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SHORT COMMUNICATION

Treatment of *Candida* infections with fluconazole in adult liver transplant recipients: Is TDM-guided dosing adaptation helpful?

Elda Righi[1,2] | Alessia Carnelutti[1] | Umberto Baccarani[3,4] | Assunta Sartor[5] | Piergiorgio Cojutti[4,6] | Matteo Bassetti[1,4] | Federico Pea[4,6]

[1]Infectious Diseases Division, Azienda Sanitaria Universitaria Integrata Santa Maria della Misericordia, Udine, Italy

[2]Infectious Diseases, Department of Diagnostics and Public Health, University of Verona, Verona, Italy

[3]General Surgery and Transplantation Unit, Azienda Sanitaria Universitaria Integrata Santa Maria della Misericordia, Udine, Italy

[4]Department of Medicine, University of Udine, Udine, Italy

[5]Microbiology Unit, Azienda Sanitaria Universitaria Integrata Santa Maria della Misericordia, Udine, Italy

[6]Institute of Clinical Pharmacology, Azienda Sanitaria Universitaria Integrata Santa Maria della Misericordia, Udine, Italy

Correspondence
Elda Righi, Infectious Diseases Division, Azienda Sanitaria Universitaria Integrata Santa Maria della Misericordia, 50, Colugna Street, Udine (UD) 33100, Italy.
Email: elda.righi@libero.it

Abstract

Background: Fluconazole represents a common antifungal option for the treatment of *Candida* infections in liver transplant recipients. Although adequate antifungal exposure is known to correlate with favorable outcomes in patients with invasive candidiasis, therapeutic drug monitoring (TDM) of fluconazole is currently not recommended.

Methods: We conducted a retrospective study including adult liver transplant recipients receiving fluconazole for invasive candidiasis and undergoing TDM. We assessed the correlation between clinical variables, fluconazole trough plasma levels (C_{min}), and outcome.

Results: Twenty-seven patients (74% males; median age 57 years) were included. Abdominal candidiasis was the most frequent infection (56%). Median duration of fluconazole therapy was 17 days (IQR 9-21). Fluconazole median C_{min} was 11.0 mg/L (range 2.4-30.6 mg/L). Five (19%) patients required TDM-guided fluconazole dose increase. All-cause in hospital mortality was 33%. Fluconazole C_{min} >11 mg/L significantly correlated with clinical success (OR 8.78, 95% CI 1.13-67.8, $P = 0.04$).

Conclusions: Our study identified decreased fluconazole C_{min} as a factor associated with negative outcomes in liver transplant recipients with *Candida* infection. TDM of fluconazole may be advisable in this patient population.

KEYWORDS

fluconazole, invasive candidiasis, liver transplant recipients, outcome, therapeutic drug monitoring

1 | INTRODUCTION

Liver transplant recipients (LTR) have an increased risk of developing invasive candidiasis (IC), a life-threatening infection associated with mortality rates up to 70%.[1-3] Prompt administration of adequate antifungal treatment has demonstrated to improve the outcome of patients with IC.[4,5] The choice of the most appropriate antifungal agent in LTR depends on various factors, including patient's pathophysiology, disease severity, and *Candida* species.[3] Recent guidelines recommend the use of fluconazole in stable patients who do not present risk factors for azole resistance.[6,7] Although therapeutic drug monitoring (TDM) is not routinely recommended due to fluconazole predictable PK profile and renal elimination,[8] TDM-guided dosing adaptation could optimize drug exposure in selected patient populations (ie, pediatric patients or those undergoing renal replacement therapies).[9,10] Fluconazole exposure in LTR may be affected by complex pathophysiological conditions and by unstable renal function. Additionally, dosing adaptation of fluconazole based only on

creatinine clearance (CrCl) estimated values might result in inappropriate exposure due to the poor performance that CrCl formulas may have in predicting glomerular filtration rate in this population.[11,12] For this reason, since several years our institution performs TDM of fluconazole in LTR with the intent of individualizing drug exposure.

