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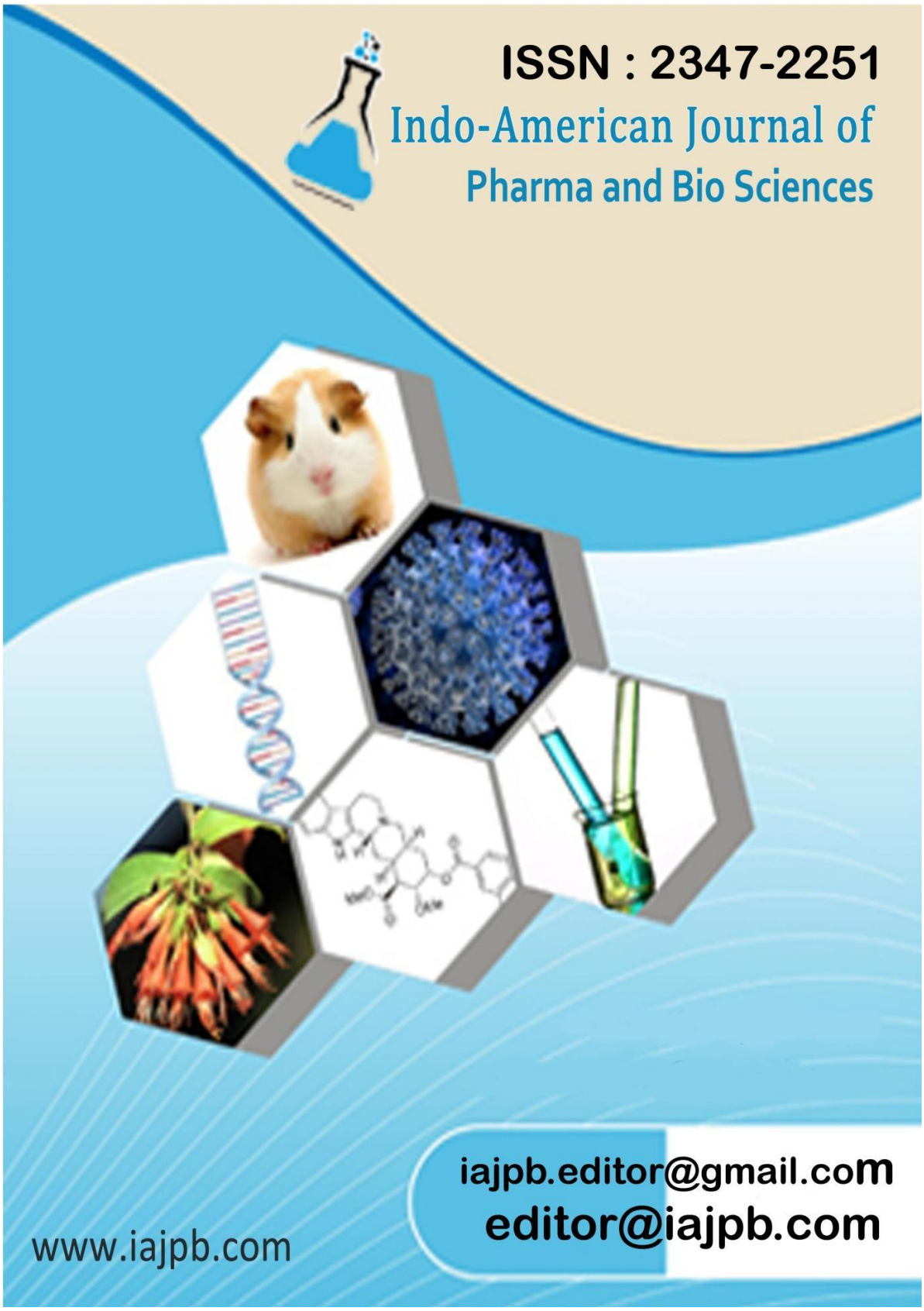

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A single- center retrospective cohort research examined the actual relationship between therapeutic drug monitoring and the antifungal medication posaconazole's clinical results.

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ABSTRACT:

Patients receiving hematopoietic stem cell transplantation (HSCT) should take posaconazole as a first line of defense against invasive fungal disease (IFD). There is a lack of data on how therapeutic drug monitoring (TDM) affects the prevention of IFD with posaconazole in retrospective investigations. Using real-world data, this research aimed to assess posaconazole's effectiveness, safety, and cost-efficiency in avoiding IFD.

