Economic Evaluation of Clinical Pharmacists' Services Provided for Solid Organ Transplant Patients: A Systematic Review



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ABSTRACT

Objective: This systematic review evaluated the economic impact of clinical transplant pharmacists' intervention for solid organ transplant patients.

Methods: A PRISMA compliant search of the literature was conducted up to 31th March 2024 using PubMed, Cochrane and Embase databases to identify the original articles published on economic outcomes of transplant pharmacists' services. The quality of each included study was assessed using the CHEERS, ROBINS-I, and RoB 2 checklists.

Results: Nine studies were included, six of which performed cost-benefit analyses and three conducted cost-saving analyses. Findings indicated that clinical pharmacist interventions led to reduced health-care cost through mechanisms such as increased cost savings, cost avoidance, and reduction in hospital length of stay. The reported range of benefit to cost ratio is 2.39 to 4.16. Some studies also highlighted the important role of pharmacists in improving patient care and clinical outcomes. Most of the pharmacists' interventions were detection and management of drug related problems and prevention of adverse drug events.

Conclusion: Findings indicates that clinical transplant pharmacist interventions in various settings, from inpatient wards to specialty clinics, pharmacies and mHealth platforms, contribute positively to economic outcomes and clinical care quality in solid organ transplant patients.

KEYWORDS: Clinical transplant pharmacist; Cost; Economic evaluation; Pharmacist; Solid organ transplantation

INTRODUCTION

olid organ transplantations (SOTs) save lives of patients facing terminal organ failures and increase both duration and quality of life of these patients [1]. More than 46,000 transplantations were performed worldwide in 2023. The most transplanted organs are kidney, liver, and heart, respectively [2]. From 2020, the average amount spent for

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ORCID: 0000-0003-2004-7845 E-mail: dashtis@sina.tums.ac.ir organ transplantation in the United States (U.S.) was US\$ 1,664,800 for heart, US\$ 878,400 for liver, and US\$ 442,500 for kidney transplantation [3]. Evidence shows that the cost of SOTs is very high for the healthcare system. Many studies in different fields have explored the role of pharmacists in reducing the healthcare system costs [4, 5]. Pharmacists have been involved in the care of transplant recipients since the early 1970s. The United Network for Organ Sharing (UNOS) and the Centers for Medicare and Medicaid Services (CMS) necessitated transplantation centers to involve a clinical transplant pharmacist in their multidisciplinary transplanta-

tion teams to meet accreditation standards. Clinical transplant pharmacists play a role in the pre-, peri-, and post-transplantation phases for inpatients and ambulatory transplant recipients or candidates [6].

The concept of "value-based care" is gaining importance. Value-based healthcare focuses on improving outcomes relative to imposed costs. A systematic review is essential to examine the financial impact of clinical transplant pharmacists' services from a health-economic perspective. This study aimed to review economic evaluation studies on pharmacists-provided services for SOT patients.

MATERIALS AND METHODS

Search Strategies and Study Selection

This systematic review was conducted based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline [7]. All studies published in PubMed, Embase and the Cochrane Library databases were identified from incepts up to 31th March 2024. Table 1 describes the study selection criteria. The adopted search strategy was based on controlled vocabulary terms such as MeSH (Medical Subject Headings), Emtree terms, and keywords. The search strategy included the main search terms "solid organ transplant", "pharmacist" and "health economic analysis". Studies issued as conference abstract, commentaries, editorials, research protocols, reviews, or studies not written in English language were excluded. Following the evaluation of titles and abstracts, relevant articles were reviewed using their full-text. Three authors independently (MSH, SDK, SHH) scrutinized the full text of qualified articles for data extraction.

Ouality Evaluation of Studies

The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) 2022 checklist, which comprises 28 questions, was used to investigate the methodological quality of the economic studies by two authors (MH and AH) [8]. Each question was assessed as "yes", "partially" or "no" and scored as 1,0.5 or 0

point, respectively. Even though the CHEERS checklist is not designed per se as a scoring instrument, the application of a scoring method for that has been used and published elsewhere [9, 10]. Twenty-eight checklist items are distributed into six primary categories (title and abstract, introduction, methods, results, discussion, and other relevant information). Studies with the scores of exceeding 75%, within the range of 50-74% and below 50% were labeled as good, moderate, and low-reporting quality studies, respectively. Although this approach will assign studies a reporting quality score, this score should not be interpreted as a reflection of the study's quality. The absence of certain items does not necessarily indicate low study quality. Therefore, the utilization of the CHEERS checklist was primarily conducted to offer supplementary insights rather than establish a weighting factor for study significance.

