JPSCR: Journal of Pharmaceutical Science and Clinical Research
Volume 10, Issue 2, Pages 190 - 202, July 2025
https://doi.org/10.20961/jpscr.v10i2.87515

ISSN 2503-331X (Online)

Adverse Drug Reactions, Treatment Adherence, and Treatment Outcomes in Drug-Resistant Tuberculosis Patients: A Single-center, Cross-sectional Study

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Received: June 4, 2024; **Accepted:** August 11, 2025; **Published:** August 19, 2025

Abstract
Drug-Resistant Tuberculosis (DRTB) is a significant global health issue due to its rapid transmission and high morbidity. The variety of medications used in DRTB treatment increases the risk of adverse drug reactions (ADRs), which can contribute to patient nonadherence and adversely affect treatment outcomes. This study aimed to describe the occurrence of ADRs, quantify medication adherence rates, and assess treatment outcomes among patients with drug-resistant tuberculosis (DRTB). Furthermore, it sought to analyse the associations between ADRs, demographic and clinical variables, medication adherence, and the associations between ADRs and treatment outcomes. Using a cross-sectional design, this study utilized medical records data and the Tuberculosis Information System (SITB) of adult DRTB patients treated at Universitas Indonesia Hospital from April 1, 2022, to February 28, 2023. A total sampling method was employed to select the research participants. Of the 65 patients, 60 (95.24%) experienced ADRs, and the Medication Refill Adherence method indicated an 89.23% adherence rate. Two patients (3.08%) were classified as successful or cured during the data collection period. Chi-square tests revealed no significant relationship between ADRs and medication adherence ($p = 0.373$) or treatment outcomes ($p = 0.120$). All demographic and clinical factors (age, gender, comorbidities, treatment combinations, and potential drug interactions) also showed no significant relationships with adherence ($p > 0.05$). In contrast, treatment combinations showed significant relationships with treatment outcomes ($p = 0.013$). These findings highlight the importance of medicines optimisation strategies, including proactive ADR management and adherence support, to improve treatment outcomes in DRTB patients.

Keywords: Adverse Drug Reactions; Drug-Resistant Tuberculosis; Medication Adherence; Treatment Outcome.

1. INTRODUCTION

Drug-Resistant Tuberculosis (DRTB) is a form of tuberculosis caused by *Mycobacterium tuberculosis* that has developed resistance to first-line anti-tuberculosis drugs, such as Isoniazid and Rifampicin (Ministry of Health of the Republic of Indonesia, 2019; World Health Organization, 2022). This condition remains a significant public health challenge due to its rapid transmission and high morbidity rates globally and in Indonesia (Tiberi et al., 2022;

Ministry of Health of the Republic of Indonesia, 2018). According to the World Health Organization (WHO)'s Global Tuberculosis Report, there were 450,000 cases of DRTB worldwide and 28,000 cases in Indonesia (World Health Organization, 2021; World Health Organization, 2022). Between January and June 2021, 657 cases of DRTB were reported in West Java, with 87 cases recorded in Depok (RSUI, 2022).

In Indonesia, the treatment of DRTB involves a combination of short- and long-term regimens using non-injectable drugs, which include both first-line and second-line anti-tuberculosis medications (Ministry of Health of the Republic of Indonesia, 2020). Due to the complexity of these drug regimens, there is a considerable risk of adverse drug reactions (ADRs). ADRs refer to harmful and unintended responses to a medication used at recommended doses for disease prevention, diagnosis, treatment, or modification of physiological functions (BPOM RI, 2020). QT interval prolongation and gastrointestinal (GI) disorders are examples of adverse drug reactions (ADRs) associated with anti-tuberculosis medications (Ifayani et al., 2023).

Research conducted in primary healthcare settings has shown that ADRs can negatively impact treatment adherence among TB patients (Seniantara et al., 2018). Aminah and Djuwita (2021) found that ADRs in DRTB patients led to nonadherence with treatment, including irregular medication use or complete cessation of therapy. Additionally, research in a regional hospital in Lampung reported that TB patients who experienced ADRs while receiving Category I anti-tuberculosis treatment were 2.143 times more likely to exhibit nonadherence compared to those who did not experience adverse reactions (Julaiha, 2015). The occurrence of ADRs can also impact treatment outcomes. According to Kurniaty (2017), there was a negative correlation between the severity of TB drug side effects and treatment success, indicating that more severe adverse effects were linked to reduced likelihood of successful treatment outcomes. Other studies have further indicated that severe side effects contribute to treatment discontinuation and are statistically associated with poor outcomes in patients with multidrug-resistant TB (Aminah and Djuwita 2021).

