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Original Article

Potential Drug Interactions in Prescriptions Corresponding to Patients after Liver Transplants

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ABSTRACT

Background: Patients that are subjected to transplants undergo various changes in their lifestyle, including a complex pharmacological treatment that needs adequate management. Therefore this study aims to analyze the potential drug interactions found in the prescriptions corresponding to transplant patients after liver transplants. **Materials and Methods:** A cross-sectional and descriptive study with a quantitative approach, developed in the Liver Transplant Outpatient Service of the Walter Cantídio University Hospital (*Hospital Universitário Walter Cantídio*, HUWC) belonging to the Federal University of Ceará (*Universidade Federal do Ceará*, UFC). A total of 31 prescriptions corresponding to patients recently subjected to transplants between July 2019 and December 2020 were analyzed. The study participants were adult patients recently subjected to transplants and aged between 18 and 75 years old at the time of the first pharmaceutical consultation, who had their medical records available, containing the medical prescriptions. The patients' pharmaco-epidemiological and clinical profile was outlined and the drug interactions were analyzed by resorting to the Micromedex 2.0® database. **Statistical analysis used:** The data were analyzed in the *Research Electronic Data Capture* (REDCap) statistical program. **Results:** There was prevalence of male patients aged between 40 and 60 years old, and the most frequent etiology of the transplants was alcoholic cirrhosis with no associated comorbidities (31.43%). The most frequent potential drug interactions were the following: tacrolimus + prednisone (27.45%), tacrolimus + omeprazole (22.55%), and tacrolimus + amlodipine (7.84%). The interactions were considered: a) regarding severity, as of 'moderate severity' (57.58%) and as of 'major severity' (39.39%); b) regarding documentation, predominantly as 'deficient' (54.55%); c) regarding the latency period: the majority was not specified (63.64%); and d) regarding the mechanism of action, the following were observed: those of a 'pharmacokinetic' origin (41.67%) and those of a of 'pharmacodynamic' origin (41.67%). **Conclusion:** Analysis of the potential drug interactions in transplanted patients is fundamental for the identification of risks, improving the safety of these patients and more assertively guiding the courses of action.

Keywords: Drug interactions, Liver transplant, Pharmaceutical Care.

Key Messages: This study may assist the multiprofessional team, especially pharmacists, in optimizing pharmacotherapy and conducting treatment of these specific patients: individuals subjected to liver transplants.

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INTRODUCTION

Liver transplant is the approach most frequently indicated for patients with liver diseases, when pharmacological treatment has shown no effectiveness.[1] Modernization of the pharmacological therapy adopted by the post-transplant protocols became more complex, generating greater potential for the occurrence of drug interactions (DIs) and for the emergence of adverse events.[2] The patients make use of immunosuppressants to avoid transplant rejection and, concomitantly, treatment is prescribed for associated comorbidities such as Diabetes Mellitus and Systemic Arterial Hypertension, in addition to medications with a prophylactic indication to prevent opportunistic infections. Very common in transplanted patients, polypharmacy potentiates the emergence of DIs, and their evaluation can assist the care team, thus promoting good quality treatment.[3] Pharmacists can contribute in a relevant way by cooperating with the patients and other health professionals, with identification of the problems related to pharmacotherapy as their first and foremost function, context in which DIs are introduced, which can excessively interfere in compliance of these patients; as well as by behaving as crucial professionals to improve the life context after the transplant. In this context, the main objective of this study was to analyze potential drug interactions found in the prescriptions corresponding to patients recently subjected to transplants and treated in the liver transplant outpatient service of a university hospital.

SUBJECTS AND METHODS

This is a descriptive and cross-sectional study with a quantitative approach, conducted from July 2019 to December 2020. The population consisted of patients in the phase immediately after liver transplant with up to one month of pharmaceutical monitoring in the Liver Transplant Outpatient Service of the Walter Cantídio University Hospital (HUWC) belonging to the Federal University of Ceará. The following inclusion criteria were applied to select the study participants: adult patients recently subjected to transplants, aged between 18 and 75 years old at the time of the first pharmaceutical consultation in the outpatient service and with up to one month after the transplant, and who had their medical records available in the outpatient service, containing the medical prescriptions. The exclusion criterion was the following: patients that did not have their medical records available to consult the pharmacotherapy prescribed.

