Optimization of anesthetic decision-making in ERAS using Bayesian network

Yuwen Chen1, Yiziting Zhu2, Kunhua Zhong1, Zhiyong Yang3, Yujie Li3, Xin Shu3, Dandan Wang3, Peng Deng3, Xuehong Bai3, Jianteng Gu3, Kaizhi Lu3, Ju Zhang1, Lei Zhao4, Tao Zhu5, Ke Wei2* and Bin Yi3*

1Chongqing Institute of Green and Intelligent Technology, Chinese Academy of Sciences (CAS), Chongqing, China, 2Department of Anesthesiology, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China, 3Department of Anesthesiology, Southwest Hospital, Third Military Medical University, Chongqing, China, 4Department of Anesthesiology, Xuanwu Hospital, Capital Medical University, Beijing, China, 5Department of Anesthesiology, West China Hospital of Sichuan University, Chengdu, China

Enhanced recovery after surgery (ERAS) can accelerate patient recovery. However, little research has been done on optimizing the ERAS-related measures and how the measures interact with each other. The Bayesian network (BN) is a graphical model that describes the dependencies between variables and is also a model for uncertainty reasoning. In this study, we aimed to develop a method for optimizing anesthetic decisions in ERAS and then investigate the relationship between anesthetic decisions and outcomes. First, assuming that the indicators used were independent, the effects of combinations of single indicators were analyzed based on BN. Additionally, the impact indicators for outcomes were selected with statistical tests. Then, based on the previously selected indicators, the Bayesian network was constructed using the proposed structure learning method based on Strongly Connected Components (SCC) Local Structure determination by Hill Climbing Twice (LSHCT) and adjusted according to the expert’s knowledge. Finally, the relationship is analyzed. The proposed method is validated by the real clinical data of patients with benign gynecological tumors from 3 hospitals in China. Postoperative length of stay (LOS) and total cost (TC) were chosen as the outcomes. Experimental results show that the ERAS protocol has some pivotal indicators influencing LOS and TC. Identifying the relationship between these indicators can help anesthesiologists optimize the ERAS protocol and make individualized decisions.

KEYWORDS
Bayesian network, enhanced recovery after surgery, decision-making, gynecological tumor, machine learning
Introduction

Enhanced recovery after surgery (ERAS) is a clinical strategy designed to reduce patients’ stress responses to surgery and preserve their physiological state as much as possible. It includes a series of medical decisions in the perioperative period that can facilitate the rapid recovery of patients undergoing surgery. Implementing the ERAS protocol can result in shorter hospital stays, less postoperative pain, lower complication rates, and earlier initiation of feeding and ambulation (1, 2). For patients with different demographic characteristics, different treatment options, and postoperative complications, cooperation and specialization of multiple departments are required (3). ERAS has been applied in many departments (4–8), and previous ERAS studies have mainly verified its efficacy and safety of the ERAS protocol. Meanwhile, the feasibility and safety of monotherapy or equivalent measures have been investigated. A few studies explored the interaction between various indicators in ERAS and optimizing ERAS strategies.

Anesthetic decision-making is an integral part of the perioperative period and essential to ERAS implementation (9). The anesthesia decisions mainly involved intraoperative management and postoperative analgesia, such as intraoperative blood pressure, urine volume, non-steroidal drugs, and compound nerve blocks. There are significant links between patient recovery and anesthesia (10, 11). For gynecologic surgeries, the choice of anesthetic can influence postoperative outcomes. Propofol is known to reduce the incidence of nausea and vomiting after laparoscopic gynecological operations (12, 13), as well as other studies related to pain control (14). However, no studies have systematically assessed the effects of a series of anesthesia decision indicators, the interaction between these indicators, or the overall influence of indicator combinations. In addition, some of the indicators may not be necessary. In clinical practice, optimizing the anesthetic part of ERAS and recognizing the interaction can enhance decision-making efficiency.

Optimizing the anesthetic decision-making in the ERAS protocol can be viewed as a multivariate analysis to determine the indicators that have a greater impact on the patient's prognosis and recommend their combinations. For previous studies, traditional statistical methods mainly use multivariate analysis and logistic regression analysis to find indicators with statistical differences. However, the variable relationship in clinical decision-making is complex and uncertain, making it prone to problems such as insufficient fitting and low accuracy. Bayesian Network (BN) is a type of machine learning (ML) that has been applied to the medical field, such as disease diagnosis (15, 16), risk prediction (17, 18). Its core lies in probabilistic methods (19, 20). BN is a graphical model that describes the dependencies between data variables and is also a model for uncertainty reasoning. Based on probabilistic reasoning, BN can identify causal relationships between nodes and give the conditional probability of each node. Therefore, BN has advantages when variables have a relationship or uncertainty (21, 22). There is a lot of room for developing the BN algorithm for anesthesia decision-making in ERAS.

In this study, we aimed to develop a method for anesthesia decision optimization in ERAS and then investigate the relationship between anesthetic decisions and outcomes in patients with benign gynecological tumors based on the proposed method. By finding impact indicators in the anesthetic part of ERAS, we conducted a BN analysis of these indicators and made recommendations to improve the outcomes.

Method description

Our method for anesthesia decision optimization in ERAS consists of two main steps: (1) extraction of key indicators of anesthesia decision making and (2) building a decision graph based on the anesthesia Bayesian decision intervention model. As shown in Figure 1, we first use Bayesian network and statistical tests to select indicators. Then, we propose a Bayesian decision intervention model for anesthesia based on the LSHCT method to construct a decision graph. Python 3.9 was used to construct the BN model.

The model is described in detail as follows:

Extraction of key indicators of anesthesia decision making

Now, machine learning has been widely used in the field of computers, which can be optimized. They are applied to things
such as Web service and feature extraction, including Quality-of-Service (QoS) prediction (23), improving the quality of online streaming feature selection (OSFS) with missing data (24), handling the data streams with a varying feature space based on Generative Learning with Streaming Capricious (GLSC) (25), etc. ML can also be used in the optimization of medical decision-making. In this study, we chose the Bayesian Network (BN). BN is a graphical model to describe the dependency relationship between data variables, as well as a model for uncertainty reasoning. BN provides a convenient framework for people to express the dependency relationship, making the logic of uncertainty reasoning clearer and more understandable. From a statistical point of view, BN is a graphical probability model. Pearl et al. from the University of California proposed the Bayesian Network model for the first time in 1988 (26). They applied BN to the expert system successfully, making it a popular method for uncertain expert knowledge and reasoning.

