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Cost benefit analysis of clinical pharmacist interventions in medical intensive care unit in Palestine medical complex: Prospective interventional study

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ABSTRACT

Background: Clinical pharmacy services in the critical health care settings have expanded dramatically.
Study problem.
Clinical pharmacy services have limited implementation in Palestine. Many intensive care units (ICUs) patients do not get the intended beneficial effects of their treatment due to treatment related problems and their consequent cost burden.
Aim: To evaluate the impact of the clinical pharmacist interventions on costs of care and safety of patient by assessing treatment related problems among medical ICUs patients in Palestine.
Methodology: A prospective interventional study was conducted at medical ICU of the major public hospital in Ramallah city over a 4-month period (between September and December 2020). Patients were randomly assigned to either an intervention or a control group (With / without clinical pharmacist involvement). Treatment related problems were identified in both study groups by the clinical pharmacist, but interventions were only provided to the intervention group. The total economic benefit included both cost savings from intervention and cost avoidance from preventable adverse drug events (ADEs) resulted from CP interventions. The primary outcomes with the clinical pharmacist interventions were net benefit and benefit to cost ratio, which were calculated using previously published methodologies and adjusted to the Palestinian settings. The analysis of CP interventions acceptance by physicians was performed.
Results: During the 4-month study period, the 117 patients admitted to the ICU were included into the analysis; 66 patients in the intervention group and 51 in the control group. The interventions made by a clinical pharmacist resulted in direct cost saving of NIS8,990.05 ($2799.63) and cost avoidance of NIS22,087.5 ($ 6878.37). Translated into a net savings of NIS188.35 ($58.65) per intervention and NIS470 ($146.36) per patient. Comparison of benefits (NIS31,077.55) ($9678.00) and costs (NIS19,043.928) ($5930.55) indicate a net economic benefit to the institution of (NIS 12,033.623) ($3747.44) and a benefit cost ratio of 1.63.
Conclusion: Integrating a clinical pharmacist in the ICU team was investment that resulted in benefits in term of cost saving and cost avoidance.

Abbreviations: CP, Clinical pharmacist; TRP, Treatment related problems; ADE, Adverse drug event; BCR, Benefit cost ratio.

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1. Introduction

Critically ill patients who are often older with multiple co-morbidities are at high risk for the occurrence of adverse drug events (ADEs) due to change in organs functions, alterations in pharmacokinetics and polypharmacy, the complexity of this process involving constantly changing doses which contributes to medication errors and adverse drug events (Fuchs et al., 2012; Kane-Gill et al., 2012; Michalets, Creger, and Shillinglaw 2015).

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Many studies have evaluated the role of the clinical pharmacists within multidisciplinary ICU team that resulted in significant reduction in the duration of stay in the ICU and ADEs and an overall cost reductions (Gallagher et al., 2014; Leape et al., 1999; Kearney et al., 2018; Rottenkolber et al., 2012; Yasunaga et al., 2016).

Clinical pharmacy services are still primitive in Palestine with only 7 PharmDs working in public hospitals delivering pharmaceutical services from centralized locations with heavy workloads (MoH 2020), which result in limited time for providing clinical pharmacy services with reasonable quality (Khdour et al. 2013). Hence many patients especially the ICU patients do not receive the desired beneficial effects of their treatment due to treatment related problems that cause both unnecessary suffering and huge costs to society (Khdour et al., 2013; MoH, 2020).

The Study aim to evaluate the cost benefit of clinical pharmacist interventions in assessing treatment related problems among medical intensive care unit patients in the Palestinian Medical Complex (PMC) in Ramallah City.

2. Methodology

A prospective interventional study was conducted for economic evaluation of clinical pharmacist's interventions in detecting and managing of treatment related problems (TRPs) as part of multidisciplinary medical intensive care unit team using cost benefit analysis model adopted from pharmacoeconomic guidelines (Tömöri, 2015) and pharmacoeconomic analysis of clinical staff pharmacist practice model (Nesbit et al., 2001).

