Original Article

Development and validation of a prognostic model for postoperative hypotension in patients receiving epidural analgesia

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Abstract

Background and Aims: Postoperative hypotension is common in adults receiving epidural analgesia. Although risk factors have been reported in the literature, prognostic models have not been developed or validated. We aimed to develop and validate a multivariable, prognostic model for postoperative hypotension in patients receiving epidural analgesia.

Material and Methods: We retrieved retrospective cohort data of adults undergoing abdominal or thoracic surgery at five hospitals between 2014 and 2023 who received epidural analgesia for at least 24 hours after surgery. A systematic literature search helped define *a priori* candidate exposures. The primary outcome was postoperative hypotension during the first 72 hours after surgery. Multiple logistic regression was performed to evaluate a multivariable model. Exposures identified as statistically significant were used for logistic regression, linear discriminant analysis, and decision-tree model of random forest. Classification error was used to compare models, and variable importance was used for random forest analysis.

Results: In total, 829 participants were included. The incidence of postoperative hypotension was 38.8%. Multivariable analysis identified the following independent prognostic factors: male sex, white race, body mass index, intraoperative hypotension, use of arterial line, bupivacaine concentration of 0.125% (vs. lower concentrations), and anesthesia duration. The error misclassification rate was 67% for multiple logistic regression, 27% for linear discriminant analysis, and 33.4% for random forest model.

Conclusion: Using retrospective cohort data, a prognostic model of hypotension produced the best performance results using linear discriminant analysis, with an error misclassification rate of 27%. Further studies are required to perform model optimization for future clinical use.

Keywords: Epidural analgesia, hypotension, prognostic model, surgery

Introduction

Epidural analgesia is an important modality after abdominal or thoracic surgeries and is also included in enhanced recovery guidelines.[1,2] Its benefits include an opioid-sparing effect, a reduced risk of respiratory and neurologic complications, and the prolongation of pain relief beyond the first 24 postoperative hours.[3,4]

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Access this article online

Quick Response Code:

Website: https://journals.lww.com/joacp

DOI: 10.4103/joacp.joacp_88_24

How to cite this article: Guerra-Londono CE, Vasquez ET, Riveros E, Noori E, Greiver D, Pillai S, *et al*. Development and validation of a prognostic model for postoperative hypotension in patients receiving epidural analgesia. J Anaesthesiol Clin Pharmacol 2025;41:286-91.

Submitted: 25-Feb-2024 **Revised:** 27-May-2024
Accepted: 05-Jun-2024 **Published:** 24-Mar-2025

Despite these clinical benefits, hypotension occurs in 30%–60% of patients receiving epidural analgesia,[5,6] more frequently than with other forms of analgesia.[7-9] Due to a strong association with harm, postoperative hypotension has been defined as any systolic blood pressure less than 90 mmHg.[6,10] The occurrence of hypotension is troubling as it often leads to a temporary interruption or a decreased dose of analgesic drugs, which may reduce their efficacy.

Understanding an individual's risk of hypotension can be useful for the patient and the anesthesiologist, particularly prior to placing an epidural catheter. In previous studies, several demographic (e.g., age and sex), surgical (e.g., type of surgery), and anesthetic factors (e.g., local anesthetic concentration and level of epidural catheter placement) have been associated with hypotension during epidural analgesia or anesthesia.[11,12] To our knowledge, a validated multivariable model specific for postoperative hypotension in patients receiving epidural analgesia has not been reported. Thus, we aimed to develop and validate a prognostic model of postoperative hypotension in adults receiving epidural analgesia after abdominal or thoracic surgery.

Material and Methods

The current study was approved and conducted in accordance with the ethical standards of the institutional review board (IRB # 15233) and the Helsinki Declaration of 1975, as revised in 2000. It is reported according to the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) statement.[13]

A retrospective cohort study was conducted at our healthcare system. This study included available electronic medical records of adults undergoing abdominal or thoracic surgeries requiring inpatient admission at any of the five hospitals between January 1, 2014, and January 20, 2023, and who received epidural analgesia as a component of their postoperative recovery. We excluded pregnant individuals, those undergoing epidural analgesia for non-surgical indications (e.g., chest trauma), and those who received an epidural only for intraoperative purposes. To ensure that participants were sufficiently exposed to epidural analgesia, we also excluded patients in whom the epidural catheter was removed in the first 24 hours. Participants in whom the epidural failed (unable to block at least two dermatomes bilaterally) were also excluded. Initially, participants were identified electronically using structured query language and then screened individually by the investigators. Epidural analgesia was performed typically using a landmark technique and dosed according to the local practices of each center, which included different concentrations of local anesthetic ranging from 0.0625% to 0.125%, with or without the use of epidural opioids. Electronic medical records were then reviewed for the first 72 postoperative hours.