Despite the importance of this issue, studies on ADRs, treatment adherence, and outcomes in DRTB patients in Indonesia remain limited. UI Hospital, a referral center for DRTB in Depok, has not conducted research in this area since it began treating DRTB patients in April 2022. This research aimed to provide data on the prevalence of ADRs, treatment adherence, and treatment outcomes, thereby contributing to medicine optimization efforts. Additionally, it seeks to examine the relationship between ADRs and demographic and clinical factors (such as age, gender, comorbidities, treatment regimens, and drug interactions) with adherence and treatment outcomes among DRTB patients at UI Hospital.

2. RESEARCH METHOD

2.1. Research design and population

This cross-sectional research utilized medical record data and the Tuberculosis Information System of DRTB patients treated at UI Hospital, West Java, from April 1, 2022, to February 28, 2023. Inclusion criteria for this research were DRTB patients aged 18 years and

above who initiated treatment at UI Hospital. Patients with incomplete data were excluded from the analysis. A total sampling method was employed to select the research participants. Ethical approval for this research was obtained from the ethics committee at UI Hospital (S-024/KETLIT/RSUI/III/2023).

2.2. Data collection

Patients who met the inclusion criteria were reviewed through their medical records to collect data on their characteristics, treatment regimens, potential drug interactions, experienced adverse drug reactions (ADRs), adherence to medication, and treatment outcomes. Clinically significant potential drug interactions were identified based on the Merrative Micromedex Drug Interaction database (2023). All adverse drug reactions (ADRs) of anti-tuberculosis regimens were identified based on clinicians' assessments documented in electronic medical records. The clinician determined treatment outcomes based on information in the electronic medical records. Patient adherence was assessed using the Medication Refill Adherence (MRA) method. This method calculates adherence by dividing the total number of days of medication supplied by the number of days evaluated during the observation period, then multiplying the result by 100. An adherence rate within the 80–120% range was considered acceptable (Hess et al., 2006).

2.3. Data Analysis

The data had been entered, coded, and verified for completeness and accuracy on Microsoft Excel before being transferred to SPSS version 25 for processing and analysis. Univariate analysis was conducted for each variable to provide a descriptive overview, with results presented as frequency distributions (%), means and standard deviations (SD), or medians and interquartile ranges (IQR), depending on the data distribution. Bivariate analysis was performed using the Chi-Square Test to assess the relationship between ADRs, treatment adherence, and DRTB treatment outcomes. ADRs were categorized as either present or absent; treatment adherence was classified as adherent or non-adherent; and treatment outcomes were grouped into successful or unsuccessful categories. If the assumptions for the Chi-Square test were not met, Fisher's Exact Test was applied. A p-value of less than 0.05 was considered statistically significant.

3. RESULTS AND DISCUSSION

A total of 76 patients were diagnosed with DRTB at the time of the research. Two patients were excluded as they were under 18 years of age. Of the remaining 73 adult DRTB patients, eight were excluded due to incomplete data, leaving 65 DRTB patients who were included in the final analysis. The sociodemographic and clinical characteristics of these patients are presented in Table 1.

The age grouping in this research follows the classification outlined by the National Institutes of Health (NIH, 2022). As shown in Table 1, 92.31% of the DRTB patients were between 18 and 65 years old, a considerably higher proportion than those over 65. This age

distribution is consistent with findings from Wibowo et al. (2021), Alateah et al. (2020), Ali et al.(2020), Khan et al.(2019), dan Wu et al.(2019), where the majority of DRTB patients were of productive age. This trend may be due to the higher rates of re-treatment cases among individuals in the productive age group (18–65 years) compared to the non-productive age group (>65 years) (Wu et al., 2019).

Table 1. Characteristics of patients with drug-resistant tuberculosis in this single-center, cross-sectional study.