2.1. Setting of the study

The study was conducted in the ICU at the Palestine Medical Complex (PMC), which has 279 beds and 86.4 % bed occupancy rate (MoH, 2020). The PMC serves as a referral hospital in the West Bank of Palestine. The Ramallah s Son Wing s ICU department has 10 adult ICU beds for both medical and surgical cases. The average length of patient s stay in MoH hospitals is 2.8 days (MoH, 2019). The average length of patient stay at Ramallah hospital ICU is 3–4 days according to Ramallah Hospital s ICU records.

2.2. Study population and sample size

All patients age over 18 and admitted to the PMC ICU during 4-month study period (between September-December 2020) for medical services were included in the study. The patients enrolled were clinical cases from emergency or the wards departments. Patients who were admitted for surgical services were excluded from the study.

2.3. Sampling method

After excluding ICU patients admitted for surgical services, patients in ICU who were admitted for medical services were randomly allocated into either a routine care service (control group) or an interventional clinical pharmacy service (intervention group) via randomization generator program. The randomization scheme was generated by using the Web site Randomization.com (Dallal, 2007). Control group to account for natural fluctuation in the absence of clinical pharmacist intervention used as baseline against which the clinical pharmacist intervention is assessed.

2.4. Data collection

The clinical pharmacist gathered all the required subjective and objective information about the patient in order to comprehend the patient's relevant medical/medication history and clinical condition. This information was collected from multiple sources; patient electronic medical files, clinical pharmacist bedside evaluation, and participation in physician round medication prescription and monitoring. The clinical pharmacist recorded the health data for each patient on a consult note form derived from a specially designed and validated Pharmaceutical Care Manual used by clinical pharmacists at the University of Jordan with modifications (AbuRuz et al., 2007).

2.5. Clinical pharmacy service / clinical pharmacist patient care process

PMC ICU does not yet offer CP services. In order to perform the study, the author acquired a volunteered clinical pharmacist (PharmD). Clinical pharmacist was available at ICU ward for five days a week from 8.00 a.m. to 3.00p.m. of the day and maintained contact with the ICU team as needed. A day of clinical pharmacist in ICU started by collection the necessary subjective and objective information about the patient prior morning round in order to understand the relevant medical/medication history and clinical status of the patient then the CP assessed the information collected and analyzed the clinical effects of the patient's therapy in the context of the patient's overall health goals in order to identify and prioritize TRPs and achieve optimal care using evidence based medicine. During morning rounds, the clinical pharmacist collaborated with the ICU team to develop an individual patient-centered care plan to discuss treatment and recommend improvements in patient treatment-related problems. Both newly admitted patients and patients who had already been admitted to the ICU for medical services were randomly allocated into groups and discussed. The CP's suggestions for altering the course of treatment were discussed. Only interventions approved by the ICU team were carried out.(American College of Clinical Pharmacy, 2012). ICU team maintained the blinding of patients with regard to whether changes were based on recommendations by the CP.

2.6. Economic analysis

Each CP intervention was assessed for drug related cost savings and cost avoidance of adverse drug events (ADEs) due to CP intervention. Benefits in terms of cost savings and cost avoidance were compared with the cost of the CP intervention to determine the net economic impact on the institution. The cost savings generated by CP interventions were compared to cost savings resulted in the control group due to physician interventions. Cost avoidance were not calculated in the control group as it was the cost avoided by eliminating the occurrence of ADEs as a consequence of the pharmacist interventions.

A. Direct cost savings analysis:

Cost savings where cost of drug therapy assumed to extend to the end of therapy with the new agent before intervention minus cost of drug therapy after intervention plus cost of drug that was used before intervention. Any increased cost of patient's therapy as a result of clinical pharmacist intervention were considered as negative cost savings. Medication costs were computed using cost prices at the Ministry of Health (General Directorate of Pharmacy, 2020). The cost of any drug therapy = The cost of drug therapy per unit * frequency per day * duration of therapy.

B. Cost avoidance analysis:

This cost is related to the clinical pharmacist interventions with potential to avoid adverse drug events (ADEs). Each intervention

was evaluated to estimate the probability of an ADE in the absence of the clinical pharmacist intervention using Nesbit methodology (Nesbit et al., 2001).