Studies' biases were evaluated using the risk of bias in non-randomized studies of interventions (ROBINS-I) tool and second version of the Cochrane risk-of-bias tool for randomized trials (RoB 2) by two authors (MSH and SDK) independently [11,12]. In ROBINS-I, judgments for each domain of bias and for overall risk of bias, are categorized as low, moderate, serious, or critical risk of bias. In RoB2, judgments can be presented as low or high risk of bias or may be expressed using some concerns. To address discrepancies between reviewers during both the study selection and quality assessment phases, we implemented a systematic resolution process. Initially, all discrepancies were identified and documented. The two independent reviewers (MSH and SDK) then engaged in a detailed discussion to understand the basis of each disagreement. This discussion was guided by predefined criteria, focusing on the inclusion and exclusion criteria for study selection and the specific items of the CHEERS 2022 checklist and bias tools. If consensus could not be reached after initial discussions, a third reviewer (SHH) was consulted to provide an additional perspective. This third reviewer's decision was considered final.

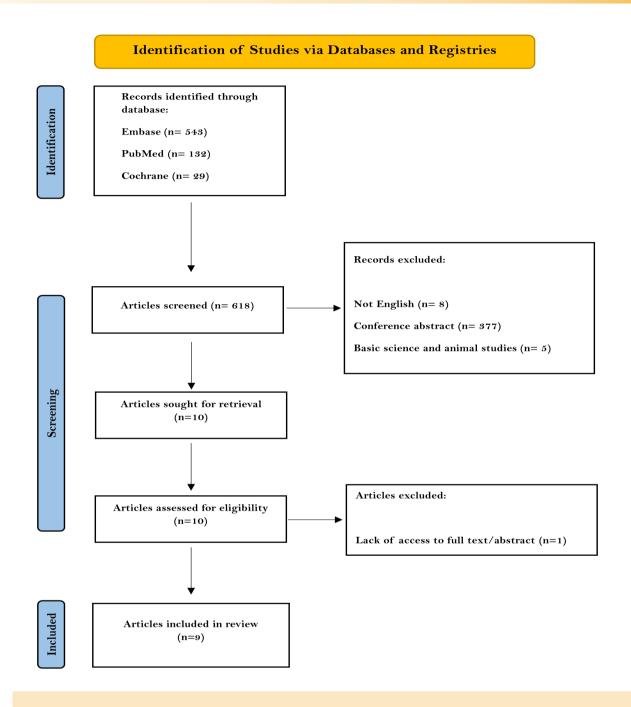


Figure 1: Study flow diagram as PRISMA guidelines.

Additionally, all decisions and rationales for resolving disagreements were meticulously recorded to ensure transparency and reproducibility. Through this structured approach, we aimed to minimize bias and ensure the robustness of our systematic review process.

RESULTS

Selected Studies

Of 704 identified articles in databases, nine studies were considered eligible for inclusion in this review (Fig. 1). Access was granted to the full text of 8 articles, but one article did not have full text available, so abstract information was used instead.

Table 1: Articles' selection cri	teria.
Population	Solid organ transplant patients in out-patient or in-patient setting
Intervention/Comparison	Studies on the economic impact of pharmacists' activities/interventions
Outcomes	Costs
Study Design	Economic evaluations (cost comparison, cost effectiveness, cost benefit)

General Characteristics of Included Studies

The general characteristics and findings of the nine included studies are summarized in Table 2. The studies encompass a variety of organ transplants, with four focusing on kidney transplants, two on liver transplants, one on kidney and/or pancreas transplants, one on heart transplantation, and one on any type of single or combined SOTs. The economic analyses employed were predominantly costbenefit analyses (CBA) in six studies, with the remaining three utilizing cost-saving analyses (CSA).

Settings and Study Designs

The included studies were conducted in diverse settings, four in hospital settings, four in outpatient settings (clinic or pharmacy), and one through a mobile health (mHealth) platform. Five studies incorporated control groups to compare the impact of pharmacists' interventions against standard care, while four studies assessed pharmacist interventions in a single cohort design without control groups. Geographically, seven studies were from the United States, while Taiwan and South Korea each contributed one study.

Quality Assessments of the Studies

The quality assessment of the studies using the CHEERS, ROBINS-I, and RoB 2 tools are shown in Tables 3 and 4. According to the CHEERS checklist, all nine studies were determined to have moderate quality. Seven studies were assessed using ROBINS-I checklist revealing six studies with a low risk of bias and one study with a moderate risk of bias. A clinical trial study was evaluated with a RoB 2 checklist with some concerns about the risk of bias.