Characteristics	Number of Patients (n=65)	Percentage (%)
Age		
18–65 years old	60	92.31
> 65 years old	5	7.69
Sex		
Male	38	58.46
Female	27	41.54
Comorbidity		
Yes	31	47.69
No	34	52.31
TB Treatment Guideline		
Short-Term	8	12.31
Long-Term	57	87.69

In terms of gender distribution, 58.46% of the DRTB patients were male, which aligns with the findings of Wibowo et al. (2021), Alateah et al. (2020), Ali et al.(2020), and Wu et al. (2019), where male patients constituted a higher percentage of DRTB cases. However, this differs from the results of Khan et al.(2019), where a higher percentage of female DRTB patients was reported. This variation suggests that gender distribution in DRTB cases may differ across regions and populations, as noted by Munir et al. (2008), indicating that gender disparities in DRTB prevalence are not universally consistent.

Regarding comorbidities, the most common condition among the patients was diabetes mellitus, affecting 61.29%, followed by digestive disorders (19.35%) and hypertension (12.90%). Similar findings were reported by Khan et al.(2019), where diabetes mellitus was identified as the most prevalent comorbidity among DRTB patients. A systematic review and meta-analysis conducted by Foe-Essomba et al (2021) also reported that diabetes is associated with an increased risk of developing tuberculosis. Complex immunological, metabolic, and clinical interactions mediate the link between diabetes and tuberculosis. Diabetes impairs multiple arms of the immune system, alters pulmonary defenses, and delays TB detection and response (Kumar et al., 2023; Madan et al., 2022; Hussain et al., 2023; WHO, 2025)

The treatment regimens used at UI Hospital have followed the latest WHO recommendations, which promote regimens without injectable drugs. This approach is associated with improved patient adherence due to the shorter treatment duration. The research found that most patients (n=57; 87.7%) were on long-term regimens, while only eight (12.3%) received short-term regimens. These patients were confirmed MDR-TB without resistance to

fluoroquinolones, had no direct interaction with pre-Extensively Drug-Resistant Tuberculosis (XDR-TB) or XDR-TB patients, had no prior treatment with second-line anti-tuberculosis drugs for ≥ 1 month, or had no extensive TB disease or extrapulmonary TB involving a critical site (meningeal, pericardial, or miliary TB). The predominance of long-term regimen use may be attributed to more re-treatment cases, where patients had developed resistance or reduced sensitivity to the drugs used in the short-term regimen (Ministry of Health of the Republic of Indonesia, 2020). Table 2 provides details on the variations in the treatment regimens used.

A total of 18 different drug regimens were administered to patients with DRTB (Table 2). The most commonly used regimen, accounting for 56.25%, was the general regimen for long-term treatment: 6 Bdq - Lfx - Lzd - Cfz - Cs / 14 Lfx - Lzd - Cfz - Cs. The combination of multiple drugs used in the treatment of DRTB, along with the presence of comorbidities, increases the likelihood of significant drug interactions, estimated at 20-40% (Palleria et al., 2013). In this research, 12 patients (18.5%) were found to be at risk of moderate to significant drug interactions (Merative Micromedex, 2023). The use of multiple drugs in DRTB treatment inherently raises the risk of significant drug interactions, consistent with previous research findings indicating a 20-40% likelihood (Palleria et al., 2013). Potential significant and moderate drug interactions identified in this study, as well as their potential effects and patient management (Table 3). (Merative Micromedex, 2023).

Table 2. Regimen of anti-tuberculosis treatment received by patients with drug-resistant tuberculosis in this single-center, cross-sectional *study*. *Description:* Bdq: Bedaquiline, Lfx: Levofloxacin, MFX: Moxifloxacin, CFZ: Clofazimine, Hdt: High-dose isoniazid, Z: Pyrazinamide, E: Ethambutol, Eto: Etionamid, Lzd: Linezolid, Cs: Cycloserine, Dlm: Delamanid, Am: Amikacin, PAS: Para-aminosalicylic acid.

