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ARTICLE

Multistate modeling for survival analysis in critically ill patients treated with meropenem

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Abstract

Appropriate antibiotic dosing to ensure early and sufficient target attainment is crucial for improving clinical outcome in critically ill patients. Parametric survival analysis is a preferred modeling method to quantify time-varying antibiotic exposure – response effects, whereas bias may be introduced in hazard functions and survival functions when competing events occur. This study investigated predictors of in-hospital mortality in critically ill patients treated with meropenem by pharmacometric multistate modeling. A multistate model comprising five states (ongoing meropenem treatment, other antibiotic treatment, antibiotic treatment termination, discharge, and death) was developed to capture the transitions in a cohort of 577 critically ill patients treated with meropenem. Various factors were investigated as potential predictors of the transitions, including patient demographics, creatinine clearance calculated by Cockcroft–Gault equation ($CLCR_{CG}$), time that unbound concentrations exceed the minimum inhibitory concentration ($fT_{>MIC}$), and microbiology-related measures. The probabilities to transit to other states from ongoing meropenem treatment increased over time. A 10 mL/min decrease in $CLCR_{CG}$ was found to elevate the hazard of transitioning from states of ongoing meropenem treatment and antibiotic treatment termination to the death state by 18%. The attainment of 100% $fT_{>MIC}$ significantly increased the transition rate from ongoing meropenem treatment to antibiotic treatment termination (by 9.7%), and was associated with improved survival outcome. The multistate model prospectively assessed predictors of death and can serve as a useful tool for survival analysis in different infection scenarios, particularly when competing risks are present.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Pharmacometric multistate models have recently been successfully applied to characterize disease progression in oncology, but rarely used for survival analysis in the field of infectious diseases.

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WHAT QUESTION DID THIS STUDY ADDRESS?

Multiple competing events occur, making it difficult to evaluate the impact of meropenem exposure on survival outcome without bias. To address this issue, multistate modeling was applied to characterize transition rates from the state of ongoing meropenem treatment to other antibiotic treatment, antibiotic treatment termination, discharge, or death.

WHAT THIS STUDY ADDS TO OUR KNOWLEDGE?

The multistate model could successfully characterize the trajectory of clinical infection from antibiotic treatment to death and discharge. Relatively high creatinine clearance and achievement of 100% time that unbound concentrations exceed the minimum inhibitory concentration contributed to a decreased risk of mortality.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

This analysis showcases the application of a pharmacometric multistate model to explore the impact of treatment on clinical outcomes within a complex infection trajectory. It offers opportunities for improved integration of infectious disease data and quantification of exposure-response relationships.

INTRODUCTION

The clinical outcome of critically ill patients with infections remains unsatisfactory even with combined and aggressive antibiotic therapy.[1] This may be owing to a pre-existing hazard of death from severe pathological burden, or inadequate antimicrobial effects due to difficult-to-achieve pharmacokinetic/pharmacodynamic (PK/PD) target attainment of antibiotics. Appropriate antibiotic dosing to ensure early and sufficient target attainment in patients in the intensive care unit (ICU) is quite challenging. Commonly used PK/PD targets were often established based on preclinical in vitro or animal studies.[2] Besides, for critically ill patients with severe infections, PK/PD targets associated with bacterial eradication and clinical cure may be higher.[3] This is because patients in the ICU are often immunocompromised and less capable of fighting infections effectively.[4] Furthermore, it has been shown that with longer half-lives, for example, in patients with reduced kidney function, meropenem PK/PD targets tend to be better associated with the overall exposure (area under the curve [AUC]) than the time above a threshold concentration.[5] Last, altered volume of distribution and drug clearance (CL) driven by profound pathophysiological changes or surgery interventions in patients in the ICU may cause substantial PK variability, so that the therapeutic dose for non-critically ill patients may not be suitable for patients in the ICU and a tailored dosing regimen might be needed.[1,6]

Because direct measurement and continuous quantification of antimicrobial effects is not feasible in patients in the ICU, clinical PK/PD analysis attempts to identify the breakpoint of a PK/PD index that best separates cure/no cure or mortality/survival subgroups.[7] Although tree-based modeling (e.g., classification and regression tree analysis [CART]) is clinically attractive due to intuitive and understandable decision rules from a heterogeneous group of predictors, such a retrospective time-collapsed approach is questionable in application.[8] The variability associated with the breakpoint value is lost, potentially leading to incorrect prediction of a patient or case to positive or negative outcome (e.g., survival or death). Instead, PK/PD models built on available in vitro or in vivo PK/PD data allow to characterize the full time-course of antibiotic exposure, bacterial killing, and resistance development, and are increasingly applied to explore diverse treatment regimens.[9] Therefore, PK/PD models are considered a more appropriate tool to investigate predictors of clinical outcome and suggest individualized antimicrobial therapy for critically ill patients.

Parametric survival analysis, a preferred time-to-event (TTE) modeling method allowing time-varying covariates evaluation and further survival simulation, typically describes the transition from the initiation of therapy to long-term clinical outcome by a single hazard function(assuming independent censoring).[10] This would induce biased estimation of the death hazard when competing (or semi-competing) events appear (e.g., antibiotic treatment termination, discharge, or death due to other causes in patients with infection). Multistate modeling, introducing multiple intermediate

states and transition-dependent hazard functions, has recently gained popularity for describing the natural progression of diseases like cancer (e.g., stable disease, response or progression, and death), and helps to mitigate the bias introduced by confounding factors (e.g., second-line treatment after disease progression).[11,12] Compared to single hazard TTE analysis, multistate modeling allows to simultaneously perform related TTE analysis (e.g., transition from stable disease to response/progression, or transition from stable disease to death/censoring).[13–15] Moreover, achieved values of relevant PK/PD indices and other covariates can be tested on all hazard functions and characterized as predictors in a prospective and transition-specific way (e.g., PK/PD target attainment on in-hospital death).

