



Population pharmacokinetics of total and unbound concentrations of caspofungin in Chinese critically ill pediatric patients

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Introduction

- Caspofungin is the first-line treatment for invasive fungal infections (IFIs) in pediatric intensive care unit (PICU) patients, yet its population pharmacokinetics, particularly for total and unbound form, remains uncharacterized in this population.^{1,2}

Objectives

- This study aimed to describe the pharmacokinetics of total and unbound caspofungin in critically ill Chinese pediatric patients and to optimize the standard dosing regimen.

Methods

Data collection

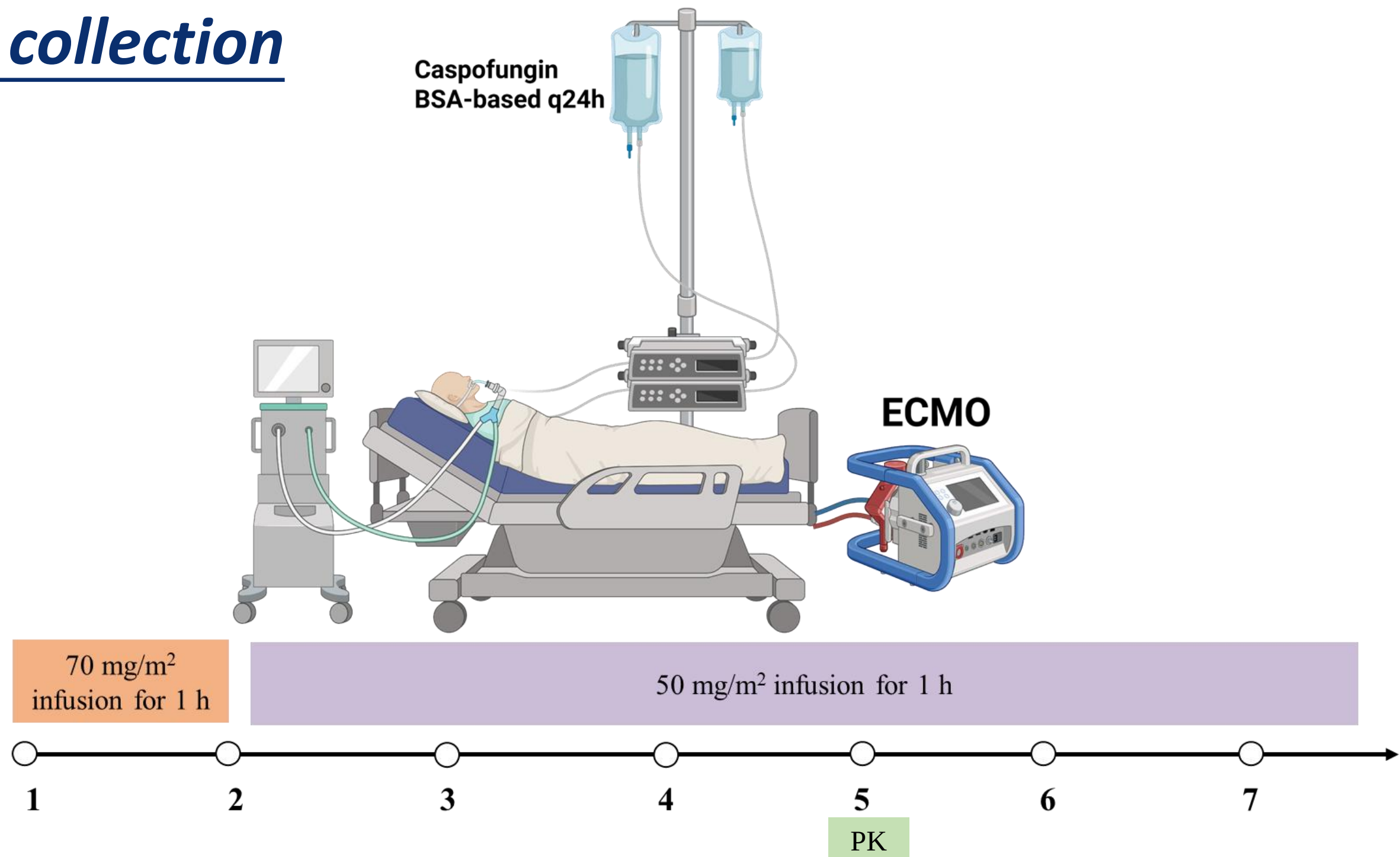


Figure 2. Clinical trail design

Population pharmacokinetic analysis

- The PopPK model was developed using the NONMEM (version 7.5.0) with theFOCE-I algorithm. Given the limited data, a linear model and a specific protein-binding model would be tested to describe PKs of total and unbound caspofungin simultaneously.
- Monte Carlo simulations were conducted to evaluate and optimize the standard dosing regimen.