Methods: Researchers from Shandong Provincial Qianfoshan Hospital, which is affiliated with Shandong First Medical University, looked at posaconazole as a fungal prevention treatment for HSCT patients in this retrospective cohort research. Based on their TDM status, patients were categorized into two groups: TDM and non-TDM. Propensity score matching (PSM) was used to examine clinical data in order to better understand the function of TDM in posaconazole prevention.

Conclusions: Following PSM, the prophylactic success rate was 100% in the TDM group compared to 52.9% in the non-TDM group ($P = 0.003$). Both groups had similar levels of gastrointestinal, liver, and kidney side effects ($P > 0.05$). When comparing the TDM group to the non-TDM group, we find that the former had reduced overall treatment costs and prescription costs.

In conclusion, real-world data show that TDM modestly lowers treatment costs and improves posaconazole's efficacy in avoiding IFD in HSCT patients.

KEYWORDS

posaconazole, therapeutic drug monitoring, invasive fungal disease, prophylactic antifungal therapy, hematopoietic stem cell transplantation

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1 Introduction

Every year, invasive fungal disease (IFD) cases rise in tandem with the numbers of patients suffering from immunodeficiency and other serious illnesses. Furthermore, hematological patients are disproportionately likely to have fungal infections, including Candida albicans, Aspergillus, and Trichophyton rubrum. For many types of cancers, both blood-related and others, the only curative therapeutic option is haematopoietic stem cell transplantation (HSCT). One of the leading causes of death after HSCT, IFD is among the most dangerous infectious consequences. The likelihood of immune-mediated rejection (IFD) is significantly increased by factors such inadequate engraftment,

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immunosuppressive medication, and protracted neutropenia following transplantation (Jenks et al., 2020). The use of antifungal medications as a preventative measure has greatly reduced the occurrence of IFD and the possibility of deaths caused by it (Marr et al., 2000; Gao et al., 2016). As a primary preventative measure, posaconazole has clear benefits. As a triazole antifungal that works across a wide range of fungal infections (Barchiesi et al., 2000; Girmenia, 2009), it is very efficient against Candida, Aspergillus, Coccidioides, and Histoplasma. The way it works is by preventing the production of ergosterol by blocking an enzyme called cytochrome P450-dependent 14α-demethylase. This process interrupts biosynthesis and changes the permeability of the

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cell membrane, which in turn prevents the growth of fungal cells (Lass-Flörl, 2011). Posaconazole is widely used in clinical settings because of its effectiveness and safety; it is highly recommended as a first-line preventative therapy for IFD by both domestic and international recommendations (Patterson et al., 2016; Maertens et al., 2018). Posaconazole, a second-generation triazole, has several great qualities: it is highly bioavailable, it has little drug resistance, and it has few medication interactions (Kwon and Mylonakis, 2007; Moore et al., 2015). However, it does have certain limitations. Xiao-Qun et al. (2011) found that this compound has a decreased risk of medication interactions due to its glucuronidation pathway metabolism and its ability to mainly inhibit the activity of CYP3A enzymes while sparing CYP2C19. The pharmacokinetics of posaconazole vary greatly from one person to another. Both posaconazole's bioavailability (F) and absorption rate constant (Ka) vary widely between studies (Dolton et al., 2014; Chen et al., 2020). Inducers of the uridine diphosphate (UDP)-glucuronosyltransferase enzyme, such phenytoin and rifabutin, may lower plasma concentrations of posaconazole, which accounts for about 17% of its metabolism (Shu et al., 2022). According to research, the therapeutic effectiveness of posaconazole is closely related to its plasma concentrations (Jang et al., 2010; Dolton et al., 2012), and the minimal plasma concentration (Cmin) that has been shown to prevent IFD is no more than

under 0.7 μg/mL, as reported by Jang et al. in 2010. Nevertheless, insufficient plasma concentrations may prevent certain patients from achieving the intended preventive benefit, which may be attributed to the significant pharmacokinetic variation (Van der Elst et al., 2015). Hence, posaconazole patients must undergo therapeutic drug monitoring (TDM) to guarantee the medicine's effectiveness and reduce resistance.

Through quantitative study of patient medication levels, TDM (a clinical pharmacy service) guarantees that drug concentrations are maintained within an effective treatment range. It entails modifying medication doses to improve therapeutic effectiveness while reducing adverse effects. By constantly checking the patient's medication concentrations using TDM, doctors can make sure the medicine stays within the therapeutic window and improve treatment results. Rapid detection of plasma concentration status is possible with TDM for patients on posaconazole to avoid IFD. According to John et al. (2019), TDM is the preferred method for antifungal prophylaxis with posaconazole.