Meropenem is a commonly prescribed beta-lactam antibiotic in the ICU because of its broad-spectrum activity and a rather favorable toxicity profile. The elimination of meropenem is determined by renal function and varies among patients in the ICU with renal failure or augmented renal CL. Meropenem displays time-dependent bactericidal activity, and its clinical efficacy correlates with the cumulative percentage of time that free plasma meropenem concentrations exceed the minimal inhibitory concentration ($fT_{>MIC}$).[16] A commonly accepted PK/PD target for meropenem in hospitalized patients is 40% $fT_{>MIC}$ and originated from mouse infection models.[16,17] However, mouse models may not reflect longer half-lives observed in humans (especially in critically ill patients) compared to mice, and thereby compromise the reliability of translating PK/PD indices from mouse models to humans. Several studies have consistently shown that critically ill patients require a higher PK/PD target,[3,18,19] specifically longer $fT_{>MIC}$ (100% $fT_{>MIC}$ or 100% $fT_{>4\times MIC}$), and some indicate a shift toward AUC/minimum inhibitory concentration (MIC) as the PK/PD index best correlated with antimicrobial response.[5,20] In addition, although PK or outcome studies of meropenem have been reported for different patient populations, a quantitative evaluation of the impact of meropenem PK/PD target attainment on clinical outcomes has been lacking.[19]

Previous non-parametric TTE analyses in retrospective studies found that patients who achieved 100% $fT_{>MIC}$ (patients in the ICU) or 100% $fT_{>4\times MIC}$ (patients with bloodstream infections) had a shorter time to discharge from ICU or negative blood culture compared with those who did not.[21,22] Similarly, a recent study compared the survival outcome for different dosing groups leading to different PK/PD targets (40% $fT_{>MIC}$, 100% $fT_{>MIC}$, and 100%$fT_{>4\times MIC}$) in a sepsis rat model.[23] Pronounced survival prolongation was observed in the treatment groups attaining 100% $fT_{>MIC}$ and 100% $fT_{>4\times MIC}$ compared to the group attaining 40% $fT_{>MIC}$, although the differences were not statistically significant due to the limited sample size (12 rats per group). In the clinical setting, a randomized clinical trial conducted in patients with sepsis showed no significant differences in microbiological/clinical cure and 28-day mortality between high meropenem dosing (2 g infusion over 3 h every 8 h, 100% patients attaining 100% $fT_{>MIC}$) and standard dosing (1 g infusion over 3 h every 8 h, 66.7% patients attaining 100% $fT_{>MIC}$).[24]

This study aimed to develop a multistate modeling framework to investigate the hazards and predictors (e.g., patient demographics, creatinine CL, $fT_{>MIC}$, and microbiology-related measures) of hospital discharge and in-hospital mortality in a large population of patients in the ICU receiving meropenem therapy.

MATERIALS AND METHODS

Patients and data

Clinical data utilized in this study is sourced from Medical Information Mart for Intensive Care (MIMIC-IV), an openly accessible database that contains de-identified and comprehensive health-related information, including diagnoses, severity scores, medication administration, demographic measurements, laboratory and microbiology test records, and further information from patients who were admitted to the ICU of the Beth Israel Deaconess Medical Center between 2008 and 2019.[25] The use of the MIMIC-IV database has been approved by Institutional Review Boards of Beth Israel Deaconess Medical Center and Massachusetts Institute of Technology, and a waiver of informed consent was granted.

Patients in the ICU with a continuous meropenem dosing history of more than 2 days were screened for inclusion, and those who underwent continuous renal replacement therapy (CRRT) or were lacking an MIC value of the infecting pathogen were excluded from the current analysis. Demographic data (like age, sex, and body weight), baseline factors (disease type and mortality risk), infected bacterial species, microbiological response (negative or positive), time-varying serum creatinine values, albumin, C-reactive protein (CRP), and antibiotic dosing records within 28 days from the first meropenem dose were extracted for each subject as potential covariates for modeling.

Pharmacokinetic model derived PK/PD index

The concentration-time profile of meropenem was predicted for each patient based on a previously published meropenem population PK model in conjunction with the

patient's dosing history and specific covariates, because meropenem concentrations were not available from the patients. In total, five two-compartment population PK models of meropenem in patients in the ICU were identified in literature,[26–30] and the PK model developed by Ehmann et al. was selected as the model most representative of the study population due to its inclusion of multiple covariate relationships based on a wide distribution of covariate values, as well as similar population characteristics as the study patients.[29] Briefly, the population PK model had been built upon densely sampled meropenem serum concentrations (1376 observations) in 41 non-CRRT critically ill patients (mostly patients with sepsis) receiving standard dosing of meropenem (1000 mg as 30-min i.v. infusions q8h). The model included three significant covariate-parameter relationships influencing meropenem pharmacokinetics, that is, creatinine clearance according to Cockcroft–Gault ($CLCR_{CG}$) on meropenem clearance, and body weight and albumin on the central and peripheral volume of distribution, respectively. The median, 5th, and 95th percentiles of age, body weight, and $CLCR_{CG}$ of the patients were 55.5 (32.0, 69.9) years, 70.5 (47.4, 121) kg, and 80.8 (24.8, 191) mL/min, respectively.

