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Original Article

Machine learning risk prediction model for bloodstream infections related to totally implantable venous access ports in patients with cancer

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ABSTRACT

Objective: This study aimed to develop and validate a machine learning-based risk prediction model for catheter-related bloodstream infection (CRBSI) following implantation of totally implantable venous access ports (TIVAPs) in patients.

Methods: A retrospective cohort study design was employed, utilizing the R software package mlr3. Various algorithms including logistic regression, naive Bayes, K nearest neighbor, classification tree, and random forest were applied. Addressing class imbalance, benchmarks were used, and model performance was assessed using the area under the curve (AUC). The final model, chosen for its superior performance, was interpreted using variable importance scores. Additionally, a nomogram was developed to calculate individualized risk probabilities, enhancing clinical utility.

Results: The study involved 755 patients across both development and validation cohorts, with a TIVAP-CRBSI rate of 14.17%. The random forest model demonstrated the highest discrimination ability, achieving a validated AUC of 0.94, which was consistent in the validation cohort.

Conclusions: This study successfully developed a robust predictive model for TIVAP-CRBSI risk post-implantation. Implementation of this model may aid healthcare providers in making informed decisions, thereby potentially improving patient outcomes.

Introduction

The totally implantable venous access port (TIVAP) is a catheter device that is utilized for patients who require long-term, recurring intravenous infusion.[1] Its primary purpose is to provide safe and reliable central venous access for the administration of various substances, including chemotherapeutic agents, blood products, and parenteral nutrition solutions.[2] This device is especially important for patients with solid tumors and hematological malignancies that require prolonged vasotoxic drug treatment.[3] Repeated punctures and infusions of strong medications can cause damage to the peripheral veins in these patients.[4] To prevent this, a central venous catheter such as the TIVAP is necessary. The TIVAP has gained widespread use in clinical practice due to its numerous advantages. It offers a secure and dependable method for catheterization, reducing the need for frequent catheter maintenance and

minimizing the risk of complications related to the catheter.[5] The implementation of TIVAP has greatly improved the care of patients requiring long-term intravenous treatments. Its use has not only enhanced the safety and efficiency of drug administration, but also alleviated the discomfort and complications associated with repeated venous punctures. Overall, the TIVAP has become an indispensable tool in clinical settings, providing a convenient and reliable means of central venous access for patients undergoing long-term intravenous therapies.[6]

Catheter-related bloodstream infection (CRBSI) is a significant complication that can arise from the use of TIVAP.[7] CRBSI is characterized by the presence of bacteremia or fungemia in patients with intravascular catheters, or within 48 hours of catheter removal, without any other apparent source of infection.[1] Tsuruta's study indicates that CRBSI is the primary reason for unplanned port removal.[8] In Lebeuax et al.'s study,[9] approximately 18% of patients with port CRBSI went on to

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develop severe sepsis or septic shock, illustrating the severity of this complication. The occurrence of CRBSI not only increases the risk of unplanned TIVAP removal but also can delay tumor treatment and prolong hospitalization, leading to poor patient outcomes.[10,11] Furthermore, it can negatively impact patient prognosis and even pose a potential threat to the patient's life.[12] Previous studies suggest that the incidence of late CRBSI in TIVAP falls between 5.6% and 9.26%, with up to 30% of TIVAP patients discontinuing anti-tumor chemotherapy due to systemic infection.[13,14] Unfortunately, currently, there are no clinically applicable tools for predicting the risk of TIVAP-CRBSI. Despite its prevalence, there is no effective way to predict the risk of TIVAP-CRBSI currently. Therefore, there is an urgent need to develop a clinically useful risk prediction tool to help identify patients at high risk of CRBSI and provide targeted interventions to mitigate this potentially life-threatening complication.