Aim of the study was to analyze the clinical characteristics and the factors associated with fluconazole trough levels (C_{min}) in a cohort of LTR treated for confirmed or suspected *Candida* infections.

2 | METHODS

2.1 | Study population

A retrospective, observational study was conducted at a 1100-bed tertiary care university hospital performing liver transplants since 2004. Adult (aged 18 and older) orthotopic LTR undergoing at least one determination of fluconazole C_{min} during the period August 2009-August 2016 were included. Only the first episode treated with fluconazole was considered for each patient. Fluconazole was administered for proven or suspected fungal infection due to *Candida* spp. Proven infection was defined as recovery of *Candida* spp from a normally sterile site in presence of signs and symptoms of infection, as previously reported.[13] Suspected candidiasis was based on clinicians' judgment in presence of risk factors for *Candida* infection along with clinical, radiological, or laboratory evidence consistent with an infectious disease process. Identification of isolates and antimicrobial susceptibility profiles were performed as previously described.[14] Patients' demographics, timing from liver transplant, site of infection, type of *Candida* strain, fluconazole dosage, fluconazole C_{min}, and outcome were collected through electronic databases. Changes in liver enzymes and kidney function during fluconazole treatment were also recorded. Clinical success during fluconazole treatment was defined as cure or significant improvement of signs and symptoms of infection along with microbiological success, defined as eradication if follow-up culture results were negative for *Candida*, or presumed eradication if follow-up blood cultures were not available but the clinical outcome was defined as success. Failure of response was defined as no significant improvement in signs and symptoms, death, or positive follow-up blood culture results. In-hospital mortality was defined as death during hospitalization in which fluconazole treatment and TDM were performed.

The local institutional review board approved the study, and written patient consent was waived because of the retrospective nature of the study.

2.2 | Fluconazole treatment and TDM

According to the Summary of Product Characteristics, fluconazole daily dose up to 400 mg/d is suggested for the treatment of IC in adult patients.[15] In presence of impaired renal function (CrCl <50 mL/min) dose reduction of 50% is recommended.[15] Fluconazole initial dosage was based on the treating physician's judgment and subsequently adjusted according to real-time TDM.

Since many years fluconazole TDM is performed at our institution by means of a validated HPLC technique and is available for all hospitalized patients receiving fluconazole upon request of the treating physician.[16] Since 2009, fluconazole levels are routinely detected and electronically recorded among LTR receiving fluconazole through monitoring of C_{min} and peak plasma levels. Based on the results of TDM, dose adjustments for LTR were recommended by an experienced clinical pharmacologist with the purpose of maintaining C_{min} close to 10 mg/L. A dose increase was suggested for fluconazole concentrations below the desired level (C_{min} <8 mg/L). Conversely, fluconazole dose was usually reduced when C_{min} was more than twice the target level. Subsequent C_{min} assessments following dose adjustments were performed in order to confirm the achievement of target C_{min}.

This approach is finalized to achieve the pharmacodynamics target of efficacy, defined as an area under the concentration-time curve/MIC (AUC/MIC) ratio >100 against all fluconazole-susceptible strains of *Candida* (MIC ≤2 mg/L, with MIC tested according to EUCAST methodology).[17,18] Fluconazole C_{min} were assessed at steady state after at least 3-5 days of treatment.

2.3 | Statistical analysis

Continuous and categorical data were reported as mean ± SEM or median (25th and 75th percentile) and frequency distributions, respectively. Categorical variables were evaluated using chi-square or, when appropriate, the two-tailed Fisher's exact test. To determine correlations between two continuous variables, a Spearman correlation coefficient was calculated. Mann-Whitney *U* test was used for comparing two groups. Logistic regression analysis was used to identify the variables correlated to clinical success among LTR with *Candida* infection. Variables with statistically significant association on univariate analysis were included in a multivariable binary logistic regression model. The area under the receiver-operating characteristic (ROC) curve and Youden's Index were calculated to established cut-off values for the variables with highest sensitivity and specificity for clinical success. Analyses were performed using SPSS v. 20.0 (IBM, SPSS). All tests were two-tailed, and a *P* value >0.05 was determined to represent statistical significance.

