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ORIGINAL PAPER

Economic Impact of Pharmaceutical Recommendations Carried Out in a Liver Transplant Unit of a University Hospital

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ABSTRACT

Introduction: Advances in medicine have provided the possibility of organs and tissues transplantation for therapeutic purposes. Transplant patients, in addition to immunosuppressive therapy, mostly undergo treatment for other comorbidities, and this polypharmacy makes the role of the pharmacist extremely important to ensure patient safety and adherence. Through pharmaceutical recommendations, the professional can reduce morbidity and mortality and thus reduce healthcare costs. **Methods:** This is an observational, retrospective descriptive study, carried out from January 2021 to December 2022, aiming to analyze the economic impact of pharmaceutical recommendations made in a liver transplant unit of an university hospital. Data collection took place from May to August 2023 through the institution's clinical pharmacy database. The economic impact was classified as effectiveness increased (EI), cost reduction (RC), and avoided risk (AR) calculated through a methodology developed and adapted to the study's reality. Medication acquisition costs were verified through the hospital's own system, and the values were adjusted according to inflation in June 2023. **Results:** A total of 363 pharmaceutical recommendations (PR) were conducted, of which the EI represented 64% (n = 231), followed by RC (20%, n = 72) and risk avoided (16%, n = 60). The total resulting value corrected by the Índice Nacional de Preços ao Consumidor Amplo (IPCA) was R$ 179,223.31, with the AE at R$ 140,414.04 and the RC at R$ 38,809.27. **Conclusion**: The importance of the clinical pharmacist in the multidisciplinary team is evident through the improvement of patient monitoring and health condition management. Through this study, we can perceive that the PR presented had a considerable financial impact, and, through the optimization of pharmacotherapy for transplant patients, an increase in therapeutic EI was obtained. The importance of developing further studies showing the impact of the quality of care provided by the pharmacy's performance is clear, to further highlight the importance of this field for healthcare assistance.

Descriptors: Pharmaceutical Recommendation; Transplant; Clinical Pharmacy.

Impacto Econômico das Recomendações Farmacêuticas Realizadas em uma Unidade de Transplante Hepático de um Hospital Universitário

RESUMO

Introdução: Os avanços na medicina proporcionaram a possibilidade do transplante de órgãos e tecidos para fins terapêuticos. Os pacientes transplantados, além da terapia imunossupressora, fazem, em sua maioria, tratamento para outras comorbidade e essa polifarmácia faz com que o papel do farmacêutico seja de extrema importância para garantir a segurança e a adesão do paciente. Por meio das recomendações farmacêuticas (RF), o profissional consegue reduzir a morbimortalidade e o tempo de internação, assim como os custos de saúde. **Métodos:** Trata-se de estudo observacional, descritivo retrospectivo, realizado no período de janeiro de 2021 a dezembro de 2022, que tem por objetivo analisar o impacto econômico das recomendações farmacêuticas realizadas em uma unidade de transplante hepático de um hospital universitário. A coleta de dados ocorreu no período de maio a agosto de 2023 com auxílio do banco de dados da farmácia clínica da instituição. O impacto econômico foi classificado como aumento de efetividade (AE), redução de custo (RC) e risco evitado (RE), calculados por uma metodologia desenvolvida e adaptada à realidade do estudo. Os custos relacionados à aquisição dos medicamentos foram verificados mediante o sistema próprio do hospital e os valores foram ajustados de acordo com a inflação de junho de 2023. **Resultados:** Foram realizadas 363 RF, das quais o AE representou 64% (n = 231), seguido por RC (20%, n = 72) e RE (16%, n = 60). O valor total resultante corrigido pelo Índice Nacional de Preços ao Consumidor Amplo (IPCA) foi de R$ 179.223,31, sendo o valor do RE de R$ 140.414,04 e da RC de R$ 38.809,27. **Conclusão:**

A importância do farmacêutico clínico na equipe multidisciplinar é evidente por meio da melhoria do acompanhamento dos pacientes, da monitorização e da gestão da condição de saúde. Por intermédio deste estudo podemos perceber que as RF apresentadas obtiveram impacto financeiro considerável e obteve-se, pela otimização da farmacoterapia dos pacientes transplantados, uma AE terapêutica. Percebe-se, ainda, a importância de se desenvolverem mais estudos que mostrem o impacto da qualidade assistencial proporcionada pela atuação da farmácia clínica, para que seja possível destacar a importância dessa seara para a assistência em saúde.

