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Risk Factors for Low Plasma Exposure to Prophylactic Posaconazole in Taiwanese Hematologic Malignancy Patients

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ABSTRACT

Posaconazole is commonly administered as antifungal prophylaxis in individuals with hematologic malignancies. Nevertheless, considerable interindividual variability in its pharmacokinetic profile can result in insufficient plasma exposure and subsequent prophylaxis failure. Evidence from real-world settings regarding the pharmacokinetics of posaconazole tablets and intravenous formulations in East Asian populations is still scarce. This study was conducted to assess plasma posaconazole concentrations and to identify factors associated with subtherapeutic exposure in Taiwanese patients. This analysis used a nested case-control design based on records from the National Taiwan University Hospital database. Adult individuals with hematologic malignancies who received posaconazole in either delayed-release oral tablet form or intravenous form and had therapeutic drug monitoring performed were eligible for inclusion. To explore determinants of low drug exposure, multivariate logistic regression modeling was conducted, defining subtherapeutic plasma concentrations as values below 0.7 μg/mL. Levels above 1.83 μg/mL were considered supratherapeutic. In the cohort of 221 patients, 24.9% had drug concentrations below the therapeutic range, whereas 24.0% exceeded the upper therapeutic limit (supratherapeutic). The multivariate logistic regression analysis identified several factors independently associated with insufficient posaconazole exposure. Being male was associated with increased odds of low concentrations (OR = 2.31). The occurrence of diarrhea also significantly contributed (OR = 2.18). Moreover, concomitant therapy with proton pump inhibitors (OR = 2.00) and prokinetic agents (OR = 2.17) was independently associated with decreased plasma posaconazole levels. Even with standard dosing regimens, both subtherapeutic and supratherapeutic posaconazole exposures continue to pose clinical challenges. Implementing therapeutic drug monitoring alongside individualized risk assessment is crucial to improving the effectiveness of antifungal prophylaxis in patients with hematologic malignancies.

Keywords: Antifungal prophylaxis, Posaconazole, Hematologic malignancies, Therapeutic drug monitoring

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Introduction

Posaconazole, a second-generation triazole antifungal, is widely used for the prevention and management of invasive fungal infections (IFIs), especially among high-risk groups such as patients with hematologic malignancies or recipients of hematopoietic stem cell transplantation [1]. Its antifungal effect is mediated through inhibition of ergosterol biosynthesis, a crucial component of fungal cell membranes, providing activity against molds including *Aspergillus* and *Mucor* species [2].

However, considerable variability in posaconazole pharmacokinetics has been documented between individuals. This variability is influenced by multiple factors, including formulation type, concomitant medications, serum albumin levels, body weight, gastrointestinal conditions, and genetic differences affecting drug metabolism [3–6]. Consequently, plasma concentrations may deviate from the desired therapeutic range, potentially compromising treatment effectiveness or increasing the risk of adverse events [7]. Evidence indicates that

achieving higher plasma concentrations is associated with improved clinical outcomes, supporting the implementation of therapeutic drug monitoring (TDM) for dose optimization [8, 9]. Current guidelines recommend target trough levels of ≥0.7 μg/mL for prophylaxis and ≥ 1.0–1.25 μg/mL for treatment, while concentrations above 3.75 μg/mL may raise safety concerns [10]. Notably, hepatotoxicity has been linked to levels exceeding approximately 1.83 μg/mL [11, 12].

Posaconazole is available in three formulations: oral suspension, delayed-release tablets, and intravenous solution. The oral suspension demonstrates inconsistent absorption that is highly dependent on food intake and can be significantly reduced in patients with gastrointestinal dysfunction or those receiving acid-suppressive therapy [13, 14]. In contrast, the delayed-release tablet provides more reliable systemic exposure due to its absorption in the small intestine and reduced sensitivity to gastric pH or dietary factors [6, 9].

The commonly recommended dosing regimen for tablet and intravenous forms consists of 300 mg twice on the first day, followed by 300 mg once daily. Nevertheless, pharmacokinetic studies have highlighted body weight as a key determinant of drug exposure [4], with additional real-world evidence suggesting that lower body weight may increase the likelihood of reaching higher plasma concentrations [15, 16]. This consideration is particularly important in Asian populations, where body weight distributions differ from those in Western cohorts, potentially leading to distinct exposure patterns.

