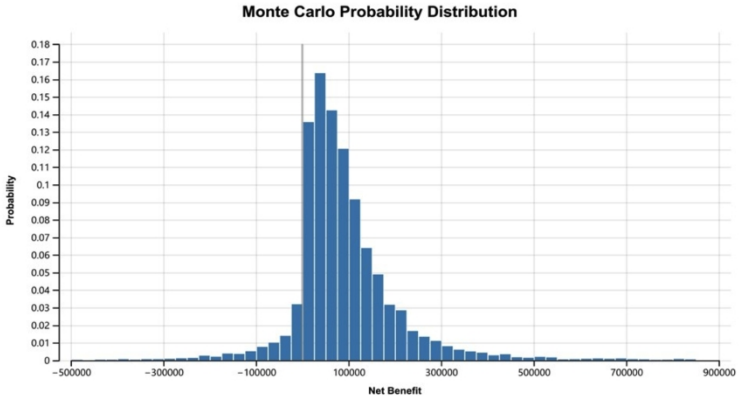


Tornado diagram illustrating the impact of various parameters on the net benefit of supplemented medication reconciliation service (one-way sensitivity analysis)

298x168mm (300 x 300 DPI)



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

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Research Article

Title: Clinical pharmacist-led medication reconciliation supplemented with medication review in chronic kidney disease admitted patients: a cost-benefit analysis

Journal: BMJ Open.

Table S1: Patient demographics and clinical characteristics of the study sample.

Variable	Study sample N(%) N = 142
Gender n (%)	
Female	53 (37.32)
Male	89 (62.68)
Age, years (M± SD)	57.16 ±15.96
BMI n (%)	
<18.5	6 (4.23)
18.5 -24.9	41 (28.87)
25-29.9	42 (29.58)
> 29.9	53 (37.32)
Marital status	
Married	109 (76.76)
Not married	33 (23.24)
Smoking status	
Yes	43 (30.28)
No	75 (52.82)
Ex-smoker	24 (16.90)
Educational level	
Not educated	20 (14.08)
School	93 (65.49)
University/higher education	29 (20.42)
Employment status	
Employed	26 (18.31)
Retired	32 (22.54)
Unemployed	84 (59.15)
Occupation	
Medical	3 (2.11)
Non-medical	64 (45.07)
No	75 (52.82)
Monthly income (JOD)	
<500	110 (77.46)
500 -1000	29 (20.42)
>1000	3 (2.11)

Reason for admission	
AKI on Top of CKD related problems	42 (29.58)
CKD/dialysis related problems	71 (50.0)
Others	29 (20.42)
CKD stage	
Stage 2	2 (1.41)
Stage 3a	3 (2.11)
Stage 3b	12 (8.45)
Stage 4	32 (22.54)
Stage 5	93 (65.5)
Years of dialysis (M± SD)	2.33 ± 3.66
Years of CKD (M± SD)	5.02 ± 6.80
Number of comorbidities (M± SD)	6.36 ± 2.18
CCI (M ± SD)	6.08 ± 2.93
Number of medications at admission (M± SD)	9.58 ± 3.07
Number of medications at discharge (M± SD)	9.24 ± 4.34
Death at discharge	5 (3.52)
Length of stay	8.94 ± 8.59

Abbreviation: BMI: Body Mass Index, M± SD: Mean ± Standard deviation, JOD: Jordanian Dinar , CKD: Chronic Kidney Disease, AKI: Acute Kidney Disease, CCI: Charlson Comorbidity Index.

One JOD is equivalent to 1.41 US Dollars (USD).

Table S2: Examples of the studied clinical cases with the probability score to cause ADEs.

A patient had a recent myocardial infarction (MI) and had previously undergone stent placement for the main coronary artery. She was taking febuxostat for gout. The clinical pharmacist recommended switching from febuxostat to allopurinol. (Black box warning)	High (0.6)
A female patient on hemodialysis, has a hemoglobin (Hb) level of 12 and a history of stroke. She was on alpha epoetin 4000 units prescribed every other day (EOD). (Black box warning)	High (0.6)
A 91-year-old female patient with CKD stage 5 (baseline serum creatinine is 500 mmol/l). Dialysis was delayed due to her age. The patient is experiencing uremia, including vomiting symptoms. She was prescribed metoclopramide 10 mg intravenously every 8 hours, which is a high dose considering her condition. Additionally, she is taking trimetazidine, which has a serious interaction with metoclopramide (category X). It is important to note that trimetazidine is contraindicated in patients with a GFR <30.	Medium (0.4)
A patient has osteoporosis and is undergoing hemodialysis. Initially, she was prescribed alendronate, but the clinical pharmacist recommended switching to denosumab. The physician stopped the alendronate as advised but could not provide denosumab due to economic issues. Subsequently, the patient visited the outpatient clinic (OPC) due to bone pain, and there she received denosumab treatment.	Medium (0.4), Low (0.1)
A patient has a CrCl (Creatinine Clearance) of 13, and he is currently taking fenofibrate. Additionally, the triglyceride level is less than 250 mg/dL.	Medium (0.4)
A patient underwent upper endoscopy, which revealed mild gastritis. There were no available tests for H. pylori, and the patient's serum creatinine level was 500 mmol/l (CrCl <15). Nevertheless, upon discharge, the patient was	Medium (0.4)

