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Cost-Effectiveness of Clinical Pharmacy Education on Infection Management among Patients with Chronic Kidney Disease in an Indonesian Hospital

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ABSTRACT

Objectives: This study evaluated the clinical and economic impacts of clinical pharmacy education (CPE) on infection management among patients with chronic kidney disease (CKD) stages 4 and 5 in Haji Adam Malik Hospital, Indonesia. **Methods:** A quasi-experimental economic evaluation comparing CPE impact on 6-month CKD mortality was conducted on the basis of payer perspective. The experimental group (n = 63) received care by health care providers who were given CPE on drug-related problems and dose adjustment. The control group (n = 80) was based on the historical cohort of patients who received care before the CPE. Measure of clinical outcome applied in this study was number of lives saved/100 patients treated. Cost-effectiveness ratios for CKD stages 4 and 5 patients without CPE and with CPE and incremental cost-effectiveness ratios (ICERs) for CKD stages 4 and 5 patients were analyzed. **Results:** Lives saved (%) in the treatment of CKD without CPE: CKD stage 4, 78.57; CKD stage 5, 57.58. Lives saved (%) in the treatment of CKD with CPE: CKD stage 4, 88.89; CKD stage 5, 65.45. Cost-effectiveness ratios for stage 4 with and without CPEs were Rp3,348,733.27 and Rp3,519,931.009, respectively. Cost-effectiveness ratios for stage 5 with and without CPEs were Rp7,137,874.93 and Rp7,871,822.27, respectively. ICERs were Rp2,045,341.22 for CKD stage 4 and Rp1,767,585.60 for CKD stage 5. **Conclusions:** Treatment of CKD stages 4 and 5 with CPE was more effective and cost-effective compared with treatment of CKD stages 4 and 5 without CPE. The ICERs indicated that extra costs were required to increase life saved in both stages.

Keywords: chronic kidney disease, clinical pharmacy education, cost-effectiveness, DRPs, infection.

Introduction

Chronic kidney disease (CKD) is a worldwide public health problem with increasing prevalence, high treatment cost, and poor outcomes [1]. In Indonesia, up to now, there is no available information regarding the accurate prevalence of CKD, but a survey carried out in a few parts of the country found that 12.5% of the population had CKD [2]. In the United States alone, the prevalence of CKD increased from 10% in the period 1988 to 1994 to 13% in the period 1999 to 2004 [3]. In fact, epidemiologic studies have demonstrated that the incidence of kidney diseases is higher in the developing countries than in the developed world. Global annual growth rate of CKD is 8% [4].

CKD is a costly disease to both patients and nations. In the United States, the cost for hemodialysis per patient per year was US $71,889 [5]. Barclay [6] found that almost a quarter of the Medicare budget was spent for the treatment of CKD. In Indonesia, the lowest cost for a single hemodialysis is about Rp500,000 (~US $53). This means that the annual cost required to treat one patient is about Rp50,000,000 excluding other costs such as those for drugs, routine blood tests, and other supporting tests [7]. Most of the risk factors of CKD could be prevented and cured if managed at early stages. The disease, however, is usually underdiagnosed and undertreated, resulting in loss of opportunities for prevention and eventually disability or death. A few studies on CKD in the United States indicated that its treatment rate was only 14.1% [3]. The diagnosis and management of CKD must always be performed as early as possible to delay the progression of loss of kidney function.

Patients with advanced stages of CKD usually have complex comorbidities and complications. One of its common complications is infection, which is the second leading cause of death of patients with CKD, especially those in stages 4 and 5 [7,8]. Its inflammatory state can further lead to the development of atherosclerosis and increased risk of cardiovascular disease. Patients with CKD also usually experience neutrophil dysfunction because of complicated problems including malnutrition, trace element deficiencies, iron overload, impaired glucose metabolism, hyperparathyroidisms, and uremic retention solutes.

Conflict of Interest: The authors have indicated that they have no conflicts of interest with regard to the content of this article.

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Furthermore, skin, dialysis water, treatment systems, and dialyzer reuse are also the possible sources of infection in patients with CKD [9]. These complications expose them to a higher risk for bacterial and viral infections. Epidemiological studies suggest that the three most frequent infectious complications experienced by patients with end-stage renal disease are urinary tract infection, pneumonia, and sepsis [9]. It was found that the mortality rate of patients treated with hemodialysis was about 100- to 300-fold than that of patients without hemodialysis [10]. As such, numerous medications are always required to treat advanced stages of CKD and its comorbidities and complications. These can further result in drug-related problems (DRPs), ineffective treatment, and inefficient resource utilization [11].