Most prior investigations in East Asian populations have focused on oral suspensions, often with limited sample sizes and insufficient assessment of factors such as protein binding and bilirubin levels [9, 17, 18]. Furthermore, research has largely emphasized subtherapeutic exposure, while supratherapeutic concentrations—relevant to drug toxicity—have received comparatively little attention [9, 17–19]. Data on the real-world use of delayed-release tablets and intravenous formulations in Taiwanese patients remain scarce.

To fill these gaps, this study presents a large-scale real-world evaluation of posaconazole plasma levels in Taiwanese patients with hematologic malignancies receiving antifungal prophylaxis. By incorporating both tablet and intravenous formulations, the analysis covers the full range of drug exposure, investigates potential associations with breakthrough IFIs, and identifies clinical factors contributing to inadequate or excessive posaconazole concentrations.

Materials and Methods

Study design and data source

This nested case-control study used data from the Integrated Medical Database of National Taiwan University Hospital. This database was established in 2013 to facilitate the use of extensive clinical data for medical services and research. It contains comprehensive outpatient, inpatient, and emergency department records, which are accessible to authorized researchers for investigative and academic purposes [20]. The study protocol was approved by the Research Ethics Committee of National Taiwan University Hospital (approval number: 202208071RINA). Because the data were deidentified, no informed consent was required. This study was conducted in accordance with the Declaration of Helsinki.

Study cohort and selection criteria

This study included individuals aged ≥18 years who received a diagnosis of a hematologic malignancy between July 1, 2016, and December 31, 2020. Diagnoses were identified using ICD-10-CM codes, including acute myeloid leukemia, myelodysplastic syndromes, and allogeneic hematopoietic cell transplantation cases. Patients received posaconazole as delayed-release tablets or the intravenous formulation for the prophylaxis of invasive fungal infections.

In Taiwan, posaconazole prophylaxis is reimbursed only for high-risk patients, including those with severe acute graft-versus-host disease or high-risk hematologic malignancies receiving intensive chemotherapy. Patients were included if they had at least one therapeutic drug monitoring (TDM) measurement after steady state (≥ 5 days after initiation) and received a standard dose of 300 mg daily.

Patients whose first TDM measurement was not performed during hospitalization were excluded. The cohort was divided into case (< 0.7 μg/mL) and control (≥ 0.7 μg/mL) groups.

Covariates

Several clinical and demographic variables were included in the analysis, including age, sex, body weight, BMI, gastrointestinal symptoms, liver and renal function, inflammatory markers, albumin level, and concomitant medications such as proton pump inhibitors, H2 blockers, prokinetics, metabolic inducers, and inhibitors. Poor oral intake was defined as minimal or no oral intake in the four days preceding TDM sampling.

Clinical outcomes

Breakthrough invasive fungal infection (IFI) was defined as an infection that occurred during antifungal prophylaxis. Due to retrospective limitations, modified EORTC/MSG criteria were used [21]. Possible IFI was defined as switching from posaconazole to another antifungal between day 5 after initiation and day 1 after discontinuation. Probable IFI required additional microbiological evidence, such as positive Aspergillus or cryptococcal antigen testing or fungal culture. Outcomes were assessed until hospital discharge, with an additional 2-week follow-up after discontinuation if applicable.

Statistical analysis

Comparisons of patient characteristics between the case and control groups were conducted to identify potential predictors of subtherapeutic posaconazole exposure. For categorical measures, results are expressed as frequencies and percentages. For continuous measures, results are given as medians together with first and third quartiles. The Shapiro–Wilk test was used to check whether continuous data followed a normal distribution. When normality held, group differences were assessed using the independent t-test; otherwise, the Mann–Whitney U test was applied. Categorical variables were examined with either the chi-square test or Fisher's exact test as appropriate. To identify factors independently associated with subtherapeutic levels after accounting for other covariates, a multivariate logistic regression model was built using backward stepwise selection for variable entry. Adjusted odds ratios (ORs) and their accompanying 95% confidence intervals (CIs) were computed. All potential predictors were initially entered into the model. At each step, the variable with the largest P value was eliminated. This procedure was repeated until only those variables with P values less than 0.15 remained. A threshold of $P < 0.05$ was used to declare statistical significance in the final model. All data management and statistical procedures were performed using SAS (release 9.4; SAS Institute, Cary, NC, USA).