prescribed amoxicillin 1g twice daily and clarithromycin 500mg twice daily without renal adjustment and without confirming the diagnosis.	
A patient has AKI on top of CKD and has been experiencing severe vomiting for over a week. Upon admission, the patient's home medication included metoclopramide 10 mg three times daily taken orally. However, after admission, the route was changed to intravenous 10 mg TID (not renal dose) without improvement, the dose was changed to metoclopramide intravenously at 20 mg three times daily, which is considered too high. The clinical pharmacist recommended discontinuing metoclopramide and administering ondansetron as an alternative.	Medium (0.4)
A patient is undergoing hemodialysis and was diagnosed with deep vein thrombosis (DVT). Upon discharge, she was prescribed a therapeutic dose of Enoxaparin. The clinical pharmacist recommended switching to apixaban.	Medium (0.4)
A patient was admitted for liver cirrhosis, baseline CrCl 32, AKI, diabetes mellitus (DM), and recently diagnosed depression. He was initially admitted while taking metformin 500mg once daily. However, upon discharge, his medication regimen included metformin 850mg three times daily, mirtazapine, spironolactone, and hydrochlorothiazide. The clinical pharmacist was unable to reach the responsible physician to discuss the changes. Consequently, the patient was readmitted after 5 days due to diarrhea and hyponatremia.	Medium (0.4)
A patient has a UTI and is currently taking ciprofloxacin, calcium carbonate, and ferrous gluconate twice daily, both at 6 pm and 6 am, all by oral route.	Low (0.1)
A patient admitted with severe hypophosphatemia; the physician initially recorded that the patient was on calcium carbonate 500mg BID. With medication reconciliation we found that the actual home dose was calcium carbonate 1g TID, along with sevelamer TID, which was obtained from outside the hospital (and was not known by the physician). Resolving these discrepancies with the physician led to a change in the diagnosis.	Low (0.1)

A patient has been taking Combivent® every 8 hours for over than 2 weeks without any valid indication.	Low (0.1)
A 32-year-old patient has type 1 diabetes mellitus (DM1), end-stage renal disease (ESRD), partial retinopathy, and uncontrolled DM with recurrent hypoglycemia. Upon admission, she was using pre-mixed insulin. The clinical pharmacist suggested switching to a basal-bolus insulin regimen.	Low (0.1)
A patient was discharged without some of his hypoglycemic and antihypertensive agents unintentionally.	Low (0.1)
A patient on HD, was on famotidine 40mg once daily at home. Was not documented.	Very low (0.01)

Table S3: Average cost avoidance per patient across cause-based domains in the PCNE classification of DRPs (Version 9.1).

Primary domain	Cause	Cost avoidance ($) Average per patient	Number of patients
Drug selection	Inappropriate drug according to guidelines/formulary	195.0	64
	No or incomplete drug treatment despite existing indication	139.5	62
	No indication for drug	71.7	32
	Inappropriate combination of drugs or drugs and dietary supplements	174.2	11
	Too many different drugs/active ingredients prescribed for indication	83.5	3
	Inappropriate duplication of therapeutic group or active ingredient	83.5	3
Dose selection	Drug dose of a single active ingredient too high	207.7	66
	Dosage regimen too frequent	83.9	63
	Drug dose too low	89.4	24
Patient transfer related (discrepancies)	Drug omission	133.6	95
	Discrepancy in the strength and/or frequency and/or number of units of dosage form and/or total daily dose	118.3	39
	Drug addition	150.0	16
	Therapeutic class substitution	24.3	18

	Drug duplication	84.4	4
	Discrepancy in the dosage form/route of administration	71.9	2
Drug use process	Inappropriate timing of administration or dosing intervals by a health professional	77.2	34
	Drug administered via wrong route by a health professional	152.4	1
Treatment duration	Duration of treatment too long	91.1	3
	Duration of treatment too short	65.3	3
Drug form	Inappropriate drug form/formulation	38.1	3
Others	Addition of a lab test	118.3	89
	No or inappropriate outcome monitoring	91.6	17

BMJ Open

Clinical pharmacist-led medication reconciliation supplemented with medication review in chronic kidney disease admitted patients: a cost-benefit analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2024-087232.R3
Article Type:	Original research
Date Submitted by the Author:	22-Dec-2024
Complete List of Authors:	Altawalbeh, Shoroq ; Jordan University of Science and Technology, Department of Clinical Pharmacy Sallam, Nahlah M.; Jordan University of Science and Technology, Department of Clinical Pharmacy Al-Khatib, Minas; Jordan University of Science and Technology, Department of Clinical Pharmacy Alshogran, Osama Y.; Jordan University of Science and Technology, Department of Clinical Pharmacy Bani Amer, Mohammad S.; Jordan University of Science and Technology, Department of Internal Medicine
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Medical management, Health services research, Health economics
Keywords:	Medication Reconciliation, Health Services, Health economics < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Health & safety < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

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Research Article

Clinical pharmacist-led medication reconciliation supplemented with medication review in chronic kidney disease admitted patients: a cost-benefit analysis

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Running Title: Cost-benefit of medication reconciliation in CKD

Number of Tables: 2

Number of Figures: 3

Keywords: Medication reconciliation, clinical pharmacist, cost-benefit, chronic kidney disease, Jordan.

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 cost-benefit ratio of medication reconciliation supplemented with medication review for inpatients with CKD, compared to 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 per-patient 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 $20,623 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 totaled $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 CKD patients is cost beneficial from the healthcare perspective in Jordan, an example of a low- and middle-income country (LMIC). This finding further confirms the pivotal role of clinical pharmacists in multidisciplinary healthcare teams.

Keywords: Medication reconciliation, clinical pharmacist, cost-benefit, chronic kidney disease, Jordan.

