postoperative pulmonary complications (PPCs) compared with propofol-based total intravenous anesthesia (TIVA). We appreciate the author's observation which is really an eye-opener and thought-provoking considering the recent promotion of TIVA based on the environmental impact of inhalational anesthesia.[2] After thorough evaluation of the study, we would like to raise certain points for further clarification and better understanding of the outcomes of this study.

First, the authors have used either one-lung ventilation (OLV) or two-lung ventilation (TLV) according to the surgeon's preference. Hypoxia is a well-known part of OLV. We are curious to know whether any patient suffered moderate-to-severe hypoxia, and if so, the duration of those events. This is very relevant as intraoperative hypoxia, especially if moderate to severe and sustained, might impact the incidence of PPCs. It is essential to preserve hypoxic pulmonary vasoconstriction (HPV) during the period of OLV which was on average 2 to 3 hours in this study. Although it is well-known that inhalational anesthetics can impact HPV, TIVA does not. A separate subgroup analysis should have been done between each agent to identify the actual impact of individual agents on PPCs. Also, OLV is known to raise the airway pressure which might have impacted the incidence of PPCs compared to TLV. Another subgroup analysis also should have been done to evaluate the impact of the ventilation techniques on PPCs.

Second, the literature related to the anti-inflammatory impact of the inhalational anesthesia and TIVA is conflicting. Propofol was found to release higher concentrations of proinflammatory cytokines (interleukin 6 [IL6], interleukin 6 [IL8], tumor necrosis factor alpha [TNF-α], etc) compared to sevoflurane, which indicates inhalational agents have an anti-inflammatory property that possibly has impacted the incidence of PPCs, as suggested by the authors.[3] In contrast, some recent evidence did not show any difference in the anti-inflammatory response as well as reduction in the incidence of PPCs between these 2 techniques.[4,5] We are a bit confused here about which one to take related to the reduction of PPCs.

Although we do appreciate the commendable work by the authors on this unsolved mystery especially when recent evidence is indicating that green anesthesia initiative-driven use of propofol-based TIVA may lead to higher mortality and inferior postoperative outcomes,[6] we think some clarification in these points are worthy to solve the ongoing dispute related to this matter.

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REFERENCES

1. Zhang YT, Chen Y, Shang KX, Yu H, Li XF, Yu H. Effect of volatile anesthesia versus intravenous anesthesia on postoperative pulmonary complications in patients undergoing minimally invasive esophagectomy: a randomised clinical trial. *Anesth Analg*. 2024;139:571–580.
2. American Society of Anesthesiologist. Green anesthesia initiative. Accessed February 24, 2024. https://www.asahq.org/education-and-career/asa-medical-student-component/green-anesthesia-initiative.
3. Schilling T, Kozian A, Senturk M, et al. Effects of volatile and intravenous anesthesia on the alveolar and systemic inflammatory response in thoracic surgical patients. *Anesthesiology*. 2011;115:65–74.
4. Yuan JL, Kang K, Li B, et al. The effects of sevoflurane vs. propofol for inflammatory responses in patients undergoing lung resection: a meta-analysis of randomized controlled trials. *Front Surg*. 2021;8:692734.
5. He LL, Li XF, Jiang JL, et al. Effect of volatile anesthesia versus total intravenous anesthesia on postoperative pulmonary complications in patients undergoing cardiac surgery: a randomized clinical trial. *J Cardiothorac Vasc Anesth*. 2022;36:3758–3765.
6. Hasselager RP, Hallas J, Gögenur I. Inhalation anaesthesia compared with total intravenous anaesthesia and postoperative complications in colorectal cancer surgery: an observational registry-based study. *Br J Anaesth*. 2022;129:416–426.

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Predictors of Failed Spinal Anesthesia After Intrathecal Injection of Local Anesthetic for Cesarean Delivery: Are We Omitting the Omission Variable Bias?

To the Editor

We read with interest the recently published article titled "The Incidence and Predictors of Failed Spinal Anesthesia After Intrathecal Injection of Local Anesthetic for Cesarean Section: A Single-Center, 9-Year Retrospective Review" by Jin et al.[1] In this retrospective review, the authors aimed to evaluate the incidence of failed spinal anesthesia (SA) for cesarean section (CS) and its predictors. They concluded that previous CS was the most significant predictor of spinal failure. Under the study conditions, we agree that it is a valid conclusion, but there is more to it than meets the eye.

