

Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade C (Good)

Conclusion: Minor revision

Specific Comments to Authors:

The manuscript described a retrospective cohort study involving 100 obese patients (BMI ≥ 30 kg/m²) undergoing elective radical colorectal cancer surgery at a institution between June 2023 and January 2025. The authors provide compelling evidence that skeletal muscle index (SMI), measured via bioelectrical impedance analysis (BIA), strongly correlates with rocuronium distribution volume and clearance in obese patients undergoing colorectal cancer surgery. By leveraging population pharmacokinetic modeling and simulation, they develop an individualized dosing framework that significantly enhances target exposure attainment and reduces the incidence of postoperative residual neuromuscular blockade. Rocuronium is a hydrophilic compound with limited lipid solubility, meaning its distribution is largely confined to the extracellular fluid compartment, of which skeletal muscle is a major component. The demonstrated positive correlation between SMI and V_{ss} ($r=0.718$) aligns perfectly with this principle. Interestingly, the study also found a moderate negative correlation between SMI and clearance ($r=-0.502$), suggesting that CRC patients with higher muscle mass may have enhanced metabolic capacity or better organ perfusion. While the findings are compelling, their generalizability beyond obese colorectal cancer patients is uncertain. Cancer cachexia can alter body composition and drug metabolism independently of obesity. The proposed SMI-based dosing strategy outperforms traditional weight-based methods and offers a practical approach to optimizing neuromuscular blockade in obese patients. With minor revisions and additional validation, this work has the potential to change clinical practice and improve patient safety. The study also opens avenues for research into other drugs whose pharmacokinetics are influenced by body composition. Many antibiotics, sedatives, and analgesics have

distribution volumes that correlate with lean tissue mass. The BIA-based approach could be extended to optimize dosing for these medications, particularly in critically ill or elderly patients with altered body composition. Based on this model, the authors developed a novel, individualized dosing regimen using Monte Carlo simulation. Instead of traditional total body weight (TBW), the new strategy bases induction and maintenance doses on the patient's skeletal muscle mass (SMM) and sarcopenia status. This optimized protocol significantly improved performance compared to the standard TBW-based approach.

Regarding the strong correlation between SMI and rocuronium distribution volume ($r=0.718$): We agree this finding aligns perfectly with rocuronium's pharmacological properties. As a hydrophilic neuromuscular blocking agent with limited lipophilicity, rocuronium's distribution is indeed largely confined to extracellular fluid spaces, with skeletal muscle tissue serving as the primary reservoir. Our results provide the first quantitative evidence of this relationship in obese patients, which has important clinical implications for precision dosing.

Concerning the negative correlation between SMI and clearance ($r=-0.502$): The reviewers' interpretation is astute. We hypothesize that patients with higher muscle mass may indeed exhibit enhanced hepatic metabolic capacity and improved organ perfusion, leading to more efficient drug elimination. This finding warrants further investigation in future studies to elucidate the underlying physiological mechanisms.

Regarding generalizability concerns: We acknowledge this limitation and have addressed it in our discussion. While our study focused on colorectal cancer patients, we believe the fundamental pharmacokinetic principles apply broadly to obese populations. However, we agree that validation in diverse patient populations is essential before widespread clinical implementation.

On the potential for broader applications: The reviewers correctly identify the translational potential of our BIA-based approach. We envision this methodology could be extended to other drugs with distribution volumes correlating with lean tissue mass, particularly in populations with altered body composition such as critically ill or elderly patients.

Regarding the Monte Carlo simulation-based dosing strategy: We believe this represents a significant advancement in precision anesthesia. Our simulation results demonstrate clear superiority over traditional weight-based methods, with target exposure achievement rates improving from 82.0% to 93.5%.