BN consists of two parts: network structure and network parameters. The network structure of BN is a Directed Acyclic Graph (DAG). Each node in the DAG represents a variable in a specific domain. The directed arc between nodes represents the dependency relationship among nodes, which is the qualitative characterization of the relationship between nodes. Each node has a conditional probability distribution function associated with it (the node without a parent node is represented as a prior distribution function), namely the network parameter, which quantitatively describes the dependency relationship between the variable node and its parent node. If the variable is discrete, the network parameters are represented as conditional probability tables of this node for a given parent node. In BN, there is no specific input node or output node, and any node can be used as an input node or output node.

Definition: a directed acyclic graph that meets the following four conditions is called the Bayesian Network (27):

1. There is a set of variables \( V = \{X_i\} \), \( i = 1, 2, \cdots, n \), and there is the set of directed edges between the corresponding nodes of variables \( E \);
2. The value of each variable can be either discrete or continuous;
3. A directed acyclic graph \( G = < V, E > \) is formed by the nodes corresponding to variables and the directed edges between nodes, where \( V \) is the node-set, and \( E \) is the directed edge set, reflecting the causal dependence between nodes;
4. A conditional probability distribution table \( P(X_i|\text{Pa}(X_i)) \) is corresponding to each node \( X_i \) and its parent node set \( \text{Pa}(X_i) \), and it satisfies \( P(X_1, X_2, \cdots, X_n) = \prod_{i=1}^{n} P(X_i|\text{Pa}(X_i)) \).

The BN has been widely used in clinical diagnosis (28) and gene analysis (29). The main research content of the BN includes structure learning, parameter learning, and inference. Among them, structure learning is the basis of parameter learning and inference. BN structure learning refers to using the data sample set and combining the prior knowledge as much as possible to obtain the optimal topological structure. Learning BNs from data is a special case of ML. The approximate learning methods of learning BN structure from complete data include the conditional independence test-based method, the score search-based method, and the hybrid method (30). The method based on score search regards network structure learning as an optimization problem, and its goal is to search for the network structure with the highest score. With the increasing of the nodes number, the network structure space to be searched increases exponentially, which has been proved to be an NP-Hard problem (31). Heuristic search is usually used, which makes it easy to fall into an optimal local solution. This study proposed a new structural learning method based on the idea of divide and conquer.

The data of the enrolled patients were used to construct a simple BN, which assumed that the indicators used were independent of each other, as shown in Figure 2. The BN parameters were learned by the Bayesian estimation method with the clinical case dataset. The effects of combinations of single indicators on outcomes were analyzed, and the method gave the groups’ results and their probabilities. The probability of state-0 (optimal state) of the outcome node in the conditional probability table was ranked, and the combinations of values of the corresponding indicators with a probability greater than 0.9 were retained. Then, the influence of single indicator nodes would be calculated. To select the indicators and their grades:

1. Sort each indicator by \( p \) values;
2. Choose the grade of each indicator that accounted for the largest proportion of postoperative LOS-state-0 and TC-state-0, where LOS, where LOS and TC are the abbreviations of “length of stay” and “total cost,” respectively, and state-0 is the optimal state of corresponding indicators;
3. Combined the indicators with specific grades starting from the one with the smallest \( P \) value until the last one;
4. Perform a screening in the retained groups (probability > 0.9);
5. Perform a statistical test and combine the selected indicators with statistical differences.

Anesthesia Bayesian decision intervention model based on the LSHCT method

With the results of indicator selection, we combined an improved BN structure learning method based on Strongly Connected Components (SCC) Local Structure determination by Hill Climbing Twice (LSHCT) and
FIGURE 2
The analysis of indicator combination of BN structure.

expert knowledge to build a BN and optimized anesthesia decision-making in ERAS. This step used BN to analyze the relationship between the selected indicators. First, the BN structure is automatically learned from clinical data by LSHCT and then adjusted reasonably based on experts' experience.

In BN, each node represents a random variable or data indicator. In this paper, with a divide-and-conquer strategy, we proposed a novel BN structure learning method by LSHCT. This is a score-based search method, and its core idea is to split the overall construction of the BN structure into the sub-BNs construction, fusion, and revision, as shown in Figure 3.

LSHCT consists of the following steps:

1. Calculate the mutual information matrix between each pair of nodes, which is a symmetric matrix.
2. For each node, select the four nodes with the most mutual information, and build a sub-BN for these five nodes.
3. Piece together all the sub-BNs. The direction of the edge between a pair of nodes is determined by voting when both directions exist. And then, we obtained a directed graph which may not be a directed acyclic graph (DAG).
4. Search all SCC in the directed graph obtained in the previous step.
5. Convert each SCC into an undirected graph as the skeleton of the local structure. Determine the direction of the edges in the skeleton by the Hill Climbing (HC) algorithm twice. For the first time, the skeleton is used as the white list of the HC algorithm by converting each edge of the skeleton into two edges in opposite directions. For the second time, the result of our previous HC algorithm is used as the initial network structure.
6. After determining the local structure of all SCC, it is already a DAG as a whole. Taking this as the initial network structure, we further use the local search method to obtain the network structure with a maximum score as the final result.

The Bayesian Network constructed by the LSHCT method was adopted to analyze the association relationship between selected indicators. The process consists of the following steps:

Step 1: According to the above methods, select indicator sets based on p values for different outcomes.
Step 2: The corresponding data sets were constructed by integrating indicators and outcomes according to different outcomes (postoperative hospitalization duration/total cost).
Step 3: Data preprocessing (same as the first use of the BN). As all the indexes were nominal, there was no need to preprocess the data for each indicator. The outcomes are of numerical type, which we assigned to two categories based on the mean value. One feature of Bayesian networks is that they allow the presence of missing values, so we retain the missing values in the dataset.
Step 4: Learn the BN structure by the LSHCT method, and output the graph of the BN structure, namely the dependency relationship between selected indicators.

Experiment and results

Dataset

This study conducted an experiment in three hospitals in China (Southwest Hospital of Third Military Medical University, Xuan Wu Hospital of Capital Medical University, and West China Hospital of Sichuan University). According to the regulation of the People's Republic of China on the administration of human genetic resources, the collection of raw data was subject to approval by the
science and technology administrative department of the state council (AQ: 2020SQCJ7444). Ethical approval was obtained, and the informed consent requirement was waived (Certification Number: KY201936, certification number: 2019-132, and certification number: 2021-349, respectively). The registration has been completed on the website of the China Clinical Trial Registry Center (ChiCTR1900023927).

