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Original Article

Effect of inflammation on voriconazole levels in patients with invasive pulmonary aspergillosis

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Abstract

Introduction: Voriconazole (VCZ) serum concentrations may be affected by many factors, such as drug-drug interactions, liver dysfunction, genetic polymorphism, and inflammation. This study aimed to determine the relationship between VCZ measured trough plasma levels and C-reactive protein levels in patients with coronavirus disease 2019 (COVID-19)-associated aspergillosis (CAPA) and invasive pulmonary aspergillosis (IPA).

Methodology: Patients who were > 18 years of age, received VCZ treatment for IPA or CAPA in our hospital between March 2020 and April 2021, and had their VCZ level monitored, were included in this retrospective study.

Results: A total of 85 patients (35 diagnosed with CAPA) were included in this study. Forty-three patients (50.6%) had VCZ levels in the therapeutic range, 4 (4.7%) were sub-therapeutic, and 38 (44.7%) were supra-therapeutic. Inflammatory markers were significantly higher in patients with supra-therapeutic levels ($p < 0.05$). Supra-therapeutic levels and VCZ-related adverse effects were significantly more frequent in CAPA patients than in IPA patients ($p = 0.011$ and $p = 0.002$, respectively).

Conclusions: Patients diagnosed with CAPA were more prone to adverse effects and supra-therapeutic VCZ levels. More frequent therapeutic drug monitoring is recommended in this patient population.

Key words: voriconazole; COVID-19-associated aspergillosis; invasive pulmonary aspergillosis; inflammation; therapeutic drug monitoring.

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Introduction

Voriconazole (VCZ), a broad-spectrum triazole antifungal agent, is recommended as the first-line agent for treating invasive fungal disease caused by *Aspergillus* spp [1]. VCZ is metabolized to VCZ N-oxide mainly by cytochrome P450 (CYP) 2C19 and CYP3A4 [2]. VCZ metabolism shows high inter-individual variability due to nonlinear pharmacokinetics and genetic variants, which may result in insufficient or toxic plasma concentrations [3]. The trough plasma level of VCZ is affected by many factors, including age, gender, drug–drug interactions, liver dysfunction, genetic polymorphism, and inflammation [2,4]. Therefore, therapeutic drug monitoring (TDM) is recommended for VCZ [5].

It has been shown that inflammation may increase VCZ plasma levels through transcriptional and non-transcriptional mechanisms [6–11]. Inflammatory cytokines can cause the downregulation of CYP enzymes and decrease the hepatic clearance of VCZ, leading to supra-therapeutic levels and potential toxicity. Studies with human hepatocytes have shown that interleukin-6 causes a 26–50% decrease in the expression of CYP2C19 enzymes [12,13].

During the recent coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), COVID-19-associated aspergillosis (CAPA) was defined as a life-threatening complication in critically ill patients with COVID-19 [14–17]. The mortality of CAPA was reported to be 53.8% to 67.4% in patients hospitalized in intensive care units (ICUs) [14,18–20]. Therefore, timely diagnosis and effective antifungal treatment are essential to improve clinical outcomes and reduce mortality [14]. It is well known that the levels of inflammatory cytokines such as interleukins and tumor necrosis factor-alpha are higher in COVID-19 patients [21]. We observed supra-therapeutic plasma

levels of VCZ in a substantial number of CAPA patients in our center, when potential factors such as errors in drug dosage, time of sampling for TDM, and organ dysfunction were excluded. In a preliminary study, we observed a mild correlation between trough levels of VCZ and C-reactive protein (CRP) [22].

In this study, we extended our observation to investigate whether this relationship between VCZ trough plasma levels and CRP was similar in the CAPA population and other patients with invasive aspergillosis.

Methodology

This study was conducted as an observational study at a tertiary care university hospital between 20 March 2020 and 15 April 2021. The study site, Hacettepe University Hospital, included an academic teaching hospital with 1040 beds, including eight ICUs (143 beds) and an oncology hospital (131 beds + 8 ICU beds). The local ethics committee reviewed and approved the study protocol (GO 21/319). Informed written consent was obtained from all patients for the study.

Patients older than 18 years who received intravenous or oral VCZ with the diagnosis of invasive pulmonary aspergillosis (IPA) were included in the study. Patients were included regardless of the COVID-19 diagnosis. Patients who received VCZ for other indications and those not monitored for drug levels were excluded.