3 | RESULTS

A total of 27 liver transplant recipients (LTR) underwent at least one fluconazole TDM during the study period. Patients' characteristics are summarized in Table 1. Twenty (74%) patients were males and 7 (26%) females. Median age was 57 years (IQR 52.0-60.3). Conditions leading to liver transplant included HCV-related cirrhosis, (12/27, 44%) alcoholic liver cirrhosis (8/27, 30%), HBV-related cirrhosis (4/27, 15%), primary biliary cirrhosis (2/27, 7%), and fulminant hepatitis B (1/27, 4%). Concomitant HCC was detected in 10 cases (37%). Median MELD score at transplantation was 17.5 (IQR 14.0-23.3) with 50% of patients presenting with Child's B disease. Risk factors

TABLE 1 Characteristics of liver transplant recipients included in the study (n = 27)

Characteristic	N = 27
Age (y, IQR)	57 (52.0-60.3)
Males (%)	20 (74)
Reason for liver transplantation (%)	
HCV-related cirrhosis	7 (26)
HCV + HCC	3 (11)
HIV/HCV + HCC	2 (7)
HBV-related cirrhosis	2 (7)
HBV + HCC	3 (11)
Alcohol-related	5 (19)
Alcohol + HCC	2 (7)
Primary biliary cirrhosis	2 (7)
Fulminant HBV	1 (4)
Charlson comorbidity score (IQR)	3.3 (2.0-4.5)
Renal impairment (%)	
Mild (CrCl 50-80 mL/min)	13 (48)
Moderate (CrCl 31-49 mL/min)	7 (26)
Severe (CrCl 10-30 mL/min)	4 (15)
Albumin g/L (IQR)	25.7 (19.0-30.3)
Creatinine mg/dL (IQR)	1.20 (0.98-1.69)
BMI (kg/m^2)	22.9 (20.6-26.9)
Site of infection (%)	
Intra-abdominal	15 (56)
Biliary	8 (30)
BSI	3 (10)
Esophageal	1 (4)
Candida species (%)	19 (70)
C albicans	11/19 (58)
C glabrata	4/19 (21)
C parapsilosis	2/19 (11)
C tropicalis	1/19 (5)
Mixed (*C albicans* and *glabrata*)	1/19 (5)
Timing from LT (d, IQR)	42 (10-406)
Median duration of hospitalization (d, IQR)	45 (29-62)
MELD score	17.5 (14.0-23.5)
Hospitalization in ICU (%)	8 (33)
Concomitant antimicrobial therapy (%)	18 (67)
Fever (%)	12 (44)
Concomitant documented bacterial infections (%)	12 (44)
Type	
BSI	7/12 (58)
Abdominal	5/12 (42)
Pathogen	
Enterococcus spp	6/12 (50)
Enterobacteriaceae	4/12 (33)
Other	2/12 (17)
Fluconazole treatment duration (d, IQR)	17 (9-21)
Concomitant immunosuppressive therapy (%)	
Tacrolimus	17 (63)
Cyclosporin A	8 (30)
Everolimus	2 (7)

Note: Results are expressed as percentage (%) or median and interquartile range (IQR).