Development of the base multistate model

Depending on the antibiotic dosing records, discharge, and survival data, subjects could transfer among five different states. The states considered were (i) ongoing meropenem treatment (S_1, receiving meropenem), (ii) other antibiotic treatment (S_2, shifting to alternative antibiotic therapy without meropenem), (iii) antibiotic treatment termination (S_3, no antibiotic therapy), (iv) discharge alive (S_4, discharge from hospital), and (v) in-hospital death (S_5). All patients were in the "ongoing meropenem treatment" state (S_1) at initiation and could then transit to any other states unidirectionally, as shown in Figure 1.

Each state represented a different compartment of the model, with the amount corresponding to the probability of occupying the state. A probability of 1 was assigned to S_1 at time 0, and then distributed across the five states according to the differential Equations 1–5. The sum of probabilities was equal to 1 at any timepoint (Equation 6). After each observation, the probabilities of all states were reset to zero, and a probability of 1 was given to the observed state. Given that the precise time of death or discharge was not available in our dataset, we have treated them similarly to other states that are interval-censored, using a 1-day interval.

$$dP_1/dt = -P_1 \bullet \left(k_{12}(t) + k_{13}(t) + k_{14}(t) + k_{15}(t)\right) \quad (1)$$

$$dP_2/dt = P_1 \bullet k_{12}(t) - P_2 \bullet \left(k_{23}(t) + k_{24}(t) + k_{25}(t)\right) \quad (2)$$

$$dP_3/dt = P_1 \bullet k_{13}(t) + P_2 \bullet k_{23}(t) - P_3 \bullet \left(k_{34}(t) + k_{35}(t)\right) \quad (3)$$

$$dP_4/dt = P_1 \bullet k_{14}(t) + P_2 \bullet k_{24}(t) + P_3 \bullet k_{34}(t) \quad (4)$$

$$dP_5/dt = P_1 \bullet k_{15}(t) + P_2 \bullet k_{25}(t) + P_3 \bullet k_{35}(t) \quad (5)$$

$$P_1 + P_2 + P_3 + P_4 + P_5 = 1 \quad (6)$$

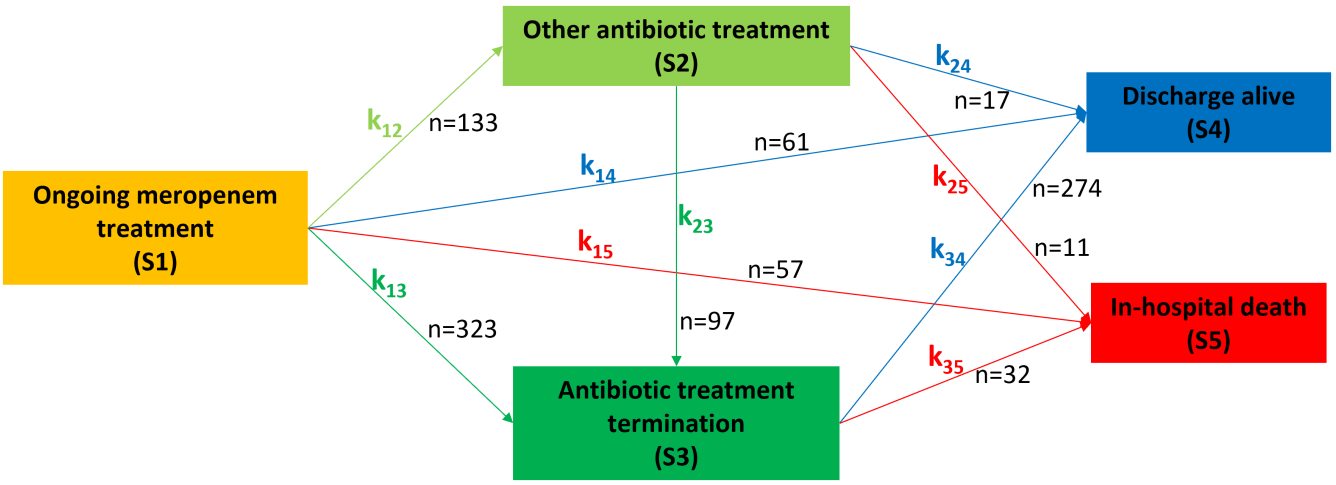

FIGURE 1 Multistate transition diagram. Each compartment represents a state, and the arrows indicate observed transitions between states. k_{ij} represents the transition rates between the states; n is the number of patients who experienced a certain transition. All patients were assumed to be in S_1 initially, and then stayed in S_1 or moved to any of the other states (S_2, S_3, S_4, S_5). All patients occupied a state at any time. Patients who did not have a discharge or death event by day 28 were right censored at their current intermediate states (3, 8, and 114 patients were censored in S_1, S_2 and S_3, respectively).

In these equations, P_n is the probability of being in state n; $k_{ij}(t)$ represents the transition hazard from state i to j at time t ($i < j$). Both constant (exponential) and time-varying k_{ij}, characterized by a Gompertz or Weibull function, were assessed (Equations 7–9).

$$k_{ij}(t) = \text{scale}_{ij} \tag{7}$$

$$k_{ij}(t) = \text{scale}_{ij} \bullet \exp\left(\text{shape}_{ij} \bullet t\right) \tag{8}$$

$$k_{ij}(t) = \text{scale}_{ij} \bullet \text{shape}_{ij} \bullet \left(\text{scale}_{ij} \bullet t\right)^{\text{shape}_{ij}-1} \tag{9}$$

where scale_{ij} was the baseline transition hazard from state i to j, t was evaluated both as time since treatment initiation or time since entering the state. An estimation of shape_{ij}less than 1 indicated a decreasing hazard, and greater than 1 an increasing hazard over time.