Two of the frequently occurring DRPs are irrational dosing (too little or too much of the drug provided to the patients) and drug interaction (comprising drug–drug, drug–food, and drug–laboratory interactions) [12]. These DRPs can worsen outcomes of patients with CKD if not managed according to established guidelines. For example, incorrect dose of many drugs such as antibiotics provided to patients with CKD can accumulate in the body, resulting in toxic effects to organs including kidneys. The progress of the kidney damage will also be accelerated [13,14]. In addition, there is an increased chance of drug interaction due to multiple drug therapy, which could lead to inefficient and ineffective treatment of the disease. An example is concomitant administration of enzyme inhibitors such as ranitidine sometimes prescribed to eliminate nausea and vomiting caused by cephalosporines, which will elevate the drugs' level in the body, exacerbate the cephalosporines' nephrotoxicity, and accelerate kidney damage. The ultimate negative outcome is death [15].

A great deal of attention has to be paid to the improvement of CKD outcomes and its treatment cost. Ernst and Grizzle [16] found that every US $1 spent on medication required US $1.77 on DRPs. Thus, to improve outcomes and minimize costs, a concrete approach needs to be taken to prevent and resolve DRPs.

The participation of pharmacists trained in clinical skills with other health care providers is crucial in optimizing drug therapy [17–19]. Such clinical skills can be imparted through a structured CPE program. This study was conducted to evaluate the impacts of clinical pharmacy education (CPE) on outcome and costs in the management of infection among patients with CKD stages 4 and 5 in Haji Adam Malik (HAM) Hospital, Indonesia.

Methods

A quasi-experimental economic evaluation comparing CPE impact on 6-month CKD mortality was conducted on the basis of *Jaminan Kesehatan Masyarakat* (JAMKESMAS) or public health insurance perspective. JAMKESMAS is a social insurance funded by the Indonesian government covering 76.4 million people (~one-third of the Indonesian population). The insurance aims to protect the poor and near-poor population from the catastrophic payment due to sickness [20]. The experimental group (n = 63) received care by health care providers who were given CPE on DRPs and dose adjustment. The control group (n = 80) was based on the historical cohort of patients who received care before the CPE.

As the perspective of the study was from the payer's point of view, only direct costs consumed by the control and experimental groups of patients with CKD were included in the economic analysis.

Clinical Pharmacy Education

Prior to the CPE, 3-month data were collected from JAMKESMAS inpatients database by using a predefined data collection form. The data were analyzed descriptively to identify antibiotic usage-associated problems and other related drugs administered to the patients. The results of this analysis were used to prepare materials for the CPE. In addition, the CPE highlighted common issues including dose adjustment according to the level of kidney function, frequently administered antibiotics for the patients, and frequently occurring drug-drug interactions as identified from the patients' medical charts. The CPE was conducted by a clinical pharmacist through a half-day formal seminar (officially scheduled and organized by the head of installation of research and development HAM Hospital) and two informal (unofficial) one-to-one discussion sessions regarding issues raised by the health care providers. The participants of the CPE were pharmacists who work at the installation of pharmacy, physicians and nurses who serve in the installation of nephrology, and other related employees selected by the head of the installation of research and development. The printed materials of the CPE were also distributed to the participants.

Data Collection

Data were extracted from 6-month JAMKESMAS database of inpatients with CKD stages 4 and 5 receiving treatment of antibiotics starting from admission until discharge for the middle of September 2009 to the middle of March 2010 as control group (n = 80) and middle of March to middle of September 2010 as experimental group (n = 63) by using a predetermined data collection form. Inclusion criteria were infectious patients with glomerular filtration rate of less than 15 ml/min/1.74m^2 surface area. Patients younger than 18 years or with cancer and human immunodeficiency virus were excluded from this study [21,22]. The data recorded on the data collection form included date of admission, medical record number, age, sex, patient conditions at admission (stage of CKD), patient condition at the end of treatment (death or survive), number and unit cost of laboratory tests, and antibiotics and other drugs administered.