The Nesbit methodology was used to determine the likelihood that a patient would be harmed if a cp did not intervene. A 7-member panel of cp specialists (3 cp specialized in main area, 6 of them had residency certification, and 6 of them had board certification) used a consensus approach to determine the chance that a patient would be harmed if no action was taken by the cp. The probability of an ADE in the absence of the intervention is set at 0, 0.01, 0.1, 0.4, or 0.6. These categories correspond to the likelihood of an ADE being zero, very low, low, medium, or high. as clarified in Table 1.

Since cost of ADE in ICU settings was not previously evaluated or calculated in Palestine, Nesbit probability score is the most appropriate method in estimating the cost avoidance of probably occurring ADE in the absence of clinical pharmacist interventions (cost avoidance).

a. Assumptions for cost of ADE in ICU settings

There were no studies in Arab world nor in developing countries to estimate the economic burden of ADEs in ICU patients. We assumed that for each ADE in ICU settings would result in longer hospital stay by one day. The cost of one day ICU stay is estimated to about NIS750() taking into consideration the high occupancy rate of the PMC and average length of ICU stay of 3–4 days by the hospital accounting department.

Moreover, the cost of providing clinical pharmacist service, is considered as a salary of newly employed clinical pharmacist plus any increased cost of therapy in the intervention group (negative cost savings).

2.7. Statistical analysis

IBM SPSS (v.26) was used to tabulate and analyze the collected data. Categorical data was expressed as proportions (%) and the continuous data as mean ± SD. Chi squared tests (for sex and patient status at discharge), APACHE score (for severity of caseses-timates ICU mortality based on a number of laboratory values and patient signs taking both acute and chronic disease into account.) and independent sample *t*-test (was used to assess the differences between the two groups at baseline).

2.8. Sensitivity analysis

For the cost-benefit analysis, one- and two-way deterministic sensitivity analysis were undertaken in the base case of the cost analysis in order to assess the impact that changes in a certain input (clinical pharmacist salary, cost of ADE) will have on the output results of an economic evaluation (Benefit to cost ratio). In addition to that, the sensitivity analysis compared the study's findings to an alternative scenario in which the Nesbit method was used to estimate cost avoidance due to routine practice in the control group. The resulting cost avoidance was then used as the baseline against which the cost avoidance of the intervention group was calculated.

Table 1
Nesbit method for calculating cost avoidance.

Probability score	Probability of ADE occurring	Explanation of the probability	Example
0.6	**high**	Harm is expected life threatening, prevented a potentially fatal or severe reaction	10x normal dose
0.4	**medium**	Harm is expected, clinically relevant, prevented a potentially serious reaction	adjustment of renal failure
0.1	**low**	Some harm is expected, but poorly clinically relevant; i.e., prevented a potentially significant reaction	2-4x normal dose
0.01	**very low**	Problem orders, clarifications, missing information etc.	
0	**zero**	Information only	

2.9. Ethical considerations

Before beginning the study, ethical approval from the research committee of Al Quds University was obtained. Moreover, the MOH provided permission to conduct the study at PMC. Furthermore, all participants were provided with an information sheet explaining the aim of the study and assurance of the confidentiality of data collected before signing the informed consent to participate in the study.

3. The results

3.1. Participants characteristics

During the study period 117 patients were admitted to ICU for medical services were included in the analysis, where 66 patients were allocated in the intervention group and 51 in the control group.

Table 2 shows patient characteristics in both groups. There is no significant difference with respect to age, sex, and APACHE 2 score, length of stay, patient status at discharge between groups (p value > 0.05). Moreover, there is no significant difference between intervention and control groups with respect to number of TRP identified by the clinical pharmacist. There were also non-life-threatening TRPs identified in control group.

3.2. Treatment related problem (TRP)

The clinical pharmacist (CP) identified 296 TRPs in both groups, 172 TRPs in the intervention group of which 7 CP interventions were rejected by the physician and the remaining and 165 CP interventions were accepted by physician and implemented in the intervention group by the ICU team on 66 patients in 8 categories as represented in Table 3.

Table 2
Characteristics of patients who were admitted to ICU for medical services.