Assessment of transition rate predictors

The ability of covariates to predict the transition rate k_{ij} was tested with a proportional hazard model. The transition hazard for an individual z with a continuous covariate X was calculated according to Equation 10.

$$k_{ij} = k_{ij,0} \bullet e^{(\beta_X \bullet (X_z - X_{\text{median}}))} \tag{10}$$

where $k_{ij,0}$ is the baseline transition hazard, β_X is the coefficient of the effect of X on the transition from state i to j. X_{median} is the population median value of X (at baseline for time-varying covariates).

Age, body weight, CLCR_{CG}, albumin, and PK/PD indices were the continuous covariates evaluated. Categorical covariates tested included sex, meropenem daily dose (1 for <2500 mg/day, 2 for 2500–4500 mg/day, and 3 for 5000–8000 mg/day), sepsis (sepsis or not), baseline mortality risk (0 or 1, determined when the patient was admitted to the hospital), combined antibiotic therapy (combination or not), bacterial susceptibility (resistant or susceptible), and microbiological response (positive or negative). CRP was not examined because large proportions (80.8%) of individual-level data were missing. Kaplan–Meier Mean Covariate plots were first examined to identify potential covariates; effects of potential covariates on specific transitions were then investigated in univariable analysis, followed by multivariable analysis if statistically significant.

Data analysis

All data extraction and exploration activities were conducted using R version 4.2.2 (R Foundation for Statistical Computing). The nonlinear mixed-effects modeling software (NONMEM, version 7.4.4)[31] was used for parameter estimation, with runs executed by Perl-speaks-NONMEM (PsN, version 5.2.0).[32] For the multistate model, LAPLACE LIKE was used for estimation and decreases in the objective function value (ΔOFV) of 6.64 ($p < 0.01$) and 10.83 ($p < 0.001$) were considered statistically significant (1 degree of freedom) for each forward addition and backward deletion, respectively. The predictive performance of the models was evaluated by visual prediction checks (VPCs). To minimize the risk of false positivity with multiple testing in predictor evaluation, case deletion diagnostics was used to identify influential individuals. If statistical significance was driven by few (≤3) influential individuals, the relationship was reported but not included in the final model.

RESULTS

Patients and data

The process of inclusion/exclusion of patients and data extraction from the MIMIC-IV database is shown in Figure 2. In brief, 577 patients (537 patients plus 40 readmissions included as unique patients) were entered in the analysis dataset and are summarized in Table 1. The median and interquartile range (IQR) of age, body weight, and CLCR_{CG} were 65.0 (54.0–74.0) years, 78.0 (64.0–94.0) kg, and 72.7 (42.9–128) mL/min, respectively. A large proportion of the subjects (50.1%) had experienced different kinds of surgeries, and only 88 patients (15.2%) suffered from sepsis. The pathogens causing the infections included mainly *Enterobacter* spp., *Pseudomonas* spp., and *Klebsiella* spp., and most of them were susceptible to meropenem (MIC ≤2 mg/L).

During ongoing meropenem treatment (S_1), 41.9% of the patients received other antibiotics targeted to Gram-negative bacteria (combined antibiotic therapy). In addition, the meropenem dosing regimen in some cases changed over time, but the reason was unclear from the database. CLCR_{CG} appeared to be relatively stable over time during the study period for most patients. The dataset for analysis was cut on day 28 after the first meropenem dose, and events at later timepoints are generally regarded as not being related to the antibiotic treatment. The median time to antibiotic treatment termination, discharge, and death event were 7.0, 12.5, and 7.0 days, respectively.

PK/PD target attainment

Meropenem concentrations at every hour were predicted based on the population PK model, and the PK/

