**Table 2.** Modeling strategies and final pharmacokinetics parameters of included studies.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study**  **(publication year)** | **Software/**  **Algorithm** | **Fixed effect parameters (RSE)** | | **Between-subject variability (%)** | **Residual unexplained variability** | **Interal validation** | **External validation** | **Simulation target** | **Modeling application** |
| Würthwein et al. (2011) | NONMEM/FOCE-I | CL (L/h) | =0.462 | 25 | prop.err = 21% | VPC GOF Bootstrap | NR | NR | Evaluate covariate effects |
| V1 (L) | =8.33 | 29 |
| Q (L/h) | =1.25 | / |
| V2 (L) | =3.59 | / |
| Würthwein et al. (2013) | NONMEM/FOCE-I | CL (L/h) | =0.411×[1+0.0102×(BW-76)] | 28.5 | prop.err=14.3% | pcVPC  SVPC GOF Bootstrap | 36 subjects/456 samples | NR | Evaluate covariate effects |
| V1 (L) | =5.85×[1+0.0102×(BW-76)] | 28.8 |
| Q (L/h) | =0.843 | / |
| V2 (L) | =6.53 | 66.8 |
| / | / | IOV(CL)=16.0% |
| / | / | COV(CL-V1)=0.802 |
| Pérez-Pitarch et al. (2018) | NONMEM/FOCE-I | Kel (h-1) | =0.0899 | 11.8 | add.error=0.0941 mg/L | GOF Bootstrap VPC | NR | AUC/MIC:  865 for *C. albicans*, 450 for *C. glabrata* and 1185 for *C. parapsilosis*.  Cmax/MEC: 10–20 for  *Aspergillus spp.* | Evaluate the efficacy of different dosages |
| Vc (L) | =6.46×(BW/75)×[1-0.233×(TP-5.6)] | 21.4 |
| K12 (h-1) | =0.494 | / |
| K21 (h-1) | =0.392 | / |
| Yang et al. (2019) | NONMEM/FOCE-I | CL (L/h) | =0.165×(BSA/0.79)1.3 | 24.2 | prop.err=19.6% | GOF VPC NPDEs Bootstrap | NR | Cmin | Evaluate the efficacy of dosing regimen; Describe PK in specific population |
| V1 (L) | =1.730×(BSA/0.79)1.5 | / |
| Q (L/h) | =0.351 | 161.6 |
| V2 (L) | =0.943 | 76.6 |
| Wang  et al. (2020) | NONMEM/NR | CL (L/h) | =0.21×(OPT/5)1.3 | 20 | Add.error=0.73mg/L | GOF VPC Bootstrap | NR | NR | Evaluate covariate effects; Describe PK in specific population |
| Vc (L) | =(2.21+SEX×0.62)×(OPT/5)0.93 | 10 |
| Vp (L) | =2.87 | 48.0 |
| Q (L/h) | =0.84×(SOFA/7)1.98 | / |
| Bailly et al. (2020) | Monolix/  SEAM | CL (L/h) | =0.98 | 42.3 | prop.err=12.2% | GOF VPC | NR | AUC/MIC ratio (250, 450, and 865);  Cmax/MIC  (5, 10, 15, and 20) | Evaluate the efficacy of different dosages |
| V1 (L) | =9.01 | 42.6 |
| Q (L/h) | =5.12 | 79.9 |
| V2 (L) | =11.9 | 77.2 |
| Niu et al. (2020) | Phoenix NLIME | CL | =0.1×(BSA/0.79)0.89×(lnAST/3.38) -0.23 | 33.3 | prop.err=26.6% | GOF  VPC  NPDEs Bootstrap | NR | AUC24/MIC | Dosing optimization against Candida spp |
| Vd | =1.36×(BSA/0.79) | 32.9 |