Data Analysis

Characteristics of the patients

The characteristics of patients with CKD were grouped and analyzed according to age, sex, and severity of the disease. Grouping of the patients with CKD on the basis of severity was performed by calculating the glomerular filtration rate applying the Modification of Diet in Renal Disease study equation [23]. Their mean values were statistically analyzed at the 95% confidence level ($P < 0.05$ is considered significant).

Cost-effectiveness analysis

Effectiveness. It has been known that CKD is a life-threatening disease [24]. Thus, final outcome is the appropriate measurement for this disease. In this study, it was measured as number of lives saved per 100 patients with CKD (percentage of patients who survived over those who were treated) in the control and experimental groups [25]. Before performing cost-effectiveness analysis (CEA), a formal testing for the effectiveness for CPE in terms of mortality was conducted and it was found that there was no statistically significant difference in terms of mortality reduction between groups with and without CPEs ($P = 0.342$).

Health care resources consumed. Components of the health care resources accounted in this study included drugs, floor stock,

routine blood test, urine test, integrated diagnostic services, treatment administration, hemodialysis service, physician visits/consultations, chemicals, emergency service, radiology service, serology service, card and ticket, blood flask, eye polyclinic, surgery, bacteriology test, and clinical pharmacy education. Other health care costs including hotel, cleaning, catering, electricity, water, and building depreciation were considered to be accounted in the hospital accommodation charge.

Steps in performing CEA. Few assumptions were made in this study: Infecting pathogens were the same among each group of patients with CKD. Patients did not suffer from other concomitants diseases because they can modify drugs provided and affect outcomes; only serious adverse events increased the cost of treatment, and each adverse event prolonged the hospital stay; there was no impact of antibiotic resistance on costs.

Direct medical costs were analyzed by multiplying the number of doses/test/service/unit given with cost per dose/test/service/unit. Direct nonmedical costs were obtained by multiplying the hospital length of stay with accommodation charge per day. In this study, the cost-effectiveness of the group with and without CPEs was compared on the basis of costs and effectiveness of treating 100 patients.

Samples with and without CPEs were stratified according to the stage of the disease (a). Percentage of patients with CKD stages 4 and 5 with and without CPEs treated (outcome/100 patients) were calculated (b). Direct costs consumed for the treatment of individual patient of CKD stages 4 and 5 with and without CPEs were calculated (c). Cumulative direct costs consumed for the treatment of exiting number of CKD stages 4 and 5 patients ($\sum C_i$) with and without CPEs were calculated (d). Each of the values obtained in point d) was converted into cost consumed to treat 100 patients (cost/100 patients) (e). Cost-effectiveness ratio of each of the subgroup treatments was calculated by dividing the value obtained in point e) by the value obtained in point b). Incremental cost-effectiveness ratios (ICERs) in the management of CKD stages 4 and 5 were analyzed by calculating $(Cost_{with\ CPE} - Cost_{without\ CPE})/(Outcome_{with\ CPE} - Outcome_{without\ CPE})$ [26].

Sensitivity analysis. In this study, one-way sensitivity analysis was undertaken to improve the quality and usefulness of the CEA. Here, drug costs were increased to 5%, 10%, and 15%. The new costs, cost-effectiveness ratios, and ICER were recalculated [25].

All calculations and result plotting were performed by using Microsoft Excel 2007 (Microsoft Corp, Redmond, WA) and SPSS for Windows (version 17; SPSS Inc, Chicago, IL).

Results

Characteristics of the patients

Characteristics of the studied populations are shown in Table 1. There were 80 patients included in the control group. Of these, 66% were men and 34% were women. The experimental group consisted of 63 patients. Sixty-three percent were men, and 37% were women. Ages of the control and experimental groups were 47.06 ± 13.80 years and 49.44 ± 13.08 years, respectively. As shown in Table 1, there was more admission of patients with CKD stage 5 in both groups compared with those with CKD stage 4. By age, there was no statistically significant difference between the experimental and control groups ($P = 0.299$). By gender, in the group without CPE, the disease was more prevalent in men than in women ($P = 0.003$). A similar result was obtained in that the disease was also more prevalent in men than in women in the group with CPE ($P = 0.031$). In the group without CPE, CKD stage 5 was more prevalent than CKD stage 4, ($P < 0.001$). Similarly, CKD stage 5 was also more prevalent than CKD stage 4 in the group with CPE ($P < 0.001$).