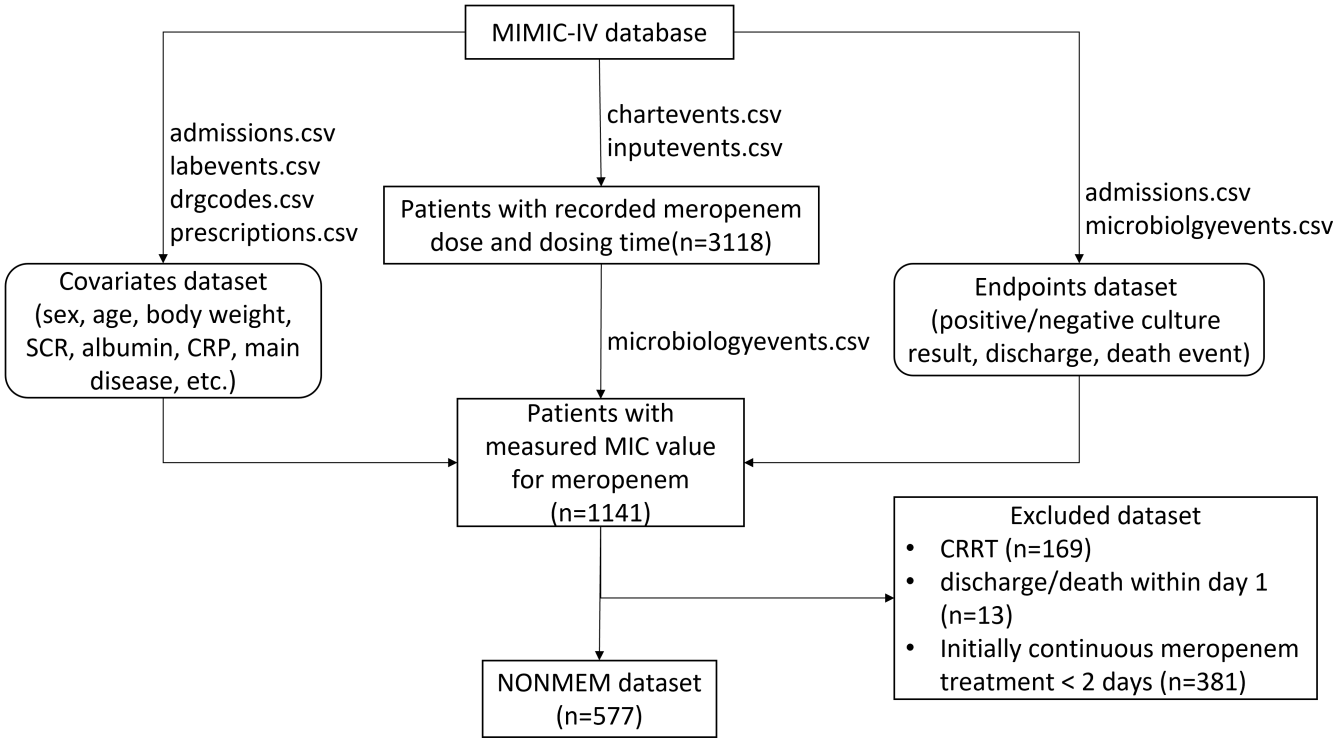

FIGURE 2 Flow chart for meropenem data extraction from the Medical Information Mart for Intensive Care (MIMIC-IV) database. CRP, C-reactive protein; CRRT, continuous renal replacement therapy; MIC, minimal inhibitory concentration; SCR, serum creatinine.

PD indices $fT_{>MIC}$, $fT_{>4\times MIC}$, and, for exploratory analysis, the area under the concentration–time curve over 24 h divided by the MIC (fAUC/MIC) were calculated for every day within the study period (28 days). Median and IQR of $fT_{>MIC}$, $fT_{>4\times MIC}$, and fAUC/MIC from day 1 and day 2 (so that every patient contributed equally) were 99.2% (84.4%–100%), 88.9% (54.5%–100%), and 361 (12.1–747), respectively. There was no statistically significant correlation between the daily dose amount of meropenem, $CLCR_{CG}$, and $fT_{>MIC}$ (Figure S1).

Base multistate model

The multistate data consisted of 1005 transitions between states, including 553 antibiotic therapy-related transitions (133 to other antibiotic treatment and 420 to antibiotic treatment termination) and 452 "absorbing" events (352 discharge alive and 100 in-hospital death; Figure 1). Three, eight, and 114 patients were right censored at meropenem ongoing meropenem treatment, other antibiotic treatment, and antibiotic treatment termination (S_1, S_2, and S_3; Figure 1). The observed transitions from ongoing meropenem treatment to other states (S_2, S_3, S_4, and S_5) were well described by Weibull functions, where shape parameters k_{12}, k_{13}, k_{14}, and k_{15} were all higher than 1, indicating increased transition hazard over time.

Predictors of transition rates

The predictor-transition relationships statistically significant in the univariable analysis are reported in Table S1. Low $CLCR_{CG}$, high age, high baseline mortality risk, meropenem daily dose, sepsis, and achieving 100% $fT_{>MIC}$ were found to significantly increase the risk of death during the univariable analysis. However, after the forward addition and backward deletion process in the multivariable analysis, only $CLCR_{CG}$ was retained on k_{15} and k_{35} as a predictor for a death event. Additionally, combined antibiotic therapy on k_{12} and k_{13}, and 100% $fT_{>MIC}$ on k_{13} were retained in the final multistate model. None of the identified relationships were driven by influential individuals according to case deletion diagnostics (Figure S1). The final multistate model provided an adequate fit to the data, as demonstrated in the VPC (Figure 3) and Kaplan–Meier plots (Figure S3). The final parameter estimates are shown in Table 2. Combined antibiotic therapy was estimated to increase k_{12} 3.42-fold and reduce k_{13} by 45.3%, meaning that patients with a combination of antibiotics initially have a lower probability to stop antibiotic treatment and to recover. Every 10% decrease in $fT_{>MIC}$ reduced the probability of antibiotic treatment termination (indicating clinical infection cure) by 9%. A 10 mL/min decrease in $CLCR_{CG}$ contributed to a 18% higher death risk through increased k_{15} and k_{35}. An example of the dataset and the NONMEM code are included in the supplementary document.

TABLE 1 Summary of patient characteristics presented as median and IQR or number of subjects (%).

Baseline characteristics	Median	IQR/number of subjects (%)
Age (years)	65.0	54.0–74.0
Body weight (kg)	78.0	64.0–94.0
Sex		
Female	230	40%
Male	347	60%
Cockcroft-Gault creatinine clearance (mL/min)	72.7	42.9–128
Albumin (g/dL)	2.6	2.1–3.0
Main diagnosis		
Sepsis	88	15.2%
Other (e.g., surgical procedures)	489	84.8%
Mortality risk		
Low	185	32.1%
High	392	67.9%
Meropenem initial daily dose[a]		
≤1500 mg	111	19.2%
1500–3000 mg	309	53.5%
3000–6000 mg	143	24.8%
≥6000 mg	14	2.4%
Combined initial antibiotic therapy[b]		
Yes	242	41.9%
No	335	58.1%
Bacterial species		
Enterobacter spp.	212	36.8%
Pseudomonas spp.	179	31.0%
Klebsiella spp.	108	18.7%
Proteus spp.	21	3.6%
Serratia spp.	14	2.4%
Acinetobacter baumannii	9	1.6%
Morganella morganii	9	1.6%
Other	25	4.3%
MIC value		
≤2 mg/L (susceptible)	467	80.9%
4–8 mg/L (moderate susceptibility)	64	11.1%
16 mg/L (resistant)	46	8.0%
Time to negative culture[c] ($n = 296$) (days)	3.0	1.0–7.0
Time to antibiotic treatment termination[d] ($n = 420$) (days)	7.0	4.0–11.0
Time to discharge ($n = 352$) (days)	12.5	8.0–18.0
Time to death ($n = 100$) (days)	7.0	4.0–14.2

Abbreviations: IQR, interquartile range; MIC, minimum inhibitory concentration.