Findings of the Included Studies *Inpatient settings*

Regarding the studies that were performed in the inpatient settings, the economic benefits reported varied among the studies. Brethauer et al. (2000) showed that rotating clinical pharmacy services in a liver transplant ward could save approximately US \$25,000 per 60-day period, leading to an annual net benefit ranging from US \$36,000 to US \$96,000 (average US \$65,000) [13]. Maldonado et al. (2013) demonstrated that the introduction of transplant pharmacists reduced the length of hospital stay (LOS) in a kidney transplant ward from 7.8 days to 3.4 days, resulting in a cost-saving of US \$279,180 without compromising 1- and 3-month mortality rates [14]. Ah et al. (2016) reported a benefit to cost ratio of 3.8 with net savings of EUR 94,009 by transplant pharmacists through the prevention of adverse drug events (ADEs) in hospitalized liver transplant recipients over 2.5 years [15]. Ravichandran et al. (2018) reported that 5-week interventions by clinical pharmacist for transplant patients resulted in cost saving of US \$36,000 per pharmacist that their extrapolation estimates an annual cost saving of US \$373,000 by each transplant pharmacist. The benefit to cost ratio in this survey was calculated to be 2.65. Most of the provided interventions by these pharmacists were pharmacokinetic evaluations and dose adjustments [16].

Ambulatory care setting

In terms of studies in the ambulatory care settings, two studies evaluated the impact of clinical pharmacy services in outpatient clinics, two in the pharmacy, and one using an electronic health technology. The first study (2000) in ambulatory care clinic was on the role of clinical pharmacist to identify kidney trans-

Table 2: General findings of included studies.	neral finding	s of include	d studie	<u>.</u>										
First Author/ country/year of publication [Ref] In-patient Setting	Study design	Type of transplanted organ	Setting	Study duration	Sample size	Gender/ Age (y)	Intervention	Type of economic evaluation	Perspective	Type of costs assessed	Cost year/ currency	Discount/ adjustment rates	Economic outcomes	Clinical outcomes
Brethauer / USA/2000 [13]	Prospective, observational, cohort	Liver	Hospital	Period 1: 45 days; Period 2: 60 days; Period 3: 50 days	IG: 739 CG: 32	Not specified/ Not specified	CG: only drug and electronic data check by hospital pharmacy IG: ward- assigned clinical pharmacist services	CBA	Institution	Direct medical costs	1999/US\$		60-day cost avoidance in IG: US\$ 20,000 to (US\$ 25,000) (average US\$25,000) Total cost for the 60-day pharmacist 60-day pharmacist 14,077 Annual net benefit of clinical pharmacy service in IG: US\$ 36,000 to US\$ 96,000 (average US\$ 65,000)	
Maldonado/ USA/2013 [14]	Retrospective, observational Case-control	Kidney	Hospital	Hospital 12 months	IG:54 CG:60	M, F/ CG: 51.4 IG: 55.0	IG: year 2011 (pharmacist assigned) CG: yea 2007 (pharmacist not assigned)	GSA	Institution	Direct medical costs and indirect costs	2011/US\$		Annual cost saving in IG: US\$ 279,180	The mean LOS decreased from 7.8 days in CG to 3.4 days in IG (Pc0.001). Improving hospital's medication management, discharge planning, and patient echtcation services for transplant recipients.

	Not available	<u></u>		ж
	Net cost-benefit: e 94,009 Benefit to cost ratio: 3.8	Cost saving of US\$ 36000 per pharmacist during 5 weeks that is extrapolated to annual cost saving of US\$ 373,000 per transplant pharmacist Benefit to cost ratio: 2.65		Cost saving for patients without Medicare coverage: US\$ 55,343 and for patients with Patients with Medicare coverage: US\$ 69,450 Total cost avoidance assuming no Medicare reimbursement: US\$ 124,793 and assuming full Medicare reimbursement: US\$ 124,793 and assuming full floor of the calculation considering salary and fringe benefit US\$ 116,640 per year Benefit US\$ 116,640 per year Benefit us assuming no Medicare reimbursement: reimbursement: reimbursement: reimbursement: 4.16:1
	Not available			
	Not available	2013/US\$		1998/US\$
	Not available	Direct medical costs		Direct medical costs
	Not available	Institution		Institution
	Ps CBA	CSA		CBA
	Not available/ Identifying DRPs CBA Not available	Pharmacist activities were medication therapy management, dosage adjustment, auntibiotic selection, laboratory evaluation, pharmacokinetic evaluation.		
	Not available/ Not available	Not specified/ Not specified		Not specified/ Not specified
	420	Not specified (350–400 per year)		61 all received clinical pharmacist service
	1 29 months	Hospital 5 weeks		12 months
	Hospital			Clinic
	Liver	kidney, pancreas, liver, or any combination		Kidn cy
ntinued.	Retrospective, descriptive	Prospective, observational, cross-sectional	žs.	Prospective, cohort
Table 2: Continued.	Ah/Korca/ 2016 [15]	Ravichandran/ USA/2018 [16]	Out-patient Setting	Chisholm/ USA/ 2000 [17]

