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Original Article

Drug-related Problems in Solid-Organ Transplant Recipients Hospitalized for COVID-19: An Experience of a Referral Tertiary Center in Iran

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Abstract

Background: Transplanted patients receiving immunosuppressive agents are at a higher risk of Coronavirus-disease-2019 (COVID-19), and their polypharmacy state makes the choice of treatment challenging. This study aimed to assess the drug-related problems (DRP) and clinical pharmacists' interventions to manage transplanted patients and candidates for transplantation with COVID-19.

Methods: This cross-sectional study was conducted in the COVID-19 intensive care unit of Shiraz Organ Transplantation Center (Iran), from March 2020 to April 2021. Patients were admitted to the COVID-19 intensive care unit based on clinical symptoms or positive polymerase chain reaction (PCR) tests. The clinical pharmacist reviewed all medications and physicians' orders on a daily basis and evaluated DRPs in accordance with the pharmaceutical care network of Europe (PCNE) classification (V 8.01). The treatment team was informed of the DRPs, and the acceptance or rejection of the intervention was also documented. Data were analyzed using SPSS (Version 25.0). In order to determine the proportion and determinants of drug-related problems, descriptive statistics and logistic regression were applied, respectively.

Results: A clinical pharmacist reviewed 631 individuals with 11770 medication orders, and 639 DRPs were found in 69% of them with an average of 1.01±1 per patient. The most commonly reported DRPs were treatment efficacy issues followed by adverse drug reactions (ADRs). A total of 982 interventions were provided at prescriber, patient, and drug levels, of which 801 were accepted, and 659 (82.27%) were fully implemented.

Conclusion: There have been considerable drug-related issues in managing transplanted patients with COVID-19. DRPs are more common in people with polypharmacy, more than three comorbidities, and hydroxychloroquine regimens.

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Keywords ● COVID-19 ● Clinical pharmacists ● Kidney transplantations ● Liver transplantations

What's Known

- Transplanted patients with coronavirus-disease-2019 are more likely to develop drug-related problems due to their polypharmacy and pharmacokinetic alteration.

What's New

- The study shows that drug-related problems had high-frequency (69% of such patients).
- Patients with polypharmacy have 1.8 times more drug-related problems.
- The most frequently reported drug-related problems were those related to treatment effectiveness.

Introduction

On March 11, 2020, the world health organization (WHO) declared the outbreak of Coronavirus Disease 2019 (COVID-19) a "pandemic" worldwide. According to epidemiological updates

from WHO, on Feb. 28, 2022, 434,154,739 cases were confirmed worldwide, causing 5,944,342 deaths.[1, 2] Patients receiving solid organ transplantation (SOT) seem to be at a higher risk of COVID-19 due to long-term use of immunosuppressive agents and additional coexisting medical comorbidities.[3, 4] Since no definitive and effective treatment for COVID-19 has yet been registered, *in vitro* evidence or successful experiences in managing affected patients are significant sources of information. Several antiviral and immunomodulatory drugs have been developed to be evaluated in clinical trials. The chloroquine/hydroxychloroquine, remdesivir, favipiravir, umifenovir, protease inhibitors (PIs) such as lopinavir/ritonavir, interferons are some of the compounds that have been investigated in these studies.[5, 6] When it comes to transplanted patients with COVID-19, maintaining the balance between decelerating viral disease and the function of the graft via a proper degree of immunosuppressive modulation acts as a double-edged sword.[7, 8] Additionally, combining the aforementioned medications with immunosuppressive agents causes various pharmacokinetic and pharmacodynamic interactions, which can sometimes lead to dangerous and even life-threatening drug-related problems (DRPs).[9]

The pharmaceutical care network of Europe (PCNE) defines DRP as "an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes".[10, 11] DRPs seem to induce harm to patients, increase healthcare costs, lengthen hospitalization time, and reduce the quality of life and potentially patients' survival. Therefore, identifying, reducing, and preventing DRPs are critical steps carried out precisely by pharmaceutical care services. In order to optimize the medication therapy and reduce re-hospitalization, the pharmacists should review the medications, identify the patients at risk of DRPs, and improve drug regimens.[11] PCNE provides a practical classification system that enables clinical pharmacists to identify DRPs in adverse drug reactions (ADRs), drug selection, dose, usage process, and interactions among several classifications with different focuses. It also helps the pharmacotherapy services in determining the root causes of problems, leading to timely interventions.[10] Patients with SOT are more likely to develop DRPs as a result of coexisting morbidity-related polypharmacy, pharmacokinetics or pharmacodynamics changes, and immune response alterations.[11]