Results and Discussion

A total of 4026 individuals with hematologic cancers were initially identified. Among these, 221 fulfilled the entry requirements and were consequently enrolled in the analysis. The case group contained 55 patients, while the control group included 166 subjects. A diagram summarizing the patient selection process is shown in **Figure 1.**

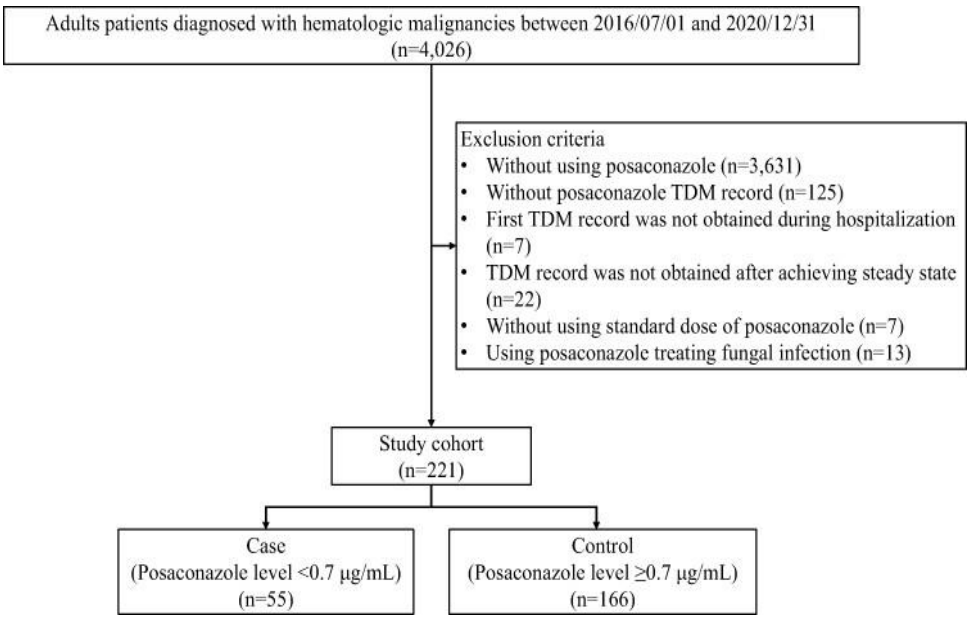

Figure 1. Flow diagram outlining how patients were selected for the study.

Table 1 Summary of patient characteristics at baseline across the entire study population. The breakdown of posaconazole concentrations was as follows: 24.9% measured below 0.7 μg/mL, 51.1% fell between 0.7 and 1.83 μg/mL, and 24.0% exceeded 1.83 μg/mL. Males made up a larger share of the case arm than the control arm (61.8% vs. 44.6%). The case group also showed greater frequencies of elevated bilirubin levels, low albumin, diarrhea, insufficient oral intake, and co-administration of PPIs or prokinetics. On the other hand, median CRP was higher in the control arm (3.61 mg/dL) relative to the case arm (2.47 mg/dL).

Table 1. Baseline demographic and clinical data for the total study cohort, along with separate columns for cases and controls.