Results

Demographic information and clinical data

- 29 patients (age: 0.33-16 years) were included. (Table 1)
- Median total and unbound concentrations were 7.475 mg/L (0.155–58.3) and 0.125 mg/L (0.00305–2.11), respectively. (Figure 2)

Table 1. Demographic and laboratory information	
Patient characteristics	Median [min, max] (n=29)
ECMO (Yes/No)	4/25
CRRT (Yes/No)	1/28
Severe Malnutrition (Yes/No)	2/27
Hypoalbuminemia (Yes/No)	2/27
Renal Transplant (Yes/No)	1/28
Age (years)	5.33 [0.330, 16.0]
Sex (Male/Female)	12/17
Weight (kg)	16.0 [4.90, 74.0]
Height (cm)	104 [54.0, 173]
BSA (m ²)	0.660 [0.286, 1.89]
White Blood Cell (10 ⁹ /L)	4.92 [0.100, 54.1]
Red Blood Cell (10 ¹² /L)	2.98 [1.95, 5.45]
Hemoglobin (g/L)	85.5 [54.0, 168]
Platelet (10 ⁹ /L)	144 [19.0, 588]
Albumin (g/L)	35.8 [24.8, 49.9]
Total Protein (g/L)	58.8 [33.3, 75.4]
Alanine Aminotransferase (U/L)	24.1 [3.51, 2510]
Aspartate Aminotransferase (U/L)	50.0 [18.3, 10900]
Total Bilirubin (umol/L)	8.50 [2.10, 329]
Direct Bilirubin (umol/L)	4.10 [1.00, 262]
Serum Creatinine (umol/L)	29.7 [6.50, 223]
Uric Acid (umol/L)	140 [6.69, 736]
Organisms isolated	
C. parapsilosis	9
C. albicans	2
C. tropicalis	1
C. guilliermondii	1