Although there have been suggestions for the use of posaconazole for prevention purposes, there has been a dearth of well controlled trials evaluating the efficacy, safety, and cost-effectiveness of TDM in the Chinese population. Therefore, we looked at HSCT patients who used posaconazole for fungal prophylaxis in the past and assessed how TDM affected the drug's effectiveness, safety, and cost-effectiveness. In order to maximize fungal prophylaxis regimens, treatment results, and survival rates for patients, our study seeks to provide a reference for the appropriate use of posaconazole in clinical practice.

2 Materials and methods

2.1 Ethical approval

The study was designed to adhere to legal requirements and the Declaration of Helsinki. Ethical approval was granted by the Ethics Committee of Shandong First Medical University (approval number R526). All methods were conducted in accordance with the relevant guidelines. Due to its retrospective nature, the institution waived the requirement for obtaining written informed consent from patients.

2.2 Study design and participants

This retrospective, single-center study enrolled HSCT patients who used posaconazole oral suspension or enteric-coated tablets for IFD prevention and underwent TDM from January 2021 to March 2024 at the First Affiliated Hospital of Shandong First Medical University.

This study was divided into two groups: The TDM group: patients who received posaconazole TDM; Non-TDM group: Patients who did not undergo posaconazole TDM.

Inclusion criteria: (1) Patients with hematological diseases undergoing HSCT; (2) Prophylaxis with posaconazole oral suspension or enteric-coated tablets; (3) TDM group: the steady state plasma concentration (≥7 days) must be monitored; Non- TDM group: Plasma

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concentrations must not have been monitored. The exclusion criteria were: (1) Incomplete data or medication information; (2) Active fungal infection; (3) Non-adherence to medical advice; (4) Patients in the TDM group whose steady-state trough concentration (≥7 days of administration) was not recorded. Data collection included: (1) Demographic data, including age, gender, and body weight; (2) Hepatic and kidney function tests, including gamma-glutamyl transferase (GGT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL), and blood urea nitrogen (BUN); (3) Posaconazole- specific data, such as usage and dosage, sampling times, and minimum concentration (Cmin) results; (4) Concomitant medications, including proton pump inhibitors (PPI) and phenytoin; (5) Pathological symptoms reported by patients, such

2.3 Drugs and reagents

Posaconazole oral suspension (Specification: 40 mg·mL-1, Trade name: Noxafil®); Posaconazole enteric-coated tablets (Specification: 100 mg, Trade name: Noxafil®); Tinidazole internal standard working solution (Concentration: 250 μg/mL); formic acid and acetonitrile were both of chromatographic grade.

2.4 Sample collection and bioanalysis

Posaconazole TDM trough concentrations were monitored. Blood samples were collected 0.5 h before the first dose of the day. The concentration of the sample collected before the first dose was defined as the $C_{min.}$

The target trough C_{min} for posaconazole is 0.7 μg/mL. After 7 days of administration, serum samples containing posaconazole were obtained from patients using EDTA tubes. Posaconazole blood concentrations were determined by HPLC. The methodology conformed to the standards set in the 2020 edition of the Chinese Pharmacopoeia (Volume IV) and the 2018 FDA Guidance on Bioanalytical Technique Validation. Only one blood concentration measurement per patient was included in the analysis.

2.5 Evaluation indicators

The clinical diagnosis of IFD was defined as at least one host factor, one clinical criterion and one microbiological criterion (Chinese Association HematologistsChinese Invasive Fungal Infection Working Group, 2020).

Host factors included: (1) recent neutropenia (neutrophil count <500/L) lasting for more than 10 days; (2) receiving allogeneic hematopoietic stem cell transplantation; (3) use of glucocorticoids (more than 0.3 mg kg d, except allergic bronchopulmonary aspergillosis) for more than 3 weeks within the past 60 days; (4) Use of T cell immunosuppressants (such as cyclosporine A, tumor necrosis factor, some monoclonal antibodies such as alemtuzumab) or nucleoside analogues within 90 days; (5) use of B cell immunosuppressive agents such as BTK inhibitors; (6) history of invasive fungal infection; (7) patients with AIDS or genetic immunodeficiency (such as chronic granulomatosis or combined immunodeficiency).