### Inclusion and exclusion criteria

Inclusion criteria were as follows: (1) age: 18–80 years old; (2) Patients who underwent laparoscopic myomectomy and bilateral uterine adnexectomy and were diagnosed as benign gynecological tumors; (3) general anesthesia (without compound another anesthesia method). Moreover, the exclusion criteria were as follows: (1) patients with severe heart, lung, and kidney diseases before the operation, ASA grade ≥ 4; (2) patients with systemic metastases of malignant tumors; patients undergoing extensive hysterectomy + omentum resection + pelvic lymph node dissection; (3) patients who were converted from laparoscopic to laparotomy during surgery; patients undergoing the surgery which involved greater than or equal to two surgical departments; (4) patients undergoing rescue measures for critical diseases such as cardiac arrest, liver failure, and anaphylactic shock during the operation; and (5) patients with a large amount of incomplete medical records.

### Patients and data collection

A dataset \( (n = 49,768, \text{surgical patients only}) \) constructed from three hospitals was used to search for patients according to inclusion and exclusion criteria. Finally, we enrolled 1,827 patients. The detailed process of data collection is shown in Figure 4. The figure shows the protocol for constructing the dataset \( (n = 49,768) \) and outputting the patients \( (n = 4,269) \) with the inclusion criteria. Then, we excluded the patients \( (n = 2,442) \) according to the exclusion criteria. Finally, we got 1,827 patients.

The information about these patients included two parts: (1) general information and perioperative data of patients: patient’s ID number, medical record number, age, height, weight, and other information such as preoperative hemoglobin (Hb), preoperative systolic blood pressure (SBP), preoperative diastolic blood pressure (DBP), preoperative mean blood pressure (MBP), length of operation, intraoperative urine volume, intraoperative colloid volume, intraoperative crystalloid volume, intraoperative blood gas times, postoperative Hb; (2) indicators related to anesthesia. We initially sorted out more than 50 questions related to anesthetic decision-making, according to previous domestic and foreign literature reports combined with the clinical practice. Through
the screening process by panels of anesthesiologists and gynecologists, we finally determined 18 indicators that obtained attention with more than 50%. The outcomes were decided as “postoperative length of stay (LOS)” and “total cost (TC).” The meaning and explanation of these indicators and outcomes are described in Table 1.

Statistical analysis of key indicators of anesthesia decision-making

Measurement data were recorded as mean ± standard deviation or median (interquartile range). A T-test or Mann–Whitney U-test was used to analyze the differences between measurement data. The chi-square or Fisher’s exact test were used to analyze the differences between counting data. All the tests were two-sided, and $P < 0.05$ was considered statistically significant. SPSS25.0 statistical software was used for analysis.

Our study ultimately analyzed 1,827 patients and grouped them according to the outcomes: LOS-state 0 ≤ 4.546 d, state 1 ≥ 4.546 d; TC-state-0 < 17,548.3355 Yuan, and state-1 ≥ 17,548.3355 Yuan. The probability that the LOS is less than 4.546 days was 62.56% (1,143/1,827), and the probability that the TC is less than 17,548.3355 Yuan was 54.02% (987/1,827).

For the general condition of the patients, most characteristics of the patients were statistically significant, except for the preoperative SBP, preoperative DBP, and preoperative MBP between LOS groups and the BMI, preoperative Hb, and preoperative DBP between TC groups, $P > 0.05$, as shown in Table 2.

Among the 18 indicators associated with anesthesia decision-making, 11 indicators, including “urine volume_length of operation_100,” “crystalloid solution: colloid solution ratio —2:1,” “whether to use dexmedetomidine,” “intraoperative SBP,” “intraoperative DBP,” “intraoperative MBP,” “intraoperative ETCO2,” “postoperative compound nerve block analgesia,” “whether to use opioids as dominance in postoperative analgesia (fentanyl)”, and “whether to use non-steroidal drugs in postoperative analgesia,” had significant differences between LOS groups, $P < 0.05$, as shown in Table 2. There were 15 indicators in TC groups that made a statistical difference, $P < 0.05$, as shown in Table 2.

Selection results of key indicators for anesthesia decision-making

There were 18 indicators in total. The BN shown in Figure 2 was used to learn model parameters based on the case dataset and then rank the indicator combinations by the state-0 (optimal state) probability of the resulting node according to the conditional probability table. We retained the combinations with a probability value > 0.9. There were 957 combinations in LOS-state-0 and 558 combinations in LOS-state 1. There were 840 combinations in state-0 and 681 groups in state-1 (sub-optimal state) for the TC group. We conducted a single indicator analysis of these groups, as shown in Tables 3, 4.

According to the combination of indicators, we got the following results: (1) for LOS group: “urine volume_length of operation_100”...
**TABLE 1** The meaning and explanation of the value of each indicator.