Descritores: Recomendação Farmacêutica; Transplante; Farmácia Clínica.

INTRODUCTION

Medicine has been exploring the concepts that permeate the limits between life and death since the 20th century. Advances in intensive medicine have made it possible to preserve organs in patients with brain death, opening space for organ and tissue transplantation for therapeutic purposes[1].

The first liver transplant in Brazil took place in São Paulo in 1968, and during the 1970s, the development of immunosuppression was observed. Thus, in 1984, liver transplantation left the experimental field and began to be considered a medical therapy[2].

The success of the transplant is directly linked to the patient's commitment to their treatment. Patients are at inherent risk of rejection, requiring them to undergo immunosuppressive therapy and be monitored for signs of rejection[3]. Furthermore, the transplant forces the patient to change lifestyle habits such as diet, hygiene, medications and health care[4].

A large proportion of transplant recipients undergo, in addition to immunosuppressive pharmacotherapy, treatment for chronic diseases, such as dyslipidemia, hypertension and diabetes, and use medications for antibacterial, antifungal and antiviral prophylaxis. Polypharmacy increases the risk of adverse reactions and drug interactions, in addition to making it difficult to use these medications[5].

Transplantation is more than an operation: it is a complex therapeutic procedure that, due to this complexity, requires the dedication of a large number of professionals[6]. A multidisciplinary approach is necessary to ensure adequate care for the transplant recipient. The pharmacist's role, mainly through his clinical role and pharmaceutical care, can reduce the risk of morbidity caused by pharmacotherapy, avoiding treatment failure and complications of combined therapy[7].

A global trend is strengthening the pharmacist's activity alongside the patient to ensure more effective care. In this way, the pharmacist takes on a more active role in therapy and patient care, highlighting the importance of their involvement in practices that help with patient safety, which is fundamental[8].

The pharmaceutical area directly linked to patient safety is clinical pharmacy, whose mission is to ensure the promotion, prevention and recovery of health and evaluate probable medication errors. In this way, the clinical pharmacist aims to optimize pharmacotherapy, providing the rational use of medications[9]. When there is a very well-implemented clinical pharmacy service, in addition to patient safety, there is a reduction in costs for the hospital. Reviews of medical records and clinical rounds carried out by the pharmacist favor appropriate recommendations for therapy, with a focus on rehabilitation and health recovery[10].

Prescription evaluation by the clinical pharmacist is critical to ensure adequate treatment and prevent, reduce and monitor adverse events. Its main objective is therapeutic success and patient safety, optimizing resources and minimizing costs[11]. Adequate pharmaceutical evaluation can result in pharmaceutical interventions, which are planned, documented, and carried out with users and health professionals to resolve or prevent disorders that may or may not interfere with pharmacotherapy, integrating the pharmacotherapeutic monitoring process. Through these interventions, the pharmacist provides guidance and promotes the rational use of medications[12].

It is estimated that for every US$1.00 invested in clinical pharmacy, US$4.81 in cost reduction (CR) and other economic benefits are obtained[13]. If there are no interventions, problems related to pharmacotherapy can compromise the effectiveness of drug therapy, increasing morbidity and mortality and hospitalization time and, consequently, health costs[14].

METHODS

Study design

This observational, descriptive study aims to observe, record and describe the characteristics of a specific phenomenon occurring in a sample or population[15]. Retrospective data was collected from records of pharmaceutical recommendations (PR) made in a liver transplant ward from January 2021 to December 2022 by clinical pharmacists from the service and resident pharmacists.