Participants characteristics	Intervention group (n = 66)	Control group (n = 51)	P value
Age mean and SD	58.30 (18.913)	64.78 (16.952)	0.057**
Gender (%) Male	59.1	54.9	0.79*
Female	40.9	45.1	
APACHE-2 score Mean, (SD)	12.14 (7.321)	13.37 (7.4)	0.369**
Length of stay Mean, (SD)	5.55 (3.347)	5.55 (3.306)	0.955**
Alive patient' (%) at discharge	65.2	76.5	0.262*
Dead patient' (%) at discharge	34.8	23.5	
TRP detected by CP (N)	165	131	0.816**
%	(2.48)	2.56	
SD	1.947	1.9	

* Chi square test.
** Two sample *t*-test.

Table 3
Frequency and percentage of TRPs detected in both groups.

TRP categories	Intervention group		Control group	
	No	%	No	%
Unnecessary drug therapy	58	34.0	17	30.0
Safety	36	21.0	4	7.0
Untreated condition	28	16.0	0	0.0
Efficacy	28	16.0	2	4.0
Miscellaneous	10	6.0	1	2.0
No TRP found	7	4.0	32	57.0
TRP on discharge	4	2.0	0	0.0
Inappropriate knowledge	1	1.0	0	0.0
Total	172	100.0	56	100.0

Many of the TRPs were detected by the clinical pharmacist during participation in the morning round with medical ICU team and many of them were prevented before reaching the patients in the intervention group. Unnecessary drug therapy related problems were the most common TRP category identified by the CP in the intervention group followed by safety and untreated condition related problems.

ICU specialist detected 56 TRPs in the control group and resolved 24 of them. Unnecessary drug therapy were the most common TRPs category observed.

3.3. Types of clinical pharmacist interventions /assessments

Table 4 shows the accepted CP assessment categories by ICU physician using evidence-based medicine. Stepping down current therapy was the most frequent type of intervention occurring (22 %). Untreated conditions that require adding pharmacological therapy (17 %) and safety issues that require dosage adjustment (17 %) were scored most.

Table 4
Categories of the clinical pharmacist' assessments and interventions by the treating ICU team in the intervention group.

Type of clinical pharmacist' assessment/ intervention	No	%
Treatment should be stepped down	37	22.0
Untreated conditions that require pharmacological therapy	30	17.0
Safety dosage regimen issues	29	17.0
The patient requires additional/ combination therapy or stepping up	16	9.0
Discontinue / drug used without indication	12	7.0
Efficacy dosage regimen issues	7	4.0
No interventions detected	7	4.0
Rejected interventions by ICU specialist	7	4.0
The patient is at high risk for developing ADR and needs monitoring or prophylaxis	6	3.0
Duplication needs to discontinue one medication	4	2.0
More effective drug was recommended	3	2.0
Unnecessary drug therapy on discharge	3	2.0
The chosen medication/s is/ are not cost effective	2	1.0
Other dosage regimen issues; e.g. (a) Dosage too low or (b) Dosage too (c) The route or dosage form is not appropriate, considering efficacy, safety and/or guidelines recommendations (d) Timing is not appropriate	2	1.0
Patient adherence problem /information only provided	2	1.0
A safer drug is recommended	1	1.0
The patient is not instructed or does not understand non-pharmacological therapy or self-care advice	1	1.0
A need for consultation	1	1.0
A need for additional or more frequent monitoring	1	1.0
The patient was discharged too early (i.e., before achieving recommended target)	1	1.0
Total	172	100.0

The clinical pharmacist most frequently advised to intervene on antibiotics group of medication (22 %). The second type of medication that necessitated the intervention of the clinical pharmacist was gastrointestinal medications specifically proton pump inhibitors (PPI) and ranitidine (16 %). For untreated hyper/hypoglycemia, the clinical pharmacist frequently recommended adding/adjusting the dose of antidiabetic insulin (NPH) (15 %). Furthermore, the anticoagulants class of medications frequently required dose adjustments by clinical pharmacists (13 %) as presented in Table 5.