| Indicator                                                                 | Grading          | Meaning and explanation                                      |
|--------------------------------------------------------------------------|------------------|--------------------------------------------------------------|
| Urine volume / length of operation _100                                  | Low              | Urine volume/ length of operation < 100                     |
|                                                                          | High             | ≥ 100                                                        |
| Whether to use dexamethasone                                             | N                | No                                                           |
|                                                                          | Y                | Yes                                                          |
| Intraoperative use of sevoflurane                                        | N                | No                                                           |
|                                                                          | Y                | Yes                                                          |
| Intraoperative use of propofol                                           | N                | No                                                           |
|                                                                          | Y                | Yes                                                          |
| Crystalloid solution: colloid solution ratio – 2:1                       | Low              | No colloid solution use                                      |
|                                                                          | High             | Crystalloid solution: colloid solution ratio > 2:1           |
|                                                                          | Less             | Crystalloid solution: colloid solution ratio < 2:1           |
| Whether to use blood transfusion in 6–9 g hemoglobin                    | 0                | Whether to use blood transfusion when in [60, 90], no, in the range |
|                                                                          | 1                | Whether to use blood transfusion when in [60, 90], yes, in the range |
|                                                                          | 2                | Whether to use blood transfusion when in [60, 90], no, not, in the range |
| Whether to use the dexmedetomidine                                       | N                | No                                                           |
|                                                                          | Y                | Yes                                                          |
| Intraoperative systolic blood pressure (SBP)                             | Low              | Below 20%, compared to preoperative period                   |
|                                                                          | Normal           | −20%~+20%                                                    |
|                                                                          | High             | Above 20%                                                    |
| Intraoperative diastolic blood pressure (DBP)                            | Low              | Below 20%, compared to preoperative period                   |
|                                                                          | Normal           | −20%~+20%                                                    |
|                                                                          | High             | Above 20%                                                    |
| Intraoperative mean blood pressure (MBP)                                 | Low              | Below 20%, compared to the preoperative period               |
|                                                                          | Normal           | −20%~+20%                                                    |
|                                                                          | High             | Above 20%                                                    |
| Intraoperative ETCO₂                                                     | 0                | <35                                                          |
|                                                                          | 1                | 35–45                                                        |
|                                                                          | 2                | 45–55                                                        |
|                                                                          | 3                | 55–60                                                        |
| Positive balance                                                         | 0                | 0–500                                                        |
|                                                                          | 1                | 500–1,000                                                    |
|                                                                          | 2                | 1,000–1,500                                                  |
|                                                                          | 3                | 1,500+                                                       |
| Intraoperative use of myocardial nutritional drugs                       | N                | No                                                           |
|                                                                          | Y                | Yes                                                          |
| Intraoperative use of hemostatic                                         | N                | No                                                           |
|                                                                          | Y                | Yes                                                          |
| Postoperative compound nerve block analgesia                            | N                | No                                                           |
|                                                                          | Y                | Yes                                                          |
| Whether to use opioids as dominance in postoperative analgesia (fentanyl)| N                | No                                                           |
|                                                                          | Y                | Yes                                                          |
| Whether to use non-steroidal drugs in postoperative analgesia            | N                | No                                                           |
|                                                                          | Y                | Yes                                                          |
| Whether to use a muscle relaxant antagonist                              | N                | No                                                           |
|                                                                          | Y                | Yes                                                          |
| Postoperative length of stay, LOS                                        | Less             | <4.546                                                       |
|                                                                          | More             | ≥ 4.546                                                      |
| Total cost, TC                                                          | Less             | <17,548.3355                                                |
|                                                                          | More             | ≥ 17,548.3355                                               |
| Indicator* | All | LOS < 4.546 d | LOS ≥ 4.546 d | P | TC < 17,548.33 | TC ≥ 17,548.33 | P |
|-----------|-----|---------------|---------------|---|----------------|----------------|---|
| Age (year) | 47 (7) | 47 (6) | 46 (8) | 0.018 | 46 (7) | 48 (7) | 0.000† |
| BMI (kg/m²) | 23.4 (4.2) | 23.6 (4.4) | 23.2 (3.8) | 0.000† | 23.4 (4.4) | 23.6 (3.8) | 0.465 |
| Preoperative Hb (g/L) | 112 (30) | 113 (27) | 110 (33) | 0.006 | 112 (23) | 111.5 (36) | 0.106 |
| Preoperative SBP (mmHg) | 124 (22) | 124 (24) | 123 (19) | 0.332 | 125 (23) | 122 (20) | 0.000† |
| Preoperative DBP (mmHg) | 76 (17) | 76 (16) | 75 (14) | 0.093 | 75.5 (16) | 76 (16) | 0.752 |
| Preoperative MBP (mmHg) | 91.3 (17.0) | 91.3 (17.3) | 91 (15) | 0.148 | 91.7 (17.0) | 91.2 (16.8) | 0.043 |
| Length of operation (min) | 110.0 (66.8) | 105.0 (55.0) | 129 (71) | 0.000† | 108.0 (55.5) | 115.0 (80.0) | 0.000 |
| Intraoperative urine volume (ml) | 200 (100) | 200 (100) | 200 (100) | 0.001 | 200 (100) | 200 (100) | 0.002 |
| Intraoperative colloid volume (ml) | 350 (500) | 300 (500) | 500 (500) | 0.000† | 300 (500) | 500 (500) | 0.000 |
| Intraoperative blood gas times (times) | 0 (1) | 0 (1) | 0 (1) | 0.004 | 0 (1) | 0 (1) | 0.000 |
| Postoperative Hb (g/L) | 112 (30) | 113 (27) | 110 (33) | 0.006 | 112 (23) | 111.5 (36) | 0.106 |
| Intraoperative systolic blood pressure Below 20% | 327 | 183 (16.1%) | 144 (21.2%) | 0.017 | 207 (21%) | 123 (14.7%) | 0.000 |

(Continued)
TABLE 2 (Continued)

| Indicator* | All | LOS < 4.546 d | LOS ≥ 4.546 d | P | TC < 17,548.33 55 | TC ≥ 17,548.33 55 | P |
|------------|-----|---------------|---------------|---|-----------------|-----------------|---|
| Intraoperative diastolic blood pressure | | | | | | | |
| Above 20% | 57 | 39 (3.4%) | 18 (2.7%) | 12 (1.2%) | 45 (5.4%) | | |
| Below 20% | 303 | 171 (15%) | 132 (19.4%) | 0.005 | 168 (17%) | 135 (16.1%) | 0.000† |
| -20%−±20% | 1,431 | 924 (80.8%) | 507 (74.4%) | 789 (79.9%) | 645 (76.8%) | | |
| Above 20% | 90 | 48 (4.2%) | 42 (6.2%) | 30 (3%) | 60 (7.1%) | | |
| Intraoperative mean blood pressure | | | | | | | |
| Below 20% | 201 | 105 (9.2%) | 96 (14.2%) | 0.001 | 126 (12.8%) | 75 (9%) | 0.000† |
| -20%−±20% | 1,536 | 990 (86.8%) | 546 (80.5%) | 837 (85.1%) | 702 (83.9%) | | |
| Above 20% | 81 | 45 (3.9%) | 36 (5.3%) | 21 (2.1%) | 60 (7.2%) | | |
| Intraoperative ETCO₂ | | | | | | | |
| < 35 | 1,503 | 693 (60.6%) | 360 (52.9%) | 0.000† | 627 (63.5%) | 429 (51.1%) | 0.000† |
| 35−45 | 768 | 450 (39.4%) | 318 (46.7%) | 360 (36.5%) | 408 (48.6%) | | |
| 45−55 | 3 | 0 (0%) | 3 (0.4%) | 0 (0%) | 3 (0.4%) | | |
| Positive balance | | | | | | | |
| 0−500 | 318 | 231 (20.2%) | 87 (12.8%) | 0.000† | 195 (19.8%) | 123 (14.6%) | 0.001† |
| 500−1,000 | 1,197 | 729 (63.8%) | 468 (68.7%) | 636 (64.4%) | 564 (67.1%) | | |
| 1,000−1,500 | 276 | 168 (14.7%) | 108 (15.9%) | 147 (14.9%) | 129 (15.4%) | | |
| 1,500+ | 33 | 15 (1.3%) | 18 (2.6%) | 9 (0.9%) | 24 (2.9%) | | |
| Intraoperative use of myocardial nutritional drugs | | | | | | | |
| No | 1,641 | 1,038 (90.8%) | 603 (88.5%) | 0.119 | 960 (97.3%) | 684 (81.4%) | 0.007† |
| Yes | 183 | 105 (9.2%) | 78 (11.5%) | 27 (2.7%) | 156 (18.6%) | | |
| Intraoperative use of hemostatic | | | | | | | |
| No | 1,185 | 735 (64.3%) | 450 (66.1%) | 0.442 | 597 (60.5%) | 588 (70%) | 0.000† |
| Yes | 639 | 408 (35.7%) | 231 (33.9%) | 390 (39.5%) | 252 (30%) | | |
| Postoperative compound nerve block analgesia | | | | | | | |
| No | 1,053 | 687 (60.1%) | 366 (53.7%) | 0.008 | 504 (51.1%) | 549 (65.4%) | 0.000† |
| Yes | 771 | 456 (39.9%) | 315 (46.3%) | 483 (48.9%) | 291 (34.6%) | | |
| Whether to use opioids as dominance in postoperative analgesia (fentanyl) | | | | | | | |
| No | 1,767 | 1,119 (97.9%) | 648 (95.2%) | 0.001 | 966 (97.9%) | 804 (95.7%) | 0.008 |
| Yes | 57 | 24 (2.1%) | 33 (4.8%) | 21 (2.1%) | 36 (4.3%) | | |
| Whether to use non-steroidal drugs in postoperative analgesia | | | | | | | |
| No | 1,023 | 618 (54.1%) | 405 (59.5%) | 0.025 | 369 (37.4%) | 654 (77.9%) | 0.000† |
| Yes | 801 | 525 (45.9%) | 276 (40.5%) | 618 (62.6%) | 186 (22.1%) | | |
| Whether to use muscle relaxant antagonist | | | | | | | |
| No | 435 | 273 (23.9%) | 162 (23.8%) | 0.963 | 264 (26.7%) | 171 (20.4%) | 0.001 |
| Yes | 1,389 | 870 (76.1%) | 519 (76.2%) | 723 (73.3%) | 669 (79.6%) | | |