A total of 167 patients were monitored by the Liver Transplant Outpatient Service; of these, 31 met the inclusion criteria, comprising the sample of this study. The variables of interest were name, gender, age, etiology of the liver disease, presence of comorbidities and medications prescribed.

The *Research Electronic Data Capture* (REDCap) statistical program was used for data processing and analysis. The drugs were classified according to the *Anatomical Therapeutic Chemical* (ATC) Classification and the IBM Micromedex 2.0® database was used for the analysis of the potential DIs. Regarding classification of the potential DIs, severity was categorized as minor, moderate and major; latency period, as fast, delayed or nonspecific; documentation, as excellent, good or deficient; and mechanism of action, as pharmacokinetic, pharmacodynamic or unknown.

The study was approved by the Research Ethics Committee of the Federal University of Ceará, under Opinion No. 3.358.115.

RESULTS

The predominant profile was that of men (61.29%, *n*=19) aged between 40 and 60 years old (38.70%, *n*=12). The main cause for the need of liver transplant was excessive alcohol consumption (26.47%, *n*=9). In addition to the liver disease diagnosis to perform the transplant, the most frequently identified comorbidities were Diabetes Mellitus (22.86%, *n*=8) and Systemic Arterial Hypertension (22.86%, *n*=8) (Table 1).

A total of 201 prescribed medications was obtained from the prescriptions analyzed (Table 2), with a mean of 6.48 medications per prescription. Tacrolimus was the immunosuppressant of choice for 100% of the patients and corresponded to 15.42% (*n*=31) of the medications prescribed. Other coadjuvant medications in maintenance of the immunosuppressant therapy were the following: prednisone (13.93%, *n*=28) and mycophenolate sodium (6.97%, *n*=14). Medications intended to prevent opportunistic infections were observed quite regularly, such as nystatin (14.93%, *n*=30) and sulfamethoxazole + trimethoprim (10.45%, *n*=21) (Table 2).

Table 1: Profile of post-transplant patients- HUWC, CE, Brazil, 2020.

Variables		n (%)
Gender	Female	12 (38,71)
	Male	19 (61,29)
Age	20 to 40 years	10 (32,26)
	40 to 60 years	12 (38,70)
	60 to 75 years	9 (29,04)
Origin of liver disease	Alcohol	9 (26,47)
	Cryptogenic cirrhosis	5 (14,71)
	NASH	4 (11,76)
	Hepatocarcinoma	3 (8,82)
	B virus cirrhosis	3 (8,82)
	C virus cirrhosis	2 (5,88)
	Budd Chiari Syndrome	2 (5,88)
	Schistosomiasis	1 (2,94)
	Hepatopulmonary Syndrome	1 (2,94)
	Polycystic Liver Disease	1 (2,94)
	Epitheloid hemangioedothelioma	1 (2,94)
	Cirrhosis due to hepatoportal sclerosis	1 (2,94)
	Secondary biliary cirrhosis	1 (2,94)
Comorbidities	Diabetes mellitus	8 (22,86)
	Systemic Arterial Hypertension	8 (22,86)
	Systemic Lupus Erythematosus	2 (5,71)
	Heart diseases	2 (5,71)
	Chronic Kidney Disease	1 (2,86)
	Dyslipidemia	1 (2,86)
	Osteoporosis	1 (2,86)
	Antiphospholipid antibody syndrome	1 (2,86)
	No comorbidities	11 (31,43)

Table 2: Frequency of drugs prescribed according to the 5th level of the ATC Classification, CE, Brazil, 2020.