Clinical pharmacists are specifically trained in pharmacotherapy evaluation and are able to identify and prevent DRPs. Many studies indicated that involving clinical pharmacists in a multidisciplinary team and implementing comprehensive medication management might reduce healthcare expenditures, as well as improving drug safety.[12-14] In this critical situation of COVID-19 control, pharmacists are extremely influential as members of the healthcare team. A published review study assessed the role of pharmacists in the COVID-19 crisis and found that pharmacists are effectively involved in different areas such as infection control, drug supply, patient care, and support for healthcare professionals.[15] Elbeddini and others also investigated the role of pharmacists in the use of telemedicine as the most accessible primary care provider in Canada.[16] Consequently, clinical pharmacists play a vital role in managing polypharmacy conditions in such transplant patients with COVID-19.

Although it has been more than a year since the outbreak of COVID-19, and the global vaccination has begun, the world is faced with emerging variants, and the disease and its treatment-related complications still continue to plague the world. Hence, this study aimed to evaluate the drug-related problems and clinical pharmacists' interventions in managing transplant patients and candidates for transplantation with COVID-19 at tertiary referral solid organ transplant hospital.

Patients and Methods

Study Design, Setting, and Patients

A cross-sectional study was conducted from March 2020 to April 2021 at Shiraz Organ Transplant Hospital, the largest referral center for solid organ transplants in the Middle East and Asia, which is affiliated with Shiraz University of Medical Sciences, Shiraz, Iran. The study was approved by the Ethics Committee of Shiraz University of Medical Sciences (#IR.SUMS.REC.1399.398). All the protocols conformed to the ethical guidelines of the Helsinki Declaration (1975). Written informed consent was obtained from all the participants. With the outbreak of COVID-19, a 30-bed intensive care unit was set up for adult transplanted patients or candidates for transplantation with confirmed COVID-19. Based on clinical presentations, radiographic findings, or positive real-time polymerase chain reaction (RT-PCR) tests, the transplanted patients or candidates for transplantation, whose COVID-19 infection was confirmed, were recruited to study. Patients who stayed for less than 48 hours or died during the study were excluded. A multidisciplinary team of internal

medicine and infectious diseases specialists as supervisors, pulmonologists, transplant surgeons, and a clinical pharmacist evaluated and managed the patients on a daily basis based on the published international and regional guidelines by scientific communities related to transplantation.[2, 7, 17] Through the patients' medical records, a clinical pharmacist carefully gathered all the demographic characteristics, length of hospitalization, clinical outcomes, and medications.

Drug-related Problems Identification

The medications of hospitalized patients were reviewed by a clinical pharmacist. All drug regimens information were individually recorded, including name, dosage form, drug class, indication, dosage, and interval. The clinical and laboratory data, such as plasma level of immunosuppressive agents, renal and hepatic function status, and the ADR of antiviral regimens (according to the Naranjo ADR probability scale),[18] were also continuously monitored, until the patient was hospitalized. Furthermore, the drug-drug interactions were identified using Micromedex online software (Micromedex® version 4.4, Ann Arbor, Michigan, United States drug interaction software mobile app available online with limited access). Polypharmacy, which is defined as regimens containing five or more drugs together,[11, 19] was also considered. The nature and incidence of DRPs were determined by evaluating patients' pharmacotherapy in terms of indication, dosage, safety, and efficacy using PCNE classification (Version 8.01).[20]

PNCE Classification

PCNE classification is a well-structured tool that provides relevant information on documented DRPs.[21] To determine the nature and number of DRPs in Version 8.01, five main domains must be evaluated.The five domains are as follows:

• "Problems": Defines as an unexpected event that can occur in the following three categories: "treatment effectiveness," "treatment safety or ADR," and "others" such as "treatment cost-effectiveness or unnecessary drug treatment."

• "Causes": Identifies the causes of DRP in eight sub-domains, such as "drug selection," "drug form," "dose selection," "treatment duration," "dispensing," "drug use process," "patient-related," and "other" such as "inappropriate drug monitoring"

• "Planned Interventions": Record the pharmacist's level of intervention to prevent or correct the DRPs.

