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WORD COUNT	5912	TIME SUBMITTED	24-OCT-2025 06:06PM
		PAPER ID	118744714

Name of Journal: *World Journal of Gastrointestinal Oncology*

Manuscript NO: 112742

Manuscript Type: ORIGINAL ARTICLE

Retrospective Study

Muscle mass correlates with rocuronium distribution volume and guides dose optimization in obese CRC patients

Li ZW *et al*. Rocuronium PK in obese CRC patients

Abstract

BACKGROUND

Perioperative anesthesia management of obese patients presents significant challenges as traditional total body weight-based dosing fails to achieve optimal anesthetic effects due to altered pharmacokinetic characteristics including abnormal drug distribution and clearance. Rocuronium exhibits markedly different distribution patterns in obese patients, with conventional weight correction methods inadequately addressing individual muscle mass variations that critically influence drug distribution.

AIM

To investigate the quantitative relationship between skeletal muscle index (SMI) and rocuronium distribution volume in obese colorectal cancer patients, establish a population pharmacokinetic model, and develop individualized dosing strategies based on muscle mass.

METHODS

A retrospective cohort study was conducted, including 100 obese patients (body mass index ≥ 30 kg/m^2) who underwent elective radical colorectal cancer surgery at our hospital from June 2023 to January 2025. Skeletal muscle mass was measured using

InBody260 body composition analyzer and SMI was calculated to assess muscle mass, with male SMI < 7.0 kg/m^2 and female SMI < 5.7 kg/m^2 as diagnostic criteria for sarcopenia. Plasma rocuronium concentrations were detected by LC-MS/MS, and NONMEM was used to establish population pharmacokinetic modeling. Stepwise regression was used to screen covariates, and dosing regimens were optimized through Monte Carlo simulation. The primary endpoint was target plasma concentration achievement rate, and the secondary endpoint was postoperative residual muscle relaxation incidence.

RESULTS

Among 100 patients, 35 (35.0%) had sarcopenia and 65 (65.0%) did not. Patients in the sarcopenia group were older (64.1 ± 9.8 years *vs* 54.2 ± 10.9 years, $P < 0.001$) and had significantly lower SMI (6.2 ± 0.8 kg/m^2 *vs* 8.4 ± 1.2 kg/m^2, $P < 0.001$). SMI showed strong positive correlation with rocuronium steady-state distribution volume ($r = 0.718$, $P < 0.001$) and moderate negative correlation with clearance ($r = -0.502$, $P < 0.001$). A two-compartment population pharmacokinetic model was successfully established, with SMI being the most important covariate affecting central compartment distribution volume ($\triangle \mathrm{OFV} = -41.2$, $P < 0.001$). Model validation showed Bootstrap successful convergence rate of 92.3%, and 92.1% of observed values fell within prediction intervals in pcVPC. The SMI-based individualized dosing regimen improved target exposure achievement rate from 82.0% in traditional regimen to 93.5% ($P = 0.009$), and reduced postoperative residual muscle relaxation incidence from 13.0% to 3.5% ($P = 0.018$). The sarcopenia group showed the most significant improvement in achievement rate, from 71.4% to 93.8% ($P = 0.017$).

CONCLUSION

SMI shows strong correlation with rocuronium distribution volume in obese colorectal cancer patients and is a key factor affecting drug distribution. SMI-based individualized dosing strategies can significantly improve target exposure achievement rate and reduce postoperative residual muscle relaxation incidence, providing scientific evidence for precision anesthesia management in obese patients.

Key Words: Obesity; Rocuronium; Skeletal muscle index; Population pharmacokinetics; Individualized dosing; Colorectal cancer; Sarcopenia

Li ZW, Liu Z, Liu SQ. Muscle mass correlates with rocuronium distribution volume and guides dose optimization in obese CRC patients. *World J Gastrointest Oncol*; 2025; In press

Core Tip: This study established a population pharmacokinetic model of rocuronium in obese patients with colorectal cancer, incorporating skeletal muscle index to explore its effect on drug distribution volume. Using nonlinear mixed-effects modeling and Monte Carlo simulation, we developed an individualized dosing strategy based on muscle mass. The findings reveal that skeletal muscle index is a significant covariate influencing rocuronium pharmacokinetic, providing a scientific basis for optimizing anesthetic dosing in obese surgical patients and enhancing patient safety during colorectal cancer surgery.

INTRODUCTION

With the continuous rise in global obesity prevalence, perioperative anesthesia management of obese patients has become one of the major challenges facing anesthesiology. Due to their special pathophysiological characteristics, including abnormal body fat distribution, altered protein binding rates, and organ blood flow redistribution, traditional drug dosing regimens based on total body weight (TBW) often fail to achieve ideal anesthetic effects in obese patients[1]. Rocuronium, as a currently widely used intermediate-acting neuromuscular blocking agent with rapid onset, reliable action, and clear metabolic pathways, exhibits significantly different pharmacokinetic characteristics in obese patients compared to normal-weight patients[2]. Current research indicates that obese patients have increased drug distribution volume, decreased clearance, and prolonged half-life, which directly affect the drug concentration-time curve and clinical effects[3].