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.[1, 2] 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 (RRT), 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 hemodialysis patients management in 2010, with an average of annual cost of $9,979 per patient.[5] A study conducted in Lebanon reported the median cost for all CKD stages per year of $4,764.02 (IQR $2,475.24 - $23,455.61) in 2019 from a society perspective.[6] Studies highly recommend implementing programs and policies to reduce progression and complications of CKD to mitigate the growing disease burden especially in countries with limited resources. [7, 8]

Patients with CKD are very vulnerable to medication discrepancies and other Drug related problems (DRPs).[9, 10] Interestingly, many serious DRPs are preventable in CKD patients.[11] Developing DRPs increased the exposure to re-hospitalization, 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 organizations 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 drug-related problems (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. [17]

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 CKD patients. Examining the costs associated with drug-related problems (DRPs) during CKD hospitalizations will further emphasize 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 cost-benefits of implementing a clinical pharmacist-led service for supplemented medication reconciliation for admitted patients with CKD in Jordan, compared to 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 stages 2-5 CKD, who were admitted to two healthcare hospitals in Jordan: King Abdullah Hospital (KAUH) and Princess Basma Hospital (PBH). A clinical

pharmacist was responsible for providing supplemented medication reconciliation to CKD-admitted patients over four months (from February to May 2023). The costs and benefits during the study period were assessed in comparison to absence of this intervention. The primary outcome measure was the net benefit generated by the supplemented medication reconciliation service provided to CKD patients 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 health care 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 summarized in the Supplemental Material (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 pre-admission medication list. The pre-admission 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 hospitalization 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 hospitalization, and new medications planned to be started upon 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 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 = reduced drug costs – (increased drug costs + increased lab 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.[18] Acute therapy duration was estimated based on the clinical scenario, while chronic medication use was calculated over three months' time horizon. Public per-unit prices of drugs were obtained from the Jordan Food and Drug Administration (JFDA).[19] 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 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 [20] 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 Supplemental Material (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.[21] 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 CKD patients. 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 cause,[22] and the Medication Discrepancy Taxonomy (MedTax) system.[23] All financial data were extracted in Jordanian Dinar currency unit (JOD) and converted to United States Dollars (USD) at a rate of (1 JOD = 1.41 USD). 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 ± 20% of the base case cost. The average service time was varied over two SD of the mean, as calculated in this study. RCC was varied in the range (0.7 to 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 the public were not actively involved in the design, conduct, reporting, or dissemination plans of this research.

Ethics approval and consent to participate

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.

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) minutes, ranging from 26 to 60.5 minutes. The total time spent by the clinical pharmacist on the supplemented medication reconciliation over the four-month intervention period was 6117.1 minutes (101.95 hours). The average duration to accomplish a primary medication reconciliation service at admission was 15.79 ± 1.74 minutes. Though, the average time for medication review during the admission was 21.6 ± 4.30 minutes (ranged from 11.6 to 35.5 minutes) per patient. Medication reconciliation time at discharge averaged 3.58 ± 1.55 minutes 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 4-month study period was $713.7 ($7 × 101.95 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 $11,210. Total cost saving = $11,210 - $7,479 - $4,198 = -$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 hospitalization days for patients with CKD in the current study [$680 multiplied by 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 low-to 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 hospitalization 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 (medications discrepancies) were found to be the third most expensive cause-based domain in the PCNE classification of DRPs (V9.1), contributing to around 25% of the total cost avoidance ($20,623; $145 per patient). The greatest

weight of discrepancies' cost avoidance was attributed to "drug omission" category ($12,694) followed by "discrepancy in frequency/strength/dose" ($4,613) and "drug addition" ($2,399), 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 (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) = $81,871]. 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).

Discussion

The major findings of the current study emphasize 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 to 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 with moderate to significant clinical impact. In a study conducted in Jordan among hospitalized 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).[24] In a study conducted in Canada, approximately half of the observed DRPs were moderate in severity in terms of causing harm to CKD patients.[25] The different scales used in severity assessment across the literature makes the comparison seems challenging. Overall, most recognized 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 CKD patients in terms of the cost-benefits associated with this service. A recent review of 47 studies among CKD patients also supports this finding; 7 studies approved the significant cost savings and 15 studies reported improvement in clinical outcomes due to clinical pharmacy care, including blood pressure, anemia, length of hospital stay, readmissions, kidney function, and other laboratory tests (i.e., 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 minutes. This is comparable to other studies that measured the time needed for medication reconciliation services: 44.4 ± 21.8,[26]

40 ±17.2 minutes,[27] and 48 minutes.[28, 29] 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 minutes (IQR 20-30 minutes).[30] The specific time for medication reconciliation at admission was roughly similar to our finding (15 minutes (IQR 10–21)) in two previous studies.[31, 32] Moreover, medication reconciliation at discharge after conducting medication reconciliation at admission was previously estimated to need approximately 3.5 minutes,[33] 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 nine studies with an average of 34.5 (±39.4) minutes.[34] This variability could be 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, 35-37] DRPs have been associated with high costs that affect patient safety and healthcare expenditures.[38]. Our study estimated the net benefit attributed to avoiding and resolving DRPs to be $81,871.15 over 4 months for a cumulative number of 142 CKD patients, averaging $576.56 per patient. Such remarkable benefit confirms the need of implementing supplemented medication reconciliation in CKD patients. Likewise, a recent retrospective cohort in the US among hemodialysis patients estimated cost saving from preventing DRPs to be $447,355 over a 6-month period of observation, attributing this benefit to performing medication reconciliation with medication review.[39] A Malaysian study measured the cost saving resulted from only dose adjustment in CKD inpatients to be $2,250 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.[40] This saved cost is considered much lower than the avoided cost resulting from renal dose adjustment in our study ($14,756 for 4 months, 94 dose adjustment interventions). An earlier prospective study