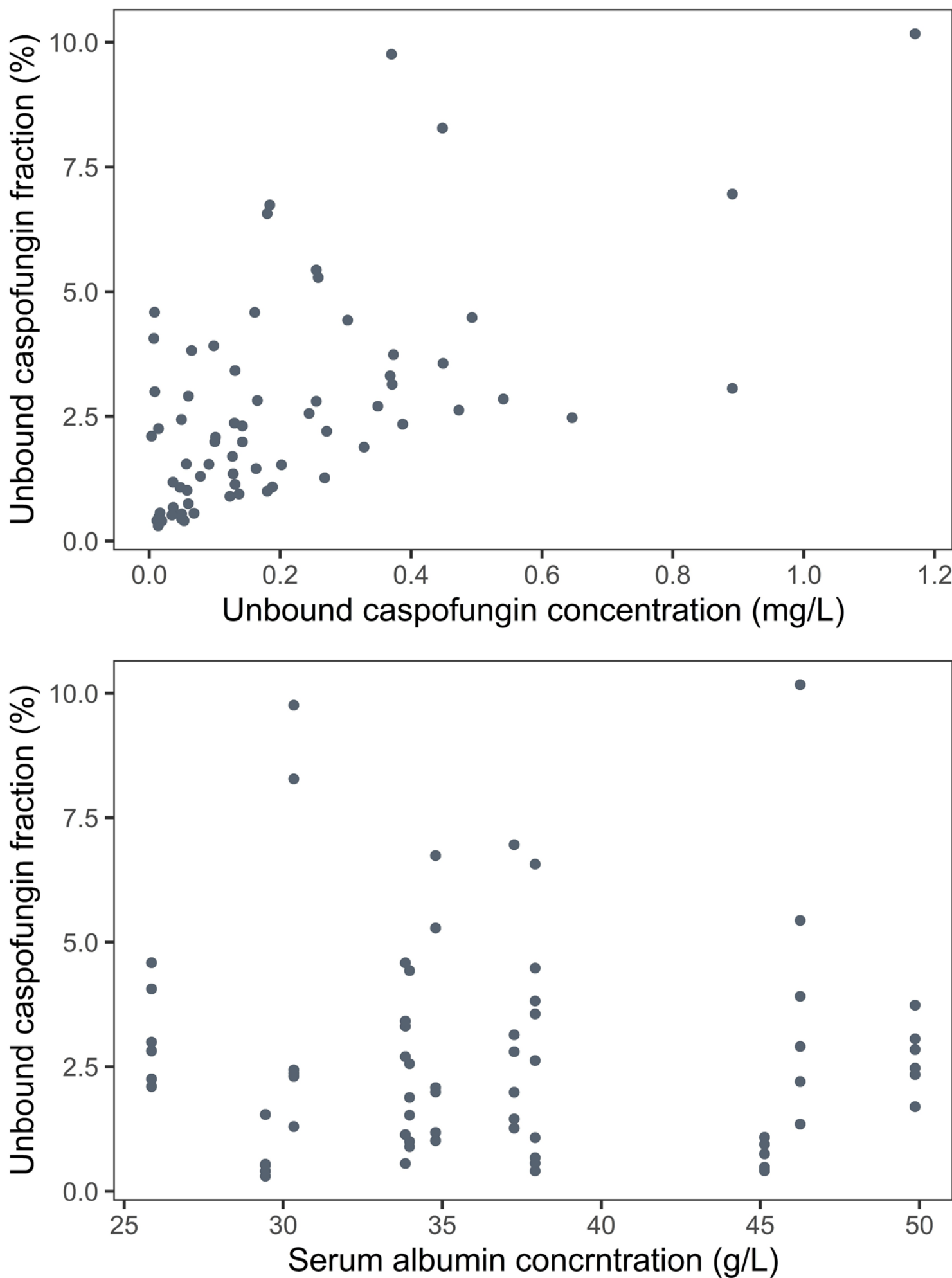


Figure 2. Caspofungin concentration profiles

Population pharmacokinetic outcomes

- The PopPK model identified BSA as a suitable parameter for dosing adjustments.
- The maximum binding capacity of caspofungin to albumin increased with rising albumin levels.
- ECMO significantly increased central distribution volume (4.91-fold) but had no significant effect on drug exposure (ECMO [n=4] vs. non-ECMO [n=25], p=0.1458).
- The final Poppk model could well describe caspofungin PK behaviour, VPC is shown in Figure 3.