The primary outcome of the model was postoperative hypotension during the first 72 hours after the end of anesthesia. This was defined as any systolic or mean arterial blood pressure less than 90 or 65 mmHg, respectively.[10]

A priori exposures were defined with the help of a systematic literature search in Medline, Scopus, Embase, and the Cochrane Library by using the terms "epidural analgesia," "hypotension," and "postoperative period." This was performed by an experienced librarian. After the screening of titles and abstracts, we reviewed 78 available publications that met the search criteria (see supplementary data). Additional exposures were hypothesized from indirect evidence or by clinical experience. Altogether, we included demographic/anthropometric (age, sex, self-identified race, body mass index), laboratory (hemoglobin, albumin) medical (cardiovascular disease and medications, diabetes, malnutrition, chronic kidney disease), surgical (center, type of surgery, invasiveness of surgery, estimated blood loss), and epidural or anesthetic exposures (ASA physical status, epidural placement level, local anesthetic concentration, type of infusion, preoperative blood pressure, and intraoperative hypotension). Intraoperative hypotension was defined as mean arterial pressure <65 mmHg for at least 5 minutes).[14] Considering that invasive blood pressure monitoring could affect the incidence and management of hypotension, we also included arterial line use (intra and postoperative) in our exposures. Data accuracy for any given exposure was assessed during and after data collection.

As a secondary objective, we planned to describe the use of epidural anesthesia in the participants, for which we also collected the duration of epidural analgesia, the time of the first episode of postoperative hypotension, and the need to discontinue (at least temporarily) the epidural due to hypotension.

According to Harrel *et al.*,[15] no more than $m/10$ predictor degrees of freedom parameters (p) should be examined to fit a multiple regression model, where m is the number of events (i.e., patients with hypotension). To study up to 24 predictors, we estimated that at least 800 patients would be required, assuming that the incidence of postoperative hypotension would be at least 30%. During a preliminary analysis, the sample size arrived at 728 participants. To perform model validation, the IRB protocol was amended to extend the dates of inclusion and maximize our sample size. The initial data query retrieved 1238 records of adults

meeting the search criteria at the five hospitals from our health system. Of these, only 829 were confirmed to meet the inclusion criteria after screening by the investigators. The details of the screening process are described in the flow diagram [Figure 1].

Whenever absent, hemoglobin values were imputed as 12 g/dL for women and 13 g/dL for men. No other imputation of data was performed.

Statistical analysis

Multiple logistic regression was performed to evaluate a multivariable model for postoperative hypotension at 72 hours. Statistical significance was defined as a *P* value less than 0.05. Exposures identified as statistically significant in the logistic regression model were used for linear discriminant analysis and the decision-tree model of random forest via simple cross-validation. The validation set was limited to 100 subjects to avoid reducing the observations to train the model. Classification error was used to compare models, and variable importance was used for random forest analysis. Statistical analyses were performed with R Studio version 4.2.2 (https://R-project.org/).

Results

The mean (SD) age of patients in our sample was 60 (13.58) years. Most participants were female 54.9% (n = 455) and of white race 67.6% (n = 560). Mean (SD) preoperative systolic and diastolic blood pressures were 129 (20) and 75.2 (13.9) mmHg, respectively. The most common ASA status was III (75%), followed by I and II (18.8%) and IV (6.2%). Epidural bupivacaine was formulated in a concentration of 0.125%, 0.1%, and 0.0625% in 85.5%, 2.5%, and 11.9% of the participants, respectively. A continuous infusion (without a patient-controlled modality) was used almost exclusively in our sample, with 97% of the sample receiving this mode of administration. Overall, epidural opioids (i.e., fentanyl) were administered in 12.8% of the patients. In all cases, epidural opioids were additives to the local anesthetics. During model development, we noted that albumin concentration was not available for most patients, for which this variable was removed. No patients in our sample received epidural clonidine or dexmedetomidine, and these variables were also removed.

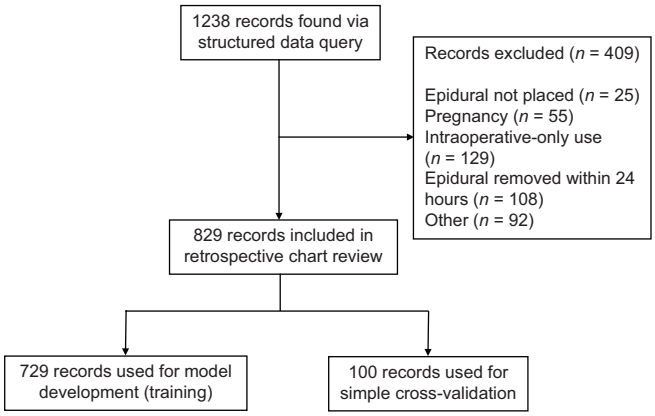

Figure 1: Flow chart diagram of the selection of patients in the study

Overall, the incidence of postoperative hypotension in our sample was 38.8%. Of the patients experiencing postoperative hypotension, most of them (87.9%) experienced the first episode during the first 24 hours after surgery, followed by 9.32% at 25–48 h, and 2.79% at 29–72 h. In addition, 32.9% of patients with postoperative hypotension required at least a temporary discontinuation of the epidural analgesia infusion.