The TIVAP-CRBSI risk prediction model is a valuable tool for estimating the likelihood of developing CRBSI after TIVAP catheterization. It belongs to the category of clinical prognostic risk prediction models. However, there is currently limited research available on the development of such a model specifically for TIVAP-CRBSI. One study conducted in 2021 by Chen[15] focused on developing a nomogram model for infusion port catheter-related systemic infection in patients with digestive tract tumors. This model incorporated four risk factors: a Karnofsky performance score (KPS) of 60 points, parenteral nutrition support, a history of diabetes, and the duration of butterfly needle usage. It is important to note that this particular model is only applicable to patients with digestive tract tumors, limiting its clinical applicability. Furthermore, the study had a small sample size, and only logistic regression analysis was employed, which increases the risk of overfitting the model. Given the limited available research and the specificity of the existing model, there is a need for further studies to develop a comprehensive and universally applicable risk prediction model for TIVAP-CRBSI. Such a model would greatly aid in identifying high-risk patients and allowing for targeted preventive measures, ultimately reducing the occurrence of CRBSI and improving patient outcomes.

Currently, traditional statistical methods such as logistic regression analysis and COX proportional hazards regression analysis are commonly used to develop clinical prediction models. However, these methods have limitations, such as strict requirements for data types, potential overfitting issues, and limited capabilities in data mining.[16] Machine learning is a scientific and technical approach that utilizes computer algorithms to learn from data and discover underlying patterns.[17] With the increasing availability of clinical informatics tools, large and complex datasets are being generated, making it challenging to collect, store, and analyze using traditional techniques.[18] As the fields of hospital information management and artificial intelligence merge, machine learning algorithms offer efficient solutions for managing and analyzing large datasets.[19] Previous reported studies have demonstrated the accuracy and effectiveness of machine learning algorithms in processing clinical data;[20,21] these studies have truly proven that using machine learning algorithms to build clinical prediction models may be the direction forward for research. Therefore, the primary goal of this study is to analyze the characteristics of the TIVAP patient cohort and employ machine learning techniques to develop a highly applicable clinical risk prediction model for TIVAP-CRBSI.

Methods

Source of data

The data for this study were obtained from a retrospective cohort of patients with tumors who received TIVAP implants, and all the necessary information for constructing the model was extracted from the medical record system. A retrospective cohort study design was utilized, where the observation period began at the time of TIVAP implantation in the research participants. The primary outcome of interest was the occurrence of TIVAP-CRBSI. Censoring was defined as the removal of the infusion port for reasons other than TIVAP-CRBSI, loss of follow-up, or failure to complete the observation period. The cohort for this study was observed from January 1, 2018, to December 31, 2022.

Participants

Participants for this study were selected through convenience sampling. All participants were cancer patients who had undergone TIVAP implantation at a cancer center affiliated with a medical university in Guangzhou, Guangdong, China. The inclusion criteria were as follows: (1) Patients diagnosed with tumors confirmed by pathological examination, (2) age $\geq$ 18 years, and (3) TIVAP implantation performed in the operating room of the center. Participants meeting the following criteria were excluded from the study: (1) Pre-existing CRBSI before TIVAP implantation, and (2) admitted after TIVAP implantation in other hospitals. All patients underwent TIVAP implantation in the same operating room at the center, and the operating surgeons held relevant qualifications, ensuring a standardized approach to TIVAP implantation among all participants.

Sample size

The sample size for this study was determined using the R software. The "pmsampsize" package utilized the sample size calculation procedure introduced by Riley in 2020 for risk prediction models.[22,23] To ensure the predictive performance of the model and avoid overfitting, the calculation of the sample size took into account the estimated coefficient of determination (R^2) of the model the anticipated number of predictive parameters to be included, and the shrinkage level required for internal validation after model development. Based on an analysis of the incidence data of TIVAP-CRBSI at our center over the years, the estimated incidence rate of TIVAP-CRBSI was found to be 9.0%. It was anticipated that 15 prediction parameters would be included in the model. Following the guidance of Riley et al., a shrinkage level of 0.90 was set for the new model. Consequently, a sample size of 700 cases was estimated as necessary for the development of the model.

Data collection

Data on patient characteristics were collected through a comprehensive review of patient hospitalization records, nursing logs, and examination and laboratory reports. The primary aim of the predictive model is to ascertain the risk of CRBSI during a patient's current hospital stay. Therefore, it is the timepoint to employ the model when the admission of patients equipped with TIVAP. To maintain the predictive model's reliability in real-world application, a standardized data collection timeline were established: (1) For patients who were diagnosed with CRBSI, data from the admission during which CRBSI was identified are documented. (2) Conversely, for patients who did not experience CRBSI by the observation's conclusion, data from their most recent admission are recorded. This structured approach ensures the predictive model's efficacy and consistency in clinical settings.