conducted medication therapy evaluation by pharmacist found that the ratio of pharmaceutical care cost to healthcare system saving is $1 to $3.98 among end-stage renal disease patients in the USA.[41] This is much smaller compared to 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 $780,000 after implementing supplemented medication reconciliation with patient education in internal medicine wards in Kansas ascribed to reducing readmissions.[42] A Chinese trial found cost saving attributed to antimicrobial dose adjustment (number of adjusted doses= 183) by a clinical pharmacist of $3,525 per patient with sepsis undergoing continuous dialysis in the ICU.[43] Wage rates and the cost of health care may differ widely across regions and institutions which make the comparison in cost is not sufficiently clear/straightforward. This also highlights the need to obtain relevant data from local or regional studies to better support the decisions of policy makers 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 $6,422.41.[44] In another study conducted in Jordan, clinical pharmacist intervention in the ICU reduced the total cost of drugs consumption by $211,574.90 over 10 months.[45] Still, the cost benefit of medication reconciliation among CKD patients 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.[46] 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.[20] 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 CKD admitted patients, with substantial cost avoidance compared to 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 toward evaluating the cost-benefit of such approaches.

Funding:

This work was supported by the Deanship of Scientific Research at the Jordan University of Science and Technology [grant number: 20220257]. The funding agency was not involved in the study design, conduct, writing, or decision to submit this article for publication.

Competing Interests:

The Authors declare that they have no conflicts of interest to disclose.

Author contributions

SA contributed to conceptualization, methodology, data curation, formal analysis, supervision, project administration, funding acquisition, and writing original draft. NS contributed to conceptualization, methodology, data curation, formal analysis, and writing original draft. MA and OA contributed to conceptualization, methodology, data curation, and writing- reviewing and editing. MB contributed to data curation and writing- reviewing and editing. SA is the guarantor for the manuscript and accepts full responsibility for the overall content.

Data availability statement

All data underlying this article are presented in the manuscript.

References

1. Small C, Kramer HJ, Griffin KA, et al. Non-dialysis dependent chronic kidney disease is associated with high total and out-of-pocket healthcare expenditures. *BMC Nephrol* 2017; 18: 3. 2017/01/07. DOI: 10.1186/s12882-016-0432-2.
2. Silva Junior GBD, Oliveira JGR, Oliveira MRB, et al. Global costs attributed to chronic kidney disease: a systematic review. *Rev Assoc Med Bras (1992)* 2018; 64: 1108-1116. 2018/12/21. DOI: 10.1590/1806-9282.64.12.1108.
3. Golestaneh L, Alvarez PJ, Reaven NL, et al. All-cause costs increase exponentially with increased chronic kidney disease stage. *Am J Manag Care* 2017; 23: S163-S172. 2017/10/06.
4. Saran R, Pearson A, Tilea A, et al. Burden and Cost of Caring for US Veterans With CKD: Initial Findings From the VA Renal Information System (VA-REINS). *Am J Kidney Dis* 2021; 77: 397-405. 2020/09/06. DOI: 10.1053/j.ajkd.2020.07.013.
5. Al-Shdaifat EA and Manaf MR. The economic burden of hemodialysis in Jordan. *Indian J Med Sci* 2013; 67: 103-116. 2013/12/12.
6. Aoun M, Helou E, Sleilaty G, et al. Cost of illness of chronic kidney disease in Lebanon: from the societal and third-party payer perspectives. *BMC Health Serv Res* 2022; 22: 586. 2022/05/04. DOI: 10.1186/s12913-022-07936-0.
7. Alshogran OY, Hajjar MH, Muflih SM, et al. The role of clinical pharmacist in enhancing hemodialysis patients' adherence and clinical outcomes: a randomized-controlled study. *Int J Clin Pharm* 2022; 44: 1169-1178. 2022/07/14. DOI: 10.1007/s11096-022-01453-0.
8. Rizk R, Hiligsmann M, Karavetian M, et al. A societal cost-of-illness study of hemodialysis in Lebanon. *J Med Econ* 2016; 19: 1157-1166. 2016/06/29. DOI: 10.1080/13696998.2016.1207653.
9. Chia BY, Cheen MHH, Gwee XY, et al. Outcomes of pharmacist-provided medication review in collaborative care for adult Singaporeans receiving hemodialysis. *Int J Clin Pharm* 2017; 39: 1031-1038. 20170821. DOI: 10.1007/s11096-017-0528-1.
10. Song YK, Jeong S, Han N, et al. Effectiveness of Clinical Pharmacist Service on Drug-Related Problems and Patient Outcomes for Hospitalized Patients with Chronic Kidney Disease: A Randomized Controlled Trial. *J Clin Med* 2021; 10 20210420. DOI: 10.3390/jcm10081788.
11. Laville SM, Gras-Champel V, Moragny J, et al. Adverse Drug Reactions in Patients with CKD. *Clin J Am Soc Nephrol* 2020; 15: 1090-1102. 2020/07/03. DOI: 10.2215/CJN.01030120.
12. Bishop MA, Cohen BA, Billings LK, et al. Reducing errors through discharge medication reconciliation by pharmacy services. *Am J Health Syst Pharm* 2015; 72: S120-126. 2015/08/15. DOI: 10.2146/sp150021.
13. Ernst FR and Grizzle AJ. Drug-related morbidity and mortality: updating the cost-of-illness model. *J Am Pharm Assoc (Wash)* 2001; 41: 192-199. 2001/04/12. DOI: 10.1016/s1086-5802(16)31229-3.
14. Alruqayb WS, Price MJ, Paudyal V, et al. Drug-Related Problems in Hospitalised Patients with Chronic Kidney Disease: A Systematic Review. *Drug Saf* 2021; 44: 1041-1058. 2021/09/13. DOI: 10.1007/s40264-021-01099-3.
15. Al Raiisi F, Stewart D, Fernandez-Llimos F, et al. Clinical pharmacy practice in the care of Chronic Kidney Disease patients: a systematic review. *Int J Clin Pharm* 2019; 41: 630-666. 2019/04/10. DOI: 10.1007/s11096-019-00816-4.
16. Onatibia-Astibia A, Malet-Larrea A, Mendizabal A, et al. The medication discrepancy detection service: A cost-effective multidisciplinary clinical approach. *Aten Primaria* 2021; 53: 43-50. 2020/10/01. DOI: 10.1016/j.aprim.2020.04.008.
17. *World Health Organization, Medication safety in transitions of care: technical report, 2019*.