• "Intervention acceptance": Describes the acceptance status of intervention.

• "Status of the DRP": Explains the outcome of DRPs, and indicates whether the problem status is "unknown", "solved", "partially solved", or "not solved".[20]

Clinical Pharmacist Interventions

Clinical pharmacist interventions were referred to all recommendations proposed by a clinical pharmacist at any stage of the pharmacotherapy process that influenced management plans. Based on the laboratory tests and the patient's clinical condition, the clinical pharmacist has daily reviewed all medication orders for patients in terms of drug-drug interactions, ADR, dose adjustment based on renal and hepatic functions, and dose adjustment of immunosuppressive agents according to their plasma levels. For early DRPs prevention, the recommendations were developed through discussions with health care professionals at the drug prescription phase. Moreover, additional interventions were presented, either verbally or in the patient's clinical file, at the prescriber, patient, and drug levels during daily monitoring and rounds. The reasons for accepting or rejecting the clinical pharmacist's recommendation have also been noted. The acceptance rate was calculated based on the intervention agreement at the prescriber level.

Statistical Analysis

Statistical analysis was performed using SPSS Version 25.0 (Armonk, NY, USA: IBM Corp.). The frequency of each type of DRP and the prescriber's acceptance rate were determined using descriptive statistics. The continuous variables were reported as mean±SD, and the categorical data were reported as percentages or frequencies. The potential risk factor of DRPs was determined using univariate and multivariate logistic regression analysis. Results were reported as odds ratios (ORs) with 95% CIs. P values less than 0.05 were considered statistically significant.

Results

During the study period, 631 individuals with COVID-19 clinical manifestations (39%) or a positive SARS-CoV-2 PCR test (61%) were recruited for final analysis; of which 232 patients (36.76%) were transplanted (133 kidney transplant recipients, 92 liver transplant recipients, three isolated small bowel transplant recipients, three multi-visceral transplants, and one Simultaneous pancreas-kidney (SPK)

transplant recipient), and 399 patients were candidates for transplantation. The demographic characteristics of these participants are summarized in table 1. More than half of the patients (63.07%) were male. The most prevalent underlying comorbidities were Cirrhosis (23.99%), diabetes mellitus (21.12%), hypertension (20.53%), and end-stage renal disease (ESRD) (19.69%). Each patient had an average of 3.71±1.10 underlying disease.

The clinical pharmacist has reviewed 11770 medication orders. On average, each patient took 5.01±3.30 drugs. Immunosuppressants (52%), antivirals and antibiotics (31%), and antihypertension (11%), were the top three prescribed drug classes. The clinical outcomes of patients and treatment options are presented in table 2. COVID-19 therapeutic management included high doses of steroids (36.67%), remdesivir (29.34%), the combination of hydroxychloroquine and lopinavir-ritonavir (13.26%), followed by tocilizumab (10.58%), the combination of hydroxychloroquine and azithromycin (5.36%), and favipiravir (4.80%), respectively. The most commonly used immunosuppressive regimens among transplanted patients were tacrolimus-based.

According to the polypharmacy definition, 429 individuals (67.99%) were in this category, however, the rate of polypharmacy was not statistically different between transplanted patients and transplant candidates (P=0.22). A total of 639 DRPs were identified from 69% of the studied patients. The mean DRPs for each patient was 1.01±1. The most commonly found types of DRPs were those related to treatment

Table 1: Demographic and clinical characteristics of COVID-19 patients who were admitted to the transplant intensive care unit (N=631) using descriptive statistics