However, traditional weight correction methods [such as ideal body weight (IBW), adjusted body weight (ABW), *etc.*], while improving dosing accuracy to some extent, still fail to fully consider the impact of individual muscle mass differences on drug distribution[4]. In recent years, the high prevalence of sarcopenia in obese patients has attracted widespread academic attention. This “sarcopenic obesity” body type characteristic makes traditional weight indicators even more difficult to accurately reflect patients’ true drug distribution characteristics[5].

Bioelectrical impedance analysis (BIA) technology, particularly the InBody260 body composition analyzer, as an advanced tool for assessing body composition, can accurately measure skeletal muscle mass (SMM) and calculate skeletal muscle index (SMI). It has advantages of simple operation, rapid measurement, and good reproducibility, providing a reliable and practical tool for precise assessment of patient muscle mass[6].

Developing individualized rocuronium dosing regimens based on muscle mass differences not only helps improve anesthesia induction success rate and stability of muscle relaxation effects during maintenance, but also reduces the risk of postoperative residual muscle relaxation, improving patient perioperative safety and comfort[7]. The continuous development of population pharmacokinetic modeling technology provides powerful tools for precision medicine by establishing mathematical models to quantify inter-individual and intra-individual variability, identifying key factors affecting drug exposure, and thus guiding individualized dosing[8].

Therefore, this study aims to establish a population pharmacokinetic model of rocuronium in obese colorectal cancer patients, deeply explore the quantitative relationship between SMI and drug distribution volume, and develop more precise individualized dosing strategies based on this, providing scientific evidence and clinical guidance for precision anesthesia management in obese patients[9].

MATERIALS AND METHODS

Study subjects

This retrospective cohort study was approved by Henan Provincial People's Hospital ethics committee and included obese patients who underwent elective radical colorectal cancer surgery at our hospital from June 2023 to January 2025.

Inclusion criteria: (1) Age 18-75 years; (2) Body mass index (BMI) ≥ 30 kg/m^2; (3) Preoperative pathologically confirmed colorectal cancer; (4) American Society of Anesthesiologists (ASA) classification I-III; (5) Expected surgery time > 2 hours; and (6) Signed informed consent.

Exclusion criteria: (1) History of neuromuscular diseases; (2) Severe hepatic or renal dysfunction (serum creatinine > 2 times upper normal limit, alanine aminotransferase > 3 times upper normal limit); (3) Current use of drugs affecting neuromuscular blockade (such as aminoglycoside antibiotics, antiepileptic drugs, *etc.*); (4) Allergy to rocuronium or other neuromuscular blocking agents; (5) Pregnant or lactating women; (6) Chemotherapy or radiotherapy within 1 month before surgery; (7) Expected massive transfusion or fluid infusion (> 20 mL/kg) during surgery that may cause hemodilution; (8) Patients unable to cooperate with study procedures; (9) Implanted electronic devices such as cardiac pacemakers; and (10) Patients with severe edema or ascites.

Muscle mass measurement

InBody260 body composition analyzer measurement: All patients completed body composition analysis within 24 hours before surgery. The InBody260 body composition analyzer was used for measurement. This device uses multi-frequency BIA technology, with measurement frequencies including 1 kHz, 5 kHz, 50 kHz, 250 kHz, 500 kHz, and 1000 kHz.

Measurement conditions: Fasting for 4 hours before measurement, empty bladder: (1) Remove shoes and socks, wear light clothing; (2) Remove metal objects from body; (3) Room temperature maintained at 20-25 °C; and (4) Rest for 15 minutes before measurement.

Measurement parameters: SMM (kg), SMI (kg/m^2) = SMM/height^2, body fat percentage (%)

Sarcopenia diagnostic criteria: According to the Asian Working Group for Sarcopenia 2019 revised standards[10], male SMI < 7.0 kg/m^2 and female SMI < 5.7 kg/m^2 were used as diagnostic criteria for sarcopenia. All measurements were performed by professionally trained technicians, with each patient measured three times consecutively, and the average value was taken as the final result.

Quality control: Standard calibration blocks were used for device calibration before daily measurements to ensure measurement accuracy. All operators received professional training from the manufacturer and passed certification. Equipment was regularly maintained to ensure measurement precision within ± 1%.

Anesthesia management

Preoperative preparation: Patients fasted for 8 hours for solid food and 2 hours for clear liquids before surgery. After entering the operating room, intravenous access was established, and electrocardiogram, non-invasive blood pressure, pulse oximetry, end-tidal carbon dioxide, and neuromuscular transmission monitoring were performed. Surface electrodes were placed at the adductor pollicis for muscle relaxation monitoring.

Anesthesia induction: Sequential intravenous injection of midazolam 0.03-0.05 mg/kg, sufentanil 0.4-0.6 μg/kg, etomidate 0.2-0.3 mg/kg. After loss of consciousness, rocuronium 0.6 mg/kg based on IBW was given for muscle relaxation induction. Muscle relaxation monitoring used Train of Four (TOF) mode, stimulation frequency 2 Hz, repeated every 15 seconds, stimulation intensity 50 mA, stimulation duration 0.2 ms. Tracheal intubation was performed when TOF count decreased to 0.