3.4. Physician decision

A total of 158 (92 %) of the CP interventions were accepted by physicians and implemented in the intervention group patients. Seven (4 %) of the CP interventions were rejected under the category of unnecessary drug therapy and miscellaneous. The rest were accepted with proposed modified plan.

In the intervention group, 59 (89 %) patients in the intervention group had at least one TRPs and 46 (69 %) patients had at least two TRPs, one patient (2 %) had 12 TRPs, while 7 patients (11 %) had no TRPs as presented in Table 6.

3.5. Cost analysis results

Over a 4-month period, 172 TRPs were identified by the CP and 165 TRPs were resolved and implemented in the intervention group resulted in direct cost saving of NIS8,990.05, cost avoidance of NIS22,087.5, and added cost on therapy (negative cost savings) of NIS3,043.93. In contrast, 56 TRPs were identified and 24 TRPs were resolved by the physician in the control group resulted in direct cost saving of NIS1,941.05.

1) Cost saving:

The majority of TRPs associated with the most cost savings generated by the CP in the intervention group were under the categories of "unnecessary drug therapy" (34 %) and "safety," (21 %) resulting in direct cost savings of (NIS4,420.3) and (NIS4,165.96) respectively.

Interventions, on the other hand, associated with most increased cost of therapy in the intervention group were for TRPs in the categories of "efficacy" (NIS1,895.63) and "untreated condition" (NIS1,102.4) as illustrated in Table 7.

There were 24 TRPs in the control group resolved by physicians and associated with a total cost saving of **NIS1,941.05** under the category of "unnecessary drug therapy" (30 %) which resulted in direct cost savings of (NIS1,853.47). The remaining resolutions were categorized under "miscellaneous" 2 % and "safety" 7 % with

Table 5
Drugs involved in the accepted clinical pharmacist interventions by the ICU team.

Drugs involved	No	%
Antibiotic (e.g., vancomycin, ceftriaxone, piperacillin-tazobactam, teicoplanin)	36	22.0
Gastro intestinal (PPI, Ranitidine)	26	16.0
Antidiabetic NPH insulin	25	15.0
Others; e.g., … SPS kayexalate for hyperkalemia.	25	15.0
Anticoagulants (enoxaparin)	21	13.0
Blood pressure and cardiac	16	10.0
Intervention not involved drugs (e.g., a need for consultation, lab monitoring, adding dextrose water for hypoglycemia ….)	9	5.0
Central nervous system	6	4.0
Sedatives and pain	1	1.0
Total	**165**	**100.0**

Table 6
Accepted clinical pharmacist interventions per patient in the intervention group.

No of interventions found in the intervention group	No of patients	%
0 accepted intervention *	7	11.0
1 accepted intervention	13	20.0
2 accepted interventions	23	35.0
3 accepted interventions	8	12.0
4 accepted interventions	5	8.0
5 accepted interventions	9	14.0
12 accepted interventions	1	2.0
Total	**66**	**100.0**

* No TRP found.

cost savings of (NIS43.92), (NIS43.3) respectively. Cost analysis results in the both groups are summarized in Table 7.

2) Cost avoidance:

The overall cost avoidance generated by the clinical pharmacist in the intervention group during the 4-month period using Nesbit methodology was **NIS22,087.5**. Most of CP interventions within low and very low probability of preventable ADE fall under the category of "unnecessary drug therapy" TRP and most of CP interventions within medium and high probability of preventable ADE fall under the category of "safety" TRPs. Cost avoidance was highest for "safety" TRPs estimated NIS9,675 followed by "unnecessary drug therapy" TRPs estimated NIS4,447.5. Cost avoidance results are illustrated in Table 8..

In the West Bank, the average monthly salary of a clinical pharmacist (Pharm D) working in public hospital is NIS4,000 according to MoH accounting department. Taking into consideration this and the negative cost saving (**NIS3,043.93**) in the intervention group, the total cost of the clinical pharmacy service totaled NIS19,043.928 during the 4-month period.