Variable	Demographic data	N (%)
Age group(years)	<40	468 (74.17)
	40–60	90 (14.26)
	>60	73 (11.57)
Gender	Male	398 (63.07)
	Female	233 (36.93)
Comorbid diseases	Diabetes mellitus	177 (21.12)
	Cirrhosis	201 (23.99)
	Hypertension	172 (20.53)
	Ischemic heart disease	59 (7.04)
	Encephalopathy	32 (3.82)
	Asthma	6 (0.72)
	End-stage renal disease received HD†	165 (19.69)
	Chronic obstructive pulmonary disease	4 (0.48)
	Deep venous thrombosis	22 (2.63)
Symptoms	Fever	331 (52.45)
	Cough	121 (19.17)
	Dyspnea	165 (26.14)
	Vomiting	83 (13.15)
	Diarrhea	58 (9.19)
	Headache	32 (5.07)
	Pharyngitis	13 (2.1)
	Rhinorrhea	8 (1.27)
	Chest pain	9 (1.43)
	Malaise	42 (6.65)
Transplantation Status	Liver transplant	92 (14.58)
	Kidney transplant	133 (21.08)
	Multi-visceral transplant	3 (0.48)
	Small bowel transplant	3 (0.48)
	SPK‡	1 (0.16)
	Candidate for transplant	399 (63.23)
Time after transplant (months)	1-3	67(10.61)
	3-6	104 (16.48)
	6-12	32 (5.07)
	>12	29 (4.61)
Ward admission	ICU	282 (44.69)
	Non-ICU	349 (55.31)

†Hemodialysis; ‡Simultaneous pancreas-kidney

Table 2: Clinical course and outcome of COVID-19 patients in Shiraz Transplant center (N=631) using descriptive statistics

Variable	Variable	N(%)
O_2 therapy	Non-Mechanical ventilation	435 (68.94)
	Mechanical ventilation	196 (31.06)
Immunosuppressive regimens	Tacrolimus+prednisolone	139 (59.91)
	Tacrolimus+prednisolone+Mycophenolic Acid (Myfortic®)	62 (26.72)
	Mycophenolic Acid+Prednisolone	24 (10.34)
	Mycophenolic Acid+Prednisolone+Cyclosporine	4 (1.72)
	Everolimus+Mycophenolic Acid	3 (1.29)
Treatment	High dose of steroids Remdesivir	260 (36.67) 208 (29.34)
	Hydroxychloroquine+Lopinavir/Ritonavir	94 (13.26)
	Tocilizumab	75 (10.58)
	Hydroxychloroquine+Azithromycin Favipiravir	38 (5.36) 34 (4.80)
Length of ICU† stay (day, Mean±SD)‡		20.09±4.12
Length of hospitalization(day, Mean±SD)‡		34.76±24.11
Mortality		113 (17.90)

†Intensive Care Unit; ‡SD Standard Deviation

effectiveness (34.12%), ADR (33.02%), and unnecessary drug treatment (17.68%). The identified DRPs, causes, and interventions according to the PCNE classification (Version 8.01) are summarized in table 3.

Based on the PCNE classification, 724 causes of DRPs were identified. The most common causes of DRPs were drug selection (27.49%), followed by patient-related causes (17.82%), drug use process (16.85%), dispensing (13.54%), and dose selection causes (12.02%). The majority of patients received an inappropriate combination of drugs or drugs and herbal medications (9.81%). Patients who administered/used drugs incorrectly (8.29%), were primarily responsible for patient-related causes. Furthermore, the majority of cases were related to drugs under-administration (7.87%) throughout the drug use process (table 3). Individuals with at least one DRP (n=82) had a significantly greater mortality rate (P<0.001) than patients without any DRPs (n=31).

A significant association between hydroxychloroquine intake, transplantation, polypharmacy, and comorbid diseases more than three with the DRPs in transplant patients or candidates for transplantation with COVID-19 was found by applying multivariable logistic regression. Table 4 summarizes the DRPs risk factors in these groups. Patients, who received five or more drugs (polypharmacy), were 2.03 times more susceptible to develop DRPs. The transplanted people were at a higher risk of DRPs than candidates for transplantation, and the existence of three or more comorbidities significantly increased the probability of such problems.

A clinical pharmacist performed 982 interventions at different levels of PCNE classification. As indicated in table 3, the majority of the interventions occurred at the prescriber level (71.08%), then at the drug level (16.80%), and finally at the patient level (12.12%). Supplementary file 1 contains several examples of interventions. In transplant patients, the most common intervention was dose adjustment of calcineurin inhibitors (CNIs) in combination with antivirals. A total of 801 interventions were accepted (81.56%), with 659 (67.11%) of them being fully implemented. The most accepted interventions were dose selection, drug selection, and treatment duration, respectively. The primary reason for the physicians' refusal of clinical pharmacist recommendations was the absence of clinical relevance and/or the rarity of clinical ADRs associated with these drug-drug interactions. After implementing the interventions, 61.21% of the problems were solved, while 22.91% were not solved.