18. Houso A, Hamdan M and Falana H. Cost benefit analysis of clinical pharmacist interventions in medical intensive care unit in Palestine medical complex: Prospective interventional study. *Saudi Pharm J* 2022; 30: 1718-1724. 2023/01/06. DOI: 10.1016/j.jsps.2022.09.017.

19. Jordan Food and Drug Administration (JFDA) http://jfda.jo/Pages/viewpage.aspx?pageID=336 (accessed July 2023).

20. Nesbit TW, Shermock KM, Bobek MB, et al. Implementation and pharmacoeconomic analysis of a clinical staff pharmacist practice model. *Am J Health Syst Pharm* 2001; 58: 784-790. DOI: 10.1093/ajhp/58.9.784.

21. Chen CC, Hsiao FY, Shen LJ, et al. The cost-saving effect and prevention of medication errors by clinical pharmacist intervention in a nephrology unit. *Medicine (Baltimore)* 2017; 96: e7883. DOI: 10.1097/MD.0000000000007883.

22. *Pharmaceutical Care Network Europe, The PCNE CLassification V 9.1. Pharmaceutical Care Network Europe, p Classification for Drug related problems*. 2020.

23. Almanasreh E, Moles R and Chen TF. The medication discrepancy taxonomy (MedTax): The development and validation of a classification system for medication discrepancies identified through medication reconciliation. *Res Social Adm Pharm* 2020; 16: 142-148. 20190414. DOI: 10.1016/j.sapharm.2019.04.005.

24. AbuRuz SM, Alrashdan Y, Jarab A, et al. Evaluation of the impact of pharmaceutical care service on hospitalized patients with chronic kidney disease in Jordan. *Int J Clin Pharm* 2013; 35: 780-789. 20130725. DOI: 10.1007/s11096-013-9806-8.

25. Quintana-Barcena P, Lord A, Lizotte A, et al. Prevalence and Management of Drug-Related Problems in Chronic Kidney Disease Patients by Severity Level: A Subanalysis of a Cluster Randomized Controlled Trial in Community Pharmacies. *J Manag Care Spec Pharm* 2018; 24: 173-181. DOI: 10.18553/jmcp.2018.24.2.173.

26. Buckley MS, Harinstein LM, Clark KB, et al. Impact of a clinical pharmacy admission medication reconciliation program on medication errors in "high-risk" patients. *The Annals of pharmacotherapy* 2013; 47: 1599-1610. 20131015. DOI: 10.1177/1060028013507428.

27. Mendes AE, Lombardi NF, Andrzejevski VS, et al. Medication reconciliation at patient admission: a randomized controlled trial. *Pharm Pract (Granada)* 2016; 14: 656. 20160315. DOI: 10.18549/PharmPract.2016.01.656.

28. Cadman B, Wright D, Bale A, et al. Pharmacist provided medicines reconciliation within 24 hours of admission and on discharge: a randomised controlled pilot study. *BMJ Open* 2017; 7: e013647. 20170316. DOI: 10.1136/bmjopen-2016-013647.

29. Neeman M, Dobrinas M, Maurer S, et al. Transition of care: A set of pharmaceutical interventions improves hospital discharge prescriptions from an internal medicine ward. *Eur J Intern Med* 2017; 38: 30-37. 20161125. DOI: 10.1016/j.ejim.2016.11.004.

30. Cornu P, Steurbaut S, Leysen T, et al. Effect of medication reconciliation at hospital admission on medication discrepancies during hospitalization and at discharge for geriatric patients. *The Annals of pharmacotherapy* 2012; 46: 484-494. 20120313. DOI: 10.1345/aph.1Q594.

31. Sebaaly J, Parsons LB, Pilch NA, et al. Clinical and Financial Impact of Pharmacist Involvement in Discharge Medication Reconciliation at an Academic Medical Center: A Prospective Pilot Study. *Hospital pharmacy* 2015; 50: 505-513. DOI: 10.1310/hpj5006-505.

32. Vira T, Colquhoun M and Etchells E. Reconcilable differences: correcting medication errors at hospital admission and discharge. *Qual Saf Health Care* 2006; 15: 122-126. DOI: 10.1136/qshc.2005.015347.