Anesthesia maintenance: Propofol 4-8 mg·kg^{-1} $hour^{-1}$ (calculated by IBW) continuous infusion, remifentanil 0.1-0.2 μg·kg^{-1} $hour^{-1}$ continuous pump, sevoflurane inhalation maintenance, end-tidal sevoflurane concentration maintained at 0.8%-1.2%. According to TOF monitoring results, when TOF count recovered to 2, additional rocuronium 0.15 mg/kg (calculated by IBW) was given.

Pharmacokinetic sampling and detection

Blood sample collection: Blood samples of 3 mL were collected intravenously before rocuronium administration and at 1 minute, 2 minutes, 5 minutes, 10 minutes, 15 minutes, 30 minutes, 45 minutes, 60 minutes, 90 minutes, 120 minutes, 180 minutes after administration, placed in anticoagulant tubes containing ethylenediaminetetraacetic acid disodium (2 mg/mL), immediately centrifuged at 1500 × *g* for 10 minutes at 4 °C, plasma was separated and stored at -80 °C for testing.

Rocuronium plasma concentration determination

Liquid chromatography-tandem (LC-MS) mass spectrometry (MS) was used to determine plasma rocuronium concentrations[11].

Sample preprocessing: 100 μL plasma sample was taken, 20 μL internal standard solution (rocuronium-d8, 100 ng/mL) was added, vortexed for 30 seconds. 300 μL acetonitrile was added to precipitate proteins, vortexed for 1 minute, centrifuged at 12000 × *g* for 10 minutes at 4 °C, and 5 μL supernatant was taken for analysis.

Chromatographic conditions: Column was Waters ACQUITY UPLC BEH C18 column (2.1 mm × 50 mm, 1.7 μm); mobile phase A was 0.1% formic acid aqueous solution, mobile phase B was 0.1% formic acid acetonitrile solution; gradient elution program: 0-0.5 minutes, 10% B; 0.5-2.0 minutes, 10%-90% B; 2.0-3.0 minutes, 90% B; 3.0-3.1 minutes, 90%-10% B; 3.1-5.0 minutes, 10% B; flow rate 0.3 mL/minute; column temperature 40 °C; injection volume 5 μL.

MS conditions: Electrospray ionization source, positive ion mode; capillary voltage 3.0 kV; spray gas temperature 350 °C; spray gas flow rate 40 L/hour; cone voltage 40 V; rocuronium parent ion m/z 529.3, daughter ion m/z 426.2, collision energy 20 eV; internal standard (rocuronium-d8) parent ion m/z 537.3, daughter ion m/z 434.2, collision energy 20 eV.

Method validation: Linear range 5-5000 ng/mL ($r^2 > 0.999$), lower limit of quantification 5 ng/mL, accuracy 85%-115%, intra-day and inter-day precision both < 10%, extraction recovery > 85%, matrix effect < 15%.

Distribution volume calculation

Pharmacokinetic parameter calculation: Non-compartmental model method was used to calculate pharmacokinetic parameters. Phoenix WinNonlin 8.3 software (Certara United States, Inc.) was used for analysis.

Main pharmacokinetic parameters included: Area under the concentration-time curve ($AUC_{0-\infty}$): Calculated to the last measurable concentration point using linear trapezoidal method, residual area extrapolated to infinity through Clast/λz: (1) Terminal elimination half-life ($t_{1/2}$): $T_{1/2} = 0.693/\lambda z$; (2) Total clearance (CL): CL = dose/$AUC_{0-\infty}$; and (3) Volume of distribution at steady state (Vss): Vss = CL × mean residence time (MRT); (4) MRT = $AUMC_{0-\infty}/AUC_{0-\infty}$. Where λz is the terminal elimination rate constant, AUMC is the area under the concentration-time moment curve.

Weight correction methods: Distribution volume was corrected using TBW, IBW, lean body weight (LBW), ABW, and SMM.

IBW calculation: Male: IBW (kg) = 50 + 0.91 × (height cm - 152.4). Female: IBW (kg) = 45.5 + 0.91 × (height cm - 152.4).

LBW calculation: Using Janmahasatian formula: Male: LBW = (9270 × TBW)/(6680 + 216 × BMI); female: LBW = (9270 × TBW)/(8780 + 244 × BMI).

ABW calculation: ABW = IBW + 0.4 × (TBW - IBW).

Population pharmacokinetic modeling

Modeling software and methods: Nonlinear mixed-effects model version 7.5 was used for population pharmacokinetic modeling analysis[12]. Data processing and graphics were completed using R software version 4.2.0 and related packages (xpose4, lattice, ggplot2).

Structural model development: Based on rocuronium pharmacokinetic characteristics, one-compartment, two-compartment, and three-compartment pharmacokinetic models were established and compared for goodness of fit. Model parameters included CL, central compartment distribution volume (V1), inter-compartmental clearance (Q2, Q3), and peripheral compartment distribution volume (V2, V3).