Search location

The study was conducted at the Walter Cantídio University Hospital in Fortaleza, state of Ceará, Brazil, located at Rua Pastor Samuel Munguba, 1290, district of Rodolfo Teófilo. The hospital is a reference in transplants, currently having a liver transplant ward with seven beds. A multidisciplinary team assists patients: doctors, nurses, clinical pharmacists, nutritionists, physiotherapists, psychologists, medical and interdisciplinary residents, and pharmaceutical residents.

Population and sample

The study population was made up of liver transplant patients hospitalized during the study period, either for the transplant or due to complications, over 18 years of age.

Data collect

Data was collected through records on specific forms and the database of the institution's clinical pharmacy unit, which is stored in Microsoft Excel® 2016.

Adaptations were made to the methodologies developed by Nesbit et al.[16], Saokaew et al.[17] and Gallagher et al.[18] to classify and calculate the economic impact related to PR to the reality of the service. The economic impact was classified as increased effectiveness (IE), cost reduction (CR) and avoided risk (AR).

The study defined IE as PR that could improve medication use and/or clinical effectiveness. In this classification, the value of R$0.00 was assigned to the economic impact, even though the recommendation increased the value of the treatment. The PR that reduced the cost was the one that reduced the value of the treatment when compared to the previously adopted therapeutic strategy without causing harm; to classify as avoided cost, PR was suggested to prevent or manage an adverse drug event (ADE)For the calculation of CR, the adapted formula was used, in which MC indicates the cost of the medicine in reais, DD is the daily dose (quantitative amount of medicine per day), DT is the days of treatment BPR is the cost of treatment before PR and APR is the cost of treatment after PR[17] (Eq. 1).

$$RC = (CM \times DDxDT)\ ARF - (CM \times DD \times DT)\ DRF \quad \text{(Eq. 1)}$$

The costs of workers, medical devices, length of stay, hospital supplies, laboratory tests, material and sterilization center, laundry, electricity and other tangible or intangible costs were not considered for the calculation, only the direct value of the medicine[19]. The unit value of the medicine was supposed to be the same as the purchase price in the year in which the PR was carried out. This value was consulted in the computerized Master® system used by the institution during the medication acquisition period.

The costs avoided with the prevention of ADE were evaluated by adapting the probability scores of its occurrence if the PR was not performed. The risks were stratified into probability levels of 0 to 1.0 (0 chance until the occurrence of ADE), with a final value of 1, when the actual occurrence of ADE or exposure of the patient to a medication known to be related to a previous ADE had been identified, according to Table 1.

Table 1. Risk stratification of the probability of occurrence of ADE.

Stratified score	Probability of occurrence of ADE
0.00	Zero
0.01	Very low
0.10	Low
0.40	Average
0.60	High
1.00	ADE

Source: Holanda[19].

The value found was listed in the closest category. To this end, research was carried out in the scientific literature in the Micromedex®, UpToDate® and Medscape® databases to analyze the probability of ADE occurring in the absence of PR. When the sources were wildly divergent, the lowest approximate value was considered. The average value of R$ 3,195.42 will be used for the hospitalization of a patient who suffered an adverse event, according to the Brazilian study carried out by Porto et al.[20], in 2010, the value being adjusted for 2023 by the Broad National Consumer Price Index (*Índice Nacional de Preços ao Consumidor Amplo- IPCA*), calculated directly on the Central Bank of Brazil website[21], considering the starting date as January 2021 and the end date as December 2022. Thus, the costs avoided will be calculated by classifying the probability of ADE occurrence multiplied by the hospitalization value of a patient with ADE[19]. For the final calculation of the economic impact, the sum of reduced and avoided costs will be considered (Eq. 2).

$$\text{Cost avoided} = \text{Probability of ADE occurrences} \times \text{Value of a patient hospitalization with ADE} \quad \text{(Eq. 2)}$$

Searched variables

We have the demographic profile, the pharmacotherapeutic profile and the profile of drug-related problems (DRP) and PR as study variables. The DRP and PR types were classified according to the terminology standardized by the institution's clinical pharmacy unit.