	Number of detected DRPs: 372 29% of DRPs had an ADE probability of-10%; 17% of DRPs were estimated to cause ADEs with moderate severity or higher	Weighted medication procession ratio was higher in IG than IG than IG than IG than IG than a with a medication gap or discontinuation was lower IG compared to Go 55 (65 vs. 142; P<0.0001)
	Annual cost savings: US\$ 4902 Annual cost avoidance: US\$ 4519 Total annual benefit: US\$ 9421 Annual cost: US\$ 3950 Benefit to cost ratio; 2.39	Mean total cost in IG: US\$ 24,315 and in CG: US\$ 10,605 and in CG: US\$ 19,194 Transplant related emergency room cost in IG: US\$ 20,75 Inpatient cost in IG: US\$ 21.80 and in CG: US\$ 21.80 and in CG: US\$ 24,529 Outpatient cost in IG: US\$ 21,80 and in CG: US\$ 24,529 Outpatient cost in IG: US\$ 24,378 Mean total health care cost in IG: US\$ 24,315 and in CG: US\$ 25,350 and in CG: US\$ 395 and in CG: US\$ 355
	Study time was between 1st March 2019 to 29th February, 2020)/US\$	2007/US \$
	Direct medical costs	Direct medical costs
	Patients/ Health care system	Health care
	Pharmacist reviewed medical records and interviewed patients to assess the effectiveness and safety of drug therapies and drug adherence, conducted medication reconciliation, identified and managed DRPs, end educated patients.	CG: traditional retail pharmacy services CBA clinical transplant pharmacy services
	M&F/ 50.9±13.5	F/ CG: 50.16 IG: 49.85
	12 months 92	12 months IG:519
	Clinic	Pharmacy
	Heart	Kidney
ontinued.	Retrospective observational, cross-sectional	Retrospective
Table 2: Continued.	Wu/Taiwan/ 2023 [18]	Tschida/USA/ 2013 [19]

Table 2: Continued

ADE: adverse drug events; CBA: cost-benefit analysis; CEA: cost-effectiveness analysis; CG: control group; CI: confidence interval; CMV: cytomegalovirus; CSA: cost-saving analysis; DRPs: drug related problems; F. Female; IG: intervention group; LOS: hospital length of stay; M: male; mo: month; RCT: randomized clinical trial; United States Dollars: US \$; ROI: return of investment; RR: risk ratio Abbreviations:

plant patients who could not afford the costs of their immunosuppressive drugs. The clinical pharmacist acted as a liaison between patients, nephrologists, and pharmaceutical companies to screen patients and introduce those who could benefit the manufacturers' medication assistance. During one year activity, clinical transplant pharmacists was estimated to save US \$124,793 if assuming no Medicare reimbursement for patients with drug cost coverage and US \$69,233 if assuming full Medicare reimbursement for those patients. Considering clinical pharmacists' time calculation, benefitcost ratios were approximately 7.5:1 and 4.16:1 for full Medicare reimbursement and no reimbursement, respectively [17]. Another study (2023) assessed the impact of pharmacist for medication therapy management in a heart transplant clinic. Providing this transplant pharmacy services and management of DRPs and prevention of ADEs by pharmacists resulted in annual cost of \$3950, cost savings of about US \$4902, cost avoidance of US \$4519 and benefit to cost ratio of approximately 2.4 $\lceil 18 \rceil$.