Cost-Effectiveness Analysis

The resources used to treat patients with CKD according to group (non-CPE and CPE) and stage (stages 4 and 5) are presented in Table 2. The direct cost consumed to treat 100 patients with CKD stage 4 without CPE was Rp276,560,978.57 with outcome or lives saved of 78.57%, whereas the direct cost consumed to treat 100 patients with CKD stage 4 with CPE was Rp297,668,900.00 with lives saved of 88.89%. Hence, cost-effectiveness ratios in the management of patients with CKD stage 4 with and without CPEs were Rp3,348,733.27 and Rp 3,519,931.00, respectively. In other words, costs per life saved were Rp3,348,733.27 and Rp3,519,931.00 for patients with CKD stage 4 with and without CPEs, respectively. Based on the analysis of ICER, however, to increase life saved from 78.57% to 88.89%, Rp2,045,341,22 of extra cost per patient was required.

Similar results were also obtained for the treatment of patients with CKD stage 5 with and without CPEs. The cost consumed by 100 patients with CKD stage 5 without CPE was Rp453,263,015.52 with outcome or lives saved of 57.58%, whereas the cost consumed to treat 100 patients with CKD stage 5 with CPE was Rp467,173,914.18 with lives saved of 65.45%. Thus, cost-effectiveness ratios of CKD stage 5 patients with and without CPEs were Rp7,137,874.93 and Rp7,871,882.87, respectively. Analysis of ICER for non-CPE and CPEs groups of CKD stage 5 indicated that Rp1,767,585.60 of extra cost per patient was required to increase live saved from 57.58% to 65.45%.

Table 1 – Characteristics of the control and experimental groups.

Demographic variable	Control group (n = 80)			Experimental group (n = 63)			P
Age (y), mean ± SD	47.06 ± 13.80			49.44 ± 13.08			0.299
Within group: applying one-sample *t* test; tested value = 0.5	Proportion	SD	P	Proportion	SD	P	
Sex:							
Male	53 (0.66)	0.48	0.003	40	0.48	0.031	
Female	27 (0.34)			(0.63)			
Severity:							
Stage 4	14 (0.17)	0.38	<0.001	23	0.37	<0.00	
Stage 5	66 (0.83)			(0.37)		1	
				8 (0.16)			
				55 (0.84)			

Table 2 – Cost-effectiveness analysis in group with and without CPEs.

Description	Without CPE		With CPE	
	Stage 4 (n = 14)	Stage 5 (n = 66)	Stage 4 (n = 8)	Stage 5 (n = 55)
Direct medical cost	Rp34,938,537.00	Rp276,918,614.00	Rp21,653,012.00	Rp243,850,649.80
Direct nonmedical cost (hotel)	Rp3,780,000.00	Rp22,235,000.00	Rp2,160,500.00	Rp13,095,003.00
Total	Rp38,718,537.00	Rp299,153,614.00	Rp23,813,512.00	Rp256,945,652.80
Cost to treat 100 patients	Rp276,560,978.57 (x_1)	Rp453,263,015.52 (x_2)	Rp297,668,900.00 (x_3)	Rp467,173,914.18 (x_4)
Outcome (hypothetical lives saved per 100 patients treated) (y)	78.57 (y_1)	57.58 (y_2)	88.89 (y_3)	65.45 (y_4)
CE ratio = x/y	Rp3,519,931.00/life saved	Rp7,871,882.87/life saved	Rp3,348,733.27/life saved	Rp7,137,874.93/life saved
	ICER			
CKD stage 4	(Cost x_3 – Cost x_1)/(Outcome y_3 – Outcome y_1) = 21,107,921.43/10.32 = 2,045,341.22			
CKD stage 5	(Cost x_4 – Cost x_2)/(Outcome y_4 – Outcome y_2) = 13,910,898.66 /7.87 = 1,767,585.60			

CKD, chronic kidney disease; CPE, clinical pharmacy education; ICER, incremental cost-effectiveness ratio.

Sensitivity Analysis

Result of the sensitivity analysis is presented in Table 3. This analysis shows that even though the acquisition costs were increased by 15%, the overall conclusions did not change. In other words, it could be concluded that the results of the CEA were robust to uncertainty on the drug cost.

Discussion

Up to now, there are still limited studies undertaken on CKD in Indonesia. This present study indicated that CPE improved effectiveness (lives saved) and decreased costs for the treatment of infection in patients with CKD stages 4 and 5 as previously mentioned. These results may have been due to a decrease in the number of drugs administered to the patients with CKD, DRPs, and their hospital length of stay. Therefore, this finding implied that CPE had positive impacts on the management of CKD.