[a]Standard meropenem dosing regimen was 1 g q8h.

[b]Meropenem combined with other antibiotics targeted to gram-negative bacteria.

[c]Time to first negative microbiology culture result.

[d]Time to antibiotic treatment termination was deemed a signal of clinical infection cure.

DISCUSSION

A multistate model was developed to jointly characterize intermediate states after ongoing meropenem treatment, such as antibiotic treatment termination (indicating clinical infection cure), and clinical end points like discharge and death of patients in the ICU receiving meropenem therapy. Transition rates between the different states

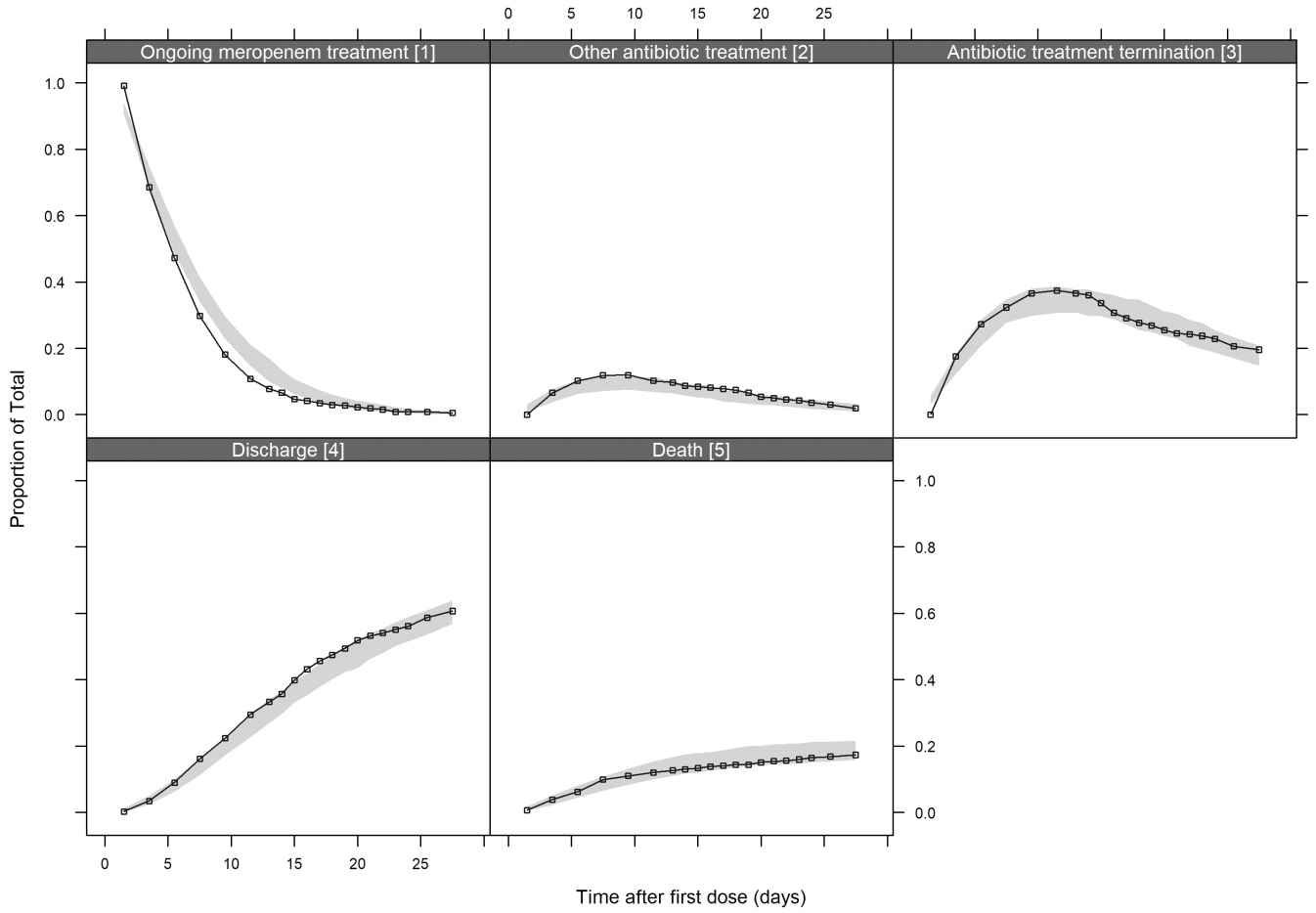

FIGURE 3 Visual predictive checks showing the proportion of patients in each state since time of the first meropenem dose. Solid lines represent the observed data and gray shaded areas indicate the 95% confidence intervals based on 500 simulations.

and transition-specific predictors were well-described by parametric hazard functions. The utilization of a multistate model framework facilitated the investigation of transition-specific predictors and enabled the concurrent characterization of the time period required for antibiotic treatment termination, hospital discharge, and death. Furthermore, this approach effectively circumvents potential bias stemming from competing events, which may arise in standard time-to-event analyses. This study exemplifies the benefit of multistate models in the area of infectious diseases, which could inspire future studies to explore and integrate intermediate events, such as microbiological response, clinical diagnosis and progression, Sequential Organ Failure Assessment (SOFA) scores, ICU stay, and mortality events over time.[14]