First, not many readers would completely agree with the conclusion that a history of CS by itself could be the most significant predictor of spinal failure (within 1 hour of initiation of SA). However, a previous CS in the presence of an inadequate spinal level at the beginning of the surgery may lead to a failure. That brings us to the most important independent variable—sensory-motor level of SA at the beginning of the surgery, which was not included in the multivariate and dominance analysis model. An inadequate sensory-motor level, despite adequate local anesthetic dose, due to various reasons, at the beginning of surgery would definitely affect the density of blockade after SA and, therefore, would influence the incidence of failed SA irrespective of the history of CS. Because this important independent variable was not included in the model, what we observe here could be the omission variable bias (OVB) that occurs when a regression model fails to include one or more important independent variables.[2] The omitted variable could be a confounding and or an interacting variable.

By omitting such a variable, the model may accidentally attribute the effect of the omitted variable (level of SA at the beginning of the surgery) to other included variables, such as the previous CS in this case (Figure). This has the potential to alter the conclusion as an incomplete regression model could show a statistically significant association between the predictors and the outcome when the true relationship is noncausal.[2] For instance, if the sensory-motor level at the beginning of the surgery had been included in the analysis, the authors could have estimated the true effect of the previous CS over the SA failure. But more importantly, the authors could have estimated the true effect of the sensory-motor level at the beginning of the surgery over the SA failure. This would shift the focus back to the basics of SA—the importance of assessing the sensory-motor level after a subarachnoid blockade before proceeding with the surgery.[3] The dominance analysis that is usually performed to estimate the relative importance of the population predictors, as clearly pointed by Budescu,[4] is conditional on the identification of the correct regression model in the first place. It is worth highlighting Budescu's remarks on model selection when the author, for the first time, described the dominance analysis: "If the model (regression) is mis-specified, the results of the dominance analysis will also be incorrect and may cause problems especially if certain predictors are incorrectly omitted from the model."[4]

Retrospective reviews, especially regression analysis, are associated with inherent limitations in the form of bias, confounding, and interactions.[5,6] In some cases, it is not possible to include all important variables for genuine reasons associated with retrospective reviews. For example, in this study, the sensory-motor level after the subarachnoid blockade was not available in the records. In such cases, the authors may discuss the possibility of whether the omitted variable is a confounder and or an effect modifier. If this is a possibility, there are a few measures the authors can take to mitigate the OVB. A detailed discussion of such measures[2] is beyond the scope of this brief communication but we should be aware that such provisions—using control variables and proxies to name a few—are available. If these measures fail, the authors may attempt to predict the direction in which the estimates are biased (over or underestimated). That said, we congratulate the authors for this important work. We believe this letter will draw attention to the significance of OVB in regression analysis and its impact on the interpretation of results and conclusions.

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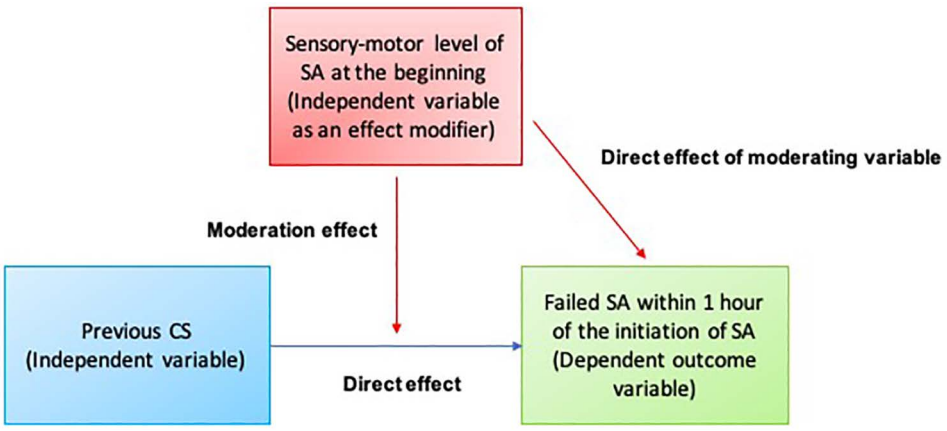

Figure. Possible moderation/interaction effect of an independent variable—sensory-motor level of SA at the beginning of the surgery—on the effect of previous CS over the outcome variable. Omission of this effect modifier in this case may induce OVB in the parameter estimate. CS indicates cesarean section; OVB, omission variable bias; SA, spinal anesthesia.