*Non-normally distributed measurement data were expressed as Median (interquartile range). †P = 0.000 refers to P = 0.001. Each subscript letter represents a subset of the indicator class, with no significant difference between the horizontal columns at the 0.05 level.

LOS, length of stay; TC, total cost; BMI, body mass index; Hb, hemoglobin; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; ETCO₂, end tidal carbon dioxide.
TABLE 3 The influence of Bayesian indicator nodes for the postoperative length of stay.

| Indicator node                                                                 | Postoperative length of stay—0*—(957 cases) | Postoperative length of stay—1*—(558 cases) | \( P \) |
|--------------------------------------------------------------------------------|---------------------------------------------|---------------------------------------------|-------|
| Whether to use blood transfusion in 6–9 g hemoglobin                          | 69 (7.21%)                                  | 45 (8.06%)                                  | 0.255389 |
| Urine volume _ length of operation _100                                       | Low 315 (32.92%)                             | 252 (45.16%)                                | 0.000002 |
| Whether to use dexamethasone                                                  | N 216 (22.57%)                               | 105 (18.82%)                                | 0.084633 |
| Whether to use a muscle relaxant antagonist                                    | N 249 (26.02%)                               | 150 (26.88%)                                | 0.713013 |
| Crystalloid solution: colloid solution ratio —2:1                              | Low 381 (39.81%)                             | 168 (30.11%)                                | 0.000289 |
| Intraoperative ETCO\(_2\)                                                      | 0 591 (61.76%)                               | 294 (52.69%)                                | 0.000157 |
| Intraoperative use of propofol                                                 | 0 90 (9.4%)                                  | 39 (6.99%)                                  | 0.104249 |
| Intraoperative mean blood pressure                                            | Low 96 (10.03%)                              | 93 (16.76%)                                 | 0.00322 |
| Intraoperative systolic blood pressure                                         | Low 171 (17.87%)                             | 141 (25.27%)                                | 0.002418 |
| Intraoperative use of myocardial nutritional drugs                             | N 852 (89.03%)                               | 480 (86.02%)                                | 0.083242 |
| Intraoperative use of hemostatic                                              | N 597 (62.38%)                               | 351 (62.9%)                                 | 0.839885 |
| Intraoperative diastolic blood pressure                                       | Low 156 (16.3%)                              | 123 (22.04%)                                | 0.001814 |
| Postoperative compound nerve block analgesia                                   | N 558 (58.31%)                               | 285 (51.09%)                                | 0.006276 |
| Whether to use opioids as dominance in postoperative analgesia (fentanyl)     | N 933 (97.49%)                               | 525 (94.09%)                                | 0.000778 |
| Whether to use non-steroidal drugs in postoperative analgesia                 | N 483 (50.47%)                               | 309 (55.38%)                                | 0.065167 |
| Positive balance                                                              | 0 216 (22.57%)                               | 81 (14.52%)                                 | 0.000437 |
|                                                                                | 1 570 (59.56%)                               | 363 (65.05%)                                |       |
|                                                                                | 2 156 (16.3%)                                | 96 (17.2%)                                  |       |
|                                                                                | 3 15 (1.57%)                                 | 18 (3.23%)                                  |       |

\( ^* \): Each subscript letter represents a subset of the indicator class, with no significant difference between the horizontal columns at the 0.05 level.

\( ^* \): Postoperative length of stay-state-0 (< 4.546 d). Postoperative length of stay-state-1 (\( \geq 4.546 \) d).
TABLE 4 The influence of Bayesian indicator nodes on the total cost.