During model development, we initially conducted a preliminary CART analysis on the study population (577 patients) to identify potentially influential covariates that may have had an impact on the survival outcome. The CART analysis indicated that patients with $CLCR_{CG}$ lower than 54.5 mL/min (identified breakpoint) would have a 61.5% higher risk of mortality compared to those with higher values (hazard ratio = 1.62), thus suggesting $CLCR_{CG}$ as a significant predictor of the event of death. However, none of the other variables, including PK/PD targets such as 100% $fT_{>MIC}$ and 100% $fT_{>4\times MIC}$, were deemed meaningful covariates. Following the CART analysis, we conducted parametric TTE modeling to evaluate the relationship between potential covariates and survival outcome. However, the TTE model could not describe the survival data well, as evidenced by a poor fit between the observed and predicted survival curves. Further exploratory data analysis hinted that intermediate competing events (other antibiotic treatment and antibiotic treatment termination) might have contributed to the suboptimal performance of the TTE model. For instance, ~61.0% of the study population were independently right-censored due to hospital discharge, which is a competing event that cannot be effectively accounted for in a TTE model. Consequently, we used a multistate model to consider the complexity of events in the dataset.

The multistate modeling analysis revealed that lower $CLCR_{CG}$ was significantly associated with a higher risk of death both during ongoing meropenem treatment and after

TABLE 2 Parameter estimates and uncertainty of the final multistate model.

Parameter	Transition	Estimated value (95% CI)	Hazard ratio[a]
$Scale_{12}$[b]	Ongoing meropenem treatment	0.0354 (0.0281, 0.0472)	–
$Shape_{12}$[b]	→ Other antibiotic treatment	1.49 (1.30, 1.68)	
$\beta_{combined\ therapy}$ on k_{12}	–	1.23 (0.860, 1.60)	Increase by 3.42-fold
$Scale_{13}$	Ongoing meropenem treatment	0.128 (0.141, 0.117)	–
$Shape_{13}$	→ Antibiotic treatment termination	1.55 (1.41, 1.69)	
$\beta_{combined\ therapy}$ on k_{13}	–	−0.791 (−1.06, −0.519)	Decrease by 45.3%
$\beta_{fT>MIC}$ on k_{13}	–	0.931 (0.533–1.33)	1.097, every 10% increase in $fT_{>MIC}$ increases the probability of stopping antibiotic treatment by 9.7%
$Scale_{14}$	Ongoing meropenem treatment	0.0317 (0.0246, 0.0449)	–
$Shape_{14}$	→ Discharge alive	1.70 (1.34, 2.06)	
$Scale_{15}$	Ongoing meropenem treatment	0.0298 (0.0227, 0.0431)	–
$Shape_{15}$	→ In-hospital death	1.62 (1.30, 1.94)	
β_{CLCR} on k_{15} and k_{35}	–	−0.0167 (−0.0221, −0.0110)	1.18, every 10 mL/min decrease in CLCR increased death risk by 18%
k_{23}	Other antibiotic treatment → Antibiotic treatment termination	0.0980 (0.0818, 0.122)	–
k_{24}	Other antibiotic treatment → Discharge alive	0.0129 (0.00810, 0.0327)	–
k_{25}	Other antibiotic treatment → In-hospital death	0.0102 (0.00635, 0.0266)	–
k_{34}	Antibiotic treatment termination → Discharge alive	0.0699 (0.0793, 0.0625)	–
k_{35}	Antibiotic treatment termination → In-hospital death	0.00645 (0.00448, 0.0115)	–

Abbreviations: CI, confidence interval; CLCR, creatinine clearance; $fT_{>MIC}$, time that unbound concentrations exceed the minimum inhibitory concentration.

[a]Hazard ratio $= \exp(\beta_{predictor} * XP)$, XP = 0.1 (10% increase) for $\beta_{fT>MIC}$, XP = 1 (combination therapy) for $\beta_{combine\ therapy}$, XP = −10 (decrease 10 mL/min) for β_{CLCR}.

[b]Weibull distribution, $k_{ij} = scale_{ij} \bullet shape_{ij} \bullet (scale_{ij} \bullet t)^{shape_{ij}-1}$, unit of k_{ij} and $scale_{ij}$ is day-1.

antibiotic treatment termination. Specifically, a 10 mL/min decrease in $CLCR_{CG}$ was found to increase the risk of death by 18%, as detailed in Table 2. Notably, $CLCR_{CG}$ emerged as the most prominent predictor of death. After incorporating $CLCR_{CG}$ into the model, other covariates that demonstrated statistically significant differences in univariable analysis, such as age, baseline mortality risk, sepsis, meropenem daily dose, and $fT_{>MIC}$, were no longer significant factors affecting the outcome of death. The recognition of $CLCR_{CG}$ as a predictor of survival outcome is plausible because impaired renal function does not only impact meropenem clearance (with lower CLCR values leading to elevated meropenem exposure), but also signifies a severe underlying pathophysiological condition, compromising the body's immune response and recovery capabilities, directly influencing mortality rates. In fact, $CLCR_{CG}$ has also been identified as a commonly reported influential predictor of survival in prior CART analyses or logistic regression models involving beta-lactams in both hospitalized and critically ill patients.[19,33] Furthermore, a time-to-death analysis (involving 406 critically ill patients infected with colistin-susceptible and carbapenem-resistant bacteria and treated with either colistin or a combination of colistin and meropenem) revealed that $CLCR_{CG}$ was linked to an increased risk of fatality in a univariable analysis; however, only SOFA score (which CLCR forms part of) and $C_{ss,avg}$/MIC (colistin trough concentrations exceeding MIC, which are highly dependent on CLCR) were retained in the final model.[34]