Clinical criteria included: (1) For lower respiratory tract fungi, the presence of at least one of the following four items on CT examination: dense, well-circumscribed lesion (with or without halo sign), air crescent sign, cavity, wedge/segmental or lobar lesion; Other filamentous fungi include: reverse halo sign; (2) For tracheobronchitis, bronchoscopy showed the following manifestations: tracheobronchial ulcers, nodules, pseudomembranes, plaques or crusts; (3) For sinus infection, at least one of the following: acute local pain (including pain radiating to the eyes), nasal ulcers with black crusts, erosion of bone from the sinuses, including intracranial spread; (4) For central nervous system: at least one of the following: imaging examination suggested focal lesions; MRICT examination showed meningeal enhancement. For disseminated candidiasis, candidemia with at least one of the following within the previous 2 weeks: hepatic/spleen bull's eye sign; An ophthalmic examination revealed progressive retinal exudation.

2.5.1 Microbiological criteria include

Direct examination: cytology, direct microscopic examination or culture: (1) The presence of at least one of the following in sputum, bronchoalveolar lavage fluid, bronchial brush or sinus aspirate indicated mold infection: the presence of fungal components showed mold, culture indicated mold; (2) Sputum or bronchoalveolar lavage fluid was positive for Cryptococcus neoformans culture or was found by direct microscopic or cytological examination.

Indirect examination: detection of antigens or cell wall components.

(1) Galactomannan test (GM test) positive serum (1,3) -B-D-glucan test (G test) positive for Aspergillus in plasma, serum, bronchoalveolar lavage fluid or cerebrospinal fluid; (2) For invasive fungal diseases (except cryptococcosis and zygomycosis): serum (1,3) -B-D-glucan test (G test) was positive; (3) For Cryptococcus, Cryptococcus capsular polysaccharide antigen was positive.

Clinical efficacy indicators were categorized as effective and ineffective prophylaxis. Effective prophylaxis was defined as the absence of fungal infection from the start of posaconazole treatment until 3 months later. Posaconazole was considered ineffective if a breakthrough fungal infection occurred during treatment or within 3 months after the use of the drug.

The safety evaluation focused on gastrointestinal disturbances (including abdominal distension, diarrhea, nausea and vomiting) as well as hepatic and renal adverse reactions, assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) (Xu et al., 2017). Among them, hepatic function and kidney function were converted into categorical variables: normal and abnormal.

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Hepatic function was considered normal if ALT levels were ≤2ULN (ULN: 50 U/L), AST levels were ≤2ULN (ULN: 40 U/L), and TBIL
levels were ≤24 μmol/L. Renal function indicators were converted
into categorical variables: Normal/Abnormal. Renal function was considered normal if the patient's creatinine clearance rate (Ccr) was ≥60 mL/min/1.73 m^2.

The economic evaluation compared incremental cost-effectiveness ratios between the two groups. Total treatment cost was calculated as the total hospitalization cost for patients. Drug cost referred to the medication cost. Drug cost ratio was the ratio of drug
cost to total treatment cost. The change in efficacy (ΔE) was the
difference between the TDM group's prophylaxis success rate and the non-TDM group's rate. The incremental cost-effectiveness ratio (ICER) for total treatment cost and drug cost was calculated as the change in cost divided by the change in efficacy.

2.6 Statistical analysis

To minimize selection bias between the TDM and non-TDM groups, propensity score matching (PSM) was performed for a total of 56 patients from both groups. Patients were matched 1:1 using the nearest neighbour method with a caliper value of 0.3. Propensity scores were computed based on gender, BMI, gastrointestinal function, hepatic function, kidney function and concomitant medication. Ultimately, 17 matching pairs were formed in each of the TDM group and the non-TDM group (n = 34).

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TABLE 1 Clinical feature between the two groups before and after propensity score matching.