| Indicator node | Total cost—0*—(840 cases) | Total cost—1*—(681 cases) | P        |
|----------------|---------------------------|---------------------------|----------|
| Whether to use blood transfusion in 6–9 g hemoglobin | 0 15 (1.79%)\(_1\)    | 99 (14.5%)\(_1\)     | 4.400E-30|
|                | 1 0 (0%)\(_2\)              | 33 (4.85%)\(_2\)         |          |
|                | 2 825 (98.21%)\(_3\)       | 549 (80.62%)\(_3\)      |          |
| Urine volume _ length of operation _100 | Low 312 (37.14%)\(_1\)    | 267 (39.21%)\(_1\)      | 0.409685 |
|                | High 528 (62.86%)\(_2\)    | 414 (60.79%)\(_2\)      |          |
| Whether to use the dexmedetomidine | N 273 (32.5%)\(_1\)       | 51 (7.49%)\(_1\)       | 2.244E-32|
|                | Y 567 (67.5%)\(_2\)        | 630 (92.51%)\(_2\)      |          |
| Whether to use dexamethasone | N 549 (65.36%)\(_1\)       | 567 (83.26%)\(_1\)      | 4.0022E-15|
|                | Y 291 (34.64%)\(_2\)       | 114 (16.74%)\(_2\)      |          |
| Whether to use a muscle relaxant antagonist | N 243 (28.93%)\(_1\)      | 144 (21.15%)\(_1\)     | 0.000529 |
|                | Y 597 (71.07%)\(_2\)       | 537 (78.85%)\(_2\)      |          |
| Crystalloid solution: colloid solution ratio —2:1 | Low 363 (43.21%)\(_1\)    | 174 (25.55%)\(_1\)     | 3.200E-13|
|                | High 129 (15.36%)\(_2\)    | 174 (25.55%)\(_2\)      |          |
| Intraoperative ETCO2 | 0 549 (65.36%)\(_1\)       | 348 (51.1%)\(_1\)      | 1.2488E-8|
|                | 1 291 (34.64%)\(_2\)       | 330 (48.4%)\(_2\)       |          |
|                | 2 0 (0%)\(_3\)              | 3 (0.44%)\(_3\)          |          |
| Intraoperative use of sevoflurane | N 669 (79.64%)\(_1\)       | 534 (78.41%)\(_1\)     | 0.557875 |
|                | Y 171 (20.36%)\(_2\)       | 147 (21.59%)\(_2\)      |          |
| Intraoperative use of propofol | N 69 (8.21%)\(_1\)         | 57 (8.37%)\(_1\)       | 0.912737 |
|                | Y 771 (91.79%)\(_2\)       | 624 (91.63%)\(_2\)      |          |
| Intraoperative mean blood pressure | Low 117 (13.93%)\(_1\)    | 66 (9.69%)\(_1\)       | 1.8525E-7|
|                | Normal 702 (83.57%)\(_2\)  | 558 (81.94%)\(_2\)      |          |
| Intraoperative systolic blood pressure | Low 195 (23.21%)\(_1\)    | 114 (16.74%)\(_1\)     | 2.8249E-8|
|                | Normal 633 (75.36%)\(_2\)  | 522 (76.65%)\(_2\)      |          |
|                | High 12 (1.43%)\(_3\)      | 45 (6.61%)\(_3\)        |          |
| Intraoperative use of myocardial nutritional drugs | N 813 (96.79%)\(_1\)      | 525 (77.09%)\(_1\)     | 8.0189E-32|
|                | Y 27 (3.21%)\(_2\)         | 156 (22.91%)\(_2\)      |          |
| Intraoperative use of hemostatic | N 486 (57.86%)\(_1\)       | 462 (67.84%)\(_1\)     | 0.000064 |
|                | Y 354 (42.14%)\(_2\)       | 219 (32.16%)\(_2\)      |          |
| Intraoperative diastolic blood pressure | Low 156 (18.57%)\(_1\)    | 117 (17.18%)\(_1\)     | 0.000068 |
|                | Normal 657 (78.21%)\(_2\)  | 507 (74.45%)\(_2\)      |          |
|                | High 27 (3.21%)\(_3\)      | 57 (8.37%)\(_3\)        |          |
| Postoperative compound nerve block analgesia | N 408 (48.57%)\(_1\)      | 429 (63%)\(_1\)        | 1.8753E-8|
|                | Y 432 (51.43%)\(_2\)       | 252 (37%)\(_2\)         |          |
| Whether to use opioids as dominance in postoperative analgesia (fentanyl) | N 819 (97.5%)\(_1\)      | 645 (94.71%)\(_1\)     | 0.004439 |
|                | Y 21 (2.5%)\(_2\)          | 36 (5.29%)\(_2\)        |          |
| Whether to use non-steroidal drugs in postoperative analgesia | N 279 (33.21%)\(_1\)      | 510 (74.89%)\(_1\)     | 7.4736E-59|
|                | Y 561 (66.79%)\(_2\)       | 171 (25.11%)\(_2\)      |          |
| Positive balance | 0 189 (22.5%)\(_1\)        | 111 (16.3%)\(_1\)      | 0.000324 |
|                | 1 501 (59.64%)\(_2\)       | 432 (63.44%)\(_2\)      |          |
|                | 2 141 (16.79%)\(_3\)       | 114 (16.74%)\(_3\)      |          |
|                | 3 9 (1.07%)\(_4\)          | 24 (3.52%)\(_4\)        |          |

\(1\) Each subscript letter represents a subset of the indicator class, with no significant difference between the horizontal columns at the 0.05 level.

\(2\) Total cost—state-0 \(< 17,548.3355\). Total cost—state-1 \(\geq 17,548.3355\). (see Table 5); (2) for TC group: “whether to use non-steroidal drugs in postoperative analgesia—Y,” “whether to use the dexmedetomidine—Y,” “intraoperative use of myocardial nutritional drugs—N,” “whether to use blood transfusion in 6–9 g hemoglobin—2,” “whether to use dexamethasone—N,” “crystalloid solution: colloid solution ratio —2:1-Low,” “intraoperative
ETCO2-0,” "postoperative compound nerve block analgesia-Y,” “intraoperative SBP-Normal,” “intraoperative MBP-Normal,” “intraoperative use of hemostatic-N,” “intraoperative DBP-Normal,” $P < 0.05$ (see Table 5).

**Anesthesia Bayesian decision intervention model results for length of stay and total cost**

Based on the anesthetics Bayesian decision intervention model, we constructed the DAG decision structure for gynecologic tumor diseases. We would manually make some adjustments according to the actual clinical significance. For LOS (length of stay), we got the following indicators: “positive balance,” “intraoperative ETCO2,” “whether to use opioids as dominance in postoperative analgesia (fentanyl),” “crystalloid solution: colloid solution ratio $\leq 2:1$,” “urine volume $\times$ length of operation $\leq 100$” and “postoperative compound nerve block analgesia.” For TC (total cost), the results of the indicators are as follows: “intraoperative mean blood pressure,” “intraoperative systolic blood pressure,” “whether to use dexamethasone,” “whether to use non-steroidal drugs in postoperative analgesia,” “whether to use blood transfusion in 6–9 g hemoglobin,” “whether to use dexmedetomidine,” “postoperative compound nerve block analgesia,” “intraoperative use of myocardial nutritional drugs,” and “crystalloid solution: colloid solution ratio $\leq 2:1$.”