Drug Regimen	Total (n=65)	Percentage (%)
Short-term		
4-6 Bdq - Lfx - CFz- Hdt - Z - E- Eto / 5 Lfx - Cfz - Z - E	8	12.50
Long-term		
6 Bdq - Lfx - Lzd - Cfz - Cs / 14 Lfx - Lzd - Cfz – Cs	36	56.25
6 Bdq - Lfx - Cfz - Cs - E / 14 Lfx - Cfz - Cs – Z	1	1.59
6 Bdq - Lfx - Lzd - Cfz - Dlm / 14 Lfx - Lzd - Cfz – Z	1	1.59
6 Bdq - Lfx - Lzd - Cfz - E / 14 Lfx - Lzd - Cfz – E	1	1.59
6 Bdq - Lfx - Cfz - Cs - Dlm / 14 Lfx - Cfz - Cs – E	2	3.17
6 Bdq - Lfx - Cfz - E - Eto /14 Lfx - Cfz - E – Eto	1	1.59
6 Bdq - Mfx - Lzd - Cfz - Cs / 14 Mfx - Lzd - Cfz - Cs	1	1.59
6 Bdq - Lzd - Cfz - Cs - E / 14 Lzd - Cfz - Cs -E	1	1.59
6 Bdq - Lzd - Cs - Z - E / 14 Lzd - Cs - Z – E	1	1.59
6 Bdq - Lzd - Cfz - Cs - Z / 14 Lzd - Cfz - Cs - Z	1	1.59
6 Bdq - Lzd - Z - E - Am / 14 Lzd - Z - E - Am	1	1.59
6 Lfx - Lzd - Dlm - Z - Eto / 14 Lfx - Lzd - Z - Eto	1	1.59
6 Lfx - Cfz - Cs - Dlm - E / 14 Lfx - Cfz - Cs - E	2	3.17
6 Bdq - Cfz - Cs - E - Z / 14 Cfz - Cs - E – Z	2	3.17
20 Lfx - Cfz - Cs - Z – E	3	4.76
20 Mfx - Lzd - Cfz - Cs – E	1	1.59
20 Cfz - Cs - Z – Dlm (6) – PAS	1	1.59

In this research, 60 out of the 65 patients (95.24%) experienced adverse drug reactions (ADRs). The most frequently reported ADRs were QT interval prolongation, affecting 36.92% of the patients. This side effect can result from using bedaquiline, clofazimine, levofloxacin, and delamanid. The second most common ADRs were gastrointestinal (GI) disorders, which nearly all anti-tuberculosis medications can cause. The development of ADRs is influenced by several factors, including the extended duration of treatment and the number of drugs taken, particularly in patients with comorbidities (Ifayani et al., 2023).

ADRs are critical to monitor as they can significantly impact patient adherence to treatment. To manage these reactions, healthcare providers may consider strategies such as close monitoring, dose adjustment, regimen modification, or even discontinuation of specific drugs (Ifayani et al., 2023). This study identified all adverse drug reactions (ADRs) of anti-tuberculosis regimens based on clinicians' assessments documented in electronic medical records. Table 4 presents the distribution of ADRs experienced by DRTB patients at UI Hospital.

The Medication Refill Adherence (MRA) analysis showed that the majority of patients (n=58, 89.2%) were classified as compliant, while 7 patients (10.77%) were deemed non-compliant. Similarly, Dewi et al. (2019) reported an adherence rate of 93.8%, while Batte et al. (2021) found a 88.1% adherence among TB patients. High adherence rates can be attributed to several factors supporting patients during treatment, including the patient's knowledge level, ease of medication access, adequate supervision by the drug-swallowing supervisor (PMO), and strong communication between patients and healthcare providers.

At the time of this research, of the 65 patients included, only 2 were recorded as having completed treatment successfully or were cured. The remaining 63 patients were categorized as having unsuccessful outcomes, including 5 deaths, 28 cases of treatment failure, and 30 patients who had not yet completed their treatment.

In this research, no significant relationship was found between adverse drug reactions (ADRs) and adherence among DRTB patients ($p > 0.05$). Similarly, other variables such as gender, age, treatment combinations, comorbidities, and potential drug interactions also did not show a significant association with adherence (Table 5). These findings are consistent with other studies, including those by Gler et al. (2012), Batte et al. (2021), and Dewi et al. (2019), which similarly reported no significant correlation between ADRs and nonadherence in TB patients. However, this contrasts with the studies of Iweama et al. (2021) and Dela et al. (2017), which found a significant link between ADRs and adherence to TB treatment. Differences in research outcomes could be attributed to variations in research conditions, such as sample size, population demographics, research settings, and assessment method for measuring medication adherence.