Data on patient characteristics, diagnostic parameters for IPA and CAPA, VCZ therapy, other medications, VCZ trough levels, and inflammatory markers were collected retrospectively. Some laboratory parameters such as serum aminotransferase levels, alkaline phosphatase, gamma-glutamyl transferase, total bilirubin, and albumin levels were recorded. Data on vasopressor requirement and use of mechanical ventilation (in the previous 24 hours on the TDM day) were also recorded.

IPA was classified as 'proven', 'probable', and 'possible' according to the European Organization for Research and Treatment of Cancer and the Mycoses Study Group (EORTC/MSG) criteria (2020) in non-ICU patients and as 'definitive', 'probable', and 'colonization' according to the criteria developed by Ashbee *et al.* in ICU patients [23,24]. All patients diagnosed with CAPA was classified as 'proven', 'probable', or 'possible' according to the 2020 European Confederation of Medical Mycology/International Society for Human and Animal Mycology (ECMM/ISHAM) consensus criteria [14].

VCZ was administered intravenously or orally at a loading dose of 6 mg/kg every 12 hours and a maintenance dose of 4 mg/kg every 12 hours [25]. It was switched to the oral route for maintenance therapy after 2 doses of an intravenous loading in patients with creatinine clearance (CrCl) below 50 mL/min due to the risk of cyclodextrin accumulation. VCZ trough level was measured at the steady state after 10 doses [6]. All patients with COVID-19 pneumonia were treated with favipiravir alone in our center.

In our center, blood samples for TDM for VCZ were routinely drawn 30 minutes before the next dose after reaching the steady state. VCZ concentrations were measured once a week in the central laboratory of our hospital. Therefore, samples were stored in the laboratory accordingly until the analysis day. Plasma VCZ level measurements were performed using a validated method (Z79010, Eureka Lab Division, Ancona, Italy) with liquid chromatography-triple quadrupole mass spectrometry (LC-MS/MS). The LC-MS/MS system consisted of a two LC-20AD pumps, a SIL-20AC/XR auto-sampler, a CTO-10ASVP column oven, a DGU-20A/3R degassing unit, Agilent C18 column, and a triple quadrupole mass spectrometer LCMS-8040 (Shimadzu, Kyoto, Japan). VCZ steady-state concentrations between 2 and 6 mg/L for the critically ill and 1–5.5 mg/L for the non-critically ill were considered the therapeutic targets [26,27]. 'Drugs.com, Drug Interactions Checker' (https://www.drugs.com/drug_interactions.html) database was used to detect potential drug-drug interactions (pDDIs) that could alter the VCZ trough levels [28]. CRP, erythrocyte sedimentation rate (ESR), and ferritin levels on the same day with the highest VCZ level (from levels on different days) were included for each patient [29,30]. Patients with pDDIs related to VCZ and those who received inappropriate VCZ doses and anti-inflammatory therapy such as tocilizumab that might affect CRP levels were excluded from the analysis. Only one VCZ trough level was included in the analysis for each patient. VCZ-related hepatotoxicity was defined as an increase in aspartate aminotransferase (AST) or alanine aminotransferase (ALT) at least 5 times the normal upper limit [31]. In patients with abnormal ALT or AST, hepatotoxicity was determined if AST or ALT value rose more than 3 times its baseline value under VCZ therapy. Absolute corrected QT (QTc) ≥ 500 msec or QTc interval prolongation ≥ 30 msec from baseline (before VCZ treatment) was considered voriconazole-related QT prolongation [32]. Other adverse effects associated with VCZ (such as visual disturbances, and hallucinations)

were common types of toxicity identified based on previous publications and considered to limit the clinical use of VCZ significantly [33].