The following criteria were adopted to evaluate the economic impact of the change in pharmacotherapy[19].

- Duration protocols at the institution or the dose and treatment time provided in the medical request for antimicrobial release.
- Diluent for intravenous infusions, taking into account the type and volume of the diluent in its original packaging sold.
- Dosage variation, considering the accumulated dose over treatment time.
- Therapy with a duration determined by institutional protocol. The treatment time was based on the days established in the protocol.
- Treatment time was not foreseen in the protocol, adopting 30 days for treating chronic health problems and 7 days for acute ones or prophylaxis.

Inclusion criteria

These pharmaceutical recommendations were accepted in the liver transplant ward from January 2021 to December 2022.

Exclusion criteria

These are pharmaceutical recommendations without complete data, such as dose, pharmaceutical form, medicine name, lack of patient data, age and gender, or outside the study period.

Statistical analysis

Data were collected and stored in an electronic database using the Microsoft Excel® 2016 program and analyzed using descriptive statistics. For numerical variables, data were presented as a simple average. Categorical variables were presented as frequency and prevalence rates in percentage, and the results will be presented in tables and figures.

Ethical aspects

The project was approved by the Research Ethics Committee of the Walter Cantídio University Hospital, under CAAE 56178022.9.00005045, following resolution No. 466 of the National Health Council (*Conselho Nacional de Saúde-CNS*) of the Ministry of Health, considering respect for human dignity and the special protection owed to participants in scientific research involving human beings.

RESULTS

During the analysis period, 363 PRs were performed involving 111 patients, 60 (54.05%) male and 51 (45.95%) female. Of these RPs, 63.63% (n = 231) were related to EI, 19.83% (n = 72) to CR and 16.52% (n = 60) to AR (Table 2).

Table 2. Demographic profile of patients involved in RP performed during the study period in a liver transplant unit of a university hospital.

Gender	n (%)	Average age (years)	PR (n)
Male	60 (54,05)	53,62	363
Female	51 (45,95)		

Source: Database of the institution's clinical pharmacy unit.

Concerning problems related to medication, the prevalence of non-prescription of necessary medicines was found to be 20.11% (n = 73), inadequate infusion time in 13.50% (n = 49), inadequate dilution/reconstitution in 13.50% (n = 49), inadequate infusion time in 13.50% (n = 49) and overdose in 13.50% (n = 47) (Table 3).

Table 3. Classification of DPR identified during the study period in a liver transplant unit of a university hospital.

DPR	n (%)
Necessary medication not prescribed	73 (20,11)
Overdose	47 (12,95)
Inadequate infusion time	49 (13,50)
Underdose	29 (7,99)
Unnecessary medication prescribed	30 (8,26)
Inadequate dilution/reconstitution	49 (13,50)
Inappropriate route of administration	18 (4,96)
Exam not requested/carried out	18 (4,96)
Others	50 (13,77)

Source: Database of the institution's clinical pharmacy unit.