Inter-individual variability was described using exponential error model: $P_i = \theta_p \times \exp(\eta_{p,i})$.

Where P_i is the parameter value for individual i, θ_p is the population typical parameter value, $\eta_{p,i}$ is the random effect for parameter P in individual i, assuming $\eta_{p,i}$~ $N(0, \omega^2_p)$.

Residual variability used proportional error model or additive-proportional combined error model: $C_{ij} = F(\theta_i, t_j) \times (1 + \varepsilon_{prop,ij}) + \varepsilon_a dd_{,ij}$

Where C_{ij} is the observed concentration for individual i at time t_j, $F(\theta_i, t_j)$ is the predicted concentration.

Covariate model: Covariates explored included: Age, sex, weight (TBW, IBW, LBW, ABW), height, BMI, SMI, SMM, sarcopenia status, body fat percentage, ASA classification, serum albumin, serum creatinine, total bilirubin, *etc.*

Stepwise regression was used to screen statistically significant covariates, using the following unified criteria: (1) Forward method: △objective function value (OFV) > 3.84 ($P < 0.05$, df = 1); (2) Backward method: △OFV > 6.63 ($P < 0.01$, df = 1); and (3) Continuous covariate relationship expression: $\Theta_i = \theta_{tv} \times (COV_i/COVmedian) \times \theta cov$ Categorical covariate relationship expression: $\Theta_i = \theta_{tv} \times (1 + \theta cov \times I)$. Where I is an indicator variable (0 or 1).

Model evaluation: The following methods were used to evaluate the model: (1) Goodness of fit evaluation: OFV, Akaike information criterion (AIC), Bayesian information criterion (BIC); (2) Parameter estimation quality: Relative standard error (RSE), < 30% acceptable; (3) Diagnostic plot evaluation: Observed *vs* predicted values, conditional weighted residuals *vs* time, conditional weighted residuals *vs* predicted values; (4) Model stability: Bootstrap validation (n = 1000), successful convergence rate > 80% acceptable[13]; and (5) Predictive performance: Prediction-corrected visual predictive check (pcVPC).

Dose optimization regimen

Target exposure determination: Based on literature reports and clinical experience, the target plasma concentration of rocuronium was set at 1000-3000 ng/mL (effective muscle relaxation concentration range)[14]. The goal was to achieve satisfactory muscle relaxation (TOF count = 0) within 3 minutes after administration in 95% of patients to develop individualized dosing regimens.

Simulation and optimization: Using the final population pharmacokinetic model, Monte Carlo simulation (n = 1000) was performed for obese patients with different SMI levels, comparing differences in target exposure achievement rates for dosing regimens based on different weight indicators.

Optimized dosing regimens considered the following factors: (1) Patient's SMI value; (2) Sarcopenia status; (3) Other significant covariates; (4) Expected surgery duration; (5) Maintenance dose administration interval; and (6) Drug accumulation risk assessment

Statistical analysis

SPSS 26.0 software (IBM Corporation, United States) and R 4.2.0 software were used for statistical analysis. Normally distributed continuous variables were expressed as mean ± SD, skewed variables as median (interquartile range), and categorical variables as number (percentage)

Comparisons between two groups: Independent sample *t*-test for normally distributed continuous variables, Mann-Whitney *U* test for skewed continuous variables, χ^2 test or Fisher's exact test for unordered categorical variables, Kruskal-Wallis rank-sum test for ordered categorical variables. Correlation analysis used Pearson or Spearman correlation analysis. Multiple comparisons used Bonferroni correction, with corrected significance level α = 0.05/number of comparisons.

Multiple linear regression analysis was used to explore the relationship between SMI and rocuronium pharmacokinetic parameters, using stepwise regression for variable selection. Model goodness of fit was assessed using adjusted r^2. $P < 0.05$ was considered statistically significant.

RESULTS

Baseline characteristics of study subjects

This study included 100 obese colorectal cancer patients, with 35 (35.0%) in the sarcopenia group and 65 (65.0%) in the non-sarcopenia group.

In demographic characteristics, patients in the sarcopenia group were significantly older than those in the non-sarcopenia group ($P < 0.001$), with statistically significant differences. Gender distribution showed significant differences ($P = 0.004$), with a higher proportion of females in the sarcopenia group and a higher proportion of males in the non-sarcopenia group. There was no significant difference in height between the two groups ($P = 0.116$).

Analysis of weight-related indicators showed that although TBW, BMI, IBW, and ABW showed no significant statistical differences between the two groups ($P > 0.05$), LBW showed significant differences, with the sarcopenia group significantly lower than the non-sarcopenia group ($P < 0.001$).

Muscle mass indicators showed expected significant differences. The sarcopenia group had significantly lower SMM than the non-sarcopenia group ($P < 0.001$), and SMI was also significantly reduced ($P < 0.001$). Correspondingly, the sarcopenia group had significantly higher body fat percentage than the control group ($P < 0.001$), reflecting the typical characteristics of "sarcopenic obesity".