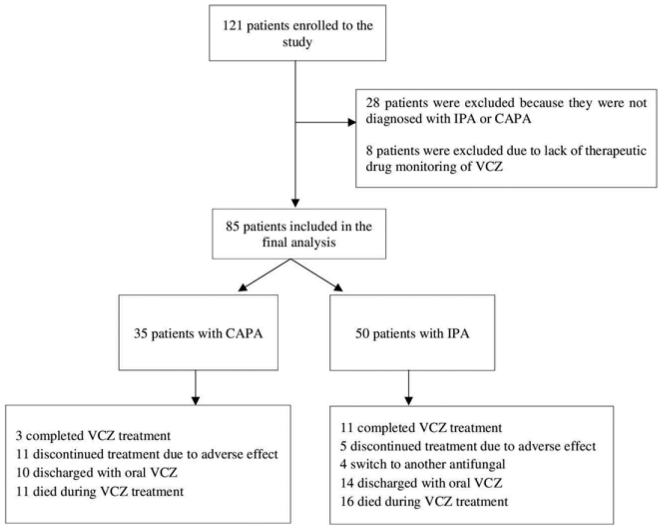
Statistical analysis was performed on IBM SPSS version 23 (IBM Corp, Armonk, NY, USA). Descriptive statistics such as mean, standard deviation, minimum, and maximum were used for numerical variables that conform to normal distribution. Percentage values and frequency tables were calculated for categorical variables. Due to the significant Kolmogorov-Smirnov tests, non-parametric tests were performed for statistical analysis. Categorical variables were compared with the χ^2 tests. Mann-Whitney U non-parametric test was used for comparing two independent groups. Tests were 2-tailed and a p value < 0.05 was considered statistically significant. Univariable and multivariable logistic regression models were used to identify risk factors that may cause supra-therapeutic voriconazole trough levels. The logistic regression models included independent variables that were found to be significant predictors (p < 0.05).

Results

One hundred and twenty-one patients were treated with VCZ during the study period (Figure 1). A total of 85 patients (35 diagnosed with CAPA and 50 with IPA) were included in the final analysis. The median age of the patients was 57 (interquartile range, IQR: 22.5) years and 64.7% were male. Demographic characteristics such as age (p = 0.077) and gender (p = 0.871) were similar in patients with CAPA and IPA. The most common comorbidities were cardiovascular diseases (51.4%) in patients with CAPA and hematological malignancy (50.0%) in patients with IPA (Table 1).

Aspergillus spp. was isolated from deep tracheal aspirates or bronchoalveolar lavage fluid cultures in 25 patients (29.4%). There was no patient with proven IPA or CAPA. The most common form of IPA was possible

Figure 1. Patient inclusion process.



CAPA: COVID-19-associated aspergillosis; COVID-19: coronavirus disease 2019; IPA: invasive pulmonary infections; VCZ: voriconazole.

Table 1. Demographic characteristics and diagnostic evaluation of patients with IPA and CAPA.

Parameter	Total (n = 85)	IPA (n = 50)	CAPA (n = 35)	*p* value
Age (years), median (IQR)	57 (22.5)	55 (21.5)	61 (19)	0.077
Gender, n (%)				
Male	55 (64.7)	32 (64.0)	23 (65.7)	0.871
Female	30 (35.3)	18 (36.0)	12 (34.3)	
Comorbidities, n (%)				
Hematological malignancies	30 (35.3)	25 (50.0)	5 (14.3)	**0.001**
Cardiovascular diseases	27 (31.8)	9 (18.0)	18 (51.4)	**0.001**
Endocrine diseases	22 (25.9)	12 (24.0)	10 (28.6)	0.636
Solid tumors	23 (27.1)	13 (26.0)	10 (28.6)	0.793
Lung diseases	15 (17.6)	9 (18.0)	6 (17.1)	0.919
Neurological diseases	9 (10.6)	6 (12.0)	3 (8.6)	0.731
Chronic kidney disease	7 (8.2)	2 (4.0)	5 (14.3)	0.119
Chronic liver disease	3 (3.5)	1 (2.0)	2 (5.7)	0.566
Hospitalization site, n (%)				
Intensive care unit (ICU)	61 (71.8)	30 (60.0)	31 (88.6)	**0.004**
Non-ICU	24 (28.2)	20 (40.0)	4 (11.4)	
Development of nosocomial infections during hospitalization, n (%)				
Presence of nosocomial infections	70 (82.4)	41 (82.0)	29 (82.9)	0.919
Voriconazole treatment				
Therapeutic/sub-therapeutic level, n (%)	47 (55.3)	31 (62.0)	16 (45.7)	0.137
Supra-therapeutic level, n (%)	38 (44.7)	19 (38.0)	19 (54.3)	
Duration of treatment, median (IQR)	20 (25)	20 (35)	19 (19)	0.235
Day for the voriconazole level monitoring, mean ± standard deviation	9 (12)	9.5 (14)	9 (7)	0.227
Mortality, n (%)				
Mortality (in hospital)	44 (51.8)	26 (52.0)	18 (51.4)	0.959
30-day mortality	32 (37.6)	17 (34.0)	15 (42.9)	0.407

Values at p < 0.05 are shown in bold. CAPA: coronavirus disease 2019-associated aspergillosis; IPA: invasive pulmonary infections; IQR: interquartile range.