Achievement of 100% $fT_{>MIC}$ increased the transition to antibiotic treatment termination, as demonstrated by a decrease in OFV of 27.8 during univariable analysis, indicating a potential clinical benefit for infection cure. Additionally, a similar effect was observed for achieving 100% $fT_{>4\times MIC}$, with a decrease in OFV of 21.6 during univariable analysis. Given their high correlation, $fT_{>MIC}$ was ultimately

chosen due to its larger reduction in OFV. The relationship between PK/PD targets of meropenem and clinical cure, defined as the resolution of all signs and symptoms caused by the infection or discontinuation of antibiotic therapy, has been previously reported in non-critically ill patients through CART analyses. These analyses included febrile neutropenic patients ($n=60$) and patients with lower respiratory tract infections ($n=101$), with significant predictors being identified as 75% $fT_{>MIC}$ or 100% $fT_{>5\times MIC}$.[35] Similarly, in critically ill patients ($n=384$) treated with eight beta-lactams, including meropenem, a positive association was observed between clinical cure and increased achievement of 50% $fT_{>MIC}$ and 100% $fT_{>MIC}$.

Furthermore, maintaining 100% $fT_{>MIC}$ was correlated with improved survival outcome also in our study. This is supported by the finding that achieving 100% $fT_{>MIC}$ increased the transition rate from ongoing meropenem treatment to antibiotic treatment termination, and the relative death rate was 10 times lower in cases of antibiotic treatment termination compared to ongoing meropenem treatment ($k_{15}/k_{14} > k_{35}/k_{34}$). This result may appear contradictory to the finding in the univariable analysis that "achieving 100% $fT_{>MIC}$ significantly increased transition rate from initial state to death." CRCL is, however, a confounding factor because a decreased CLCR is associated with an increased risk of death and patients with low CLCR that have a higher chance to achieve 100% $fT_{>MIC}$. In line with our result, a machine learning-based efficacy analysis of three beta-lactams (cefepime, meropenem, and piperacillin) in critically ill patients ($n=735$) showed that PK/PD predictors were the primary predictors of clinical cure. The key PK/PD predictor of composite outcome (28-day survival and clinical cure on day 10) was 100% $fT_{>4\times MIC}$ in the first 24 h, followed by 100% $fT_{>MIC}$ over 10 days of therapy. However, it is important to note that the 95% confidence interval of the estimated values of $\beta_{fT>MIC}$ on k_{13} included 1, suggesting a low discriminatory power. This observation may be attributed to the skewed distribution and high attainment of the desired PK/PD targets within the studied patient population. In addition, we found that the target of *f*AUC/MIC was non-influential for any of the transitions in the univariable analysis. Similarly, in the study by Alshaer et al.,[36] none of the *f*AUC/MIC and *f*AUC/4×MIC parameters showed benefits in terms of clinical outcomes.

Our analysis revealed that patients who received combined antibiotic therapy had a lower probability of discontinuing antibiotic treatment. This may be attributed to the fact that patients treated with combined antibiotics generally have more severe infections or life-threatening syndromes, resulting in a reduced likelihood of discontinuing antibiotic treatment. Although the microbiological response was evaluated as a potential predictor of transitions between states, such as hospital discharge and death, it did not show any significant impact. This could be due to the intermittent nature of the microbiological response in our dataset, which occasionally oscillated between positive and negative within a few days. To mitigate this, we only considered the first microbiological response for each patient, which might have introduced some degree of bias. Additionally, we observed that the time to the first MIC report did not significantly contribute to the transition from ongoing meropenem treatment to other antibiotic therapy, indicating that changes in the administered antibiotics may be primarily driven by clinical considerations other than the MIC results, particularly because most of the infecting bacteria were found to be susceptible to meropenem.

We acknowledge several limitations of our study. First, the database did not include meropenem concentration data for the analyzed patients. Instead, we relied on a population PK model based on patient demographics and renal function to estimate individual PK parameters and to calculate PK/PD targets with available MIC values, which might have introduced some potential bias in the multistate modeling. Second, PK/PD predictors were only considered for meropenem. The impact of combined antibiotic therapy is not fully understood and could have contributed to the bacterial killing effect. Additionally, various factors beyond the efficacy of antibiotics, including different surgical procedures, may affect clinical end points and might have disguised a robust association between PK/PD predictors and survival. Finally, our study included critically ill patients who received meropenem treatment for at least 2 days and who had available MIC test results, enabling $fT_{>MIC}$ calculations and covariate analyses on clinical outcomes. The results may hence not be applicable to the population with shorter treatment durations and non-randomly missing MIC.

In summary, our study presents a pharmacometric multistate model for analyzing survival outcomes in critically ill patients receiving meropenem treatment. Our results suggested reduced $CLCR_{CG}$ as the primary predictor of death events. Achievement of 100% $fT_{>MIC}$ contributed to an increased likelihood of discontinuing antibiotic treatment and a decreased risk of mortality. The multistate framework used in this study serves as an important example of how to approach the analysis of infectious diseases from a longitudinal perspective. Our findings may have significant implications for cross-end point bridging, patient selection, and dose optimization in the field of antimicrobial therapy.

AUTHOR CONTRIBUTIONS

Y.P. wrote the manuscript. F.X. and L.E.F. designed the research. Y.P. performed the research. All authors analyzed the data.

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CONFLICT OF INTEREST STATEMENT

The authors declared no competing interests for this work.

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SUPPORTING INFORMATION

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

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