33. Al-Jazairi AS, Al-Suhaibani LK, Al-Mehizia RA, et al. Impact of a medication reconciliation program on cardiac surgery patients. *Asian Cardiovasc Thorac Ann* 2017; 25: 579-585. 20171012. DOI: 10.1177/0218492317738382.

34. Fernandes BD, Almeida P, Foppa AA, et al. Pharmacist-led medication reconciliation at patient discharge: A scoping review. *Res Social Adm Pharm* 2020; 16: 605-613. 20190801. DOI: 10.1016/j.sapharm.2019.08.001.
35. Centers for Disease Control and Prevention. Chronic Kidney Disease in the United States, 2023. Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention; 2023. Available at: https://www.cdc.gov/kidneydisease/publications-resources/ckd-national-facts.html.
36. prevention Cfdca. Chronic Kidney Disease in the United States, 2021. 2021.
37. Nguyen-Thi HY, Le-Phuoc TN, Tri Phat N, et al. The Economic Burden of Chronic Kidney Disease in Vietnam. *Health Serv Insights* 2021; 14: 11786329211036011. 20210728. DOI: 10.1177/11786329211036011.
38. Slawomirski L, Auraaen A and Klazinga NS. The economics of patient safety: strengthening a value-based approach to reducing patient harm at national level. 2017.
39. Daifi C, Feldpausch B, Roa PA, et al. Implementation of a Clinical Pharmacist in a Hemodialysis Facility: A Quality Improvement Report. *Kidney Med* 2021; 3: 241-247 e241. 20210210. DOI: 10.1016/j.xkme.2020.11.015.
40. Hassan Y, Al-Ramahi RJ, Aziz NA, et al. Impact of a renal drug dosing service on dose adjustment in hospitalized patients with chronic kidney disease. *The Annals of pharmacotherapy* 2009; 43: 1598-1605. 20090923. DOI: 10.1345/aph.1M187.
41. Manley HJ and Carroll CA. The clinical and economic impact of pharmaceutical care in end-stage renal disease patients. *Semin Dial* 2002; 15: 45-49. DOI: 10.1046/j.1525-139x.2002.00014.x.
42. Anderegg SV, Wilkinson ST, Couldry RJ, et al. Effects of a hospitalwide pharmacy practice model change on readmission and return to emergency department rates. *Am J Health Syst Pharm* 2014; 71: 1469-1479. DOI: 10.2146/ajhp130686.
43. Jiang SP, Zhu ZY, Ma KF, et al. Impact of pharmacist antimicrobial dosing adjustments in septic patients on continuous renal replacement therapy in an intensive care unit. *Scand J Infect Dis* 2013; 45: 891-899. 20130912. DOI: 10.3109/00365548.2013.827338.
44. Al-Qudah RA, Al-Badriyeh D, Al-Ali FM, et al. Cost-benefit analysis of clinical pharmacist intervention in preventing adverse drug events in the general chronic diseases outpatients. *J Eval Clin Pract* 2020; 26: 115-124. 20190624. DOI: 10.1111/jep.13209.
45. Aljbouri TM, Alkhawaldeh MS, Abu-Rumman AE, et al. Impact of clinical pharmacist on cost of drug therapy in the ICU. *Saudi Pharm J* 2013; 21: 371-374. DOI: 10.1016/j.jsps.2012.12.004.
46. Abushanab D, Gulied A, Hamad A, et al. Cost savings and cost avoidance with the inpatient clinical pharmacist interventions in a tertiary cancer care hospital. *J Oncol Pharm Pract* 2023: 10781552231160275. 20230322. DOI: 10.1177/10781552231160275.

Figure Legends:

Figure 1: The cost-benefit analysis model.

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

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

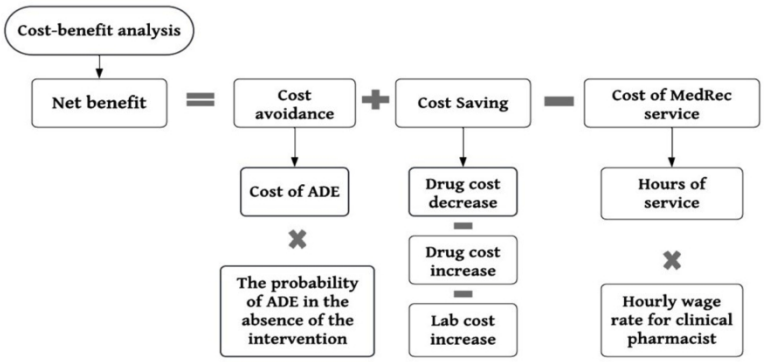
Table 1: Cost avoidance per cause-based domains in the PCNE classification of DRPs (V9.1).

Primary domain	Cause	Cost avoidance ($)	Total ($)
Drug selection	Inappropriate drug according to guidelines/formulary	12,480	25,588
	No or incomplete drug treatment despite existing indication	8,646	
	No indication for drug	2,296	
	Inappropriate combination of drugs or drugs and dietary supplements	1,916	
	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	13,710	21,141
	Dosage regimen too frequent	5,284	
	Drug dose too low	2,147	
Patient transfer related (discrepancies)	Drug omission	12,694	20,623
	Discrepancy in the strength and/or frequency and/or number of units of dosage form and/or total daily dose	4,613	
	Drug addition	2,399	
	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	2,625	2,777
	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	10,532	12,088
	No or inappropriate outcome monitoring	1,557	
Total			83,052

Table 2: Results of cost-benefit analysis

Outcome	Total ($)	Average per patient $ (M± SD)
Intervention cost over 4 months	714	5± 1
Impact on the cost of DRPs	-83,052	-585± 308
Impact on medication costs		
Reduced drug costs	-11210	-79± 85
Increased drug costs	7479	53± 67
Increased lab costs	4198	30± 29
Net benefit over the study period (4 months) [a]	81,871	577
Benefit to cost ratio [b]	115.7:1	

M± SD: Mean ± Standard deviation. The total number of patients is 142.
a: The benefits of the intervention include cost avoidance (reduced cost of DRPs) + cost savings (reduced drug costs – (increased drug costs + increased lab costs). Net benefit = The benefit of the intervention – Intervention cost over 4 months.
b: Benefit to cost ratio = The benefits of the intervention / Intervention cost over 4 months.



