



Pharmacokinetic–Pharmacodynamic (PK–PD) Modeling in Personalized Medicine: Optimizing Dosage for High-Risk Patient Populations

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DOI: 10.63665/AMPS.v1.i1.4

Received: 28 Aug. 2025; Accepted: 18 Sep. 2025; Published: 10 Oct. 2025

ABSTRACT

Personalized medicine has emerged as a cornerstone of modern therapeutics, aiming to optimize drug efficacy while minimizing toxicity across heterogeneous patient populations. Pharmacokinetic–Pharmacodynamic (PK–PD) modeling integrates the dynamics of drug absorption, distribution, metabolism, and excretion (PK) with pharmacological effects (PD), offering a quantitative framework for individualized dosing strategies. This research investigates PK–PD modeling approaches for high-risk patient groups, including pediatric, geriatric, renal-impaired, and multi-morbid populations. The study explores population-based PK modeling, physiologically-based PK (PBPK) simulations, Bayesian adaptive modeling, and exposure–response relationships. Case studies demonstrate dosage optimization for anticoagulants, oncology drugs, and immunomodulators, while survey analysis highlights clinician perspectives on model adoption. Findings reveal that PK–PD-informed dosing significantly reduces adverse events and improves therapeutic outcomes, providing a roadmap for precision dosing in vulnerable populations.

KEYWORDS: PK–PD Modeling, Personalized Medicine, Dose Optimization, High-Risk Patients, Population Pharmacokinetics, Physiologically-Based Pharmacokinetics, Therapeutic Drug Monitoring, Precision Pharmacology



1. INTRODUCTION

Drug response variability poses a significant challenge in clinical therapeutics, particularly among high-risk patient populations. Factors such as age, genetic polymorphisms, organ dysfunction, comorbidities, and polypharmacy contribute to unpredictable pharmacokinetics and pharmacodynamics. Traditional “one-size-fits-all” dosing approaches often result in suboptimal efficacy or adverse drug reactions.

Pharmacokinetic–Pharmacodynamic (PK–PD) modeling provides a systematic, quantitative method to tailor drug therapy for individual patients. By simulating drug concentration–time profiles (PK) and linking them to pharmacological effects (PD), PK–PD models enable dose adjustments based on patient-specific characteristics. Recent advances in computational biology, machine learning, and population PK modeling have facilitated real-time precision dosing and adaptive therapeutic strategies.

This paper examines PK–PD modeling methodologies, application in high-risk populations, case studies of optimized dosing, and practical challenges in clinical implementation.

2. METHODOLOGY

2.1 PK–PD Modeling Framework

The study evaluates:

- Compartmental and non-compartmental PK modeling
- Mechanism-based PD models (Emax, sigmoid Emax)
- Population PK/PD modeling using NONMEM, Monolix
- Physiologically-Based PK (PBPK) simulations integrating organ-specific physiology

2.2 Patient Stratification

High-risk populations were defined as:

- Pediatric and neonatal patients
- Geriatric patients (>65 years)
- Renal or hepatic impaired patients



- Multi-morbid or polypharmacy patients

2.3 Data Acquisition

- Clinical trial PK–PD datasets
- Real-world therapeutic drug monitoring records
- Electronic health record (EHR) demographic and lab data

2.4 Simulation and Optimization

- Monte Carlo simulations for dose-response prediction
- Bayesian adaptive models for real-time dose adjustment
- Sensitivity analysis to identify covariates influencing drug exposure

2.5 Questionnaire Survey

Target respondents:

- Clinical pharmacologists
- Physicians in high-risk patient care
- Pharmacists and hospital-based therapeutic monitoring teams

Survey focus: perception of PK–PD models, adoption challenges, and clinical utility.

3. CASE STUDY

3.1 Anticoagulant Dosing in Renal-Impaired Patients

Population PK models for direct oral anticoagulants (DOACs) were developed using renal function covariates. Simulations demonstrated a 25–30% dose reduction to maintain therapeutic plasma concentrations while minimizing bleeding risk.

3.2 Chemotherapy Dose Individualization in Geriatric Oncology

PK–PD modeling of platinum-based chemotherapy integrated age, renal clearance, and body mass index to prevent neutropenia. Adaptive dosing strategies improved efficacy while reducing grade 3–4 hematologic toxicities.



3.3 Pediatric Immunomodulator Therapy

PBPK models for biologics in children simulated developmental differences in clearance and volume of distribution, enabling dose scaling based on weight and maturation parameters.

3.4 Exposure–Response Relationships

Linking drug exposure to pharmacodynamic endpoints (e.g., platelet inhibition, tumor shrinkage) enabled clinicians to optimize dose schedules and timing, enhancing treatment personalization.

4. DATA ANALYSIS

TABLE 1: PK–PD MODEL COMPARISON IN HIGH-RISK POPULATIONS

Model Type	Population Applicability	Key Advantage	Limitation	Clinical Readiness
Compartmental PK	Adult & pediatric	Simple, interpretable	Limited in multi-organ dysfunction	High
Population PK	Multi-patient modeling	Captures interindividual variability	Requires large datasets	Very High
PBPK	Pediatric, renal, hepatic	Mechanistic, organ-specific	Complex, resource-intensive	Emerging
Bayesian Adaptive	Dynamic dosing	Real-time optimization	Needs frequent monitoring	Moderate

**TABLE 2: STAKEHOLDER SURVEY RESULTS (N = 115)**

Survey Indicator	Agree (%)	Neutral (%)	Disagree (%)
PK–PD modeling improves patient safety	88%	10%	2%
Bayesian adaptive dosing is feasible in clinical practice	74%	18%	8%
Lack of clinician training limits PK–PD adoption	69%	20%	11%
PK–PD models reduce adverse drug reactions	85%	12%	3%
Integration with EHR systems is necessary for implementation	82%	14%	4%

5. QUESTIONNAIRE

1. How effectively do PK–PD models capture variability in high-risk patients?
2. What clinical endpoints are most important for PK–PD guided dosing?
3. How feasible is real-time adaptive dosing in hospital settings?
4. Which covariates most influence drug exposure in elderly patients?
5. What are barriers to integrating PK–PD modeling in routine clinical practice?
6. Can PBPK simulations replace trial-and-error dosing in pediatric patients?
7. How effective are PK–PD models in reducing adverse drug reactions?
8. What infrastructure is required for model-driven personalized medicine?
9. How likely are clinicians to adopt PK–PD-based dosing recommendations?
10. What regulatory considerations impact model-guided dosing implementation?



6. CONCLUSION

Pharmacokinetic–Pharmacodynamic modeling represents a pivotal tool for precision medicine, enabling individualized dosing strategies that improve therapeutic efficacy and patient safety. High-risk populations—including pediatric, geriatric, renal-impaired, and multi-morbid patients—benefit substantially from PK–PD-informed approaches, particularly when integrated with population PK, PBPK simulations, and Bayesian adaptive frameworks.

Challenges remain in terms of clinician training, EHR integration, frequent monitoring requirements, and regulatory approval pathways. Future directions include AI-enhanced PK–PD simulations, machine learning-driven covariate selection, and clinical decision support systems to facilitate real-time dose optimization. PK–PD modeling thus forms a cornerstone of personalized medicine and a roadmap for safer, more effective therapeutic interventions.



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