3) Cost benefit analysis

The interventions made by clinical pharmacist resulted in direct cost saving of NIS8,990.05 and cost avoidance of NIS22,087.5 totaled NIS31,077.55 during the study period. Translated into total cost savings of NIS188.35 per CP intervention. Comparison of benefits (NIS31,077.55) and costs (NIS19,043.928) indicates a net economic benefit to the institution of (NIS12,033.323) and a benefit-cost ratio of 1.63 as reported in Table 9.

3.6. Sensitivity analysis

The cost-benefit ratio remained positive in all measured scenarios in the one-way sensitivity analysis. The economic model was insensitive to uncertainty in the clinical pharmacist salary. Varying the salary within the established limits (NIS2492 - NIS5500) did not push the benefit-cost ratio below 1:1. The largest variance was found in cost assigned to an ADE cost. However, varying the cost estimates within the established limits (extended length of stay due to ADE between 1 and 30 days) had no effect on the benefit-cost ratio falling below 1:1. The benefit-cost ratio became 1:1 if the cost of an ADE was reduced to NIS343.75 (LOS 11 hrs.).

Table 8
Cost avoidance analysis per TRP category in the Intervention group.

TRP categories	No. of interventions by CP	%	Cost Avoidance (NIS)
Safety	36	21.0	9,675
Unnecessary drug therapy	58	34.0	4,447.50
Untreated condition	28	16.0	3,300
Efficacy	28	16.0	3,225
Miscellaneous	10	6.0	1,207.50
TRP on discharge	4	2.0	232.5
No TRP found	7	4.0	0
Inappropriate knowledge	1	1.0	0
Total	**172**	**100.0**	**22,087.50**

Table 9
Cost benefit outcome analysis.

	Variable	Formula for calculations	Results
A	Cost saving (NIS)	Cost of drug therapy assumed to extend to the end of therapy with the new agent before intervention) minus (cost of drug therapy after intervention plus cost of drug that was used before intervention).	8,990.05
B	Cost avoidance (NIS)	(The probability of an adverse drug event in the absence of the intervention) multiple by * (ADE cost).	22,087.5
C	Cost of service (NIS)	(Clinical pharmacist salary) plus (any increased cost of treatment due to intervention; negative cost saving).	19,043.928
D	Benefits (NIS)	A + B	31,077.55
E	Net benefit (NIS)	D– C	12,033.623
F	Benefit to cost ratio (BCR)	D / C	1.63
G	Return on investment (ROI)	E / C *100 %	63 %
H	Benefit / intervention (NIS)	D/165	188.35
I	Benefit/patient (NIS)	D/66	470.87

Table 7
Direct cost savings results in both groups.

Groups	Intervention group				Control group **		
TRP categories	**No. of interventions by CP**	**%**	**Cost savings (NIS)**	**Added cost (Negative cost) NIS**	**No. of interventions by physicians**	**%**	**Cost saving (NIS)**
Unnecessary drug therapy	58	34.0	4420.30	19.52	17	30.0	1853.47
Safety	36	21.0	4165.96	26.38	4	7.0	43.30
Untreated condition	28	16.0	0.00	1102.40	0	0.0	0.00
Efficacy	28	16.0	11.94	1895.63	2	4.0	0.36
Miscellaneous	10	6.0	78.20	0.00	1	2.0	43.92
No TRP found	7	4.0	0.00	0.00	32	57.0	0.00
TRP on discharge	4	2.0	313.65	0.00	0	0.0	0.00
Inappropriate knowledge	1	1.0	0.00	0.00	0	0.0	0.00
Total	**172**	**100.0**	**8990.05**	**3043.93**	**56**	**100.0**	**1941.05**

**Only the positive cost saving included in analysis.

Varying the salaries and cost estimates simultaneously within the established limits did not push the benefit-cost ratio below 1:1. The benefit-cost ratio became 1:1 if the cost of an ADE was reduced to NIS343.75 (LOS 11 hrs.) at salary estimate of NIS4000.

Based on the scenario analysis that accounted for resolving TRPs under the usual course of care in the control group, the consequential total cost savings (cost saving and cost avoidance) in the control group were NIS3,441.05 during 4-month period. The adjusted final cost avoidance of the study intervention was, therefore, **NIS20,588** (i.e., NIS22,087.5 minus NIS1,500), translating into a net benefit of **NIS10,533.623** and a benefit-to-cost ratio of **1.55** during the 4-month period.