The cost-benefit analysis model

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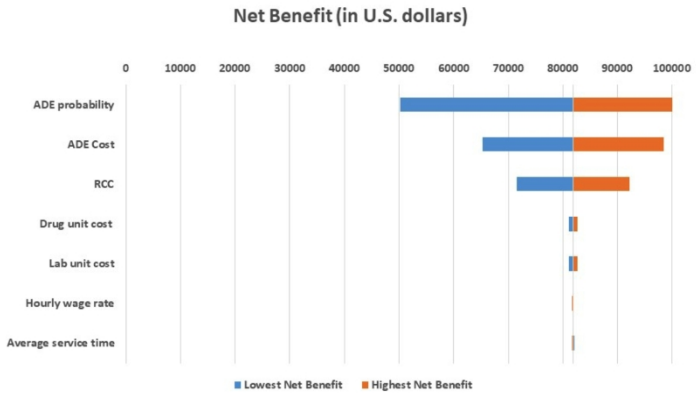

Tornado diagram illustrating the impact of various parameters on the net benefit of supplemented medication reconciliation service (one-way sensitivity analysis)

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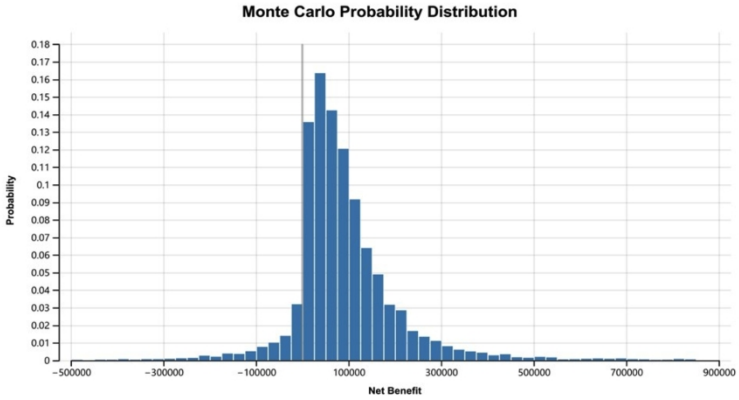

Probabilistic sensitivity analysis evaluating the net benefit of supplemented medication reconciliation service

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Research Article

Title: Clinical pharmacist-led medication reconciliation supplemented with medication review in chronic kidney disease admitted patients: a cost-benefit analysis

Journal: BMJ Open.

Table S1: Patient demographics and clinical characteristics of the study sample.

Variable	Study sample N(%) N = 142
Gender n (%)	
Female	53 (37.32)
Male	89 (62.68)
Age, years (M± SD)	57.16 ±15.96
BMI n (%)	
<18.5	6 (4.23)
18.5 -24.9	41 (28.87)
25-29.9	42 (29.58)
> 29.9	53 (37.32)
Marital status	
Married	109 (76.76)
Not married	33 (23.24)
Smoking status	
Yes	43 (30.28)
No	75 (52.82)
Ex-smoker	24 (16.90)
Educational level	
Not educated	20 (14.08)
School	93 (65.49)
University/higher education	29 (20.42)
Employment status	
Employed	26 (18.31)
Retired	32 (22.54)
Unemployed	84 (59.15)
Occupation	
Medical	3 (2.11)
Non-medical	64 (45.07)
No	75 (52.82)
Monthly income (JOD)	
<500	110 (77.46)
500 -1000	29 (20.42)
>1000	3 (2.11)

Reason for admission	
AKI on Top of CKD related problems	42 (29.58)
CKD/dialysis related problems	71 (50.0)
Others	29 (20.42)
CKD stage	
Stage 2	2 (1.41)
Stage 3a	3 (2.11)
Stage 3b	12 (8.45)
Stage 4	32 (22.54)
Stage 5	93 (65.5)
Years of dialysis (M± SD)	2.33 ± 3.66
Years of CKD (M± SD)	5.02 ± 6.80
Number of comorbidities (M± SD)	6.36 ± 2.18
CCI (M ± SD)	6.08 ± 2.93
Number of medications at admission (M± SD)	9.58 ± 3.07
Number of medications at discharge (M± SD)	9.24 ± 4.34
Death at discharge	5 (3.52)
Length of stay	8.94 ± 8.59

Abbreviation: BMI: Body Mass Index, M± SD: Mean ± Standard deviation, JOD: Jordanian Dinar , CKD: Chronic Kidney Disease, AKI: Acute Kidney Disease, CCI: Charlson Comorbidity Index.

One JOD is equivalent to 1.41 US Dollars (USD).

Table S2: Examples of the studied clinical cases with the probability score to cause ADEs.