Two other outpatient studies were done in the pharmacy settings. Tschida et al. (2013) compared economic outcomes between transplant specialty and traditional retail pharmacy services for kidney transplant patients. The specialty pharmacy services resulted in a significant reduction in total healthcare costs by about 13% and transplant-related medical costs by 30% [19]. Byrns et al. (2016) evaluated the financial impact of clinical pharmacistsled managing of cytomegalovirus (CMV) infections among transplant recipients in pharmacy setting and revealed a cost saving of US \$4,000 per case of CMV viremia [20]. Additionally, Taber et al. (2021) demonstrated that a clinical pharmacist-led mHealth system for kidney transplant patients significantly reduced hospitalization rates and associated costs. The annual net estimated cost saving was reported to be US \$368,839 [21].

Table 3: CHEERS checklist evaluation.	cklist	eva	luatio	on.																								
First author, year of publication [Ref]	1	6	ಣ	2 3 4 5 6 7	5	2 2	∞	6	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	Reporting quality based on % score*
Brethauer, 2000 [13]	Y	Ь	Y	Y P Y Y N Y Y N	Z	Y	7	Z	Z	Y	Y	Y	Y	Y	Z	Z	Z	Z	Z	Z	Y	Y	Z	Z	Ь	Z	Z	Moderate
Chisholm, 2000 [17]	Y	Y	Y	Y Y Y N Y Y Y	Z	Y	Λ ,	Z	Z	Y	Y	Y	Y	Y	Z	Z	Z	Z	Z	Z	Y	Υ	Z	Z	Ь	Y	Z	Moderate
Maldonado, 2013 [14]	Z	Y	Y	N Y Y Y Y Y N	Y	Y		Z	Z	Y	Y	Y	Y	Y	Z	Z	Z	Z	Z	Z	Y	Y	Z	Z	Y	Y	Y	Moderate
Tschida, 2013 [19]	Z	Y	Y	Y Y Y Y Y N	Y	Y	7	Z	Z	Y	Y	Y	Y	Y	Z	Y	Z	Z	Z	Z	Y	Λ	Z	Z	Λ	Y	Z	Moderate
Byrns, 2014 [20]	Z	Y	Y	N Y Y Y P Y Y	Y 1	Α .	Λ .	Z	Z	Y	Y	Y	Y	Λ	Z	Y	Z	Z	Z	Z	Λ	Υ	Z	Z	Υ	Y	Y	Moderate
Ravichandran, 2018 [16]	Z	Y	Y	N Y Y N Y Y N	Z	Y	~	Z	Z	Y	Y	Y	Y	Λ	Z	Z	Z	Z	Z	Z	Λ	Υ	Z	Z	Υ	Y	Y	Moderate
Taber, 2021 [21]	Y	Y	Y	Y Y Y Y Y	Y	Y	Y /	Z	Z	Y	Y	Y	Y	Λ	Z	Y	Z	Z	Z	Z	Y	Υ	Z	Z	Υ	Y	Y	Moderate
Wu, 2023 [18]	Y	Y	Y	Y Y Y Y Y Y N	Y	Y	Z	Z	Z	Υ	Y	Λ	Y	Y	Z	Y	Z	Z	Z	Z	Λ	Y	Z	Z	Y	Z	Y	Moderate

*Studies were assigned 1 point per item for Yes, 0.5 for partially reported, and 0 for No. Percentage score was calculated after the exclusion of "not applicable" item.

Y: reported, P: partially reported, N: not reported, NA: not applicable

Abbreviations:

DISCUSSION

This systematic review represents the first comprehensive evaluation of health economic studies focusing on clinical transplant pharmacist interventions for SOT patients. Despite broad inclusion criteria designed to capture any study reporting a health-related cost, this review highlights a scarcity of rigorous economic evaluations in this field. None of the nine identified studies conducted a thorough health economic evaluation, limiting the robustness of the findings.

The main finding of this review is that clinical transplant pharmacist interventions, regardless of the setting—whether hospital, clinic, pharmacy, or digital health—show potential for reducing healthcare costs through mechanisms such as cost savings, cost avoidance, and shortened hospital length of stay (LOS) and a reported range of benefit to cost ratio of 2.39 to 4.16. However, these findings should be interpreted cautiously due to the varied quality of the included studies.