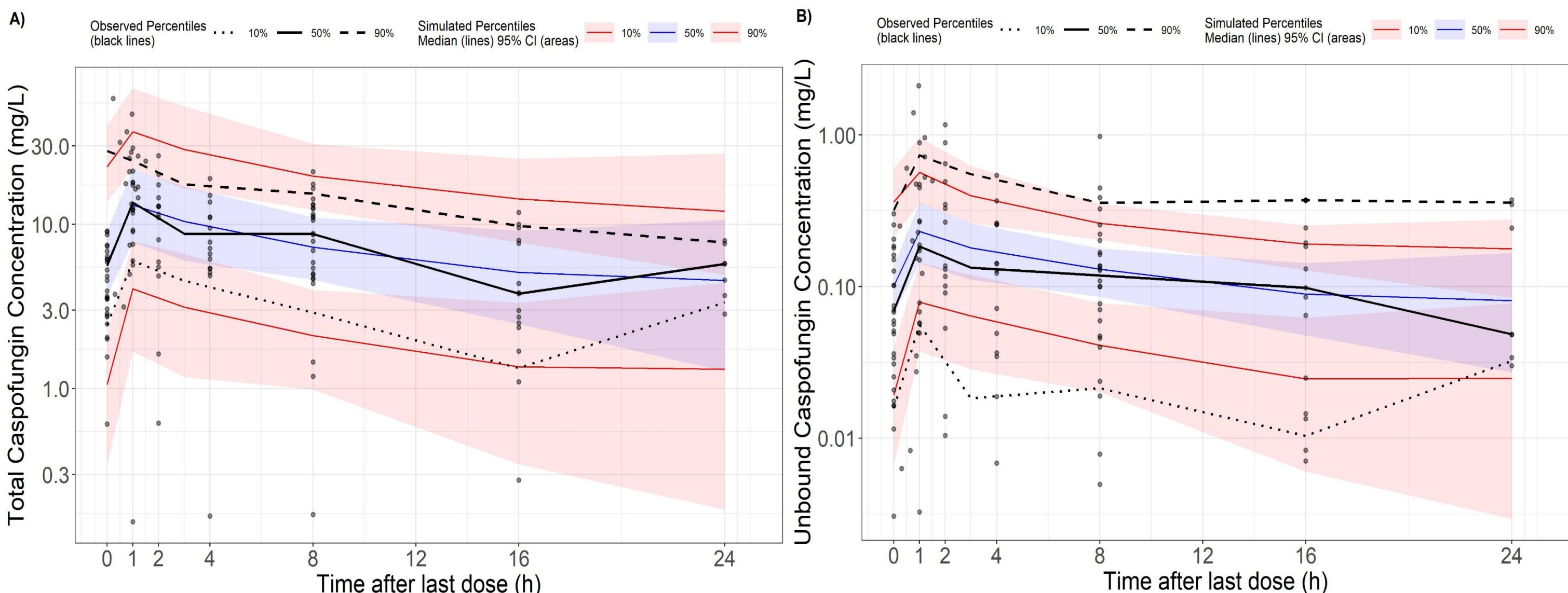


Figure 3. the VPC plot of total and unbound caspofungin concentrations

Evaluation of unbound concentration prediction ability

- The model-derived approach demonstrated higher accuracy in predicting unbound caspofungin concentrations (MPE -48.85%) than the method assuming a constant unbound fraction of 3% (MPE -186.03%).(Figure 4)

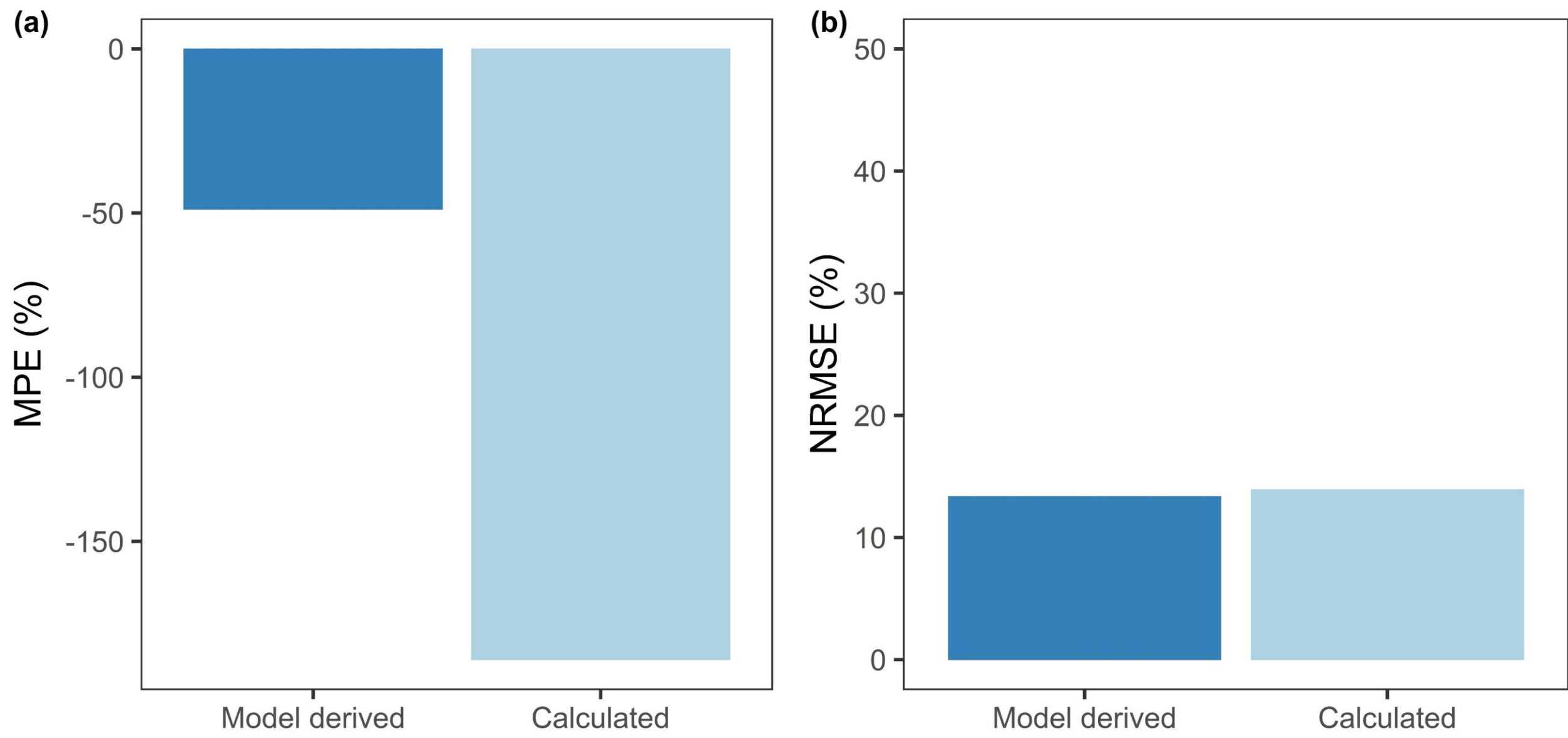


Figure 4. The bias (a) and imprecision (b) in the prediction of free caspofungin concentrations