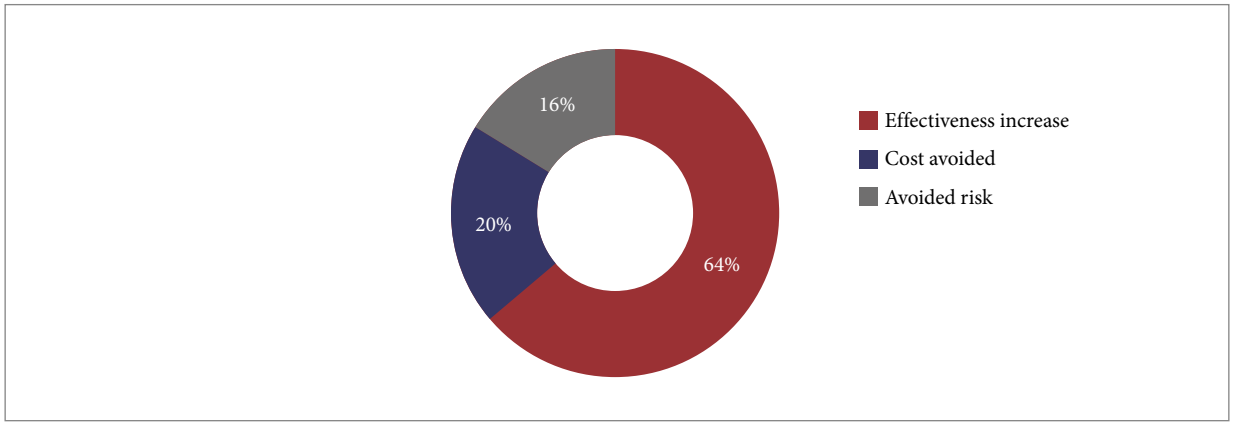
The most prevalent PRs, according to their classification, during the study period were: inclusion of medication in 20.11% (n = 73), adequacy of dose in 19.83% (n = 72), adequacy of infusion time in 13.77% (n = 50), adequacy of dilution/reconstitution in 13.22% (n = 48) and medication suspension in 12.67% (n = 46) (Table 4).

Table 4. Classification of PR was performed during the study period in a liver transplant unit at a university hospital.

PR Classification	n (%)
Dose adequacy	72 (19,83)
Inclusion of medication	73 (20,11)
Adequacy of infusion time	50 (13,77)
Medication replacement	11 (3,03)
Medication suspension	46 (12,67)
Adequacy of dilution/reconstitution	48 (13,22)
Adequacy of the route of administration	12 (3,31)
Adequacy of scheduling	13 (3,58)
Referral to other professionals	18 (4,96)
Others	20 (5,52)

Source: Database of the institution's clinical pharmacy unit.

It is observed that the most significant clinical impact was EI (64%, n = 231), followed by CR (20%, n = 72) and AR (16%, n = 60), as shown in Fig. 1.



Source: Database of the institution's clinical pharmacy unit.

Figure 1. Clinical impact values.

During the study period, CR pharmaceutical interventions reduced R$38,809.27, while AR interventions totaled R$140,414.04. Thus, the sum of CR and AR resulted in R$ 179,223.31 (Table 5).

Table 5. Economic impact of pharmaceutical interventions adjusted to the June 2023 IPCA.

Economic impact	IPCA of July 2023 (R$)
Cost reduction	38.809,27
Avoided risk	140.414,04
Total	179.223,31

Source: Database of the institution's clinical pharmacy unit.

DISCUSSION

The risks associated with patients are generally directly linked to problems that arise during the various phases of hospital health care, including the prescription, dispensing and administration of medications. The first step to avoiding these problems is admitting their existence, which can make patient care safer. Since 1999, the Institute of Medicine of the United States of America has addressed these problems and ways to avoid them, involving pharmacists in these approaches through analyzing pharmacotherapy and pharmaceutical interventions[22].

The characterization of liver recipients in this study corroborates the study of other authors from different parts of Brazil. Aguiar et al.[23] demonstrated the predominance of males (80%) and the age group of 40 to 59 years, highlighting the similarity with the current study, in which, of the total number of patients, 54.05% were male and in this age group, with an average of 53.62 years.

A study carried out in 2010 showed that 68.8% of DPR was necessary, 28% was related to safety and 2.5% to effectiveness[24]. In 2019, Oliveira et al.[25] also showed that problems related to "necessary medication not prescribed" are most prevalent (26.2%), followed by underdosing (14.3%) and overdose (13.4%). Such studies corroborate the values obtained by this study, in which the most prevalent DPR were "necessary medication not prescribed" (20.11%, n = 73), followed by inadequate infusion time and dilution (13.50%, n = 49) and overdose (12.95%, n = 47).