Abbreviations: BSI, bloodstream infection; CrCl, creatinine clearance; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; LT, liver transplant.

associated with development of IC included the use of broad-spectrum antibiotics within 30 days prior of the start of fluconazole (24/27, 89%), recent (<6 months) abdominal or biliary tract surgery (14/27, 52%), severe renal impairment (4/27, 15%), and concomitant CMV reactivation (3/27, 11%). *Candida* infection was microbiologically confirmed in 19 (70%) cases, and *C albicans* represented the most frequently isolated species (58%). All strains were reported as susceptible to fluconazole. Intra-abdominal infections accounted for 56% of infections (three peritonitis and 12 abdominal collection), followed by cholangitis (8/27, 30%), bloodstream infections (3/27, 11%), and esophagitis (1/27, 4%). Concomitant bacterial infections were reported in 12 (44%) patients.

Median time from transplantation to the initiation of fluconazole treatment was 42 days (IQR 10-406). Median duration of fluconazole therapy was 17 days (IQR 9-21). All patients received intravenous fluconazole. Overall, median maintenance dose of fluconazole (after an initial loading dose between 800 and 200 mg) ranged from 2.7 to 7.27 mg/kg/d. Fluconazole was dosed according to the Summary of Product Characteristics (SPC) in 24 patients (85%), while 4 (15%) patients with normal renal function received an initial dose below 6 mg/Kg/d according to the treating physician's judgment. All patients received concomitant immunosuppressive therapy.

Fluconazole C_{min} ranged from 2.4 to 30.6 mg/L. Median fluconazole C_{min} was 11.0 (7.9; 15.6) mg/L at first TDM and 11.6 mg/L (8.1; 16.6) after TDM-guided dosage adjustments. Overall, 18 (67%) patients achieved fluconazole C_{min} above 10 mg/L during treatment and 15 (56%) of these had C_{min} >11 mg/L. Five out of 27 (19%) patients did not achieve fluconazole C_{min} >8 mg/L in the first determination and required dose increase. After dose adjustments, fluconazole C_{min} >8 mg/L was achieved in 25 (93%) patients. Two patients did not achieve concentrations >8 mg/L during treatment: one was an HIV-positive patient receiving fluconazole for esophageal candidiasis and one was a patient hospitalized in ICU with candidemia receiving fluconazole doses up to 500 mg/d. Median fluconazole dose (initial or after dose adjustment) resulting in C_{min} concentration >8 mg/L was 4.2 mg/kg/d (IQR, 3.5-5.8). The four patients receiving reduced

fluconazole doses had median C_{min} of 8.83 mg/L (IQR 4.8-10.5) at steady state and all reached C_{min} >9 mg/L during treatment. No changes in CrCl or liver enzymes were detected during fluconazole treatment. In 12 (44%) patients with high fluconazole C_{min} (more than twice the target level), dose reduction was performed and fluconazole C_{min} maintained >10 mg/L.

Fluconazole dose significantly correlated with C_{min} (rs = 0.560, P = 0.002), while other parameters such as age, albuminemia, BMI, and CrCl did not appear significantly associated with fluconazole levels (Table S1).

Table 2 compares fluconazole C_{min} in different patient groups. Although decreased levels of fluconazole were documented for patients with low albuminemia (<20 g/L) and high BMI (>25), the univariate analysis did not show significant influence of demographic or laboratory parameters on fluconazole C_{min}.

Dosing adaptation of concomitant immunosuppressive therapy was required in 17/27 (63%) patients: 11/17 (65%) receiving tacrolimus (TAC), 5/8 (63%) receiving cyclosporine A (CsA), and 1/2 (50%) treated with everolimus (EVR). Mean percentage dose reduction was 42% for TAC, 36% for CsA, and 13% for EVR.

In five cases (three BSI and two biliary infections), microbiological cultures were available at the end of antifungal treatment, and all documented *Candida* eradication. Median fluconazole C_{min} among patients with microbiological eradication was 10.7 mg/L (IQR 8.3-15.5). Eight (30%) patients were admitted in the ICU and 3 (11%) patients presented with sepsis. None of the patients received renal replacement therapy or treatment with extracorporeal membrane oxygenation (ECMO) while receiving fluconazole.