Simulation results

- Simulations suggest that using total caspofungin concentration as the target for dose prediction may lead to overdosing in patients with hypoalbuminemia.
- The current BSA-based dosing regimen could ensure adequate drug exposure in critically ill pediatric patients with high variability, while also eliminating the need for dose adjustments in ECMO patients. (Figure 5)

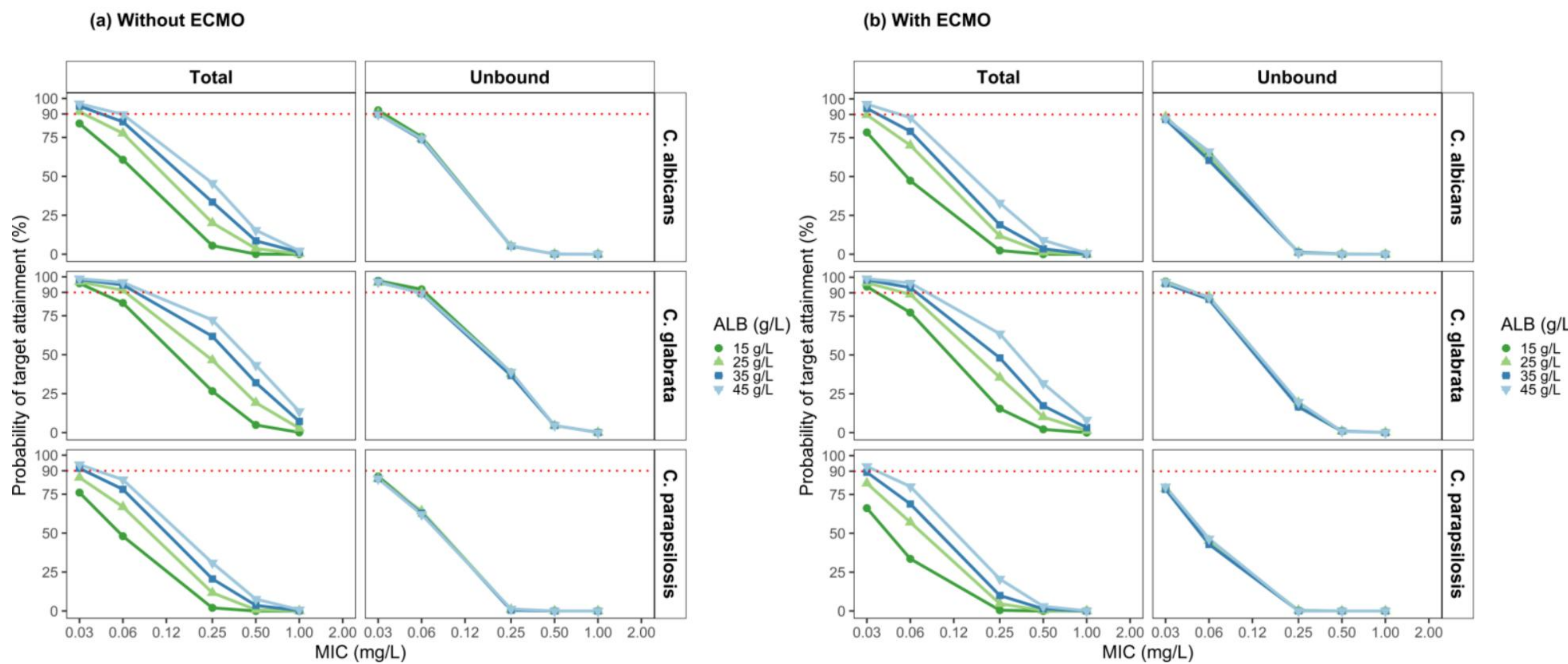


Figure 5. PTA plot of different patients

Conclusion

- Our study generated new evidence to inform dosing in critically ill pediatric patients and, for the first time, reaffirmed the adequacy of current dosing guideline for pediatric patients receiving ECMO treatment.

Reference

1. ISHIWADA N, et al. Nationwide survey of neonatal invasive fungal infection in Japan. Med Mycol, 2018, 56(6): 679-86.
2. Prevalence and attributable health burden of chronic respiratory diseases, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Respir Med, 2020, 8(6): 585-96..

