**Table 3.** Investigated and identified covariates in population pharmacokinetic models of included studies.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study**  **(Publication year)** | **Tested covariates** | | | **Covariate selection criteria** | | **Significant covariates** | | | |
| **Demographic** | **Laboratory tests** | **Co-administration** | **Forward inclusion** | **Backward elimination** | **CL** | **V1** | **Q** | **V2** |
| Würthwein et al. (2011) | SEX AGE, Weight, BSA | TBIL, CLCR | liposomal amphotericin B | p<0.001 | p<0.001 | NR | NR | NR | NR |
| Würthwein et al. (2013) | dose, SEX, AGE, Weight | TBIL, CLCR | NR | p<0.05 | p<0.01 | Weight | Weight | NR | NR |
| Pérez-Pitarch et al. (2018) | AGE, SEX, Weight | TP, SCR, TBIL, CLCR | NR | p<0.05 | p<0.01 | NR | Weight,  TP | NR | NR |
| Yang et al. (2019) | AGE, Weight, BSA | SCR, ALB | NR | NR | p<0.05 | BSA | BSA | NR | NR |
| Wang  et al. (2020) | AGE, SEX, Weight, BMI, ECMO, OPT, 24-h fluid balance | SOFA, ALT, AST, ALB, TBIL, CLCR, PCT | NR | p<0.05 | p<0.01 | OPT | SEX | SOFA | NR |
|
| Bailly et al. (2020) | AGE, Weight, ECMO | ALB, PAL, TBIL, AST, ALT, SCR, SOFA | NR | NR | NR | NR | NR | NR | NR |
| Niu et al. (2020) | BSA, Weight, | CR, eGFR, ALB, TBIL, DBIL, ALT, AST, γ-GT | NR | p<0.05 | P <0.01 | BSA, AST | BSA | NR | NR |
| Borsuk-De Moor  et al. (2021) | AGE, Weight, Height, SEX, ECMO, CRRT. Survival, dose | SOFA, PCT, UF, ELWI, Cardiac Output, ALB, TP, Liver Failure | NR | NR | p<0.01 | NR | NR | NR | NR |
| Li et al. (2021) | SEX, AGE, Weight | ALT, AST, TBIL, ALB, CLCR | NR | p<0.05 | p<0.01 | ALB, TBIL | Weight | NR | NR |
| Gastine et al. (2022) | Weight, AGE, BSA, SEX, RACE | ALB, CLCR | Acyclovir,  Vancomycin,  Dexamethasone | P<0.05 | P<0.01 | Weight | Weight | Weight | Weight |
| Wu. et al. (2022) | AGE, SEX, Weight, Height, BMI, ECMO, CRRT | ALB, CLCR, AST, ALT, DBIL, TBIL, PCT, PLT, SCR, TP | NR | P<0.05 | P<0.001 | ALB | NR | NR | NR |
| Pressiat et al. (2022) | AGE, SEX, Weight, BMI | ALB, TP, TBIL, SCR, CLCR, SOFA, WBC, CRP, MELD, PT | NR | P<0.05 | NR | NR | NR | NR | NR |
| Yang  et al. (2022) | Weight, CMT, SOP, SOT, ICU | ALB, MM, CYC, MET | NR | P<0.05 | P<0.001 | Weight, ALB | Weight, ALB | NR | NR |

BMI: body mass index; BSA: body surface area (calculated according to the formula of Mosteller); ALB: albumin; eGFR: the estimated glomerular filtration rate; CLCR: creatinine clearance (determined according to the formula of Cockcroft and Gault); SCR: serum creatinine; PCT: procalcitonin ; TP: total protein; TBIL: total bilirubin; DBIL: direct bilirubin; Hb: Hemoglobin; AST: aspartate aminotransferase; ALT: alanine aminotransferase; PAL: phenylalanine ammonia-lyase; ECMO: extracorporeal membrane oxygenation; CRRT: continuous renal replacement therapy; SOFA: sequential organ failure assessment; OPT: operative time; ELWI, extravascular lung water index; UF: ultrafiltration rate; PLT: platelet; WBC: leukocyte count; CRP: C-reactive protein; MELD: model for end-stage liver disease; PT: prothrombin time; HT: heart transplantation; NR: not reported.