Simple cross-validation was employed by dividing the sample into training (n = 729) and validation (n = 100) sets. The multiple regression model identified some exposures for the outcome variable of postoperative hypotension [Table 1]. Out of the variables associated with the outcome, intraoperative hypotension, white race, and arterial line use were inversely related to postoperative hypotension, whereas a bupivacaine concentration of 0.125% was associated with postoperative hypotension when compared with lower concentrations (i.e., 0.0625% and 0.1%). As continuous variables, body mass index and duration of anesthesia were significantly associated with the outcome, but the effect was small, as reflected by both OR being close to 1. In addition, white race was associated with a reduced likelihood of postoperative hypotension.

Using a multiple logistic regression model, we found that the misclassification error rate was high at 67%. To further explore a linear model based on Bayesian probability, a linear discriminant model was used. The variables included in the model were the same as identified as significant by the linear regression model. In contrast to the multiple logistic regression model, the misclassification error rate was 27%. Considering

Table 1: Multiple logistic regression model for 72-hour hypotension

Independent exposure	Odds ratio (95% Confidence Limit)	*P*
Body mass index	1.1 (1.06–1.013)	0.002
Male sex	2.19 (1.56–3.1)	<0.0001
White race	0.46 (0.30–0.71)	0.0003
Intraoperative hypotension	0.54 (0.38–0.77)	0.0006
Arterial line use	0.38 (0.27–0.54)	<0.0001
Bupivacaine concentration of 0.125%	2.19 (1.34–3.59)	0.0018
Anesthesia duration	0.998 (0.997–0.999)	0.001

that the goal of the study was to find a good prediction model, linear discriminant analysis outperformed multiple logistic regression. The overall classification performance can be observed on the receiver operating characteristic (ROC) curve of the model [Figure 2]. Finally, we explored the performance of a nonlinear method to fit the data by using a random forest model. The error rate observed with the model was 33.4%, higher than the linear discriminant analysis but better compared to logistic regression. Regarding variable importance, arterial line use, intraoperative hypotension, and body mass index contributed the most to the accuracy of the model. On the contrary, anesthesia duration, body mass index, and arterial line use had the highest contribution to node purity in the model. According to the reported coefficients, the formula based on latent discriminant analysis is as follows:

Y (hypotension or no_change) =0.378*BMI +0.880351125*SexMale - 1.097845987*RaceWhite - 0.976637838*Aline - 0.658459114*IntraopHypotension - 0.002847539*AnesthesiaDuration + 0.857*bupi_0.125%.

Discussion

This study found that the most important prognostic factors for postoperative hypotension in adults receiving epidural analgesia after abdominal or thoracic surgeries were sex, body mass index, race, perioperative arterial line use, intraoperative hypotension, bupivacaine concentration, and anesthesia duration. Based on error misclassification rates, we found that a model based on latent discriminant analysis performed better than logistic regression or random forest models. We consider our findings to be relevant as they represent an initial step toward predicting an individual's risk of postoperative hypotension when receiving epidural analgesia.

Some of the exposures (e.g., body mass index, sex, and bupivacaine concentration) found in our multivariable analysis had been previously reported in studies concerning intra

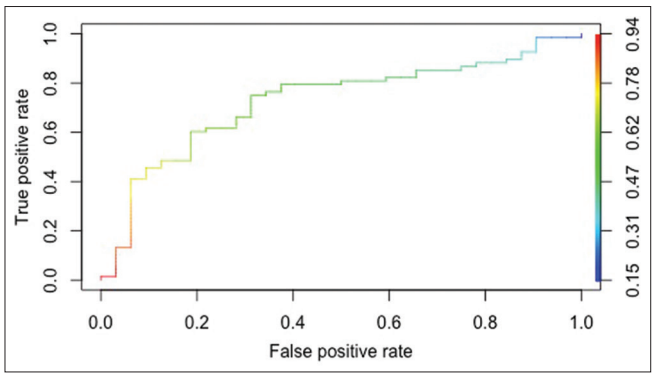

Figure 2: Receiver operating characteristic curve for the latent discriminant analysis model

or postoperative hypotension in patients receiving epidural analgesia.[12,16,17] In contrast, our study also found that arterial line use and intraoperative hypotension were inversely associated with postoperative hypotension. This finding may be related to the fact that continuous blood pressure monitoring can reduce intraoperative hypotension[18] or that intraoperative drops in blood pressure may trigger early and sustained interventions that reduce the risk of postoperative hypotension. Intraoperative hypotension is of utmost concern among anesthesiologists and has been independently associated with worse postoperative mortality.[19]