As indicated by analysis of ICER, extra costs were needed to improve outcome in the treatment of both stages. This analysis is essential to undertake in any pharmacoeconomic study because it can be used as a guidance to decide whether such amount of money is an acceptable or reasonable amount to pay by the policymaker [27]. In this case, to decide whether to include CPE into the management of CKD depends on, to large extent, budget limitation provided by JAMKESMAS as the payer. Extrapolated ICERs for the management of CKD stages 4 and 5 patients would be equal to about US $216.81 and 187.36, respectively. These values are less than the estimated Indonesian gross domestic product per capita for year 2010, US $4500 [28,29]. Therefore, based on the World Health Organization-choice threshold, the ICERs are cost-effective.

Sensitivity analysis demonstrated that increasing acquisition costs did not affect the result of CEA. In other words, it could be concluded that the results of this analysis are robust to uncertainty or the management of patients with CKD with CPE is more cost-effective compared with that of those without CPE.

This finding supports other studies undertaken by research groups in few hospitals in several countries, but focusing on different outcomes. A literature review undertaken on 14 randomized controlled studies with different settings indicated that clinical pharmacy intervention reduced DRPs to various levels [30]. A review conducted by Salgado et al. [31] summarized that pharmacists' interventions in the management of CKD have shown positive impacts on the treatment outcomes. With regard

Table 3 – Result of the sensitivity analysis.

Description	Without CPE		With CPE	
	Stage 4 (n = 14)	Stage 5 (n = 66)	Stage 4 (n = 8)	Stage 5 (n = 55)
Direct cost to treat 100 patients (x) at increased:				
5% of acquisition cost	Rp276,461,028.50	Rp459,742,172.70	Rp301,232,650.60	Rp469,900,342.00
10% of acquisition cost	Rp348,930,950.30	Rp464,770,852.00	Rp304,796,401.30	Rp472,622,099.20
15% of acquisition cost	Rp493,860,119.80	Rp469,799,531.40	Rp308,360,151.90	Rp475,343,855.90
Outcome (lives saved per 100 patients treated) (y)	78.57 (Y_1)	57.58 (Y_2)	88.89 (Y_3)	65.45 (Y_4)
CE ratio (x/y) in Rp/life saved at increased:				
5% of acquisition cost	3,518,658.00	7,984,407.00	3,388,824.96	7,179,531.59
10% of acquisition cost	4,441,020.00	8,071,741.00	3,428,916.65	7,221,116.87
15% of acquisition cost	6,285,606.00	8,159,074.00	3,469,008.35	7,262,702.15
ICER at increased:	Stage 4		Stage 5	
5% of acquisition cost	Dominant		Dominant	
10% of acquisition cost	Dominant		Dominant	
15% of acquisition cost	Dominant		Dominant	

CPE, clinical pharmacy education; ICER, incremental cost-effectiveness ratio.

to economic outcomes, the review included a finding of a study on the impact of renal drug dosing service on dose adjustment in hospitalized patients with CKD. The finding indicated that cost avoidance amounted to US $2250 during a period of 4 months in 2007 [32]. An anemia educational program performed by pharmacists for patients with CKD had significant effects on the patients' energy, daily activities, and general well-being [33]. Another pharmaceutical care intervention performed by Wang et al. [34] in renal transplant clinics made 55 recommendations, of which 81.8% were classified as clinically significant. A randomized controlled study conducted on 104 patients with end-stage renal disease found that drug use, rate of hospitalization, and cost were lower in the group with pharmaceutical care compared with those receiving standard care [35]. A conclusion could be drawn that CPE has positive impacts on CKD management.

This study was limited by the relatively small sample size and CPE sessions. A number of factors including bacterial resistance to antibiotics, variability of the infecting bacteria, complications, and comorbidities of the disease were not accounted and assumed to be similar for all patients in this study. These factors could affect the patients' mortality and hospitalization; hence, these need to be properly addressed in the future.

Conclusions

CPE improved effectiveness and efficiency of CKD management. Thus, involvement of clinical pharmacists in the team of multidisciplinary health care providers is important to obtain optimal services. This finding should be considered by the policymakers in the HAM Hospital and other hospitals in general.

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