Medicines	Code ATC	n	%
tacrolimus	L04AD02	31	15,42
nystatin	A07EA02	30	14,93
prednisone	H02AB07	28	13,93
omeprazole	A02BC01	23	11,44
sulfamethoxazole + trimethoprine	J01EE01	21	10,45
sodium mycophenolate	L04AA06	14	6,97
amlodipine	C08CA01	8	3,98
entecavir	J05AF10	3	1,49
furosemide	C03CA01	3	1,49
warfarin	B01A003	3	1,49
acetylsalicylic acid	B01AC06	3	1,49
metformin	A10BA02	3	1,49
folic acid	B03BB01	3	1,49
isoniazid	J04AC01	2	1,00
human anti-hepatitis B immunoglobulin	J06BB04	2	1,00
losartan	C09CA01	2	1,00
propranolol	C07AA05	2	1,00
ferrous sulphate	B03AA07	2	1,00
pyridoxine	A11HA02	2	1,00
calcium carbonate	A12AA04	2	1,00
regular human insulin	A10AB01	1	0,50
insulin glargine	A10AE04	1	0,50
insulin aspart	A10AB05	1	0,50
insulin degludec + liraglutide	A10AE56	1	0,50
glibenclamide	A10BB01	1	0,50
pantoprazole	A02BC02	1	0,50
saccharomyces boulardii	A07FA02	1	0,50
atenolol	C07AB03	1	0,50
escitalopram	N06AB10	1	0,50
topiramate	N03AX11	1	0,50
benzathine benzylpenicillin	J01CE08	1	0,50
ciprofloxacin	J01MA02	1	0,50
linagliptin	A10BH05	1	0,50
hydroxychloroquine	P01BA02	1	0,50
Total		**201**	**100,00**

Table 3: Frequency of potential drug interactions (drug-drug) identified from the prescriptions of recently transplanted patients and their potential risks- CE, Brazil, 2020.

Drug interactions	n	%	Potential risks related to interactions
tacrolimus + prednisone	28	27,45	Decreased blood concentration of tacrolimus
tacrolimus + omeprazole	23	22,55	Increased blood concentration of tacrolimus
tacrolimus + amlodipine	8	7,84	Increased blood concentration of tacrolimus
tacrolimus + acetylsalicylic acid	3	2,94	Acute renal failure
prednisone + acetylsalicylic acid	3	2,94	Increased risk of ulcerations and decreased ASA concentrations
prednisone + warfarin	3	2,94	Increased or decreased exposure to warfarin
omeprazole + warfarin	3	2,94	Increased anticoagulant effects
omeprazole + propranolol	2	1,96	Increased exposure to propranolol
sulfamethoxazole/trimetropine + warfarin	2	1,96	Increased exposure to warfarin
prednisone + isoniazid	2	1,96	Decreased effectiveness of Isoniazid
prednisone + propranolol	2	1,96	Decreased concentration of propranolol
glibenclamide + propranolol	1	0,98	Alteration of glucose metabolism, causing hyper or hypoglycemia
metformin + propranolol	1	0,98	Alteration of glucose metabolism, causing hyper or hypoglycemia
metformin + insulin degludec/liraglutide	1	0,98	Hypoglycemia
acetylsalicylic acid + metformin	1	0,98	Hypoglycemia
atenolol + insulin glargine	1	0,98	Alteration of glucose metabolism, causing hyper or hypoglycemia
atenolol + regular insulin	1	0,98	Alteration of glucose metabolism, causing hyper or hypoglycemia
losartan + insulin glargine	1	0,98	Hypoglycemia
losartan + regular insulin	1	0,98	Hypoglycemia
losartan + sulfamethoxazole/trimetropine	1	0,98	Hyperkalemia
sulfamethoxazole/trimetropine + insulin glargine	1	0,98	Hypoglycemia
sulfamethoxazole/trimetropine + regular insulin	1	0,98	Hypoglycemia
sulfamethoxazole/trimetropine + Insulin degludec/liraglutide	1	0,98	Hypoglycemia
metformin + insulin liraglutide/degludec	1	0,98	Hypoglycemia
tacrolimus + escitalopram	1	0,98	QT interval prolongation
omeprazole + escitalopram	1	0,98	Increased exposure to escitalopram
omeprazole + ferrous sulfate	1	0,98	Decreased iron bioavailability
prednisone + ciprofloxacin	1	0,98	Increased risk of tendonitis and tendon rupture
tacrolimus + ciprofloxacin	1	0,98	Increased blood concentrations of tacrolimus; QT interval prolongation
ferrous sulfate + sodium mycophenolate	1	0,98	Decreased effectiveness of mycophenolate sodium
tacrolimus + hydroxychloroquine	1	0,98	QT interval prolongation
calcium carbonate + hydroxychloroquine	1	0,98	Decreased exposure to hydroxychloroquine
acetylsalicylic acid + furosemide	1	0,98	Nephrotoxicity and reduced diuretic efficacy
Total	**102**	**100,0**	

Regarding the Dis (Table 3), 33 different potential DIs were identified, which were found 102 times, with those containing tacrolimus appearing the most, with 62.74% (*n*=64). The drug interactions most frequently identified were as follows: tacrolimus + prednisone (27.45%, *n*=28), tacrolimus + omeprazole (22.55%, *n*=23) and tacrolimus + amlodipine (7.84%, *n*=8). Regarding the frequencies of the potential DIs identified in the study, 60.78% (*n*=62) involved interactions with tacrolimus and, in relation to the risks associated with them, it was verified that they especially involved a reduction or increase in tacrolimus concentration, as described in the table below.