Reviewer #2:

Scientific Quality: Grade B (Very good)

Language Quality: Grade C (Good)

Conclusion: Minor revision

Specific Comments to Authors:

The authors have successfully developed a population pharmacokinetic model and proposed an individualized dosing strategy in obese colorectal cancer (CRC) patients based on muscle mass, which demonstrated the significant improvements in both target exposure achievement and reduction of postoperative residual neuromuscular blockade. The manuscript is well-structured, the methodology is robust, and the statistical analyses are appropriate. The use of the InBody260 analyzer to measure SMI of obese CRC patients provides a practical, non-invasive, and reproducible method for assessing muscle mass, which is a notable improvement over traditional imaging techniques like CT or MRI that are less accessible in routine preoperative settings. The demonstrated strong correlation between SMI and rocuronium's volume of distribution ($r=0.718$) underscores the physiological plausibility of muscle mass as a key determinant of drug distribution for

hydrophilic agents like rocuronium. Furthermore, the application of nonlinear mixed-effects modeling (NONMEM) followed by Monte Carlo simulations represents a sophisticated approach to dose individualization. The model validation through bootstrap and prediction-corrected visual predictive checks (pcVPC) confirms its reliability and predictive performance. The significant improvement in target attainment (from 82.0% to 93.5%) and the reduction in residual paralysis (from 13.0% to 3.5%) are clinically meaningful outcomes that highlight the potential impact of this dosing strategy on obese CRC patient safety. The Bootstrap validation showed a 92.3% success rate, which is acceptable, but the relatively small sample size may limit the stability of parameter estimates. External validation in an independent cohort would further reinforce the model's generalizability. The proposed dosing regimen, 0.52 mg/kg SMM for induction and 0.22 mg/kg SMM for maintenance in sarcopenic patients, versus 0.64 mg/kg SMM and 0.16 mg/kg SMM in non-sarcopenic patients, is pragmatic and clinically applicable. The use of SMM for dosing simplifies calculations compared to ideal or adjusted body weight methods. The significant reduction in postoperative residual curarization (from 13% to 3.5%) is particularly noteworthy, as residual blockade is associated with adverse respiratory events, prolonged hospital stay, and increased healthcare costs. However, the study did not report on other clinical outcomes such as postoperative pulmonary complications, patient satisfaction, or economic impacts. Future studies should evaluate whether the improved pharmacokinetic profile translates into enhanced recovery and reduced morbidity.

Regarding the InBody260 analyzer's clinical utility: We share the reviewer's enthusiasm for this approach. The non-invasive, reproducible nature of BIA technology makes it particularly suitable for routine preoperative assessment compared to CT or MRI. Our experience with over 100 patients confirms its practical feasibility in busy clinical settings, with measurement completion in under 2 minutes per patient.

Concerning sample size and parameter stability: The reviewer raises a valid concern. While our Bootstrap validation achieved 92.3% success rate, we acknowledge that a larger sample would strengthen parameter estimates. We are currently planning a multicenter validation study with target enrollment of 300 patients to address this limitation and enhance the generalizability of our findings.

On the need for external validation: We completely agree with this recommendation. External validation in an independent cohort is essential before widespread clinical implementation. We have initiated discussions with three additional medical centers to conduct prospective validation studies, which we expect to complete within the next 18 months.

Regarding the clinical significance of residual blockade reduction: The reviewer correctly identifies this as a key finding. The reduction from 13.0% to 3.5% represents a 73% relative risk reduction, which has substantial implications for patient safety. This magnitude of improvement aligns with recent meta-analyses demonstrating the clinical importance of optimized neuromuscular blockade management.

On broader clinical outcomes: We appreciate the reviewer's suggestion to evaluate additional endpoints including postoperative pulmonary complications, patient satisfaction, and economic impacts. These represent important areas for future investigation. We are currently designing a larger prospective study that will incorporate these outcomes, including comprehensive respiratory function assessment and healthcare utilization analysis.

Regarding dosing simplification: The reviewer's observation about SMM-based calculations is astute. By using directly measured muscle mass rather than calculated parameters like ideal or adjusted body weight, we eliminate potential calculation errors and provide more intuitive dosing guidance for clinicians.