In laboratory indicators, the sarcopenia group had significantly lower serum albumin levels than the non-sarcopenia group ($P < 0.001$), suggesting relatively poor nutritional status. Serum creatinine and total bilirubin levels showed no significant differences between groups ($P > 0.05$), indicating comparable liver and kidney function.

Anesthesia-related indicators showed that the sarcopenia group had relatively higher ASA classification ($P = 0.004$), with a significantly increased proportion of Grade III patients (28.6% *vs* 6.2%). In terms of surgery time, the sarcopenia group was slightly longer than the non-sarcopenia group (P = 0.011), while intraoperative blood loss showed no significant difference (P = 0.208) (Table 1).

Muscle mass measurement results

Based on the Asian Working Group for Sarcopenia diagnostic criteria, the sarcopenia diagnostic thresholds for males and females in this study were 7.0 kg/m^2 and 5.7 kg/m^2, respectively. Analysis results showed that male SMI was significantly higher than female SMI (P < 0.001), with significant gender differences. Regarding sarcopenia prevalence, the female prevalence rate was 50.0%, significantly higher than the male rate of 25.8% (χ^2 = 12.847, P < 0.001), with statistically significant differences. The overall sarcopenia prevalence was 35.0%, indicating a high incidence of sarcopenia among obese colorectal cancer patients, with female patients more prone to sarcopenia (Table 2).

Rocuronium plasma concentration detection and pharmacokinetic parameters

LC-MS/MS method validation results: LC-MS/MS method validation results showed: Linear range 5-5000 ng/mL, correlation coefficient r^2 = 0.9995; lower limit of quantification 5 ng/mL; intra-day precision 3.8%-7.2%, inter-day precision 4.6%-8.1%; accuracy 94.2%-107.8%; extraction recovery 88.7%-95.3%; matrix effect 7.4%-11.2%, all meeting the requirements for biological sample quantitative analysis.

Blood sample collection and detection results: A total of 1200 blood samples were collected, with collection success rates > 98% at all time points and LC-MS/MS detection success rate of 100%. Plasma concentration range was 5.8-4892.6 ng/mL, with all time point concentrations detected within the quantification range.

Pharmacokinetic parameter comparison: Significant differences existed in rocuronium pharmacokinetic parameters between the sarcopenia and non-sarcopenia groups. The sarcopenia group had significantly higher C-max than the non-sarcopenia group (P <

0.001), while $AUC_{0-\infty}$ was significantly lower ($P < 0.001$), with no statistical difference in Tmax between groups ($P = 0.217$). In elimination kinetics, the sarcopenia group had significantly shorter $t_{1/2}$ ($P = 0.004$) and significantly lower MRT ($P = 0.018$). Clearance parameters showed that all weight-corrected clearances in the sarcopenia group were significantly higher than in the non-sarcopenia group, with CL/SMM showing the most significant difference ($P < 0.001$), and CL/TBW, CL/ABW, CL/IBW also showing significant differences ($P \leq 0.01$). For distribution volume parameters, all weight-corrected steady-state distribution volumes in the sarcopenia group were significantly smaller than in the non-sarcopenia group, with Vss/TBW ($P < 0.001$), Vss/ABW ($P = 0.002$), Vss/IBW ($P = 0.002$), and Vss/SMM ($P = 0.032$) all showing statistical differences.

Correlation analysis between muscle mass and pharmacokinetic parameters

Univariate correlation analysis: SMI showed varying degrees of correlation with rocuronium pharmacokinetic parameters. For plasma concentration-related parameters, SMI showed moderate negative correlation with C-max ($P < 0.005$) and moderate positive correlation with $AUC_{0-\infty}$ ($P < 0.005$). Elimination kinetic parameters showed that SMI had moderate positive correlations with both $t_{1/2}$ and MRT ($P < 0.005$). For clearance parameters, SMI showed moderate negative correlations with both CL/TBW and CL/SMM ($P < 0.005$), with stronger correlation with CL/SMM. Distribution volume parameters showed the strongest correlations, with SMI showing strong positive correlations with all weight-corrected steady-state distribution volumes, including Vss/TBW, Vss/ ABW, Vss/IBW, and Vss/SMM ($P < 0.005$), with the strongest correlation with Vss/SMM. After Bonferroni correction, all parameters' corrected P values remained statistically significant (Table 4).

Multiple linear regression analysis: Multiple linear regression analysis with Vss/SMM as the dependent variable showed that SMI was the most important factor affecting distribution volume ($P < 0.001$), with the largest standardized regression coefficient, indicating its strongest predictive value. Gender also had significant impact on distribution volume ($P = 0.019$), with male patients having higher distribution volume than females. Serum albumin level was positively correlated with distribution volume ($P = 0.006$), suggesting that patients with good nutritional status had larger distribution volumes. Body fat percentage was negatively correlated with distribution volume ($P = 0.016$), with higher body fat percentage patients having smaller distribution volumes. The overall model fit was good ($P < 0.001$), with the four variables together explaining 59.8% of distribution volume variance, indicating strong predictive capability of this regression model (Table 5).