Of the potential DIs identified, 57.58% (*n*=19) and 39.39% (*n*=13) were considered as of moderate and major severity, respectively (Table 4). The documentation that served as the basis for the diverse information about the DIs was mostly considered as deficient (54.55%; *n*=18). Regarding the mechanism for the DI occurrences, 41.67% (*n*=15) involved pharmacokinetics and pharmacodynamics. Regarding the latency period, there was predominance of unspecified action initiation, with 63.64% (*n*=21).

DISCUSSION

The study allowed verifying that the patients who recently underwent transplant procedures are subjected to polypharmacy and, consequently, are more prone to suffering adverse events due to potential drug interactions.

Among the medications used, the most frequently prescribed pharmacological group was that of immunosuppressants (22.39%). This pattern was expected, as they are responsible for preventing or reversing

Table 4: Classification of potential drug interactions in terms of severity, documentation, mechanism of emergence and latency period - CE, Brazil, 2020.

Classification Criteria	n	%
Gravity		
Larger	13	39,39
Moderate	19	57,58
Smaller	1	3,03
Documentation		
Excellent	2	6,06
Good	13	39,39
Bad	18	54,55
Mechanism		
Pharmacokinetic	15	41,67
Pharmacodynamic	15	41,67
Unknown	6	16,66
Latency period		
Nonspecific	21	63,64
Retarded	10	30,30
Fast	2	6,06

transplant rejection by the recipient, inhibiting or reducing the immune system response to the graft's alloantigens.[4]

Various immunosuppressant classes were developed and transplantation centers worldwide adopt different immunosuppression protocols; in most cases, an association of a calcineurin inhibitor, together with a corticosteroid and an antimetabolic agent or mTor protein inhibitors, is prescribed as maintenance immunosuppression therapy.[5]

Tacrolimus was the immunosuppressant prescribed for all the study patients. According to the Clinical Protocol and Therapeutic Guidelines on Immunosuppression in Liver Transplant in adults, it is proved that the choice of using tacrolimus is superior to cyclosporine both in improving survival of the patient and of the transplanted organ and in preventing acute rejection after the transplant, although it does present increased risks of causing Diabetes Mellitus.[6]

It was observed that tacrolimus was present in most of the potential DIs found in the prescriptions analyzed and that all these interactions were classified as of major severity; considering that the tacrolimus blood concentrations can be altered both due to its concomitant use with other medications and to other factors such as genetics, time since the transplant, age and diet. This medication has a narrow therapeutic index, which requires monitoring of the serum levels.[7] The transplanted patients of this study undergo monitoring the day before the outpatient medical consultation; consequently, the results are already available to evaluate if the immunosuppression levels are as expected, and this attitude leaves the multiprofessional team at ease to better conduct the patient's pharmacotherapy.

In relation to the DIs analyzed that can reduce the tacrolimus blood concentration, concomitant use with prednisone stands out, which can result in changes in the immunosuppression level to values below the expected, causing transplant rejection.

A number of drugs that can increase tacrolimus concentrations were identified in the study, namely: omeprazole, amlodipine and ciprofloxacin. The interaction can potentiate the occurrence of toxicity, hypertension, acute kidney injury and electrolyte disorders, in addition to neurobehavioral side effects, such as cephalea, tremors, coma, delirium and psychosis.[7] The mechanism takes place through inhibition of the CYP3A enzymes by the presence of omeprazole or of ciprofloxacin, consequently inhibiting metabolization of tacrolimus. On the other hand, the interaction mechanism with amlodipine is still unknown.