Moreover, ADRs are not the sole factor influencing nonadherence; other factors not examined in this research, such as education level, lifestyle, domicile, occupation, and psychological support, may also play a role (Ausi et al., 2021; Dewi et al., 2019). Nonetheless, ADRs remain a concern for healthcare providers, as patients experiencing ADRs were found to

have a 3.056 times higher risk of nonadherence compared to those without ADRs. However, the p-value was greater than 0.05.

Table 3. Major and moderate drug-drug interactions in drug-resistant tuberculosis patients in this single-center, cross-sectional *study*. *Description*: Bdq: Bedaquilin, Lfx: Levofloxacin, CFZ: Clofazimin, Z: Pirazinamid, Eto: Etionamid, Dlm: Delamanid, Ods: Ondansetron, Dpr: Domperidone, Mfm: Metformin, Glq: Gliquidone, Ins: Insulin, Gmp: Glimepiride, Lnz: Linezolid, Scf: Sucralfate, Iron supp: Iron supplement, Atc: Antacid, Dcf: Diclofenac, Mfn acid: Mefenamic acid. [Source: Merative Micromedex, reprocessed].

Severity	Potential Effects	Patient Management	Drugs Involved (n)
Major	Increases the risk of QT prolongation	Dose reduction, temporary discontinuation of the medication, or substitution with an alternative drug	1. Bdq-Cfz (55) 2. Bdq-Lfx (50) 3. Cfz-Lfx (53) 4. Lfx-Dlm (6) 5. Cfz-Dlm (5) 6. Bdq-Ods (5) 7. Lfx-Ods (3) 8. Cfz-Ods (3) 9. Lfx-Dpr (2)
Major	Hepatotoxicity	Discontinue the drug until the clinical condition improves. If no improvement is observed, substitute with an alternative drug.	1. Eto-Z (9)
Major	Increases the risk of serotonin syndrome	Monitoring of the patient's clinical condition or substitution with an alternative drug	1. Lnz-Ods (3)
Major	Increases the risk of blood glucose fluctuations	Monitoring of blood glucose levels	1. Lfx-Mfm (2) 2. Mfx-Mfm (1) 3. Lfx-Glq (1) 4. Lfx-Ins (1) 5. Lfx-Gmp (1)
Moderate	Lowers levofloxacin effectiveness	Continue the current therapy	1. Lfx-Scf (6) 2. Lfx-Iron supp(4) 3. Lfx-Atc (1)
Moderate	Increases the risk of seizures	Continue the current therapy	1. LfxNa-Dcf
Moderate	Increases the risk of hypoglycemia	Monitoring of blood glucose levels	1. Lfx-Mfm (2) 2. Mfx-Mfm (1) 3. Lfx-Glq (1) 4. Lfx-Ins (1) 5. Lfx-Gmp (1)
Moderate	Increases plasma concentration of ethambutol	Continue the current therapy	1. E-Dlm (2)
Moderate	Lowers the plasma concentration of clofazimine	Continue the current therapy	1. Cfz-Atc (1)
Moderate	Increase the risk of seizures	Continue the current therapy	1. Lfx-Mfn acid (1)

Regarding treatment outcomes, no significant relationship was observed between ADRs and patient outcomes. Similarly, other variables (gender, age, comorbidities, and potential drug interactions) did not show significant associations, except for the treatment combination variable ($p = 0.013$). These results align with studies conducted by Gler et al. (2012) in the Philippines and Nair et al. (2017) in India, which reported no significant relationship between ADRS and treatment outcomes in DRTB patients.

Table 4. Adverse Drug Reactions (ADR) distribution among drug-resistant tuberculosis patients in this single-center, cross-sectional study.

ADRs	Total (n=60)	Percentage (%)
QT Prolongation	24	36.92
Gastrointestinal Disorders (nausea, vomiting, dyspepsia, loss of appetite)	23	35.38
Anemia	15	23.08
Electrolyte Imbalance (Hyperkalemia, Hypokalemia, Hyponatremia	13	20
Joint Disorders (Arthritis, Gout, Arthralgia)	12	18.46
Nervous Disorders (Peripheral Neuropathy, Tingling, Optic Neuropathy)	12	18.46
Eye Disorders (Myopia, Astigmatism, Presbyopia, Dry Eyes)	10	15.38
Hyperuricemia	9	13.85
Allergies	9	13.85
Skin Disorders (Discoloration, Dry Skin)	9	13.85
Anxiety Disorders and Depression	7	10.77
Insomnia	6	9.23
Hypoalbuminemia	6	9.23
Thrombocytopenia	4	6.15
Muscular System Disorders (Tendinitis)	3	4.62
Endocrine Disorders (Hyperthyroidism)	2	3.08
Hearing Disorders	1	1.54