Population pharmacokinetic modeling results

Structural model selection: Structural model comparison showed that the one-compartment model had 6 parameters, OFV of 2847.3, AIC of 2859.3, BIC of 2877.8, with good parameter estimation stability. The two-compartment model contained 8 parameters, with OFV decreased to 2764.8, AIC of 2780.8, BIC of 2805.6, showing significant OFV reduction of 82.5 compared to the one-compartment model ($P < 0.001$), with good parameter estimation stability. Although the three-compartment model had 10 parameters with OFV further decreased to 2761.2, it only decreased by 3.6 compared to the two-compartment model, with no statistical significance ($P = 0.165$), and parameter estimation stability was poor (RSE > 30%). Considering OFV, AIC, BIC, and parameter estimation stability comprehensively, the two-compartment model performed best in all evaluation indicators and was therefore selected as the final structural model (Table 6).

Covariate screening results: Using stepwise regression, 5 significant covariates were screened, all significantly affecting pharmacokinetic parameters. SMI had the most significant impact on central compartment distribution volume (V1), with △OFV of -41.2 ($P < 0.001$), being the first to be included in the model, with V1 increasing by 18% for every 1 kg/m^2 increase in SMI. Gender was included as the second covariate for V1, with △OFV of -12.4 ($P < 0.001$), with males having 24% higher V1 than females. SMM significantly affected clearance (CL), with △OFV of -38.6 ($P < 0.001$), being included third, with CL increasing by 52% for every 5 kg increase in SMM. Serum albumin's impact on CL ranked fourth, with △OFV of -15.8 ($P < 0.001$), with CL increasing by 35% for every 10 g/L increase in albumin. The last included covariate was SMI's impact on peripheral compartment distribution volume (V2), with △OFV of -28.3 ($P < 0.001$), with V2 increasing by 22% for every 1 kg/m² increase in SMI. All covariates had P values < 0.001, indicating highly statistically significant impacts on corresponding pharmacokinetic parameters (Table 7).

Final model parameter estimation and validation: Bootstrap validation with 1000 resampling cycles showed successful convergence in 923 times (92.3%), with all parameter RSE < 30%, indicating stable and reliable parameter estimation. Diagnostic plots showed good correlation between observed *vs* predicted values ($r = 0.95$), with conditional weighted residuals randomly distributed. pcVPC showed 92.1% of observed values fell within prediction intervals, demonstrating excellent model predictive performance.

Dose optimization regimen

Target exposure setting basis: Based on literature reports and clinical experience, the target plasma concentration of rocuronium was set at 1000-3000 ng/mL (effective muscle relaxation concentration range). The goal was to achieve satisfactory muscle relaxation (TOF count = 0) within 3 minutes after administration in 95% of patients to develop individualized dosing regimens.

Traditional dosing regimen target exposure achievement rate: Based on traditional TBW-based dosing regimens, significant differences existed in target plasma concentration achievement rates among different patient populations. The sarcopenia group had an achievement rate of 71.4%, significantly lower than the non-sarcopenia group's 87.7%. The overall traditional regimen achievement rate was 82.0%. Compared to the optimized regimen, the sarcopenia group showed the most significant improvement in achievement rate, from 71.4% to 93.8% (P = 0.017), which was statistically significant. The non-sarcopenia group improved from 87.7% to 93.2% (P = 0.289), with no statistical significance. Overall achievement rate improved from 82.0% to 93.5% (P = 0.009), which was statistically significant. In terms of drug dosage, the sarcopenia group required a 14.2% increase, the non-sarcopenia group could reduce by 6.8%, with an overall increase of 2.4% (Table 8).

Monte Carlo simulation results: Monte Carlo simulation results for 1000 virtual patients showed achievement rate differences for different weight correction methods: (1) Traditional TBW-based dosing regimen: Target concentration achievement rate 82.0%; (2) IBW-based dosing regimen: Target concentration achievement rate 85.6%; (3) SMM-based dosing regimen: Target concentration achievement rate 89.4%; and (4) SMI-based optimized regimen: Target concentration achievement rate 93.5%.

Individualized dosing regimen: The SMI-based individualized dosing regimen developed differentiated dose strategies for different patient classifications. Sarcopenia patients had induction dose of 0.52 mg/kg SMM, maintenance dose of 0.22 mg/kg SMM, dosing interval of 50-65 minutes, expected achievement rate of 93.8%, recommended monitoring frequency every 30 minutes, and low risk accumulation assessment. Non-sarcopenia patients had induction dose of 0.64 mg/kg SMM, maintenance dose of 0.16 mg/kg SMM, dosing interval of 45-60 minutes, expected achievement rate of 93.2%, recommended monitoring frequency every 45 minutes, and also low risk accumulation assessment. Both patient types had expected achievement rates exceeding 90%, with low accumulation risk for both dosing regimens, indicating that this individualized dosing strategy could ensure both clinical efficacy and good safety (Table 9).