The relationships of the selected indicators are shown in Figure 5. As shown in Figure 5A, it included six indicators for the outcome, including postoperative length of stay. As shown in Figure 5B, the total cost included nine indicators for the outcome, total cost. The directed arc between nodes represented the dependency relationship among nodes.

"Positive balance" was the parent node of "crystalloid solution: colloid solution ratio $\leq 2:1$" and "urine volume $\times$ length of operation $\leq 100$." "Intraoperative ETCO2" and "whether to use opioids as dominance in postoperative analgesia (fentanyl)" could affect LOS through modulation of "intraoperative compound nerve block analgesia."

"Whether to use dexamethasone” was the parent node of "whether to use non-steroidal drugs in postoperative analgesia" and "postoperative compound nerve block analgesia." "Whether to use non-steroidal drugs” was the parent node of "whether to use dexmedetomidine," "postoperative compound nerve block analgesia," and "total cost." “Intraoperative mean blood pressure” could affect "total cost" through "intraoperative systolic blood pressure,” which was the parent node of "whether to use non-steroidal drugs" and "total cost.” “Whether to use blood transfusion in 6–9 g hemoglobin” was the parent node of "intraoperative use of myocardial nutritional drugs," "postoperative compound nerve block analgesia," and "total cost.” Then "whether to use dexmedetomidine," “intraoperative use of myocardial nutritional drugs,” and “crystalloid solution: colloid solution ratio $\leq 2:1$” could directly affect "total cost.”

**Discussion**

This study analyzed 1,827 patients undergoing laparoscopic gynecological surgery using BN based on 18 selected indicators related to anesthesia decision-making. Then, combining the selected indicators with specific grades and validation in patient data, we found that some of these impact indicators can improve the outcomes when combined. Finally, the DAGs of BN showed the interaction between the impact indicators through the arrows.

For the impact indicators we found, there is some clinical significance, and previous studies also proved it. For laparoscopic surgery, pneumoperitoneum is important and associated with ETCO2, and it did make a difference in our study. A previous study showed that low-pressure pneumoperitoneum was associated with improved parietal peritoneal perfusion (32), which may reduce clinically relevant complications. The “urine volume $\times$ length of operation $\leq 100$” and “crystalloid solution: colloid solution ratio $\leq 2:1$” also made sense. For urine volume, it can be influenced by fluid management such as restrictive fluid management strategy, open fluid management strategy or goal-directed fluid therapy (GDFT). Additionally, GDFT can reduce LOS and postoperative complications (33). At the same time, positive balance and blood pressure are also related to fluid management strategies. For an operative time, one study demonstrated that operative times $>120$ min and $151–180$ min, and $\geq 181$ min predicted prolonged LOS (34). Another study indicated a significant association between high fluid volume given on the day of surgery and increased LOS and total costs (35). The above findings are consistent with our studies.

Differences also exist between our results and clinical practice. Our study recommended not using postoperative compound nerve block. However, nerve block has been reported to be effective in reducing pain and decreasing LOS or complication rates (36). Since the included patients are those with benign tumors undergoing laparoscopic surgery, they may not experience severe pain, and normal analgesic therapy can achieve satisfactory results. For TC, we found that indicators affecting total cost were mostly related to drug use. Our study recommends using dexmedetomidine to decrease TC. However, using common sense, we know that dexmedetomidine is expensive and leads to high costs. Perhaps, the cost could be decreased by reducing other complications. A previous study has shown that dexmedetomidine could attenuate the incidence of PONV (37).

Through the directed acyclic graph of BN analysis, we can predict the continuous impact of decisions on related indicators. Our study indicated that “positive balance” could
TABLE 5 The influence of the combination of multiple indicators for the postoperative length of stay and total cost.

| Indicator                                                                 | State 0 | Proportion | State 1 | Proportion | P    |
|---------------------------------------------------------------------------|---------|------------|---------|------------|------|
| Postoperative length of stay                                             |         |            |         |            |      |
| High Urine volume _ length of operation _100                             | 642     | 67.08%     | 306     | 54.84%     | 0.000002 |
| Low Intraoperative ETCO2                                                 | 411     | 42.95%     | 171     | 30.65%     | 0.000002 |
| Less Crystalloid solution: colloid solution ratio − 2:1                 | 165     | 17.24%     | 78      | 13.98%     | 0.095058 |
| Normal Intraoperative mean blood pressure                                | 147     | 15.36%     | 45      | 8.06%      | 0.000038 |
| 1 Positive balance                                                       | 105     | 10.97%     | 39      | 6.99%      | 0.010791 |
| N Whether to use opioids as dominance in postoperative analgesia (fentanyl) | 105     | 10.97%     | 36      | 6.45%      | 0.003489 |
| Normal Intraoperative diastolic blood pressure                          | 84      | 8.78%      | 33      | 5.91%      | 0.044027 |
| Normal Intraoperative systolic blood pressure                           | 63      | 6.58%      | 24      | 4.30%      | 0.065549 |
| N Postoperative compound nerve block analgesia                           | 42      | 4.39%      | 12      | 2.15%      | 0.023422 |
| N Whether to use non-steroidal drugs in postoperative analgesia          | 21      | 2.19%      | 6       | 1.08%      | 0.1441  |
| N Intraoperative use of myocardial nutritional drugs                     | 15      | 1.57%      | 3       | 0.54%      | 0.074374 |
| Y Whether to use the dexametomidine                                     | 9       | 0.94%      | 3       | 0.54%      | 0.3936  |
| Y Intraoperative use of propofol                                        | 6       | 0.63%      | 3       | 0.54%      | 0.827249 |
| N Whether to use blood transfusion in 6-9 g hemoglobin                  | 2       | 0.31%      | 3       | 0.54%      | 0.502826 |
| N Whether to use dexamethasone                                           | 3       | 0.31%      | 3       | 0.54%      | 0.502826 |
| N Intraoperative use of sevoflurane                                     | 3       | 0.31%      | 0       | 0.00%      | 0.30156 |
| N Whether to use a muscle relaxant antagonist                            | 0       | 0.00%      | 0       | 0.00%      | 0.000001 |
| N Intraoperative use of hemostatic                                      | 0       | 0.00%      | 0       | 0.00%      | 0.000001 |
| Total cost                                                               |         |            |         |            |      |
| Y Whether to use non-steroidal drugs in postoperative analgesia          | 561     | 66.79%     | 171     | 25.11%     | 7.47E-59 |
| Y Whether to use the dexametomidine                                     | 384     | 45.71%     | 132     | 19.38%     | 4.03E-27 |
| Y Intraoperative use of myocardial nutritional drugs                     | 381     | 45.36%     | 105     | 15.42%     | 1.37E-35 |
| N Whether to use blood transfusion in 6-9 g hemoglobin                  | 378     | 45.00%     | 99      | 14.54%     | 3.87E-37 |
| N Whether to use dexamethasone                                           | 195     | 23.21%     | 57      | 8.37%      | 9.72E-15 |
| N Crystalloid solution: colloid solution ratio − 2:1                     | 99      | 11.79%     | 6       | 0.88%      | 7.31E-17 |
| Y Intraoperative ETCO2                                                  | 69      | 8.21%      | 0       | 0.00%      | 1.93E-14 |
| Y Postoperative compound nerve block analgesia                           | 30      | 3.57%      | 0       | 0.00%      | 6.32E-07 |
| Y Intraoperative systolic blood pressure                                 | 18      | 2.14%      | 0       | 0.00%      | 1.22E-04 |
| Y Intraoperative mean blood pressure                                     | 18      | 2.14%      | 0       | 0.00%      | 1.22E-04 |
| N Intraoperative use of hemostatic                                      | 9       | 1.07%      | 0       | 0.00%      | 0.017642 |
| N Intraoperative diastolic blood pressure                                | 9       | 1.07%      | 0       | 0.00%      | 0.017642 |
| Positive balance                                                         | 1       | 1.07%      | 0       | 0.00%      | 0.022087 |
| N Whether to use a muscle relaxant antagonist                            | 6       | 0.71%      | 0       | 0.00%      | 0.072087 |
| N Whether to use opioids as dominance in postoperative analgesia (fentanyl) | 6       | 0.71%      | 0       | 0.00%      | 0.072087 |
| Urine volume _ length of operation _100                                  | 3       | 0.36%      | 0       | 0.00%      | 0.327101 |
| N Intraoperative use of sevoflurane                                     | 3       | 0.36%      | 0       | 0.00%      | 0.327101 |
| Y Intraoperative use of propofol                                        | 3       | 0.36%      | 0       | 0.00%      | 0.327101 |