Discussion

To the best of our knowledge, this is the first study to investigate the DRPs and clinical pharmacy interventions in transplanted patients and transplant candidates with COVID-19. The present study shows a high-frequency of DRPs in the management of transplanted patients and candidates for transplantation with COVID-19. Drug-related problems are significant public health concerns in patients' pharmacotherapy, especially in those with chronic diseases. DRPs have always been a problem for transplanted patients or candidates due to comorbidity associated with polypharmacy and pharmacokinetic changes.

Table 3: Identified drug-related problems (DRPs), causes, and interventions according to the PCNE classification v8.01 using descriptive statistics

Classifications		N (%)
Problems	P1. Treatment effectiveness	218 (34.12)
	P1.1. No effect of drug treatment	127 (19.87)
	P1.2. Effect of drug treatment not optimal	65 (10.17)
	P1.3. Untreated symptoms or indication	26 (4.07)
	P2. Treatment safety	211 (33.02)
	P2.1. Adverse drug event (possibly) occurring	211 (33.02)
	P3. Others	210 (32.86)
	P3.1. Unnecessary drug-treatment	113 (17.68)
	P3.2. Problem with cost-effective treatment	97 (15.18)
Causes	C1. Drug selection causes	199 (27.49)
	C1.1. Inappropriate drug (within guidelines but otherwise contra-indicated)	21 (2.90)
	C1.2. Inappropriate combination of drugs or drugs and herbal medication	71 (9.81)
	C1.3. Inappropriate duplication of a therapeutic group or active ingredient	44 (6.08)
	C1.4. No drug treatment in spite of existing indication	39 (5.39)
	C1.5. Too many drugs prescribed for an indication	24 (3.31)
	C2. Drug form causes	27 (3.73)
	C2.1. Inappropriate drug form	27 (3.73)
	C3. Dose selection causes	87 (12.02)
	C3.1. Drug doses too high	59 (8.15)
	C3.2. Drug dose too low	15 (2.07)
	C3.3. Dose timing instructions wrong, unclear, or missing	13 (1.80)
	C4. Treatment duration causes	37 (5.11)
	C4.1. Duration of treatment too long	22 (3.04)
	C4.2. Duration of treatment too short	15 (2.07)
	C5. Dispensing causes	98 (13.54)
	C5.1. Prescribed drug not available	62 (8.56)
	C5.2. Prescribing error (necessary information missing)	36 (4.97)
	C6. The drug use process causes	122 (16.85)
	C6.1. Drugs not administered at all	51 (7.04)
	C6.2. Drug under administered	57 (7.87)
	C6.3. Drug over administered at all	14 (1.93)
	C7. Patient-related causes	129 (17.82)
	C7.1. Patient uses unnecessary drug	55 (7.60)
	C7.2. Patient administered/uses the drug in a wrong way	60 (8.29)
	C7.3. Patient cannot afford a drug	14 (1.93)
	C8. Other causes	25 (3.45)
	C8.1. No or inappropriate outcome monitoring	25 (3.45)
Interventions	I1. At prescriber level	698 (71.08)
	I1.1. Prescriber informed only	558 (56.82)
	I1.2. Prescriber asked for information	140 (14.26)
	I2. At patient level	119 (12.12)
	I2.1. Patient (drug) counseling	76 (7.74)
	I2.2. Patient referred to a prescriber	29 (2.95)
	I2.3. Spoken family member/caregiver	14 (1.43)
	I3. At drug level	165 (16.80)
	I3.1. Dosage changed	123 (12.53)
	I3.2. New drug started	18 (1.83)
	I3.3. Drug stopped	24 (2.44)
Intervention acceptance	Intervention accepted	801 (81.56)
Intervention Implementation	Intervention accepted and fully implemented	659 (67.11)
	Intervention accepted and partly implemented	63 (6.42)
	Intervention accepted but not implemented	52 (5.30)
	Intervention accepted, implementation unknown	27 (2.75)

Percentages are calculated based on the total number of each section

Table 4: Determinants of drug-related problems (DRPs) among transplanted patients and candidates for transplantation with COVID-19 using logistic regression