This study observed that the most suggested PRs were those related to the inclusion of medication, followed by dose adjustment and infusion time adjustment. A study published in 2019 showed that, among the main recommendations made by the pharmacist in a transplant unit, dose adequacy ranked third among the most prevalent and infusion time adequacy[26].

When evaluating the results by transplant specialty, it was observed that, in liver transplantation, there were a more significant number of recommendations related to dose adjustment, dilution/reconstitution and adjustment of infusion time[26], which partially corroborates the results shown by this study.

Another study carried out in a hospital in Ribeirão Preto, state of São Paulo, from 2017 to 2018, in a hematopoietic stem cell transplant unit, showed that among the most prevalent recommendations was the inclusion of medication, showing that this recommendation is standard not only in solid organ transplantation but in cell transplantation[27].

Martins[28] showed, through a study in a kidney transplant outpatient clinic, that PR increased the effectiveness or quality of therapy, improving the patient's health problems. This way, PR generated by DPR detection can increase patient safety and help reduce medication adverse outcomes. [29].

Although only a tiny percentage of interventions performed by clinical pharmacies are related to CR, a cost minimization analysis revealed that these interventions have the potential to result in significant savings without harming patient outcomes[30]. Arantes et al.[11] identified total savings of R$72,648.39 over 7 months. This value includes both direct and indirect costs and was obtained through the implementation of a prescription evaluation center (*central de avaliação de prescrição-CAP*) in seven wards and 10 intensive care units (ICU). This panorama allowed for a significant reduction in costs despite the considerable number of beds in these units, showing the vital role of the clinical pharmacist. The R$ 38,809.27 value presented by this study is of great importance, considering that the unit analyzed has only seven beds compared to that given by Arantes et al.[11].

The study conducted by Nascimento et al.[31] showed that the adverse events related to the identified medications resulted in a financial impact of R$ 96,877.90 for the institution participating in the research, for society and the Unified Health System (Sistema Único de Saúde-SUS). Of these events, 25 could have been avoided. The data from this study identified that, of the 363 recommendations, an avoided cost of R$ 140,414.04 was obtained, representing the ability to prevent or minimize adverse effects of PR.

The study has some limitations, such as the exclusion of specific interventions due to lack of data, the retrospective study design, the need to adapt the methodology to the Brazilian reality, and the limited time allocated to this type of research, which requires greater precision with the data. Furthermore, the need for more similar studies, both in the field of transplants and the pharmaceutical area, makes it challenging to discuss the results found regarding economic impact.

Therefore, this work brings novelties by showing the economic impact of clinical pharmacy in assisting liver transplant patients and applying a methodology for the financial analysis of RP, making it possible to use it in other centers with different profiles of patients.

CONCLUSION

Based on the results highlighted in this study, we can infer that the PR presented had a considerable financial impact. Furthermore, optimizing pharmacotherapy for liver transplant patients increased therapeutic effectiveness.

The recognition of the clinical pharmacist's importance as part of the multidisciplinary team was evident, as it contributed to improving patient follow-up, monitoring and management of their health conditions, resulting in a higher quality of care and management of health resources.

Finally, the importance of developing more studies on the topic addressed is highlighted to demonstrate the impact on the quality of care provided by the performance of clinical pharmacy.

CONFLICT OF INTEREST

Nothing to declare.

AUTHOR'S CONTRIBUTION

Substantive scientific and intellectual contributions to the study: Nascimento L, Alcântara JM, Barros A; **Data analysis and interpretation:** Nascimento L, Alcântara JM, Barros A, Cavalcante C; **Article writing:** Nascimento L, Alcântara JM, Barros A, Oliveira MG; **Critical revision:** Nascimento L, Alcântara JM, Barros A, Oliveira MG; **Final approval:** Nascimento L, Alcântara JM, Barros A, Oliveira MG.

DATA AVAILABILITY STATEMENT

Data will be available upon request.

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