Features	All patients			Propensity-matched patients		
	TDM (n = 30)	Non-TDM (n = 26)	P value	TDM (n = 17)	Non-TDM (n = 17)	P value
Gender, n (%)			0.206			0.732
Men, n (%)	20 (66.7)	13 (50.0)		10 (58.82)	8 (47.06)	
Women, n (%)	10 (33.3)	13 (50.0)		7 (41.18)	9 (52.94)	
BMI(IQR)	15.84 (14.68,17.86)	15.91 (14.93,17.86)	0.339	16.97 (14.80,19.08)	15.98 (15.07,17.49)	0.384
Albumin, g/L, median (IQR)	40.70 (36.08,45.03)	42.70 (39.75,46.15)	0.104	40.70 (36.10,44.00)	43.50 (39.30,46.40)	0.233
NEUT, $\times 10^9$cells/L, median (IQR)	1.27 (0.04,2.69)	2.48 (0.34,2.48)	0.111	1.05 (0.025,2.12)	0.50 (0.15,3.09)	0.863
Liver[a], n (%)			0.002			>0.999
Normal	21 (70.0)	26 (100.0)		16 (94.1)	17 (100)	
Abnormal	9 (30.0)	0 (0)		1 (5.9)	0 (0)	
Gastrointestinal[b], n (%)			0.838			>0.999
Normal	20 (66.7)	18 (69.2)		10 (58.82)	9 (52.94)	
Abnormal	10 (33.3)	8 (30.8)		7 (47.06)	8 (47.06)	
Kidney[c], n (%)			0.464			NA
Normal	30 (100)	25 (96.2)		17 (100)	17 (100)	
Abnormal	0 (0)	1 (3.8)		0 (0)	0 (0)	
Concomitant medications, n (%)						
Omeprazole			0.757			>0.999
Yes	7 (23.3)	7 (26.9)		4 (23.5)	4 (23.5)	
No	23 (76.7)	19 (73.1)		13 (76.5)	13 (76.5)	
Phenytoin			>0.999			>0.999
Yes	2 (6.7)	2 (7.7)		2 (11.8)	2 (11.8)	
No	28 (93.3)	24 (92.3)		15 (88.2)	15 (88.2)	
Metoclopramide			>0.999			NA
Yes	1 (3.3)	0 (0)		0 (0)	0 (0)	
No	29 (96.7)	26 (100)		17 (100)	17 (100)	
Cyclosporin/Tacrolimus			0.158			0.485
Yes	26 (96.7)	26 (100)		15 (88.2)	17 (100)	
No	4 (3.3)	0 (0)		2 (11.8)	0 (0)	

[a]Hepatic function was considered normal if ALT, levels were ≤2ULN(ULN: 50 U/L), AST, levels were ≤2ULN(ULN: 40 U/L), and TBIL, levels were ≤24 μmol/L.
[b]Gastrointestinal function was considered normal if the patient did not experience any of the following: nausea, vomiting or diarrhea.
[c]Renal function was considered normal if the patient's creatinine clearance rate (Ccr) was ≥60 mL/min/1.73 m2.
NA: statistical testing was not performed because the outcome had no variability.

Continuous variables were presented as mean ± SD or median (IQR) and categorical variables as numbers and percentages. Differences in baseline characteristics between the TDM and non-TDM groups were examined using t-tests or Mann–Whitney U tests for continuous variables and Pearson's χ^2 test or Fisher's exact test for categorical variables. The significance level was set at $p < 0.05$. All statistical tests were conducted using SPSS version 22.0 software (SPSS Inc.).

3 Results

3.1 Patient information

According to the inclusion criteria, a total of 44 patients were included in the TDM group and 30 patients were included in the non-TDM group. According to the exclusion criteria, in the TDM group, 4 cases were excluded due to the presence of active fungal infections during the baseline period, 4 cases were excluded due to the lack of steady-state concentration data, and 4 cases were excluded due to incomplete data information. In the non-TDM group, 2 cases were excluded due to active fungal infections during the baseline period, and 2 cases were excluded due to incomplete data and information. Therefore, there were ultimately 30 patients in the TDM group and 26

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patients in the non-TDM group.

The baseline characteristics of the included patients are shown in Table 1. Prior to matching, there were 30 patients in the TDM group and 26 in the non-TDM group. No statistical differences were observed between the groups in terms of gender, BMI, albumin levels, NEUT, gastrointestinal functions, kidney functions, and concomitant medication (Omeprazole, phenytoin, metoclopramide, Cyclosporin/Tacrolimus) ($P > 0.05$). However, significant difference was noted in hepatic function ($P < 0.05$). After PSM, the TDM group