Variables	OR¶(95%CI#) Univariate	P value	OR(95%CI) Multivariate	P value
Sex	0.75 (0.44-1.23)	0.88	-	-
Age more than 50 years	2.75 (0.51-3.00)	0.09	-	-
Polypharmacy	2.99 (1.10-5.76)	0.039	2.03 (1.88-2.91)	0.039
CNI†-based immunosuppressive regimen	1.70 (0.44-1.92)	0.18	-	-
Comorbid diseases more than three	1.79 (1.60-3.29)	<0.001	1.65(1.50-2.77)	0.021
Transplantation	1.33 (1.19-3.98)	<0.001	1.96 (1.44-2.85)	0.046
Remdesivir-based regiment	1.88 (0.33-1.91)	0.68		
High dose of corticosteroid based regimen	1.10 (0.60-1.32)	0.10		
HCQ‡ -based regimen	3.91(1.82-9.10)	<0.001	2.81 (2.33-5.72)	<0.001
Lopinavir-ritonavir based regimen	1.33 (0.66-2.09)	0.07	-	
Length of ICU§ stay	1.27 (0.96-1.71)	0.81	-	
Length of hospital stay	1.44 (0.19-1.70)	0.29	-	

†Calcineurin inhibitor; ‡Hydroxychloroquine; §Intensive care unit; ¶Odds ratio, #Confidence interval

For many years, clinical pharmacists have been providing valuable advice to optimize patients' pharmacotherapy and improve clinical and economic outcomes. Due to their polypharmacy status, their collaboration in a multidisciplinary team is critical in managing patients, especially those with chronic diseases.[22] Since the beginning of the SARS-CoV-2 outbreak, pharmacists have played a key role in various areas, including drug distribution, drug information, pharmaceutical care development, and drug registration research.[15] The lack of definitive treatment, the existence of numerous morbidities, and prolonged ICU stays have doubled the importance of proper pharmacotherapy, especially in transplant patients for whom the immunosuppressant receiving and clinical condition should be balanced. The high acceptance rate of the present study reflects a long-standing and trustworthy relationship between clinical pharmacists and multidisciplinary teams. Since the inception of our center, a board-certified clinical pharmacist with extensive knowledge of organ transplantation has offered his recommendation and provided trustworthy cooperation.

We found a rather high frequency of DRPs in 69% of the studied patients with a mean of 1.01±1, while two other studies at the internal medicine ward in Turkey[23] and among admitted geriatric patients in Ethiopia[11] reported the average value of 1.63 and 1.90, respectively. These discrepancies might be attributed to differences in study designs, study populations, and study duration. There are various criteria for identifying and classifying the DRPs, and those studies that used the PCNE standards found more DRPs due to their multiple sub-domains of classification. Furthermore to date, no DRPs analysis has been performed in COVID-19 patients to be compared.

According to our findings, the most common subset of DRPs was treatment effectiveness (34.12%). The appropriate drug selection in the COVID-19 population varies depending on the stages of the disease (viral or inflammatory). For example, taking corticosteroids during the viral phase leads to more virus replication and worsens the patients' condition. On the other hand, the late start of antiviral drugs, especially in the fourth week of infection, can be ineffective.[24, 25] In studies in Ethiopia (10%)[26] and India (40.6%),[27] ineffective drug treatment contributed to a lower proportion of DRPs, while a Canadian (51.3%)[28] research indicated more ineffective drug therapy.

According to our findings, ADR is the second most frequent subtype of DRPs (33.02%). In contrast, studies conducted in Ethiopia (2%),[26] Canada (6.8%),[28] and Singapore (25%)[29] indicated lower ADR of all DRPs. In comparison to a study by Sun and others, we consider the usage of some antivirals for COVID-19 management, such as hydroxychloroquine and lopinavir-ritonavir, as our complicating drugs. In patients with COVID-19, the length of hospital stay, the amount of the hospital drugs used, underlying diseases, and receiving lopinavir-ritonavir are all the risk factors for ADRs.[30]

Drug selection causes accounted for 27.49% of all DRPs causes, especially in the subset of inappropriate combination therapy (9.81%). The most common inappropriate combination therapy was hydroxychloroquine with remdesivir or non-vitamin K antagonist oral anticoagulants (NOACs) with PIs. Changes in serum levels of the CNI class by PIs (tacrolimus with lopinavir-ritonavir) and hydroxychloroquine (cyclosporine with hydroxychloroquine) were among the most commonly observed pharmacokinetic interactions.