Linear discriminant analysis (LDA) outperformed logistic regression in prediction accuracy for postoperative hypotension. This method has been shown to be more stable than logistic regression. Model stability has been attributed to the fact that LDA models the distribution of each exposure individually in each of the outcome classes and then uses Bayes' theorem to calculate probability.[20] On the contrary, although the classification error rate of the random forest model was lower than the error calculated for multiple regression, it was still outperformed by LDA. This finding suggests that a linear function underlying data modeling in our study has a better bias-variance trade-off than non-linear approaches. Furthermore, the less-than-optimal performance of linear models may be due to the lack of inclusion of some unidentified or unavailable variables (e.g., dermatomal spread). Future research should focus on identifying or including such exposures. Overall, LDA is a good prognostic model for postoperative hypotension with a correct classification rate of 73% and an acceptable ROC curve.

During the selection of candidate exposures, we found important limitations in the existing evidence. For instance, we noted that hypotension was rarely a prespecified study outcome and rather reported as a side effect. Moreover, most studies lacked a definition of hypotension or used different definitions, such as a systolic blood pressure decrease larger than 20 mmHg from baseline.[21] Finally, many exposures were reported only after unadjusted analysis, likely explaining why they were not present in our final model.

Epidural analgesia remains popular for adults undergoing major abdominal or thoracic surgery because it can provide continuous and titratable analgesia beyond the first postoperative day.[22] Unfortunately, the sympathetic blockade associated with this technique often results in hypotension.[22] As epidural catheters are inserted prior to surgery, predicting hypotension at this stage is clinically meaningful because it informs patients and clinicians in a timely fashion.

Our study has several strengths. First, it should be noted that exposures were defined *a priori* via a systematic literature search

and included patient, surgical, procedural, and pharmacologic variables. Second, we used data from different hospitals within our network to increase the heterogeneity of the sample and include differences in clinical practice (e.g., local anesthetic concentration and neuraxial opioids). Moreover, the incidence of hypotension and several exposures found in our study were consistent with the literature.[22] Third, we used known methods to arrive at the final model and compared the performance of different linear and non-linear methods for simple cross-validation.

We are aware of several limitations in our study. First, the source of data was retrospective, which can be prone to selection and reporting bias. Fortunately, vital signs are routinely collected and electronically recorded in the medical record, allowing us to use objective definitions of hypotension. Second, while we could not standardize the frequency of blood pressure monitoring, we accounted for planned continuous perioperative blood pressure monitoring by including the use of arterial lines and the presence of intraoperative hypotension. Nonetheless, we know disease severity and surgical complexity are embedded in the decision to use continuous invasive blood pressure monitoring. Third, given that model development was prioritized in our study, the total sample used for the validation set was significantly affected.

Hypotension is multifactorial in nature.[14] As such, it is possible that unlisted factors, such as postoperative fluid management and dermatomal coverage, could have played a role in the incidence of hypotension.[23] It must be noted that we included multiple exposures, including type of surgery, invasiveness, ASA score, and comorbidity, as potential predictors, but none of these remained in the final model.

Conclusion

This study developed and validated a multivariable prognostic model for postoperative hypotension during the first 72 hours in patients receiving epidural analgesia after abdominal or thoracic surgery was developed and validated. The use of latent discriminant analysis provided the best performance, with an error misclassification rate of 27%. Arterial line use, intraoperative hypotension, and body mass index contributed the most to the accuracy of the model. Future studies can help optimize our current model, increase the validation sample, and provide more accurate clinical guidance.

Acknowledgements

A preliminary analysis was presented at the American Society of Anesthesiologists Annual Meeting, New Orleans on October 22nd, 2022.

Ethical statement

The present study was approved by the Institutional Review Board at Henry Ford Health (Detroit, Michigan, USA) on November 19th, 2021, under IRB# 15233, as notified by the IRB's Chairman (Jonathan K Ehrman, Ph.D). An amendment for extension of the timeframe of inclusion was also approved on January 18th, 2023.

Financial support and sponsorship

All funding required for this study was provided by the Department of Anesthesiology, Pain Management, and Perioperative Medicine at Henry Ford Health and the Department of Anesthesiology and Perioperative Medicine at the Medical College of Georgia, Augusta, Georgia, USA.

Conflicts of interest

Dr. Guerra-Londono declares investigator-initiated grant funding from GE healthcare (unrelated to the topic of this manuscript) and travel arrangements and site primary investigator duties with Edwards Lifesciences for an ongoing clinical trial (unrelated to the topic of this manuscript). Other authors declare no conflicts of interest.

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