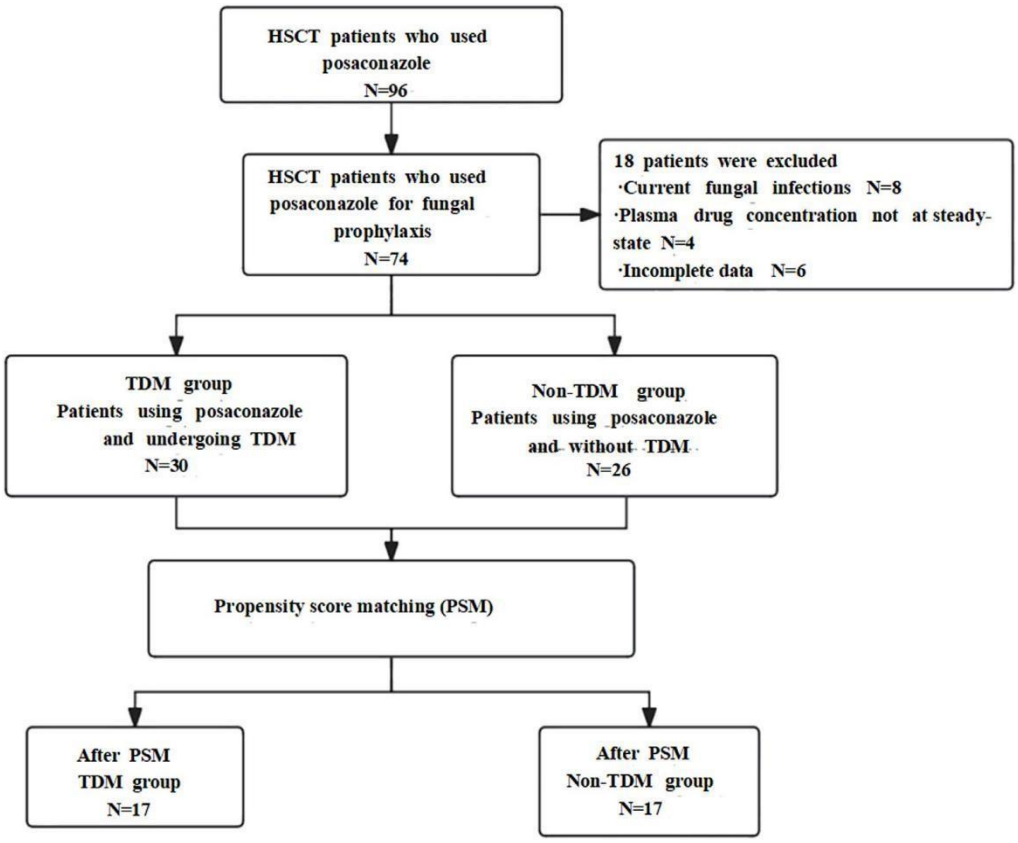

FIGURE 1
Flowchart of case selection and results.

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comprised 17 patients and the non-TDM group 17 patients. Post- PSM, no statistical differences were noted between the groups in any variables (P > 0.05), indicating that baseline disparities had been addressed, rendering the groups comparable. All patients had no active fungal infection at the baseline period. The specific inclusion process is shown in Figure 1.

3.2 Comparison of prophylactic effectiveness after matching

After PSM, 17 patients (100%) in the TDM group achieved successful prophylaxis. In the non-TDM group, 9 patients (52.9%) were successful, and 8 patients (47.1%) failed. The chi-square test indicated a statistically significant difference between the two groups (P = 0.003), as shown in Table 2. In the non-TDM group, 6 out of 8 patients who failed in prophylaxis had Aspergillus infection, and both G test and GM test were positive. In the other 2 cases, only G test was positive and the fungal species could not be determined.

3.3 Safety analysis after PSM

Adverse events occurred in 7 patients in the TDM group (41.2%). Among them, 2 patients had gastrointestinal adverse reactions and 5 patients had abnormal liver function. Adverse reactions occurred in 6 patients in the non-TDM group (35.3%).

TABLE 2 Comparison of clinical outcomes between the two groups after propensity score matching analysis.

Group	Clinical outcomes	
	Success	Failure
TDM, n (%)	17 (100)	0 (0)
Non-TDM, n (%)	9 (52.9)	8 (47.1)
χ^2 value	10.462	
P value	0.003	

There were 1 case of rash, 3 cases of gastrointestinal adverse reactions and abnormal liver function, and 2 cases of abnormal liver function. No statistically significant differences were found in the rates of gastrointestinal and liver adverse events between the groups (P > 0.05), though a increase in the incidence of adverse events was observed in TDM group, as depicted in Table 3. No adverse events related to the kidneys and cardiovascular system occurred in either group of patients.

3.4 Cost-effectiveness analysis

Incremental cost-effectiveness ratios (ICER) were used to compare the medical costs of the TDM and non-TDM groups.

TABLE 3 Comparison of adverse events rates between the two groups.

Group	Skin function[a]		Gastrointestinal funtion[b]		Hepatic function[c]		Total	
	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal
TDM, n (%)	17 (100.0)	0 (0.0)	15 (88.2)	2 (11.8)	12 (70.6)	5 (29.4)	10 (58.8)	7 (41.1)
Non-TDM, n (%)	16 (94.1)	1 (5.9)	14 (82.4)	3 (17.6)	12 (70.6)	5 (29.4)	11 (64.7)	6 (35.3)
χ^2 value	1.030		0.234		0.151		0.515	
P value	>0.999		>0.999		>0.999		0.721	

[a]Skin disorders mainly refer to rashes.
[b]Gastrointestinal function indicators were converted into categorical variables: Normal/Abnormal. Gastrointestinal function was considered normal if the patient did not experience any of the following: nausea, vomiting or diarrhea.