The American Society of Health-System Pharmacists (ASHP) guidelines on pharmacy services in SOT teams designated pharmacy services in any phase of transplantation. Clinical transplant pharmacists can reduce medical expenses through pharmacological and nonpharmacological evaluations, direct care of organ transplant recipients, patient education, prevention and identification of DRPs, and prevention of ADEs. Various studies in other medical settings have shown that pharmacists can be effective in reducing health-related costs. A systematic review by Malet-Larrea et al. consisting of 13 articles about cost-effectiveness of providing professional pharmacy services for ambulatory patients with chronic diseases such as depression, type 2 diabetes, respiratory and cardiovascular disorders in community pharmacy concluded a general trend toward cost-effectiveness of professional pharmacy services compared with the usual care [22]. A systematic review by Noormandi et al. about clinical and economic impacts of clinical pharmacists' interventions in Iran showed that most clinical pharmacist interven-

Table 4: Risk of bias assessment with ROBINS-I and F	assessment with	ROBINS-I and R	RoB 2 tools.					
First author, year of publication [Ref]	Baseline confounding	Selection of participants	Classification of intervention	Deviation from intended intervention	Missing data	Measurement of outcomes	Selection of reporter results	Overall risk of bias
The risk of bias in non-randomized studies of interventions	ı-randomized studie		(ROBINS-I) assessment tool	ssment tool				
Brethauer, 2000 [13]	Low	N	Low	NI	Low	Low	Low	Low
Chisholm, 2000 [17]	Low	Low	Low	NI	Low	Low	Low	Low
Maldonado, 2013 [14]	Low	Low	Low	N	Low	Low	Low	Low
Tschida, 2013 [19]	Moderate	Low	Low	N	Low	Moderate	Low	Moderate
Byrns, 2014 [20]	Low	Low	Low	N	Low	Low	Low	Low
Ravichandran, 2018 [16] Low	Low	Low	Low	N	Low	Low	Low	Low
Wu, 2023 [18]	Low	Low	Low	NI	Low	Low	Low	Low

The risk of bias for randomized trials (RoB 2) assessment tool

Overall risk of bias	Some concerns
Selection of the reported result	Low
Measurement of the outcome	Low
Missing outcome data	Low
Deviation from intended intervention	Some concerns
Randomization process	Low
First author, year of publication [Ref]	Taber, 2021 (21)

Abbreviations: ROBINS-I: Low risk, Moderate risk, Serious risk, Critical risk, NI (No information) RoB 2: Low risk, Some concerns, High risk

tions and activities were regarding designing institution-based drug protocols, improving drug utilization pattern, as well as detection, prevention, and management of DRPs. That review supported the beneficial role of clinical pharmacists in the improvement of quality, safety, efficiency and economic of patients' pharmaceutical care in Iran [23]. Another systematic review by Price et al. about economic evaluations of pharmacist services in different inpatient and outpatient settings showed that the findings of 57 out of 75 included studies were either dominant or cost-effective using a willingness-to-pay threshold of NZ \$46 645 per quality-adjusted life-years (QALY). The most economical pharmacists' interventions were medications evaluations, pharmacist involvements to improve patients' adherence, and pharmacist oversight of conditions such as type 2 diabetes, hypertension, and adjustment of warfarin therapy. Furthermore, that review concluded that investment in expanding pharmacist services, particularly those focused on long-term chronic health conditions would be valuable [24]. A cost-consequence analysis of pharmacist roles in eighteen medical outpatient clinics in Australia found that although clinical pharmacists' services necessitate reimbursement costs, they also improve medication management and prevent DRPs that decrease health-related costs [25]. A systemic review including 14 studies about economic evaluation of pharmacist-led digital health interventions supports the short-term cost-effectiveness of these types of pharmaceutical care services [26]. In concordance with previous systematic reviews in other patient population settings, the findings of the present review support the development of clinical transplant pharmacist services from the health-economic perspective.

Some limitations of this review and the included studies are noteworthy. The absence of a long-term horizon in the cost evaluations limits the applicability of the findings for assessing sustainable economic benefits. Many studies claimed to perform cost-benefit analyses but often measured only direct medical costs and benefits, falling short of true comprehensive evaluations.

Future research should focus on long-term economic evaluations to assess sustained impacts of clinical transplant pharmacist interventions. More comprehensive economic evaluations, including direct, indirect, and intangible costs, are needed. Interdisciplinary collaboration among healthcare professionals will enrich study quality, and incorporating digital health technologies could provide innovative insights. These approaches will strengthen the evidence base for the economic and clinical benefits of clinical transplant pharmacist services.

In conclusion, this systematic review suggests that integrating clinical transplant pharmacists into SOT healthcare teams, in various settings from inpatient wards to specialty clinics and pharmacies, can yield economic and clinical benefits. Healthcare institutions, systems, and insurers may consider these initial findings as a justification for including clinical transplant pharmacists. Nonetheless, given the overall moderate quality of the studies, further high-quality studies are essential for a definitive assessment of their cost-effectiveness.

CONFLICTS OF INTEREST: None declared.

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