Combinations of tacrolimus with escitalopram, ciprofloxacin or hydroxychloroquine can cause prolongation of the QT interval. It is necessary to monitor this interval in patients that make use of this drug combination and to observe if there is cardiac arrhythmia, dizziness, palpitations or irregular heart rhythm. Consequently, it is also recommended to monitor the magnesium, potassium and calcium blood levels in these patients. In a study conducted in the Netherlands that investigated if QT prolongation alerts caused by drug interactions resulted in requests for electrocardiograms (ECGs) and if these ECGs, in turn, were clinically relevant, it was verified that they were only requested for 33% of the patients after the alert, and high prevalence of QT prolongation was also observed, which is clinically relevant. This study also highlighted the importance of pharmacists through interventions such as reminding the prescribing professionals about the need to check the QT intervals after initiating the combination of medications that prolong the QT interval.[8]

In another study, which involved renal transplant patients and compared immunosuppression regimes between 7 months and 1 year after the transplant, it was observed that the group of recipients treated with immunosuppressant therapy + hydroxychloroquine presented 2 times more risk of abnormal ECGs or QT prolongation and ventricular arrhythmias than those who did not use the antimalaric.[9]

Consequently, it becomes evident that caution is required in the management of patients that present DIs involving tacrolimus, in order to avoid or minimize possible harms to health. The Protocol and Therapeutic Guidelines available for liver transplant in adults do not address DIs among the main drugs used in association with the immunosuppressant therapy.

It is emphasized that metabolization of drugs can be altered in patients recently subjected to liver transplants, as they are still undergoing the organ regeneration process, due to factors inherent to the transplantation procedure, such as ischemia reperfusion, acute rejection, infection and toxicity of the medications. One of the biochemical changes in regeneration of the organ is the negative regulation of the P450 cytochrome system, which is responsible for the metabolization of most immunosuppressants. In a study conducted with animals to investigate if the liver regeneration process affects the immunosuppressants' pharmacokinetics, it was observed that metabolism of tacrolimus was inhibited during regeneration of the organ.[10]

Another frequently used pharmacological group among the study patients was that of corticosteroids. Their use is fundamental for induction and maintenance of the immunosuppressant therapy. Although efficacy of these medications in initial regimes is indisputable, their long-term use after the emergence of tacrolimus is under debate, needing more follow-up and monitoring studies.[11]

Nystatin was the most frequently prescribed medication of the anti-infectives group and did not present any interaction with the other medications analyzed in the database used. Antibacterial sulfamethoxazole + trimethoprim also stands out from the list of drugs identified in the prescriptions. A potential interaction of this sulfonamide with different insulins was observed during the study, in which there is an increased risk for hypoglycemic action.

Regarding the risks arising from the DIs analyzed, the risk of hypoglycemia was observed quite frequently. The need to increase the

glucose monitoring frequency is demonstrated and, when necessary, to adjust the dose of the antidiabetic agents.

Antiacids were prescribed with certain frequency, with omeprazole standing out among them. According to Maguire *et al.* (2012), the interaction between proton pump inhibitors and tacrolimus is not so well-elucidated; in addition, in this study, the author advocates that omeprazole and esomeprazole must be avoided in patients that make use of tacrolimus. He also presents other drugs, such as rabeprazole, as a safer treatment option than omeprazole, as it undergoes a mainly non-enzymatic metabolism with renal elimination of its metabolites.[12]

Medications to treat cardiovascular diseases were prescribed, diseases that represent one of the most common causes of mortality in the long-term period after a transplant; and the etiology of the liver disease also plays a role in the profile of the risk factors for the development of a CVD. According to a study conducted in Minas Gerais, it was concluded that the risk of a cardiovascular event occurring in the subsequent ten years in patients subjected to liver transplants is 9.5% higher than the value cited in the literature for the general Brazilian population. The importance of the multiprofessional health teams in the care and assistance provided to these patients was also emphasized, mainly males and of advanced age.[13]

In this study, amlodipine was the most frequently prescribed medication for hypertension control. It is a potent CYP3A inhibitor, leading to an increase in the tacrolimus blood levels; thus, the recommendation is to monitor the tacrolimus levels.[14] It also belongs to the first-choice class for the treatment of hypertensive liver transplant patients. The guidelines intended for these individuals are changes in the eating habits and physical activities. In case there is a need to change the immunosuppressant, resorting to mycophenolate mofetil is an option, or reducing the use of corticosteroids for blood pressure control.[15]