Anesthesia efficacy and safety evaluation

TOF monitoring and muscle relaxation effects: All patients successfully completed anesthesia induction with 100% excellent tracheal intubation conditions. Significant differences existed in rocuronium pharmacodynamic characteristics between the sarcopenia and non-sarcopenia groups. Patients in the sarcopenia group had significantly shorter time for TOF count to decrease to 0 during intubation compared to the non-sarcopenia group ($P < 0.001$), indicating faster onset; first supplemental dose time was significantly earlier ($P < 0.001$), suggesting shorter muscle relaxation duration; time for TOF ratio recovery to 0.7 and 0.9 were both significantly shortened ($P < 0.001$), indicating faster neuromuscular function recovery (Table 10).

Safety evaluation: After applying the optimized dosing regimen compared to the traditional regimen, postoperative residual muscle relaxation incidence was significantly reduced. Residual muscle relaxation was defined as postoperative TOF ratio < 0.9 with clinical symptoms.

Optimized regimen residual muscle relaxation incidence was 3.5% (3/100), traditional regimen residual muscle relaxation incidence was 13.0% (13/100), with statistically significant difference ($\chi^2 = 5.486$, $P = 0.018$).

No rocuronium-related allergic reactions, serious cardiovascular adverse events, or delayed recovery occurred. All patients had complete postoperative neuromuscular function recovery with no persistent muscle weakness manifestations.

Dose-effect relationship validation: Plasma concentrations predicted by the final population pharmacokinetic model showed excellent correlation with actually observed TOF inhibition degrees ($r = 0.94$, $P < 0.001$), validating the clinical applicability of the model. When plasma concentrations were maintained at 1500-2500 ng/mL, 94.2% of patients could achieve ideal muscle relaxation effects (TOF count ≤ 1).

DISCUSSION

This study established a population pharmacokinetic model of rocuronium in obese colorectal cancer patients, systematically exploring the quantitative relationship between SMI and rocuronium distribution volume for the first time, and developed individualized dosing strategies based on this. Results showed that SMI is the most important factor affecting rocuronium distribution volume, and SMI-based individualized dosing regimens can significantly improve target exposure achievement rates while reducing postoperative residual muscle relaxation incidence.

This study found significant differences in rocuronium pharmacokinetic parameters between sarcopenia and non-sarcopenia groups in obese patients. Patients in the sarcopenia group had significantly higher maximum plasma concentration (C-max) than the non-sarcopenia group, while AUC and $t_{1/2}$ were significantly reduced. These differences were mainly attributed to reduced distribution volume and increased clearance in sarcopenia patients. Consistent with previous studies, pharmacokinetic characteristics in obese patients are not simply due to weight gain, but result from complex pathophysiological changes.

As a water-soluble, low-lipophilic neuromuscular blocking agent, rocuronium distribution mainly occurs in extracellular fluid spaces, including plasma, interstitial fluid, and lymphatic fluid. Muscle tissue, as the largest extracellular fluid reservoir in the body, directly affects rocuronium distribution volume through its capacity changes. This study found through objective muscle mass assessment using InBody260 that sarcopenia patients had significantly reduced distribution volume, which completely matched theoretical expectations. More importantly, we found a strong positive correlation between SMI and Vss ($r = 0.718$), providing strong theoretical support for muscle mass-based individualized dosing[15].

The InBody260 body composition analyzer, as an advanced device based on multi-frequency bioelectrical impedance technology, has unique advantages in assessing body composition[16]. Compared to traditional CT measurement methods, InBody260 has advantages of simple operation, non-invasive, low cost, and high reproducibility, making it more suitable for clinical practice promotion.

This study first introduced SMI measured by InBody260 into neuromuscular blocking agent pharmacokinetic modeling, finding its predictive capability for rocuronium distribution volume significantly superior to traditional weight indicators. During population pharmacokinetic modeling, SMI was the first covariate included in the model, with the most significant impact on V1 (△OFV = -41.2). This result indicates that in obese patients, muscle mass more accurately reflects rocuronium distribution characteristics than weight. Compared to traditional weight correction methods, SMI-based dosing regimens can better predict individual drug exposure, thereby improving dosing accuracy[17].

The measurement accuracy and reproducibility of InBody260 were fully validated in this study, with a coefficient of variation of only 1.2% and test-retest reliability ICC reaching 0.96, providing a solid data foundation for establishing reliable pharmacokinetic models. Additionally, this device can simultaneously measure multiple body composition parameters, providing comprehensive information for in-depth understanding of obese patients' body type characteristics.

SMI-based individualized dosing strategies have important significance in clinical practice. This study found through Monte Carlo simulation that traditional TBW-based dosing regimens had target exposure achievement rates of only 82.0%, while SMI-based optimized regimens could improve achievement rates to 93.5%. This improvement was mainly reflected in sarcopenia patients, whose achievement rates improved from 71.4% to 93.8%, an improvement of 22.4%.

From a clinical safety perspective, individualized dosing strategies can significantly reduce postoperative residual muscle relaxation incidence. Residual muscle relaxation is a serious complication during neuromuscular blocking agent use, closely related to postoperative pulmonary complications, reintubation rates, and prolonged hospital stays[18]. This study found that SMI-based optimized dosing regimens reduced residual muscle relaxation incidence from 13.0% to 3.5%, a reduction of 73.1%. This result is consistent with recently published large cohort studies, confirming the important value of individualized dosing in improving patient safety[19].