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[c]Hepatic function indicators were converted into categorical variables: Normal/Abnormal. Hepatic function was considered normal if ALT, levels were ≤2ULN(ULN: 50 U/L), AST, levels were ≤2ULN(ULN: 40 U/L), and TBIL, levels were ≤24 μmol/L.

TABLE 4 Incremental cost-effectiveness analysis between the two groups.

Group	Average total cost (¥)	Average total drug cost (¥)	Drug cost ratio	Effective rate	ICER (total cost)	ICER (total drug cost)
TDM	199540.01	111346.26	49.89%	100%	−520.70	−512.17
Non-TDM	224064.83	135469.55	58.45%	52.9%		
P value	0.616	0.459				

The results showed that in the TDM group, the *per capita* total cost was reduced by 24524.82 yuan, the *per capita* total drug cost was reduced by 24123.29 yuan, and the compliance rate was increased by 47.1%. ICER can save 520.70 yuan of hospitalization cost and 512.17 yuan of drug cost for every 1% increase in the target rate, which has absolute advantages (Table 4). Sensitivity analysis confirmed that even if the test cost increased by 10%, the ICER(total cost) was −97.05 yuan, which still maintained the economic advantage and supported the clinical promotion of TDM.

4 Discussion

Invasive fungal infections have emerged as a leading cause of mortality among HSCT patients, significantly affecting transplantation outcomes and long-term patient prognosis (Busca and Pagano, 2016; Li et al., 2017; Otto and Green, 2020). With the use of prophylactic antifungal drugs and immunosuppressive agents, the epidemiology of these infections has shifted. The prevalence of *Candida* infections has declined, while that of Aspergillus infections has risen (Schmiedel and Zimmerli, 2016; Souza et al., 2021). Thus, when selecting prophylactic antifungal medications, consideration of various potential drug-resistant strains is necessary. This study was retrospective and included patients with baseline biases, which were mitigated by employing PSM to reduce selection bias. The PSM method ensures comparability of baseline data between groups, enhancing the reliability of the results.

PASS software (15.0.5) was used to calculate the sample size of the two groups, and the results showed that with the effective rate of 100% in the TDM group and 52.9% in the non-TDM group (Target power set to 0.9, alpha set to 0.05), the sample size of each group should be at least 12 cases. In this study, there were 17 cases in the TDM group and 17 cases in the non-TDM group after PSM, which met the sample size requirements.

The study revealed a prevention success rate of 100% in the TDM group, compared to 52.9% in the non-TDM group. The clinical prophylactic efficacy of the TDM group was significantly greater than that of the non-TDM group (P = 0.003). This suggests that TDM can enhance the clinical efficacy of posaconazole. Thus, based on TDM results, the posaconazole dosing regimen may be adjusted to maintain drug concentrations within the target range, optimizing efficacy and minimizing toxicity. This finding aligns with previous studies (Lewis et al., 2019), which have shown that hospitals implementing TDM for posaconazole report superior treatment outcomes.

In the TDM group, 8 of 17 patients achieved the target prophylactic concentration of posaconazole (≥0.7ug/mL). In order to prevent adverse events and save drug costs, the dose of 300 mg qd was adjusted to 100 mg qd. The prevention of this child was effective, and no adverse events occurred. Among the 9 cases whose initial concentration was below the target, 3 cases had the dose increased, and 6 cases with very low concentration were adjusted to other antifungal drugs. All children in the TDM group were successfully prevented from fungal infection.

Posaconazole is highly safe, with an adverse reaction rate lower than that of voriconazole (Cornely et al., 2007). The principal adverse events to posaconazole are hepatic and gastrointestinal function abnormalities, which are typically mild, with serious adverse event rates ranging from 6% to 13% (Cornely et al., 2007; Ullmann and Jeffrey, 2007; Winston et al., 2011). To date, no adverse events directly related to posaconazole drug concentrations have been reported, making discontinuation due to adverse effects uncommon (Dolton et al., 2014). This study investigated the effect of hepatic enzyme inducer (phenytoin) and P-glycoprotein inhibitor (omeprazole, cyclosporine) on the plasma concentration of posaconazole and its clinical significance. The results showed that phenytoin as a UDP-glucosidase inducer significantly reduced posaconazole concentrations (<0.7 μg/mL in both patients with combination therapy), which was consistent with expectations and suggested strict monitoring during clinical combination therapy. The effect of P-gp inhibitors was bidirectional: although omeprazole may increase intestinal absorption through P-gp inhibition, its inhibition of gastric acid was dominant. Only 1 case of 4 cases combined with omeprazole reached the standard concentration (≥0.7 μg/mL). Cyclosporine as a P-gp inhibitor can theoretically increase the concentration of P-gp. In this study, the concentration of 8 patients in the TDM