IPA for non-ICU patients with hematological malignancy according to consensus criteria (Supplementary Table 1).

VCZ trough levels were within the therapeutic range in 43 patients (50.6%), supra-therapeutic in 38 (44.7%), and sub-therapeutic in the remaining 4 patients (4.7%). The rate of hospitalization in the ICU was similar in patients with supra-therapeutic and therapeutic/sub-therapeutic levels ($p = 0.724$). Adverse effects such as hallucinations, elevated serum aminotransferases, and prolongation of the QTc interval were observed in 28 (32.9%) patients. Adverse effects were significantly higher in patients with supra-therapeutic levels than the remaining (14.9% and 55.3%, $p < 0.001$) (Table 2).

VCZ-related adverse effects were observed more frequently in the CAPA group compared to IPA patients without COVID-19 [20.0% (n = 10) in IPA patients versus 51.4% in CAPA patients (n = 18), $p = 0.002$]. Hepatotoxicity was also more frequent in patients with CAPA [16.0% (n = 8) in IPA patients versus 42.9% (n = 15) in CAPA patients; $p = 0.006$] and QTc prolongation was detected only in one patient with CAPA. Two of 4 patients who developed VCZ-related hallucinations were in the CAPA group. Additionally, due to adverse effects, VCZ was discontinued in 5 IPA and 11 CAPA patients.

Inappropriate VCZ dosing and pDDIs with VCZ were observed in 5 patients each. pDDIs contributed to high VCZ trough levels in 3 patients with supra-therapeutic trough levels. Esomeprazole (40 mg twice daily), pantoprazole (40 mg twice daily), and clarithromycin (500 mg twice daily) were used in these patients. Five patients who received high doses of VCZ without adjustment based on body weight had supra-therapeutic levels.

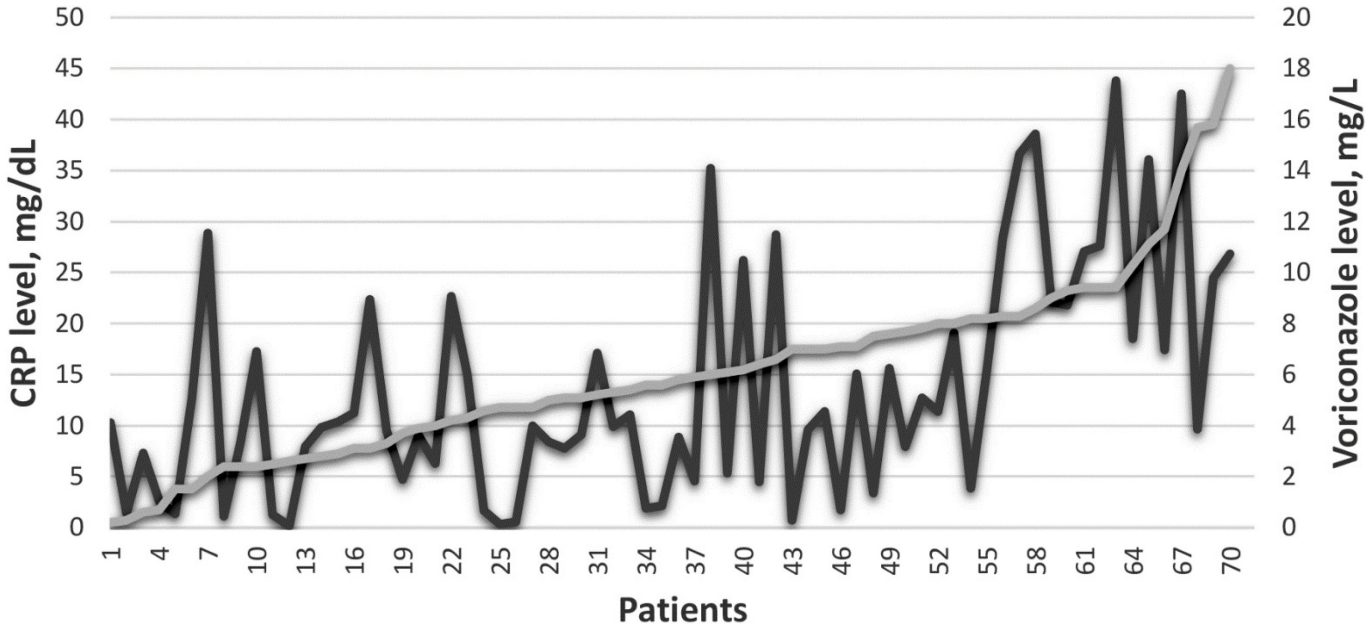
CRP and VCZ levels for each patient are presented in Figure 2. Fifteen patients with pDDIs, inappropriate dosage, or receiving anti-inflammatory therapy were excluded from this analysis to determine the effects of inflammation. Eight patients with COVID-19 pneumonia who received pulse steroids or tocilizumab