Characteristics	P-value	Posaconazole level < 0.7 μg/mL (n = 55)	Posaconazole level ≥ 0.7 μg/mL (n = 166)	All patients (n = 221)
Age, (years) (Q1. Q3)	0.892	54 (44, 63)	54 (41, 64)	54 (41, 64)
Male (sex), n (%)	0.027	34 (61.8)	74 (44.6)	108 (48.9)
Posaconazole concentration, μg/mL	-			
Mean ± SD		0.51 ± 0.12	1.57 ± 0.70	1.30 ± 0.76
Median (Q1, Q3)		0.52 (0.42, 0.60)	1.39 (1.03, 1.98)	1.11 (0.70, 1.79)
Posaconazole concentration by group, n (%)	-			
< 0.7 μg/mL		55 (100)	0 (0)	55 (24.9)
0.7–1.82 μg/mL		0 (0)	113 (68.1)	113 (51.1)
≥ 1.83 μg/mL		0 (0)	53 (31.9)	53 (24.0)
Median weight, kg (Q1, Q3)	0.917	60.3 (53.4, 69.7)	62.3 (53.9, 71.3)	61.9 (53.6, 71.0)
Median BMI, kg/m^2 (Q1, Q3)	0.273	22.7 (20.6, 25.1)	23.4 (21.4, 25.6)	23.2 (21.2, 25.5)
ALT ≥ 120 U/L, n (%)[a]	1.000	2 (3.6)	7 (4.2)	9 (4.1)
T-Bil ≥ 1.2 mg/dL, n (%)[b]	0.091	15 (27.3)	28 (16.9)	43 (19.5)
Median eGFR, mL/min/1.73 m^2 (Q1, Q3)[c]	0.773	126.9 (105.0, 146.1)	115.9 (92.7, 144.5)	119.1 (95.3, 144.9)
Albumin < 3.5 g/dL, n (%)[d]	0.093	30 (54.6)	69 (41.6)	99 (44.8)
Median CRP (Q1, Q3)[e]	0.070*	2.47 (0.97, 4.56)	3.61 (1.65, 8.59)	3.20 (1.48, 7.50)
With loading dose, n (%)	0.704	18 (32.7)	59 (35.5)	77 (34.8)
Intravenous posaconazole use, n (%)	0.473	4 (7.3)	7 (4.2)	11 (5.0)
Poor intake, n (%)	0.252	19 (34.6)	44 (26.5)	63 (28.5)
Diarrhea, n (%)	0.137	17 (30.9)	35 (21.1)	52 (23.5)
Proton pump inhibitors use, n (%)	0.129	33 (60.0)	80 (48.2)	113 (51.1)
H_2-receptor antagonists use, n (%)	0.532	11 (20.0)	40 (24.1)	51 (23.1)
Prokinetics use, n (%)	0.209	15 (27.3)	32 (19.3)	47 (21.3)
With metabolic inducer, n (%)[f]	0.080	4 (7.3)	28 (16.9)	32 (14.5)
With metabolic inhibitor, n (%)[g]	1.000	0 (0)	1 (0.6)	1 (0.5)

Notes: *The Mann–Whitney U test served as the analytical method. [a]: A total of 221 patients had ALT measurements taken before TDM; [b]: Pre-TDM total bilirubin values were obtainable from 220 individuals; [c]: Data on eGFR before TDM existed for all 221 patients; [d]: Albumin levels measured before TDM were present for 187 subjects; [e]: CRP results collected before TDM were accessible for 192 patients; [f]: Lorazepam and rifampin fell into the category of posaconazole metabolism inducers; [g]: Cobicistat was identified as a metabolism inhibitor for posaconazole. Abbreviations: ALT = alanine aminotransferase; BMI = body mass index; CRP = C-reactive protein; eGFR = estimated glomerular filtration rate; NA = not applicable; Q1 = first quartile; Q3 = third quartile; T-Bil = total bilirubin.

Table 2 summarizes the outcomes of univariate and multivariate regression procedures. When each potential predictor was examined individually, only being male was significantly associated with subtherapeutic posaconazole concentrations. After entering all eligible covariates into a backward stepwise regression, six factors were retained in the final multivariable model. From these six, four demonstrated statistically meaningful associations with elevated risk of insufficient posaconazole exposure: male gender (OR = 2.31, 95% CI = 1.17–4.56), presence of diarrhea (OR = 2.18, 95% CI = 1.04–4.54), concurrent PPI administration (OR = 2.00, 95% CI

= 1.01–4.66), and receipt of prokinetic medications (OR = 2.17, 95% CI = 1.01–4.66). Turning to infectious endpoints, the case group exhibited numerically higher proportions of breakthrough invasive fungal infections (30.9% versus 20.5%) and in-hospital mortality (10.9% versus 7.2%) compared with the control arm **(Table 3).**

Table 2. Univariate and multivariable logistic regression results identifying predictors of subtherapeutic posaconazole levels (data shown in table format).