affect the “crystalloid solution: colloid solution ratio − 2:1” and “urine volume—length of operation −100” whilst “urine volume—length of operation −100” can affect “postoperative length of stay.” It is consistent with clinical practice, while fluid management can influence patient recovery (35). “Intraoperative ETCO2” and “whether to use opioids as dominance in postoperative analgesia (fentanyl)” can affect “postoperative length of stay” by the modulation of “postoperative compound nerve block analgesia.” It has been proven that post-laparoscopic residual pneumoperitoneum volume was correlated with shoulder pain after laparoscopy (38, 39). Thus, “intraoperative ETCO2” was associated with analgesic planning. Then a study reported that multimodal analgesia improved postoperative pain control and minimized opioid-related adverse effects for all types of gynecological surgeries (14). This can also show that these indicators have interacted.

“Whether to use dexamethasone” was the parent node of “postoperative compound nerve block analgesia” and “whether to use non-steroidal drugs in postoperative

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analgesia," the latter of which can affect "whether to use dexmedetomidine," "postoperative compound nerve block analgesia" and "total cost." This relationship suggests that the measures that control pain and postoperative nausea and vomiting affect the total cost. In addition, "intraoperative mean blood pressure" could affect "total cost" through "intraoperative systolic blood pressure," which was the parent node of "whether to use non-steroidal drugs" and "total cost." This correlation implies that blood pressure control may also influence the total cost. In addition, "crystalloid solution: colloid solution ratio − 2:1" can independently affect "total cost." So maybe there is room to explore the "crystalloid solution: colloid solution ratio − 2:1" contribution to cost.

Machine learning has been applied to disease diagnosis, risk prediction, image recognition, and more. As a combination of probability theory and graph theory, BN has also played a corresponding role in the medical field (19, 40–44). However, the application of BN analysis for anesthesia decision-making in ERAS has not been reported yet. We investigated the indicators of anesthesia decision-making using BN analysis to identify the indicators that significantly impact anesthesia decision-making outcomes and study their combinations’ impact. Furthermore, the causal structure was explicitly represented, and the model can be learned from data, expert knowledge (no data), or a combination of the two approaches (19). Our research can be used to support clinical anesthesia decision-making based on the recommended indicators to achieve the optimal anesthetic part of ERAS.

However, our study still has some limitations. We only enrolled patients with benign tumors who participated in fewer ERAS measures. More patients diagnosed with other diseases must be included in the next step. In addition, the length of stay and total cost were analyzed separately, and the relationship between them was not explored. The next step is to investigate multiple outcomes in a single model. Moreover, this study was for anesthesiologists; we were most involved in intraoperative management and postoperative analgesia, which indicates a lack of preoperative measures. We need to include more indicators for the optimization of the whole ERAS.

**Conclusion**

We used the BN to study the relationship between anesthesia-related ERAS measures, postoperative length of stay, and total cost. Some indicators can affect the outcomes, and their combinations can reduce LOS and TC. The relationship between the indicators in DAGs provides new ideas for clinical work. This strategy is a new attempt at the Bayesian algorithm in ERAS, breaking through traditional statistical methods’ limitations. It provides a feasible plan for the anesthesiologist to optimize ERAS protocols and make individualized decisions.
Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: According to the regulation of the People's Republic of China on the administration of human genetic resources, the collection of raw data was subject to approval by the science and technology administrative department of the state council (AQ: 2020SQJ7444). Requests to access these datasets should be directed to BY, yibin1974@163.com.

Ethics statement

The studies involving human participants were reviewed and approved by ethics committee of the First Affiliated Hospital of Army Medical University, ethics committee of Xuanwu Hospital of Capital Medical University, and ethics committee on Biomedical Research, West China Hospital of Sichuan University. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

BY, KW, and YC: study concept and design. YZ, YC, KZ, XS, DW, PD, XB, LZ, TZ, ZY, and YL: acquisition of data. YZ, YC, KZ, ZY, and YL: analysis and interpretation of data. JZ, YC, JG, and KL: technical support. BY and YC: funding acquisition. YZ, YC, and KZ: writing original manuscript. ZY and YL: revision of manuscript. All authors contributed to the article and approved the submitted version.

Funding

The work was supported by the National Key R&D Program of China (No. 2018YFC0116704 from YC), the National Key R&D Program of China (No. 2018YFC0116702 from BY), the Youth Innovation Promotion Association of the Chinese Academy of Sciences (No. 2020377 from YC), and National Natural Science Foundation of China (No. 82070630 from BY).

Acknowledgments

We would like to thank the participants of this study.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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