Potential DIs involving warfarin were found in the study, and their management should also occur at the prescription moment. Adjustment of the patient's warfarin dose is mandatory, with a strict follow-up and monitoring from treatment initiation to avoid the risk of hemorrhage and toxicity or sub-therapeutic level of this anticoagulant.[16] One of the tools used in DI research in the population in use of warfarin is the International Normalized Ratio (INR), a monitoring tool to assess both efficacy and bleeding risk, although in some interactions such as the warfarin + omeprazole association there is risk of bleeding associated with warfarin, regardless of the INR level.[17]

From the classification of the DIs, it was observed that a large percentage corresponds to major severity and that most of them presented both deficient documentation and unspecified latency period. The aforementioned reveals a genuine need to conduct more consolidated and in-depth clinical studies to assess the actual impairment that these interactions can cause in the patient's therapy, even more in transplanted patients that require more specific care measures, such as dose adjustment and continuous pharmacotherapeutic monitoring. Consequently, identifying and classifying the potential DIs becomes crucial for adequate management.

The importance of the health team's role in knowing the impact caused by these problems related to pharmacotherapy is evidenced, as well as of monitoring the patients and evaluating any signs and symptoms that might arise. At the prescription moment, or even in the pharmaceutical consultation with these transplanted patients, electronic alert records for the identification of potential DIs according to severity are not applied yet. This tool proved to be relevant in the clinical practice, assisting in access to the information and efficiency of the process, as well as reducing harms caused by drug interactions in other scenarios.[18-19]

Inclusion of a pharmacist in the transplantation team was increased in this context, mainly due to the fact that the profession has become a necessary component, as an accreditation standard for transplantation centers. Pharmacists working in this scenario need substantial knowledge in relation to pharmacotherapy from the Intensive Care Unit to the outpatient monitoring, as well as they should actively participate in the discussion about which therapeutic regimes are more suitable for each individual, collaborating with the team and always seeking updates as better and safer treatments are incorporated.[20] In the study locus, the pharmacist is part of the multiprofessional health team and has the opportunity to contribute to optimizing the therapy offered to the patient.

The opportunity to conduct the outpatient pharmaceutical consultation during the most critical period after the transplant turns the moment into an essential time to create a bond between the health professional and the patient, in addition to opening a space to clarify doubts and provide the due guidelines about the pharmacological therapy, which can change the entire life context of the patients for their benefit. During this outpatient consultation, the pharmacist in charge develops an instrument with pharmaceutical guidelines containing all the medications and their respective dosage information, according to the medical prescription and to the schedule suggestions to be followed by the patient, in order to prevent and avoid possible drug interactions. However, in case the interactions arise from the course of action, the outpatient service should be immediately sought to obtain guidelines for the patient and management of the DIs, thus reducing the problems related to use of the medications.

In general, and considering the entire support provided by the multiprofessional team of the outpatient service, especially the pharmaceutical care adopted, the results suggest that lifetime monitoring with the pharmacist is fundamental. In addition to that, the need arises to better structure the routine of the service offered in the patients' follow-up after the transplant, with the objective of investigating these potential DIs prior to the emergence of the adverse reactions they cause.

It is evident that transplantation success goes beyond the surgical process; it also requires comprehensive care after the procedure, by means of actions performed both by the patients themselves and by the multiprofessional team, which should implement proper management based on the clinical experience. The pharmacist's performance in the transplantation process was strongly evidenced and is fundamental to ensure better health management of the transplanted patients, mainly during the period immediately after the transplant, due to the many changes in the life of these individuals.

CONCLUSION

Transplantation success is related to proper management of the pharmacotherapy, mainly in monitoring of the DIs associated with the immunosuppressants, which can cause transplant rejection or toxicity risks.

Among the most frequently prescribed medications, tacrolimus stood out as the immunosuppressant of choice for all the study patients. Most of the associations with this immunosuppressant were considered as of 'moderate severity' and 'major severity'. In an approach to processes, documentation and recording must be improved. Thus, more rigorous surveillance regarding safe use of tacrolimus is suggested.

Knowing the drug combinations associated with a greater potential for DIs facilitates identification of the symptoms and manifestations they cause. In addition to that, such knowledge becomes crucial to prevent possible drug-related adverse events that may compromise the transplanted patients' health, with the possibility of avoiding possible negative outcomes by implementing certain actions, such as medication

substitutions, dose adjustments and schedule changes between the drugs and, consequently, improving patient safety.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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