Table 2. Effects demographic and clinical characteristics on voriconazole levels.

	Total (n = 85)	Classification of voriconazole trough levels (mg/L)		*p* value
		Therapeutic/ Sub-therapeutic level (n = 47)	Supra-therapeutic level (n = 38)	
Age (years), median (IQR)	57.0 (22.5)	55.0 (21.0)	60.5 (25)	0.085
Gender, n (%)				
Male	55 (64.7)	31 (66.0)	24 (63.2)	0.788
Female	30 (35.3)	16 (34.0)	14 (36.8)	
Co-infections, n (%)				
SARS-CoV2 PCR positivity	35 (41.2)	16 (34.0)	19 (50.0)	0.137
Presence of nosocomial infections	70 (82.4)	36 (76.6)	34 (89.5)	0.122
Hospitalization site, n (%)				
Intensive care unit (ICU)	61 (71.8)	33 (70.2)	28 (73.7)	0.724
Non-ICU	24 (28.2)	14 (29.8)	10 (26.3)	
Administration route, n, (%)				
Intravenous	60 (70.6)	31 (66.0)	29 (76.3)	0.297
Oral	25 (29.4)	16 (34.0)	9 (23.7)	
Comedications and potential drug-drug interactions during follow-up				
Presence of drug-drug interactions, n (%)	5 (5.9)	2 (4.3)	3 (7.9)	0.652
Number of co-medications (mean ± standard deviation, SD)	11.5 ± 4.46	11.4 ± 4.64	11.7 ± 4.26	0.759
Inflammation markers, median (IQR)				
CRP, mg/dL (n = 70)*	10.0 (17.90)	9.5 (8.44)	22.1 (21.73)	**0.001**
ESR, mm/hr (n = 59)*	36.5 (41.00)	30.0 (34.00)	37.0 (64.50)	**0.002**
Ferritin, ng/mL (n = 25)*	1011.8 (1744.53)	1800.0 (1569.00)	753.3 (1718.40)	0.365
Adverse effect, n (%)				
Yes	28 (32.9)	7 (14.9)	21 (55.3)	**< 0.001**
No	57 (67.1)	40 (85.1)	17 (44.7)	
Trough levels of voriconazole, mean ± standard deviation (SD)				
The highest level (mg/L)	6.0 ± 3.46	4.0 ± 1.44	8.9 ± 2.81	**< 0.001**
Number of total levels	3.1 ± 3.01	2.3 ± 1.66	3.9 ± 3.60	**0.010**
Day of VCZ treatment at VCZ level monitoring day, mean ± SD	14.8 ± 15.71	12.3 ± 13.28	17.9 ± 17.98	0.117
Day of COVID-19 at VCZ level monitoring day, mean ± SD, (n = 33)	29.6 ± 21.22	28.8 ± 22.94	30.2 ± 20.28	0.849
Mortality, n (%)				
Mortality (in hospital)	44 (51.8)	22 (46.8)	22 (57.9)	0.309
30-day mortality	32 (37.6)	17 (36.2)	15 (39.5)	0.755

*Patients with pDDI: inappropriate dose and anti-inflammatory therapy were excluded from the analysis. *Values at p < 0.05 are shown in bold.* ESR: erythrocyte sedimentation rate; COVID-19: coronavirus disease 2019; CRP: C-reactive protein; IQR: interquartile range; PCR: polymerase chain reaction; SARS-CoV2: severe acute respiratory syndrome coronavirus 2; SD: standard deviation; VCZ: voriconazole.