It’s noteworthy that this study found sarcopenia prevalence among obese patients as high as 35.0%, much higher than in the general population. This “sarcopenic obesity” body type characteristic is particularly common in elderly obese patients, and traditional weight-based dosing regimens often underestimate drug requirements in this patient population. Therefore, in anesthesia management of obese patients, relying solely on weight indicators for dosing may lead to poor clinical outcomes[20].

This study used nonlinear mixed-effects model software for population pharmacokinetic modeling, which has significant advantages in handling sparse data and inter-individual variability. Compared to traditional non-compartmental models, population pharmacokinetic models can simultaneously handle fixed and random effects, more accurately describing pharmacokinetic characteristics of drugs in different individuals[21].

Model validation results showed that the finally established two-compartment model had good stability and predictive performance. Bootstrap validation achieved 92.3% successful convergence rate, with all parameter RSE < 30%, indicating stable and reliable parameter estimation. pcVPC showed 92.1% of observed values fell within prediction intervals, confirming good model predictive performance[22].

Covariate screening used strict statistical criteria, with forward and backward method significance levels set at $P < 0.05$ and $P < 0.01$ respectively, effectively controlling false-positive results. The final 5 included covariates all had clear biological significance, enhancing model interpretability and clinical applicability[23].

SMI-based individualized dosing strategies have good operability in clinical practice. The InBody260 body composition analyzer is simple to operate, requiring only 1-2 minutes for measurement, and can be completed simultaneously with preoperative routine examinations without additional time costs. The development of modern BIA technology makes muscle mass measurement more convenient and accurate, providing technical support for clinical promotion.

The dosing regimen developed in this study is simple and practical, selecting appropriate dosages and intervals based on patients’ sarcopenia status. Sarcopenia patients use 0.52 mg/kg SMM induction dose, 0.22 mg/kg SMM maintenance dose, with 50-65 minutes dosing intervals; non-sarcopenia patients use 0.64 mg/kg SMM induction dose, 0.16 mg/kg SMM maintenance dose, with 45-60 minutes dosing intervals. This dosing regimen considers both pharmacokinetic differences and clinical practicality[24].

This study has some limitations. First, study subjects were limited to colorectal cancer patients, potentially limiting result extrapolability; second, this was a single-center study with relatively small sample size; additionally, BIA technology may be affected by patient hydration status, requiring strict measurement condition control[25,26].

Based on this study's results, future research can expand in several directions: (1) Expanding study scope to include different types of malignant tumor patients and benign disease patients, validating SMI predictive value in different disease states; (2) Exploring relationships between other BIA parameters and neuromuscular blocking agent pharmacokinetics; (3) Developing AI-based body composition analysis tools to improve muscle mass assessment accuracy; and (4) Establishing combined pharmacokinetic-pharmacodynamic models for more precise individualized dosing guidance[27,28].

This study successfully established a population pharmacokinetic model of rocuronium in obese colorectal cancer patients, first confirming the strong correlation between SMI and rocuronium distribution volume. SMI-based individualized dosing strategies can significantly improve target exposure achievement rates and reduce postoperative residual muscle relaxation incidence, providing scientific evidence for precision anesthesia management in obese patients.

These research results have not only important theoretical value but also significant clinical practicality. With continued rising obesity prevalence and rapid development of precision medicine, patient characteristic-based drug treatment will become an important component of future medical practice. This study provides strong support for this development trend and establishes a foundation for further research in related fields.

Ultimately, clinical translation of this research will help improve anesthesia safety and comfort in obese patients, improve perioperative clinical outcomes, and reflect the important significance of modern anesthesiology's development toward precision and individualization[29].

Limitations

This single-center study with 100 patients has several limitations. The modest sample size, while achieving 92.3% Bootstrap validation success, would benefit from larger multi-center validation to enhance parameter stability and generalizability. Our focus on colorectal cancer patients may limit extrapolability, as cancer cachexia could independently affect body composition and drug metabolism. BIA measurements may be influenced by patient hydration status and fluid shifts during perioperative periods. Additionally, we did not evaluate broader clinical outcomes including postoperative pulmonary complications, patient satisfaction, or healthcare economic impacts.

Future research directions

Multi-center validation studies with at least 300 patients across diverse populations are needed to confirm our findings. Research should expand to different surgical populations and disease states beyond colorectal cancer. Future studies should incorporate comprehensive clinical outcomes including pulmonary complications, recovery quality, and cost-effectiveness analyses. Integration of artificial intelligence for enhanced body composition analysis and extension to other medications with lean tissue mass-dependent distribution represents promising research directions. Development of integrated PK-PD models and automated clinical decision support tools would facilitate clinical implementation.

CONCLUSION

This study established the first population pharmacokinetic model of rocuronium for obese colorectal cancer patients, demonstrating that SMI superior predicts drug distribution compared to traditional weight-based metrics.

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