According to our findings, polypharmacy, the existence of more than three comorbidities, transplantation, and receiving hydroxychloroquine are all substantial risk factors for developing DRPs. The transplanted population frequently experienced polypharmacy due to post-transplant complications, multiple immunosuppressive regimens, and receiving prophylactic antimicrobial agents. In confirmation, a study by Shafiekhani and colleagues mentioned that each kidney transplant recipient received approximately 11 medications,[13] and some other studies have also identified polypharmacy and comorbidity as the risk factors for DRPs.[31, 32] Besides, Eichenberger and others reported that transplant patients are more prone to develop DRPs.[22]

In the present study, more than 81.56% of the clinical pharmacist interventions were approved, while approximately 67.11% were fully implemented. In this research, the most common intervention performed by the clinical pharmacist was dose adjustment of CNIs in transplant patients taking antivirals. Considering previous research, simultaneous use of CNIs, especially tacrolimus and PIs, can significantly increase tacrolimus blood levels, and a 1/20th–1/50th reduction in daily dose is recommended when starting or changing PI therapy.[33] Cyclosporine plasma levels are also increased when PIs and hydroxychloroquine are used simultaneously.[2] In severe cases of COVID-19 with significant extensive lung involvement, it is also recommended to discontinue the other immunosuppressant class, mTOR inhibitors (e.g., everolimus), due to their pulmonary side effects such as pneumonitis and interstitial lung disease.[34]

Additionally, with the introduction of emergent therapeutic options such as interleukin-6 antagonists, i.e., tocilizumab, a number of pharmacotherapeutic issues should be considered. These include administration and continuation in patients with hepatic dysfunction or leukopenia,[2] for which a clinical pharmacist performed several interventions on dose adjustment or therapy discontinuation in the current study.

On the other hand, since the majority of the prescribed drugs in our study were corticosteroids, and these drugs are used in COVID-19 therapy at higher-than-usual doses, the side effects and adverse effects monitoring should be part of the interventions provided by clinical pharmacists. The side effects and adverse effects of these drugs in their high doses include hypertension, elevated blood sugar levels, and secondary bacterial or fungal infections, which should be monitored. Furthermore, based on the potential interaction (Type X) of everolimus and PIs, it should not be used concurrently with lopinavir-ritonavir.[35] Considering the two clinical conditions in transplant candidates, ESRD or end-stage liver failure, which induced changes in pharmacokinetic and pharmacodynamic parameters,[36] as well as the risk of graft rejection in transplant patients, drug dose adjustment based on clinical status is reasonable. In the current study, clinical pharmacist interventions included dose adjustments of antivirals such as remdesivir, antibiotics, and analgesics such as NSAIDs, as well as a reduction of the maximum daily dose of acetaminophen used for fever control in COVID-19 patients with ESRD, acute tubular necrosis (ATN), or chronic hepatic impairment in hospital settings. Furthermore, since the majority of the studied patients were polypharmacy, clinical pharmacists' recommendations were critical in reducing drug interactions between antiviral agents and other drugs.

With the emphasis on DRPs among the COVID-19 patients, this study has some limitations that should be noticed. The economic effects and cost-effectiveness of clinical pharmacist's interventions have not been evaluated. This is a relatively small-scale study from one center with a short duration and no independent clinical panel. A larger study is required to assess the clinical outcomes and DRPs consequences of accepted and rejected clinical pharmacist's interventions. It is also suggested that future research investigate the relationship between the severity of COVID-19 and the incidence of DRPs.

Conclusion

The present study shows a high-frequency of DRPs in the management of transplanted patients and transplant candidates with COVID-19. DRPs are more common in the transplanted population, and patients with polypharmacy, more than three comorbidities, and hydroxychloroquine regimens are more prone to manifest the problems. The mutual collaboration of clinical pharmacists and physicians is deemed vital in identifying, preventing, and resolving DRPs.

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Authors' Contribution

S.A: Conception, design of the work, acquisition and analysis of data, drafting and revising the manuscript; F.Sh: Analysis and interpretation of data; revising the manuscript; M.Sh: Conception, design of the work, acquisition, analysis and Interpretation of data, drafting and revising the manuscript. All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of Interest: None declared.

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