4. Discussion

During the 4-month study period, the 117 patients admitted to the ICU were included into the analysis; 66 patients in the intervention group and 51 in the control group. The interventions made by a clinical pharmacist resulted in direct cost saving of NIS8,990.05 ($2799.63) -compared to the control group NIS1,941.05 ($575.40)- and cost avoidance of NIS22,087.5 ($ 6878.37). Translated into a net savings of NIS188.35 ($58.65) per intervention and NIS470 ($146.36) per patient. Comparison of benefits (NIS31,077.55) ($9678.00) and costs (NIS19,043.928) ($5930.55) indicate a net economic benefit to the institution of (NIS 12,033.623) ($3747.44) and a benefit cost ratio of 1.63.

To our knowledge, this is the first prospective interventional study in a Palestinian hospital that economically assesses clinical pharmacist interventions to resolve TRPs in ICU patients within multidisciplinary team. A few studies have been done in the Middle East to examine the economic impact of disease-specific clinical pharmacy services in ICU settings (Aljbouri et al., 2013).

To persuade policy and decision makers that a clinical pharmacist will generate a positive "return on investment" in ICU settings, clinical pharmacists must demonstrate the economic value of their interventions to institutions by avoiding costs rather than generating revenues. In this study, the aim was to assess the cost benefit of the clinical pharmacist interventions for resolving treatment related problems as part of a multidisciplinary medical intensive care unit (MICU) team.

A wide variety of TRPs were enrolled in this study, with the clinical pharmacist. The fact that 46 patients (69 %) in the intervention group had at least two TRPs, highlights the magnitude of the problem.

The proportion of accepted interventions in this study is 91.9 % which is comparable with a study conducted in a Jordanian general hospital's internal medicine department (91 %) (AbuRuz et al., 2011). Similar to a study by Mahmoodpoor et al., (2018), in which intensivists accepted (93.6 %) of clinical pharmacist recommendations in the ICU of Shohada hospital in Tabriz. Despite the fact that clinical pharmacy service was not yet a formal service in all these hospitals, the high acceptance rate of this study interventions reflects the high quality of the recommendations made by the clinical pharmacist. This can be attributed to the clinical pharmacist "comprehensive medication management approach" which entails optimizing patient medication by assessing the appropriateness, safety and efficacy of each patient's medications and actively participating in patient care rounds collaboratively with the ICU team (American College of Clinical Pharmacy, 2012).

The most common TRPs associated with the most direct cost saving due to clinical pharmacist interventions were unnecessary drug therapy (34 %) that necessitated stepping down (22.5 %) and safety related problems (21 %) that required dosage adjustment (17 %). Antibiotics, PPI and anticoagulants represented the majority of drugs requiring dose adjustment by the clinical pharmacists based on individual renal function. These results are consistent with those of other researchers; (Reinau et al., 2019) who found that the most frequent types of pharmacist interventions were dose adjustment (24.0 %), followed by drug discontinuation (23.5 %). Gallagher and colleagues (Gallagher et al., 2014) found that the most common types of CP interventions were medication omissions (65.93 %), followed by dosage adjustments (21.61 %). These types of TRPs reflect a problem in ICU patients medication prescribing and monitoring, emphasizing the importance of clinical pharmacists in optimizing prescriptions that will contribute to the avoidance of preventable ADRs and associated costs in ICU patients.

The Nesbit method produces the most accurate published estimate of the cost of an ADE (Bates et al., 1997; Chen et al., 2017; Kopp et al., 2006; Nesbit et al., 2001). The probability categories used in the cost-avoidance calculation in the absence of intervention were conservative, with the maximum probability of an ADE set at 0.6. In this study,the majority of estimated probability scores were low, which is consistent with most relevant studies using the same method (Al-Qudah et al., 2019; Bosma et al., 2018; Gallagher et al., 2014).