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REFERENCES

1. Jin SY, Munro A, Aidemouni M, McKeen DM, Uppal V. The incidence and predictors of failed spinal anesthesia after intrathecal injection of local anesthetic for cesarean delivery: a single-center, 9-year retrospective review. *Anesth Analg*. 2024;138:430–437.
2. Wilms R, Mäthner E, Winnen L, Lanwehr R. Omitted variable bias: a threat to estimating causal relationships. *Methods Psychol*. 2021;5:100075.
3. Keita H, Deruelle P, Bouvet L, et al; French Practice Bulletin Taskforce: "Préconisations - insuffisance d'analgésie au cours de la césarienne sous anesthésie périmédullaire: prévention - prise en charge immédiate et différée". Raising awareness to prevent, recognise and manage acute pain during caesarean delivery: the French Practice Bulletin. *Anaesth Crit Care Pain Med*. 2021;40:100934.
4. Budescu DV. Dominance analysis: a new approach to the problem of relative importance of predictors in multiple regression. *Psychol Bull*. 1993;114:542–551.
5. Vetter TR, Mascha EJ. Bias, confounding, and interaction: lions and tigers, and bears, Oh My! *Anesth Analg*. 2017;125:1042–1048.
6. Senthilnathan M, Ravi R, Sivakumar RK, Majella MG, Chidambaram V. Aspirin use, mechanical ventilation, and inhospital mortality in coronavirus disease 2019: Are we missing something? *Anesth Analg*. 2021;133:e31–e33.

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In Response

We thank Ravi et al[1] for their thoughtful response to our article "The Incidence and Predictors of Failed Spinal Anesthesia After Intrathecal Injection of Local Anesthetic for Cesarean Delivery: A Single-Centre, 9-Year Retrospective Review." They have brought up concerns about not including the sensory-motor level of spinal anesthesia in our regression model when assessing for predictors of failed spinal anesthesia.[2] Ravi et al suggest that "inadequate spinal level" could be a confounding or interacting variable and should have been included in the predictive model. We acknowledge the reasonableness of their critique and agree that the sensory-motor level of spinal anesthesia is an important independent variable. However, we feel it is unlikely a confounding variable between previous cesarean delivery and failed spinal anesthesia due to the reasons outlined below.

First, any retrospective study assessing the association between a predictor and an outcome is at risk of omitting an important confounding variable. Naturally, the list of possible confounding variables is near-infinite, so the onus is on researchers to draw on their content knowledge to identify them as best as possible.[3] We believe that although "inadequate spinal level" is a predictor of failed spinal anesthesia, it is unrelated to "previous cesarean delivery." Therefore, it does not fit the definition of a confounder.[3] Second, it is challenging to incorporate inadequate sensory-motor spinal level into a statistical model considering the subjectivity in testing and lack of consensus on the best testing method.[4,5]

Third, we believe that the sensory-motor spinal level is unlikely to be different in parturient with previous cesarean delivery and first cesarean delivery in our data due to the following reasons. At our tertiary care stand-alone obstetric, high-risk academic hospital, obstetric anesthesia care is provided by a specialized physician anesthesiologist with a relatively homogeneous practice. Most anesthesiologists use 12 mg hyperbaric bupivacaine with 10 µg fentanyl and 100 µg preservative-free morphine unless indicated otherwise, for example, extremes of patient height or gestational age.[6] It is our standard practice to perform a sensory-motor evaluation of the spinal anesthesia before the start of the surgery.

While the method of sensory and motor block testing was not consistently documented in our records, its practice is consistently applied. Our spinal anesthetic block testing involves pinprick testing to the T6 dermatomal level and verification testing with cold to the T4 dermatome level in the event of uncertainty. In addition, the motor block is routinely assessed as a surrogate measure of block density. Finally, obstetricians always perform a skin pinch test (Alis test) at the level of the incision area before the start of the surgery. If after 10 to 15 minutes of spinal anesthetic injection, sensory dermatomal block remains below the T4 to T6 level, and the motor block is inadequate, our standard of care is not to proceed with surgical incision and perform an alternate anesthetic. The alternate anesthetic can be a combined spinal epidural or de novo epidural catheter, depending on the patient and procedural factors or general anesthesia for more urgent surgery. It is unlikely that surgery would proceed without evidence of adequate sensory-motor blockade.

We have no reason to believe that block height levels would differ between patients having primary or repeat cesarean deliveries. Yet, our study suggests that those having repeat cesarean deliveries are at higher risk for spinal anesthesia failure. We hypothesized that scarring from previous deliveries might