Risk factor	P-value	Adjusted logistic regression OR (95% CI)	P-value	Posaconazole ≥ 0.7 μg/mL (n = 166)	Posaconazole < 0.7 μg/mL (n = 55)
Male sex, n (%)	0.016*	2.31 (1.17–4.56)	0.027	74 (44.6)	34 (61.8)
Median age, years (Q1, Q3)			0.892	54 (41, 64)	54 (44, 63)
Median BMI, kg/m² (Q1, Q3)			0.273	23.4 (21.4, 25.6)	22.7 (20.6, 25.2)
Median CRP (Q1, Q3)	0.069	0.95 (0.90–1.00)	0.070#	3.61 (1.65, 8.59)	2.47 (0.97, 4.56)
ALT ≥ 120 U/L, n (%)			1.000	7 (4.2)	2 (3.6)
Total bilirubin ≥ 1.2 mg/dL, n (%)	0.058	2.16 (0.97–4.78)	0.091	28 (16.9)	15 (27.3)
Albumin < 3.5 g/dL, n (%)			0.093	69 (41.6)	30 (54.6)
Received loading dose, n (%)			0.704	59 (35.5)	18 (32.7)
Reduced oral intake, n (%)			0.252	44 (26.5)	19 (34.6)
Diarrhea, n (%)	0.038*	2.18 (1.04–4.54)	0.137	35 (21.1)	17 (30.9)
Use of proton pump inhibitors, n (%)	0.049*	2.00 (1.01–4.66)	0.129	80 (48.2)	33 (60.0)
Use of H2-receptor antagonists, n (%)			0.532	40 (24.1)	11 (20.0)
Use of prokinetic agents, n (%)	0.048*	2.17 (1.01–4.66)	0.209	32 (19.3)	15 (27.3)

Notes: The Mann-Whitney U test was applied for between-group comparisons. A P-value < 0.05 indicated statistical significance. Abbreviations: ALT = alanine aminotransferase; BMI = body mass index; CRP = C-reactive protein; OR = odds ratio; Q1 = first quartile; Q3 = third quartile; T-Bil = total bilirubin.

Table 3. Breakthrough IFI incidence and mortality outcomes in case versus control groups.

Results	Posaconazole L < 0.7 μg/mL (n = 55)	Posaconazole L ≥ 0.7 μg/mL (n = 166)
All breakthrough IFI, n (%)	17 (30.9)	34 (20.5)
Possible IFI, n (%)	11 (20.0)	23 (13.9)
Probable IFI, n (%)	6 (10.9)	11 (6.6)
In-hospital mortality, n (%)	6 (10.9)	12 (7.2)

Abbreviation: IFI, invasive fungal infection.

In this investigation, we examined real-world plasma posaconazole levels in Taiwanese patients with hematologic cancers receiving antifungal prophylaxis and identified key predictors of insufficient drug exposure. Across the cohort, 24.9% did not reach the recommended preventive trough target of 0.7 μg/mL or higher, despite being on standard dosing of the delayed-release tablet or the intravenous formulation. Independent factors linked to subtherapeutic levels included male sex, diarrhea, and concurrent use of PPIs or prokinetic agents. Hyperbilirubinemia showed a trend toward lower exposure, while inflammatory markers trended toward higher levels, though neither reached statistical significance.

The multivariable analysis confirmed that being male, having diarrhea, and taking PPIs or prokinetics each raised the risk of inadequate posaconazole concentrations. These results align with earlier work showing that PPI use

increases the likelihood of subtherapeutic exposure, likely by raising gastric pH and thereby reducing posaconazole solubility and absorption, even with the delayed-release tablet [18, 22]. Although this tablet formulation was designed to overcome pH-related absorption issues, some patients still experience impaired uptake while on PPIs, making continued TDM advisable. In our data, diarrhea and prokinetic use (e.g., metoclopramide) were also tied to lower drug levels. Bui *et al*. similarly found that both diarrhea and regular metoclopramide use were associated with subtherapeutic posaconazole concentrations [23]. The proposed mechanism for diarrhea involves shortened gastrointestinal transit time, which limits drug dissolution and intestinal uptake [23]. Prokinetics may accelerate stomach emptying and gut motility, thereby reducing the drug's contact time with absorptive surfaces in the small intestine [24]. Together, these observations suggest particular care and frequent monitoring for patients with gut dysfunction or those taking drugs that affect motility.

Male sex emerged as another independent predictor of low posaconazole levels in our cohort. One previous study also reported that men were more prone to subtherapeutic concentrations than women [23]. This difference may stem from sex-related variations in body composition—specifically, higher body weight in men (69.0 vs. 55.5 kg, $P < 0.001$) which could lead to a larger volume of distribution and, consequently, lower plasma levels in males. However, posaconazole is highly lipophilic, and greater body weight in men does not necessarily equate to more body fat; it may instead reflect increased muscle and bone mass. Prior studies have noted that male sex remains a risk factor for subtherapeutic posaconazole levels even after adjusting for weight, suggesting additional contributors, such as differences in hepatic metabolism or gastric transit time [22, 23].