The limitations of the present study include its cross-sectional design, which restricts the ability to establish causal relationships between adverse drug reactions, medication adherence, and treatment outcomes. The relatively small sample size and limited number of patients who had completed treatment at the time of data collection may reduce the statistical power and generalizability of the findings. Additionally, the study relied entirely on retrospective data from medical records and the SITB database, which may not fully capture patient-reported ADRs or psychosocial factors influencing adherence. However, the strength of the present study lies in its use of real-world clinical data drawn from both medical records and the national Tuberculosis Information System (SITB), providing a comprehensive and practical overview of adverse drug reactions (ADRs), medication adherence, and treatment outcomes among DRTB patients.

Table 5. Results of chi-square test analysis between adverse drug reactions and other variables with medication adherence and treatment outcomes in patients with drug-resistant tuberculosis. *Description*: Chi-square test (*).

	Medication Adherence (n=65)							Treatment Outcomes (n=65)						
Variable	Adherent	**%**	Non-adherent	**%**	**P**	**OR**	**95%CI**	**Successful**	**%**	**Unsuccessful**	**%**	**P***	**OR**	**95%CI**
ADRs					0.373	3.056	0.273–34.190					0.120	0.05	0.002-1.009
- Yes	55	90.2	6	9.8				1	1.6	60	98.4			
- No	3	75	1	25				1	25	3	75			
Sex						1.063	0.218–5.187					1	0.703	0.402-11.752
- Male	34	89.5	4	10.5	1			1	2.6	37	97.4			
- Female	24	88.9	3	11.1				1	3.7	26	96.3			
Age					0.445	2.250	0.215–23.546					1	-	-
- 18–65	54	90	6	10				2	3.3	58	96.7			
years	4	80	1	20				0	0	5	100			
old														
- >65 years														
old														
Treatment					0.583	-	-					**0.013**	-	-
- Short-term														
- Long-term	8	100	0	0				2	25	6	75			
	50	87.7	7	12.3				2	0	57	100			
Comorbidity					0.708	0.700	0.144– 3.409					0.238	-	-
- Yes														
- No	28	87.5	4	12.5				2	6.3	30	93.8			
	30	90.9	3	9.1				0	0	33	100			
Drug					1	1.404	0.153–12.844					0.338	4.727	0.274-81.488
interaction														
potential	11	91.7	1	8.3				1	8.3	11	91.4			
- Yes	47	88.7	6	11.3				1	1.9	52	98.1			
- No														

Furthermore, using a total sampling method minimized selection bias within the study setting, and applying an objective adherence measurement (Medication Refill Adherence) enhanced the reliability of the adherence data. The study also explored multiple variables—demographic, clinical, and pharmacological—allowing for a multifactorial analysis of potential influences on adherence and treatment outcomes.

4. CONCLUSION

Based on the results of this research, it can be concluded that the characteristics of drug-resistant tuberculosis (DRTB) patients at UI Hospital predominantly include males of productive age, with no comorbidities, and a reliance on long-term treatment combinations. A significant proportion of these patients experience the risk of adverse drug reactions (ADRs), with the most prevalent form being QT interval prolongation. The analysis of medication adherence, as measured by the Medication Regimen Adherence (MRA) calculation, indicates that the majority of patients fall into the category of compliant with their DRTB treatment. During the research period, two patients were classified as successful or cured, both of whom were on short-term treatment combinations. Notably, the research found no statistically significant relationship between ADRS and medication adherence, nor between ADRs and treatment outcomes. Additionally, no other demographic or clinical factors exhibited significant associations with medication adherence or outcomes, except the treatment combination variable. Nevertheless, it remains imperative for healthcare professionals to prioritize education, along with the prevention and management of ADRs, as part of medicines optimisation strategies to mitigate the risks of nonadherence and treatment failure among DRTB patients.

ACKNOWLEDGMENT

Gratitude is expressed to UI Hospital for providing support and facilities to complete this research.

CONFLICT OF INTEREST

The author declares no conflict of interest in the implementation of this research or the publication of the data from this research.

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