Recurrent *Candida* biliary or abdominal infections within 3 months from the previous episode were reported in 2 (7%) patients. Switch of antifungal treatment from fluconazole to caspofungin or voriconazole was performed in 4/27 (15%) cases (three patients with *C glabrata* and one with *C parapsilosis* infection) due to worsening conditions. Overall all-cause in-hospital mortality was 9/27 (33%). Median time from fluconazole therapy initiation and death was 44 days (IQR 32-80). In 4/9 (44%) cases, mortality appeared related to the presence of candidiasis.

Mortality was significantly higher among patients with lower fluconazole C_{min} either at first TDM (8.5 mg/L, IQR 5.7-10.7 and 12.7 mg/L, IQR 8.9-20.2, P = 0.02) or at subsequent occurrences (10.4 mg/L, IQR 7.10-11.1 and 15.1 mg/L, IQR 8.9-21.1, P = 0.03; Figure S1). Univariate analysis showed that mortality was significantly higher among patients with decreased serum albumin levels (P = 0.04) and those hospitalized in the ICU (P = 0.01) (Table 3). Although mortality was higher for fluconazole MIC >1 mg/L vs MIC ≤1 mg/L (50% vs 22%, respectively, P = 0.52), the difference was not statistically significant.

Clinical success was documented in 15 (56%) patients. Univariate analysis identified serum albumin >20 g/L and fluconazole C_{min} >11 mg/L as factors associated with clinical success (Table 4). Multivariate analysis showed that only C_{min} >11 mg/L was an independent factor significantly associated with clinical success (OR 8.78, 95% CI 1.13-67.8, P = 0.04).

Areas under the receiver-operating characteristic (ROC) curve showed that fluconazole C_{min} >11 mg/L had highest sensitivity, specificity, and Youden's Index in predicting clinical success (Table S2 and Figure S2).

4 | DISCUSSION

As previously reported, we observed high (>30%) in hospital mortality in LTR with *Candida* infections.[1,19] The intrabdominal site was also confirmed to be a common site for candidiasis among LTR.[14] Fluconazole still represents the drug of choice in the treatment of candidiasis for patients who are clinically stable and did not report recent exposure to azoles.[6,7,20] Furthermore, the role of fluconazole in deep-seated infections is supported by its excellent tissue penetration.[21] We previously showed that intra-abdominal penetration of fluconazole was very high in three LTR with intra-abdominal candidiasis (eg, two cases of cholangitis and one of peritonitis), ranging from 50% to 85%.[16] In the same study, TDM-guided fluconazole therapy was performed with maintenance of plasma C_{min} at around 15 mg/L for 14 days, resulting in clinical resolution of the infection.[16]

TDM of fluconazole is generally not recommended due to its approximately linear and predictable PK behavior, so that dosing adaptations based on CrCl estimates are considered appropriate in clinical practice.[10] However, it should not be overlooked that in LTR the reliability of CrCl in predicting renal function was shown to be poor.[11] Fluconazole TDM-guided dosing adjustments may be advisable in this population since adaptation based only on CrCl estimates could result in inaccurate fluconazole exposure. We also confirmed that in LTR low fluconazole maintenance dosages (100-200 mg daily) appeared sufficient to achieve optimal probability of target attainment against *C albicans*.[12,16]

Liver toxicity associated with fluconazole use has been reported.[15,22] No clear association between fluconazole concentrations and liver function, however, has been documented to justify fluconazole TDM for toxicity purposes.[10] In our study, drug reduction was

TABLE 2 Fluconazole median C_{min} (mg/L) in different patient groups

Characteristic	Yes	No	*P* value
Male sex	10.7 (7.9; 13.4)	12.8 (6.3; 17.1)	0.66
ICU admission	11.0 (6.3; 16.0)	10.9 (8.6; 19.2)	0.83
Serum albumin <20 g/L	7.9 (6.2; 10.5)	12.4 (8.9; 19.3)	0.07
CrCl <50 mL/min	13.8 (7.5; 22.4)	11.0 (7.4; 12.7)	0.32
BMI >25	7.9 (6.2; 11.0)	12.4 (8.6; 19.3)	0.60
MELD >15	12.6 (9.1; 17.6)	9.6 (6.2; 13.2)	0.24