Figure 2. CRP and voriconazole levels for each patient.



Patients are ranked from smallest to largest according to their voriconazole level. CRP: C reactive protein.

therapy to control the hyper-inflammatory response associated with COVID-19 had VCZ trough levels within the therapeutic target range. Inflammatory markers were significantly higher in patients with supra-therapeutic levels (p = 0.001 for CRP and p = 0.004 for ESR). According to multivariate analysis, every 1 mg/dL increase in CRP levels increased the risk for supratherapeutic levels 1.130-fold. In addition, SARS-CoV-2 polymerase chain reaction (PCR) positivity increased the risk of supratherapeutic levels by 11.027-fold (Table 3).

Supra-therapeutic VCZ trough levels were similar in patients with CAPA and IPA (p = 0.137). However, when the analysis was repeated by excluding patients with pDDIs, inappropriate doses, and anti-inflammatory therapy; supra-therapeutic levels were significantly higher in patients with CAPA than in IPA [65.4% (n = 17) in CAPA versus 34.1% (n = 15) in IPA, p = 0.011)]. In patients with supra-therapeutic levels, the dose of VCZ was reduced by 50% in 12 patients with IPA and 8 patients with CAPA. In 66.7% (n = 8) of the patients with IPA and 25.0% (n = 2) patients with CAPA in whom VCZ doses were reduced, VCZ levels were found to be in the therapeutic range in repeated measurements.

Discussion

In this study, we found that inflammatory markers, especially CRP, were higher in patients with supra-therapeutic VCZ trough values. Patients with CAPA had higher VCZ levels and were more prone to adverse effects than patients with IPA. To the best of our knowledge, this is the first study to compare the VCZ trough levels in patients with CAPA and IPA.

Inflammation may affect VCZ concentrations with various mechanisms, apart from pDDI and genetic polymorphisms [4,34]. The effect of inflammation on VCZ levels has been shown in many studies. In a retrospective study by Van Wanrooy *et al*., a significant correlation was found between VCZ trough levels and

Table 3. Risk factors for supra-therapeutic voriconazole trough levels according to the logistic regression analysis (n = 70)*.

	Univariable analysis		Multivariable analysis	
	OR (95% CI)	***p* value**	**OR (95% CI)**	***p* value**
Age	1.020 (0.991-1.049)	0.188	1.024 (0.969–1.082)	0.402
CRP level	1.102 (1.041-1.167)	**0.001**	1.130 (1.042–1.226)	**0.003**
Day of VCZ treatment at VCZ level day	1.016 (0.979-1.055)	0.392	1.088 (1.006–1.176)	**0.034**
Mechanical ventilation	1.000 (0.390-2.561)	1.000	2.702 (0.444–16.443)	0.281
Positivity for SARS-CoV2 PCR	3.652 (1.316-10.132)	**0.013**	11.027 (1.815–67.013)	**0.009**
Presence of nosocomial infections	2.183 (0.515-9.251)	0.289	1.038 (0.057–18.888)	0.980
Inotropic drug treatment	2.013 (0.664-6.106)	0.217	2.188 (0.298–16.076)	0.442

*Patients with pDDI: inappropriate dose and anti-inflammatory therapy were excluded from the analysis. *Values at $p < 0.05$ are shown in bold.* CRP: C-reactive protein; OR: odds ratio; PCR: polymerase chain reaction; SARS-CoV2: severe acute respiratory syndrome coronavirus 2; VCZ: voriconazole.

CRP concentrations in linear regression analyses ($p < 0.001$). It was reported that for every 1 mg/L increase in CRP level, the VCZ concentration increased by 0.015 mg/L [9]. In another prospective study in patients with hematological malignancies, VCZ levels were significantly associated with CRP levels ($p < 0.001$) [35]. In a retrospective case-control study conducted in the hematology unit, inflammation (for median CRP levels > 96 mg/L) was a significant risk factor for the occurrence of supra-therapeutic VCZ levels in multivariate analysis ($p < 0.01$) [10]. In our study, we observed that a 1 mg/dL increase in CRP level and positive SARS-CoV-2 PCR might increase the risk for supra-therapeutic levels by 1.130 times and 11.027 times, respectively.