Our results showed that both low albumin and high bilirubin levels affected posaconazole exposure. Posaconazole is more than 98% bound to plasma proteins, so its total concentration depends heavily on albumin levels [2]. In individuals with hypoalbuminemia, total measured drug levels may appear falsely low even when the active unbound portion stays within therapeutic bounds. Some evidence suggests that using only total concentrations for TDM in such patients could lead to unnecessary dose increases and greater toxicity [25]. Hence, total values should be adjusted using albumin-based correction formulas (e.g., Cadj = Ctotal × 4.4/Alb), as is done for phenytoin [25]. Elevated total bilirubin may also interfere with posaconazole's protein binding. Bilirubin competes for the same albumin-binding sites, potentially displacing posaconazole and increasing its free fraction [26]. As with hypoalbuminemia, this rise in free drug corresponds to a drop in measured total concentration, which could be mistaken for subtherapeutic exposure.

Our findings also highlight the clinical relevance of both subtherapeutic and supratherapeutic posaconazole levels. In this cohort, roughly one quarter of patients had inadequate exposure, consistent with real-world data showing that many individuals fail to reach target levels even with the tablet formulation [27]. Although baseline features were not adjusted, the case group had numerically higher rates of breakthrough IFIs and in-hospital death compared with the control group, which aligns with studies linking lower posaconazole levels to greater fungal infection risk [8, 9]. High concentrations were also observed, with about 25% of patients exceeding 1.83 μg/mL—a threshold previously tied to an increased chance of liver injury [11]. While current guidance sets the upper limit at 3.75 μg/mL, hepatotoxicity has been reported at lower levels in hematologic malignancy populations, underscoring the need for individualized risk assessment rather than fixed cutoffs [10].

We also examined whether systemic inflammation alters posaconazole pharmacokinetics. Inflammatory states, often marked by elevated CRP, tend to suppress the activity and expression of liver drug metabolizing enzymes and transporters, notably CYP3A4 [28]. This inflammation-driven downregulation is well described with voriconazole, leading to higher plasma levels and greater toxicity during inflammatory episodes [29]. Although posaconazole shares structural features with voriconazole, their metabolic pathways differ considerably. Posaconazole undergoes minimal cytochrome P450-mediated breakdown and is cleared chiefly by glucuronidation via UGT enzymes, especially UGT1A4 [2]. Systemic inflammation is also known to reduce UGT activity, potentially impairing glucuronidation-based elimination [28]. Nevertheless, no meaningful correlation between CRP and total posaconazole concentration was observed in our data. Consistent with our results, a prospective study by Märtson and colleagues found no significant association between CRP levels and posaconazole trough concentrations [30].

Several limitations should be acknowledged. First, the retrospective, single-center nature of this work may limit generalizability. Second, only total posaconazole levels were measured, without free drug concentrations, which may lead to misinterpretation in patients with altered protein binding. Third, outcome definitions differed from standard EORTC/MSG criteria due to data constraints and were not adjusted for baseline differences, so they

should be interpreted cautiously. Finally, genetic polymorphisms and hepatic enzyme activity were not assessed, although they may influence posaconazole disposition.

Conclusion

A substantial number of Taiwanese individuals with hematologic cancers fail to reach the recommended posaconazole target level even when receiving standard doses. Our analysis identified male sex, diarrhea, and concurrent use of PPIs or prokinetics as factors linked to a higher likelihood of subtherapeutic exposure. Systemic inflammation, however, appears to have little influence on posaconazole levels. Both insufficient and excessive concentrations occur frequently in this population. Notably, those with subtherapeutic exposure showed numerically higher rates of breakthrough invasive fungal infections than did patients achieving adequate levels, though these exploratory results were not adjusted for baseline differences. Taken together, these findings underscore the need for individualized dose adjustment and vigilant monitoring to achieve effective prophylaxis in this vulnerable group.

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Conflict of Interest: None

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Ethics Statement: The Institutional Review Board at National Taiwan University Hospital approved the study protocol (approval code: 202208071RINA). Given this circumstance ,the research was retrospective in design, and the usual requirement to obtain informed consent was set aside. Any data points that could identify individual patients were eliminated from the dataset before any analysis commenced. This study followed the ethical guidelines outlined in the Declaration of Helsinki.

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