Note: Median fluconazole C_{min} reported in the table were measured at first therapeutic drug monitoring; target of C_{min} was 10 mg/L, with dose increase recommended for C_{min} <8 mg/L. Results are expressed as median and interquartile range (IQR) of fluconazole median C_{min} (mg/L). Abbreviations: BMI, body mass index; ICU, intensive care unit; MELD, model for end stage liver disease.

suggested for high fluconazole C_{min} (eg, more than twice the target level) in order to maintain a concentration target around 10 mg/L. In our study, fluconazole C_{min} up to 31 mg/L were not associated with changes in liver or renal function during treatment.

TABLE 3 Univariate analysis of factors associated with in-hospital mortality

Factor	Lived (18)	Died (9)	*P* value
Male sex (%)	13 (87)	7 (78)	1.00
Age (y, IQR)	54.0 (51.8-59.0)	60.0 (54.0-62.5)	0.32
Charlson score (IQR)	4.0 (2.8-5.0)	3.0 (2.0-3.8)	0.08
BMI, kg/m^2 (IQR)	22.3 (20.6-23.9)	26.8 (22.0-28.0)	0.08
Time from LT(d, IQR)	160 (14.0-432.0)	40 (3.0-137.5)	0.11
Serum albumin, g/L (IQR)	26.3 (23.8-31.2)	19.0 (16.0-25.3)	**0.04**
CrCl, ml/min (IQR)	57.9 (39.3-68.3)	73.6 (49.7-88.2)	0.20
Concomitant bacterial infection (%)	7 (47)	5 (56)	0.68
Concomitant bacterial BSI (%)	4 (27)	3 (33)	0.65
Non *albicans Candida* (%)	4/12 (33)	4/6 (67)	0.31
Median MELD score (IQR)	14.5 (10.0-18.0)	17.0 (15.0-20.0)	0.10
[a]Mean fluconazole C_{min}, mg/L (IQR)	12.7 (8.9-20.2)	8.5 (5.7-10.7)	**0.02**
ICU stay (%)	2 (13)	6 (67)	**0.01**
Median hospital stay (d, IQR)	33.0 (21.8-55.5)	62.0 (47.0-134.5)	0.07

Note: Results are expressed as percentage (%) or median and interquartile range (IQR).
Abbreviations: BMI, body mass index; BSI, bloodstream infections; CrCl, creatinine clearance; ICU, intensive care unit; LT, liver transplant; MELD, model for end stage liver disease.
[a]Measured at first therapeutic drug monitoring. Statistically significant values are shown in bold.

The PK/PD parameter that best predicts the outcome for fluconazole is the AUC/MIC ratio.[23,24] AUC/MIC ratios ≥55.2 were generally associated with favorable clinical outcomes,[16] but higher target values (>100) have been advocated for certain categories of patients, such as pediatric and critically ill patients, especially those receiving hemofiltration.[10,25,26] Our fluconazole C_{min} target was set at around 10 mg/L. Although rough, the approach of targeting C_{min} at this value is in line with the intent of achieving AUC/MIC ratio of at least 100 against all of the fluconazole-susceptible (EUCAST clinical breakpoint 2 mg/L) strains of *Candida* spp [10 mg/L × 24 h ours)/2 mg/L = 120]. A previous study including pediatric patients receiving fluconazole showed increased microbiological eradication rates for fluconazole C_{min} >11 mg/L.[9] Although we could not confirm a positive impact of C_{min} on *Candida* eradication due to the limited number of patients with repeated microbiological cultures, we observed that comparable cut-off value (C_{min} >11 mg/L) were associated with clinical success in our study. Although decreased C_{min} were more common among patients with *Candida* infection who died during hospitalization compared to survivors, the small sample size and potential confounding factors prevented us from drawing conclusions about the impact of fluconazole concentrations on mortality. Finally, although increased fluconazole MICs appeared correlated with higher mortality rates, this result was not statistically significant, probably because of the limited number of patients enrolled in the study.