| Borsuk-De Moor  et al. (2021) | NONMEM/FOCE-I | CL day 1 | =0.563×(BW/70)0.75 | 24.7 | prop.err=19.9% | pcVPC GOF  Bootstrap | NR | AUC24/MIC  (*C. albicans* (AUC/MIC 865), *C. glabrata* (AUC/MIC 450), and *C. parapsilosis*  (AUC/MIC 1185)) | Evaluate covariate effects; Describe PK in specific population |
| CL day 2 | =0.737\*(BW/70)0.75 | 24.7 |
| CL day 3 | =1.01×(BW/70)0.75 | 24.7 |
| V1 day 1 | =6.04×(BW/70) | 28.6 |
| V1 day 2 | =7.32×(BW/70) | 28.6 |
| V1 day 3 | =7.70×(BW/70) | 28.6 |
| Q | =1.31 | / |
| V2 | =5.13 | 49.4 |
| Cor-CL-V1 | =0.868 | / |
| Li et al. (2021) | NONMEM/FOCE-I | CL | = 0.323×0.89×(35/ALB)1.27  (if TBIL ≤ 22 μmol/L)  =0.323× (35/ALB)1.27×(TBIL/22)0.265  (if TBIL >22 μmol/L) | 22.4 | prop.err=24% | pcVPC  GOF NPDEs | NR | AUC/MIC  (*>*865 for *Candida albicans*,  *>*450 for *Candida glabrata* and *>*1185 for *Candida parapsilosis*) | Evaluate covariate effects |
| Vc | =6.77× (WT/70)1.08 | / |
| Q | =0.923 | / |
| Vd | =4.58 | / |
| Gastine et al. (2022) | NONMEM/FOCE-I | CL(/70kg) | =0.790 | 27.5 | prop.err=19.4% | GOF VPC Bootstrap | NR | AUC24/MIC (865, 450 and 1185 for C. albicans, Candida  glabrata and Candida parapsilosis), fAUC24/MIC  (10-20) | Assess extended twice-weekly dosage using caspofungin |
| Vc(/70kg) | =7.75 | 31.5 |
| Q(/70kg) | =1.20 | / |
| Vp(/70kg) | =5.29 | 15.1 |
|  |  | IOV(CL)=17.2% |
| Wu et al. (2022) | NONMEM/NR | CL | = 0.385×(ALB/37.42)-1.01 | 33.5 | prop.err=13.4% add.error=0.213mg/L | GOF Bootstrap VPC NPDE | NR | AUC/MIC  (The target AUC/MIC values for C. albicans, C. glabrata, and C. parapsilosis were greater than 865, 450, and 1,185, respectively) | Evaluate covariate effects |
| V1 | =4.27 | 67.5 |
| Q | =2.85 | 0.0 |
| V2 | =6.01 | 47.7 |
| Pressiat et al. (2022) | Monolix/ FOCE-I | CL | =0.38 | 33.0 | prop.err=36% | GOF pcVPC | NR | fAUC24/MIC  (25.9, 13.5, and 35.5 for C. albicans, C. glabrata, and Candida  parapsilosis, respectively) | Analyze the PK/PD of caspofungin in specific population |
| V1 | =6.24 | 59.0 |
| Q | =2.58 | / |
| V2 | =6.44 | 107.0 |
| Keff13 | =0.08 | 54 |
| Keff31 | =0.26 | / |
| Yang  et al. (2022) | NONMEM/ | CL | =0.32×(1+0.46×ALB\*)×(1+0.98×WT\*)  (ALB\*=1, ALB<35 g/L;  ALB\*=0, ALB≥35 g/L;  WT\*=1, WT≥70 kg,  WT\*=0, WT< 70 kg) | 29.2 | prop.err=19.3% | Bootstrap  GOF pcVPC | NR | fAUC24/MIC  (fAUC24/MIC ≥20, fAUC24/MIC ≥7 and fAUC24/MIC ≥7 for  C. albicans, C. parapsilosis and C. glabrata) | Evaluate covariate effects; Describe PK in specific population |
| V1 | =13.31×(1+0.49×ALB\*)×(1+0.24×WT\*)  (ALB\*=1, ALB<35 g/L;  ALB\*=0, ALB≥35 g/L;  WT\*=1, WT≥70 kg,  WT\*=0, WT< 70 kg) | 59.2 |

CL: clearance; Q: intercompartmental clearance; V1: central volume of distribution; V2: peripheral volume of distribution.