A patient had a recent myocardial infarction (MI) and had previously undergone stent placement for the main coronary artery. She was taking febuxostat for gout. The clinical pharmacist recommended switching from febuxostat to allopurinol. (Black box warning)	High (0.6)
A female patient on hemodialysis, has a hemoglobin (Hb) level of 12 and a history of stroke. She was on alpha epoetin 4000 units prescribed every other day (EOD). (Black box warning)	High (0.6)
A 91-year-old female patient with CKD stage 5 (baseline serum creatinine is 500 mmol/l). Dialysis was delayed due to her age. The patient is experiencing uremia, including vomiting symptoms. She was prescribed metoclopramide 10 mg intravenously every 8 hours, which is a high dose considering her condition. Additionally, she is taking trimetazidine, which has a serious interaction with metoclopramide (category X). It is important to note that trimetazidine is contraindicated in patients with a GFR <30.	Medium (0.4)
A patient has osteoporosis and is undergoing hemodialysis. Initially, she was prescribed alendronate, but the clinical pharmacist recommended switching to denosumab. The physician stopped the alendronate as advised but could not provide denosumab due to economic issues. Subsequently, the patient visited the outpatient clinic (OPC) due to bone pain, and there she received denosumab treatment.	Medium (0.4), Low (0.1)
A patient has a CrCl (Creatinine Clearance) of 13, and he is currently taking fenofibrate. Additionally, the triglyceride level is less than 250 mg/dL.	Medium (0.4)
A patient underwent upper endoscopy, which revealed mild gastritis. There were no available tests for H. pylori, and the patient's serum creatinine level was 500 mmol/l (CrCl <15). Nevertheless, upon discharge, the patient was	Medium (0.4)

prescribed amoxicillin 1g twice daily and clarithromycin 500mg twice daily without renal adjustment and without confirming the diagnosis.	
A patient has AKI on top of CKD and has been experiencing severe vomiting for over a week. Upon admission, the patient's home medication included metoclopramide 10 mg three times daily taken orally. However, after admission, the route was changed to intravenous 10 mg TID (not renal dose) without improvement, the dose was changed to metoclopramide intravenously at 20 mg three times daily, which is considered too high. The clinical pharmacist recommended discontinuing metoclopramide and administering ondansetron as an alternative.	Medium (0.4)
A patient is undergoing hemodialysis and was diagnosed with deep vein thrombosis (DVT). Upon discharge, she was prescribed a therapeutic dose of Enoxaparin. The clinical pharmacist recommended switching to apixaban.	Medium (0.4)
A patient was admitted for liver cirrhosis, baseline CrCl 32, AKI, diabetes mellitus (DM), and recently diagnosed depression. He was initially admitted while taking metformin 500mg once daily. However, upon discharge, his medication regimen included metformin 850mg three times daily, mirtazapine, spironolactone, and hydrochlorothiazide. The clinical pharmacist was unable to reach the responsible physician to discuss the changes. Consequently, the patient was readmitted after 5 days due to diarrhea and hyponatremia.	Medium (0.4)
A patient has a UTI and is currently taking ciprofloxacin, calcium carbonate, and ferrous gluconate twice daily, both at 6 pm and 6 am, all by oral route.	Low (0.1)
A patient admitted with severe hypophosphatemia; the physician initially recorded that the patient was on calcium carbonate 500mg BID. With medication reconciliation we found that the actual home dose was calcium carbonate 1g TID, along with sevelamer TID, which was obtained from outside the hospital (and was not known by the physician). Resolving these discrepancies with the physician led to a change in the diagnosis.	Low (0.1)

A patient has been taking Combivent® every 8 hours for over than 2 weeks without any valid indication.	Low (0.1)
A 32-year-old patient has type 1 diabetes mellitus (DM1), end-stage renal disease (ESRD), partial retinopathy, and uncontrolled DM with recurrent hypoglycemia. Upon admission, she was using pre-mixed insulin. The clinical pharmacist suggested switching to a basal-bolus insulin regimen.	Low (0.1)
A patient was discharged without some of his hypoglycemic and antihypertensive agents unintentionally.	Low (0.1)
A patient on HD, was on famotidine 40mg once daily at home. Was not documented.	Very low (0.01)

Table S3: Average cost avoidance per patient across cause-based domains in the PCNE classification of DRPs (Version 9.1).

Primary domain	Cause	Cost avoidance ($) Average per patient	Number of patients
Drug selection	Inappropriate drug according to guidelines/formulary	195.0	64
	No or incomplete drug treatment despite existing indication	139.5	62
	No indication for drug	71.7	32
	Inappropriate combination of drugs or drugs and dietary supplements	174.2	11
	Too many different drugs/active ingredients prescribed for indication	83.5	3
	Inappropriate duplication of therapeutic group or active ingredient	83.5	3
Dose selection	Drug dose of a single active ingredient too high	207.7	66
	Dosage regimen too frequent	83.9	63
	Drug dose too low	89.4	24
Patient transfer related (discrepancies)	Drug omission	133.6	95
	Discrepancy in the strength and/or frequency and/or number of units of dosage form and/or total daily dose	118.3	39
	Drug addition	150.0	16
	Therapeutic class substitution	24.3	18

	Drug duplication	84.4	4
	Discrepancy in the dosage form/route of administration	71.9	2
Drug use process	Inappropriate timing of administration or dosing intervals by a health professional	77.2	34
	Drug administered via wrong route by a health professional	152.4	1
Treatment duration	Duration of treatment too long	91.1	3
	Duration of treatment too short	65.3	3
Drug form	Inappropriate drug form/formulation	38.1	3
Others	Addition of a lab test	118.3	89
	No or inappropriate outcome monitoring	91.6	17