Univariate analysis showed that hypoalbuminemia appeared associated with poor outcomes. No significant correlations, however, were shown between fluconazole C_{min} and albumin serum levels in our cohort. As previously reported, the unbound fraction of fluconazole should not be affected by hypoalbuminemia since only a small moiety (12%) of fluconazole molecules is bound to plasma protein.[27] Hypoalbuminemia, however, has been linked with increased mortality among patients on liver transplant waiting list.[28,29] There is currently no consensus to support albumin supplementation in this patient population.[30,31]

In conclusion, the findings of a statistically significant association between fluconazole C_{min} >11 mg/L and clinical success appear

TABLE 4 Univariate and multivariate analysis of factors associated with clinical success

	Univariate analysis		Multivariate analysis	
Characteristic	OR (95% IC)	*P* value	OR (95% IC)	*P* value
Age <60 y	0.80 (0.16-4.02)	0.78		
Charlson score <4	1.36 (0.28-6.58)	0.70		
Mean CrCl >50 mL/min	0.63 (0.12-3.32)	0.58		
[a]Fluconazole C_{min} >11 mg/L	13.0 (1.92-87.99)	**0.01**	8.76 (1.13-67.77)	**0.04**
No ICU stay	0.35 (0.06-1.93)	0.23		
Albuminemia >20 g/L	14.0 (1.37-142.89)	**0.03**	8.31 (0.66-104.26)	0.10

Note: Variables with statistically significant association on univariate analysis (fluconazole C_{min}, albuminemia) were included in a multivariable binary logistic regression model.
Abbreviations: CrCl, creatinine clearance; ICU, intensive care unit.
[a]Measured at first therapeutic drug monitoring. Statistically significant values are shown in bold.

to support our choice of performing TDM in LTR with candidiasis, although the results should be interpreted with caution due to the limited number of patients enrolled in the study. To the best of our knowledge, however, this is the first study analyzing the potential role of fluconazole TDM in improving clinical outcomes of liver transplant recipients with candidiasis.

Our study has several limitations. Firstly, due to the retrospective nature of the study and the site of *Candida* infections, that was abdominal in the majority of cases, a systematic assessment of the microbiological resolution of the infection was unfeasible. Secondly, the analysis of the association between fluconazole levels and outcome among severely ill (eg, ICU admitted) patients or patients with *non albicans* candidiasis was unfeasible due to the limited sample size. Thirdly, the retrospective nature of the study limits the generalizability of the findings, considering that other factors other than *Candida* infection could have been implicated in patients' outcome. This, however, represents a common limitation in studies assessing the outcome of patients with invasive candidiasis that is often affected by multiple confounders such as patients' complexity and multiple comorbidities. Finally, we recognize that TDM based only on C_{min} determination is a rough measurement and did not allow an appropriate estimation of AUC, potentially causing underestimation of drug exposure.

In conclusion, our study suggests that TDM of fluconazole C_{min} may be advisable in LT recipients with suspected or documented candidiasis. Prospective studies in larger cohorts are warranted to confirm the utility of TDM in LTR and to further analyze the correlation between fluconazole exposure and clinical outcome.

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CONFLICT OF INTEREST

The authors have no conflict of interest.

AUTHOR CONTRIBUTION

ER and FP designed the study, collected and analyzed the data, and wrote the manuscript; AC, UB, AS, PC, MB contributed to laboratory and clinical data collection and to the critical revision of the manuscript.

ORCID

Elda Righi https://orcid.org/0000-0001-8718-1200

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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