Earlier studies' estimates of the ADE cost price differed. While Rottenkolber and colleagues (Rottenkolber et al., 2012) estimated the mean excess treatment of ADE patients equal €970 ($1,153.4), Nesbit and colleagues estimated ADE cost price as $5006 (Nesbit et al., 2001). A scoping review conducted with 38 cost intervention categories ranging from ($55.45 to $19,897.16) (Hammond, Gurnani, et al., 2019).

There was clear evidence of the value of CP interventions. The savings resulted from managing treatment related problems significantly outweighed the costs of clinical pharmacist involvement described in this study. Total cost savings (benefits) was estimated to be NIS31,077.55 ($9,857.55), similar favorable results were found with a retrospective study estimated a potential saving of €10,905 ($12,982.62) as a result of pharmacist interventions regarding antimicrobials in ICU over 5-month in Spain (Leache et al., 2019). These findings highlight the critical role of CP in enhancing the quality of treatment offered, as well as lowering TRP patient suffering and associated costs to health institutions and society.

It may be unreasonable to compare the benefit-cost of this study to studies conducted in other countries because the medication costs, clinical pharmacist salaries and medical service costs differ greatly. Moreover, many of the variations are possibly due to different methodologies or cost calculations. For example, Al Qudah and colleagues found in their RCT CBA study the BCR of cp interventions in outpatient settings equate 5.98 (Al-Qudah et al., 2019). Similarly a retrospective study, which compared the number of pharmacist interventions 1 year before and after a clinical pharmacist was deployed in a nephrology ward in Taiwan found the benefit/cost ratio increased from 4.29 to 9.36 after the on-ward deployment of a clinical pharmacist(Chen et al., 2017). Quality improvement research was carried out in the Netherlands at a general teaching hospital (GTH) and a university hospital (UH). The cost benefit for each accepted intervention was $139.48 (GTH) and $159.40 (UH). (Bosma et al., 2018) compared to study results; the CP generated benefits of NIS188.35 ($59.74) per intervention. This large disparity can be explained by the higher cost price used for an ADE as well as the fact that pharmacist salary expenditures were not included in their study. Regardless of the cost savings recorded in published studies, they all support the clinical pharmacist's importance in ICU.

The ACCP estimated that a benefit of $16.70 was realized for every $1.00 invested in clinical pharmacy programs (SCCM-ACCP, 2000). Compared to our study, the clinical pharmacist generated a benefit of NIS2 for every NIS1.00 invested in clinical pharmacy program in ICU; which is within the range of (1.05:1 to 25.95:1) reported by Touchette et al., (2014) work but lower when compared with the BCR of Nesbit et al., (2001), that ranged from 3.1 to 13.33.

In February 2016, a PharmD job description was created in Palestine. However, clinical pharmacy services are still rudimentary with only 7 PharmDs working in public hospitals delivering pharmaceutical services from centralized locations (MoH, 2020), and many decision makers resist the employment of PharmDs due to current economic crises. This study provides an evidence to decision makers that clinical pharmacy services are a worthwhile investment; by employing a benefit-cost analysis model, which is used to decide whether to implement one specific intervention or program, and can be determined if net benefits are greater than zero and BCR is greater than one (Tömöri, 2015). According to the conclusions of this study (Net Benefit: NIS12,033.623, BCR: 1.63), cp service is a good investment that should be introduced in ICU.

Accurate data on the cost of a preventable ADE are not available in Palestine was the main limitation in the study. As a result, cost avoidance calculations were based on estimated ADE probabilities rather than real economic data.

5. Recommendation

The Palestinian Ministry of Health should take a more active role in integrating clinical pharmacists into the health system and promoting their interactions with other specialties, which will alleviate the current serious problem of "clinical pharmacist unemployment "and quality of patient care provided. For future research**,** we recommend to conduct more long-term studies with larger sample sizes and for longer periods of time. Also involve more hospitals and clinical pharmacists in the study, allowing them to practice in a variety of patient care settings.

6. Conclusions

Integrating a clinical pharmacist in the ICU team was an investment that resulted in cost savings and cost avoidance. With further formalizing clinical pharmacy services at hospital and integrating the clinical pharmacist as part of the critical care team, an even higher economic benefit is anticipated.

7. Consent to participate

Informed consent was obtained from all individual participants included in the study.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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