gYri oeut pal.reached the target rate of 50%. Of note, although these drug interactions significantly affected posaconazole exposure, there was no statistically significant difference in the incidence of adverse events between the two groups, possibly because of: (1) the small sample size made it difficult to detect differences; (2) The fluctuation of posaconazole concentration did not reach the threshold of significantly affecting the safety; (3) The non-TDM group may avoid extreme high concentration due to empirical medication. TDM was of great value in this study, identifying not only the risk of undertreatment (sub-target concentration) in

PHT co-users, but also potential overdose cases (4.58 μg/mL) in

omeprazole co-users, suggesting that TDM can optimize individualized dosing and balance efficacy and safety. Therefore, TDM is recommended for patients combined with hepatic enzyme inducers or P-gp inhibitors to avoid treatment failure or drug toxicity, especially in high-risk groups.

In this study, treatment costs in the TDM group were significantly lower than those in the non-TDM group. Cost-effectiveness analysis indicated that the TDM group offered better economic value. For every unit increase in efficacy, total treatment costs for patients in the TDM group were

520.70 yuan lower than for those in the non-TDM group, and drug costs were 512.17 yuan lower. From the perspective of pharmacokinetic/pharmacodynamic (PK/PD) optimization, TDM achieves cost control at multiple levels by precisely adjusting the administration schedule of posaconazole. First, by avoiding the "trial and error" process of empirical administration, TDM significantly reduces the costs of subsequent rescue therapy and adverse effect management by reducing treatment failure due to insufficient dose (e.g., breakthrough fungal infection) or toxic effects caused by overdose (e.g., liver injury). The lower drug costs in the TDM group in this study reflect that PK/PD-guided dose optimization (e.g., timely dose escalation for phenytoin users and dosage modification for omeprazole users) can reduce exposure to ineffective drugs. Second, TDM shortened the time window to reach the target concentration, and avoided prolonged hospitalization caused by delayed efficacy by early identification of patients with low concentration (such as 2 phenytoin users), which explained the economic advantage of a total treatment cost reduction of 520.70 yuan per 1% improvement in efficacy. More important, concentration- based prophylaxis (e.g., in patients undergoing hematopoietic stem-cell transplantation) can reduce the incidence of invasive

fungal disease and essentially circumvent costly rescue therapies. These mechanisms together show that the economic value of TDM is not only reflected in the savings in direct drug costs, but also from1tCh.3e3i9mfpphroarv2e0m25en1t59i2n76t7he overall efficiency of diagnosis and treatment brought by PK/PD optimization, which provides clinicians with both accurate and cost-effective decision- making tools.

This study also has limitations: on one hand, PSM can only balance known impact factors and cannot adjust for unknown factors, which may introduce bias into the results. On the other hand, the factors considered in the matching process are relatively limited, such as not including the patient's economic status, which could also influence the results.

The innovative aspect of our study is the exploration of TDM's role in prophylactic antifungal treatment with posaconazole. We found that TDM contributes to optimizing treatment regimens, enhancing therapeutic outcomes, and reducing economic burdens on patients. Additionally, we utilized the PSM method to minimize selection bias, thus enhancing the reliability of our results. Our findings offer a new perspective for the rational use of posaconazole in clinical practice, expected to further improve treatment efficacy and patient survival rates.

5 Conclusion

The purpose of this study was to examine the relationship between the use of posaconazole topical masked by a topical medication (TDM) and clinical outcomes in children who had undergone hematopoietic stem cell transplantation and had been prescribed the medication to prevent fungal infections. Patients in the TDM group had a far lower risk of fungal infections, fewer hospitalizations, and lower medication costs compared to those in the non-TDM group. It may be concluded that TDM can guarantee posaconazole's efficacy while also easing patients' financial burden. There was no statistically significant difference, however, between the groups on the occurrence of adverse events. In order to maximize the effectiveness and economy of the medicine, we suggest regular transdermal monitoring (TDM) for HSCT children who are prescribed posaconazole for fungal prophylaxis.

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