The findings of our study suggest that patients with CAPA had higher VCZ levels and a higher risk of VCZ-related adverse effects, probably due to increased systemic inflammation in severe COVID-19. Le Daré *et al*. reported that inflammation might significantly affect the VCZ trough levels. VCZ metabolites were decreased during the inflammatory period compared with the non-inflammatory period (VCZ N-oxide/VCZ < 0.3 versus VCZ N-oxide/VCZ >1) despite the adjustment of VCZ dosing [36]. In another study, VCZ trough levels were significantly higher in patients with CAPA compared to patients without COVID-19 [median (interquartile range): 5.8 (4.75–6.75) to 2.4 (0.99–4.60)), $p = 0.001$], and a positive correlation was found between VCZ baseline levels and CRP levels ($r = 0.443$, $p < 0.001$) [22]. Contrary to these findings, in a retrospective study by Reizine *et al.* that compared CAPA and influenza-associated pulmonary aspergillosis patients treated with VCZ, the therapeutic levels of VCZ were reached later, and sub-therapeutic levels were more frequent in patients with CAPA. The conflicting findings of this study were due to pDDI or patients receiving anti-inflammatory therapies [37].

In our study, patients with supra-therapeutic VCZ levels were more prone to VCZ-related adverse effects ($p < 0.001$). Similar to our study, in a retrospective multicenter study conducted by Bienvenu *et al*., VCZ levels were significantly higher in critically ill patients who experienced VCZ-related adverse effects than patients who did not (5.8 mg/L vs. 2.7 mg/L, respectively; $p = 0.03$) [38]. Several meta-analyses have demonstrated a link between voriconazole exposure and adverse effects [39].

Previous studies have shown that proton pump inhibitors (PPIs) can increase VCZ exposure due to the inhibition of CYP2C19 [40,41]. In the study by Cojutti *et al*., the authors pointed out that the potency of CYP inhibition was dose-dependent for PPIs. This study showed that VCZ levels were significantly lower in patients receiving oral pantoprazole at 20 mg/day than in patients receiving intravenous pantoprazole at 80 mg/day ($p = 0.03$) [41]. In our study, supra-therapeutic levels occurred in 3 out of 5 patients who received high-dose PPIs (80 mg omeprazole or 80 mg pantoprazole) while 35 patients (43.8%) who did not receive high-dose PPI had supra-therapeutic VCZ levels.

A limitation of this study is its retrospective nature, which limits access to data. In addition, interleukin-6 levels, which may reflect inflammation in CAPA patients, were not routinely monitored, and simultaneous ferritin levels were measured only in a few patients. Therefore, we could only explain some of the variability for VCZ pharmacokinetics. Another limitation was that VCZ trough levels are measured only once a week in our center which may have caused delayed VCZ dose adjustments in case of supratherapeutic concentrations. No testing for genetic polymorphism was routinely performed in many centers in Turkey, including our center.

Conclusions

Our findings confirm that the inflammation reflected by CRP levels was associated with supra-therapeutic VCZ levels. Patients with CAPA were also more prone to supra-therapeutic levels and VCZ-related adverse effects. Clinicians should consider the inflammatory status of patients on VCZ therapy to prevent VCZ-related adverse effects and therapeutic drug monitoring should be used more frequently in CAPA patients.

Authors' contributions

PBE and EK: data analysis and writing-original draft of the manuscript; PBE, AGE, AP, and ACI: study design and review of manuscript. KD, GM, and OU: review and editing the manuscript.

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Annex – Supplementary Items

Supplementary Table 1. Diagnostic classification for IPA/CAPA.

Diagnostic criteria	IPA (n = 50)	CAPA (n = 35)
EORTC/MSG criteria (2020), (n = 20)		
Possible	12 (60.0)	-
Probable	6 (30.0)	-
Proven	0 (0.0)	-
Not classified	2 (10.0)	-
ICU criteria (2006), (n = 30)		
Colonization	27 (90.0)	-
Probable	3 (10.0)	-
Definitive	0 (0.0)	-
ECMM/ISHAM criteria (2020), (n = 35)		
Possible	-	1 (2.9)
Probable	-	12 (34.3)
Proven	-	0 (0.0)
Not classified	-	22 (62.8)

CAPA: COVID-19-associated aspergillosis; COVID-19: coronavirus disease 2019; ECMM/ISHAM: European Confederation of Medical Mycology/International Society for Human and Animal Mycology; EORTC/MSG: European Organization for Research and Treatment of Cancer and the Mycoses Study Group; ICU: intensive care unit; IPA: invasive pulmonary infections.