Outcome

The diagnostic criteria used for TIVAP-CRBSI in this study included:[10,24–26] (1) A higher number of colony-forming units (CFU) per milliliter in the infusion port blood sample culture compared to peripheral blood, (2) a colony count of greater than 1000 CFU in the infusion port blood sample culture, and (3) positive culture of the catheter tip. Additionally, catheter tip culture after TIVAP removal was considered clinically significant when 15 colony units were formed and when 10^3; CFU/mL was achieved. Since all the data used in this study were obtained retrospectively from medical records, the outcome diagnosis occurred prior to data collection, and the determination of predictors did not impact the diagnosis of patient outcomes.

Predictors

A comprehensive literature review was conducted to identify risk factors associated with portrelated bloodstream infections. Databases such as PubMed, Web of Science, CINAHL, Cochrane Library, AHRQ American Guide Network, Registered Nurses' Association of Ontario (RNAO), and Scopus were searched systematically for relevant studies published between January 2012 and August 2022. The studies identified key risk factors associated with CRBSI related to TIVAP include elevated levels of C-reactive protein, concurrent surgical procedures alongside TIVAP implantation, the hospital environment, patient demographics, and a history of hematologic malignancies.[5,9,13,14] In addition, neutropenia, total parenteral nutrition (TPN), chronic steroid use, invasive procedures, postoperative antibiotics, and preoperative antibiotics have also been confirmed as independent predictors of TIVAP-related CRBSI.[27] Based on the literature review, we expanded some potential predictors to include three dimensions: patients' basic conditions, TIVAP-related characteristics, and disease treatment-related information. To ensure the validity of the predictors and avoid omissions, we used the Delphi expert consultation method to revise the candidate predictors through email inquiries. After two rounds of correspondence, we identified a list of potential candidate predictors containing 41 features. The results of the Delphi expert correspondence are shown in Supplementary material 1.

Missing data handling

When processing missing data, cases with a missing data rate greater than 20% were initially excluded from the analysis. To address the remaining missing values, we used predictive mean matching (PMM) for multiple imputation. Missing values in the dataset were replaced by the average of the five imputed values generated through multiple imputations.

Construction of machine learning-based risk prediction model

Data processing

The researchers began by preprocessing the data, which involved applying logarithmic transformation to features with asymmetrical distributions. Afterward, all features were standardized. In this research, we applied the Z-score normalization technique to standardize select continuous variables. This method transforms raw data into standardized scores by recalibrating data points of varying magnitudes or distributions to a uniform scale, characterized by a mean of 0 and a standard deviation of 1. Through this process, each data point is recalculated to indicate the number of standard deviations it deviates from the mean of the original dataset. Z-score normalization facilitates equitable comparisons across data measured on different scales, rendering the data suitably formatted for analysis with machine learning algorithms.

Candidate predictor screening

Since most of the data included in this study are clinical data, multicollinearity between variables is likely to exist. To effectively identify predictors with significant predictive power for the target variables, the least absolute shrinkage and selection operator (LASSO) regression analysis was used in the training cohort for multivariate analysis. During the implementation of the LASSO regression analysis, all potential explanatory variables were first standardized to eliminate the effects of different dimensions. Then, the optimal regularization parameters (i.e., penalty coefficient) were determined by cross-validation to balance the bias and variance of the model, allowing for the selection of the most critical independent screening indexes for model prediction.

Learner selection

To construct the prediction model, the R software package "mlr3" was used, utilizing built-in algorithms such as logistic regression, naive Bayes,

K nearest neighbor, classification tree, and random forest. Each algorithm was applied to the preprocessed and standardized dataset to build the respective prediction models. The hyperparameter tuning strategies employed in the construction of our machine learning models are detailed in Supplementary material 2.

Benchmarks

First, we address the class imbalance issue by employing an over-sampling technique, which increases the number of minority class samples to achieve balanced classes. Specifically, the "class balancing" adjustment technique is utilized to oversample the minority class samples. This oversampled dataset is then applied to each learning algorithm, creating a collection of models trained specifically on the balanced data. To evaluate the performance of these models, we use stratified 5-fold cross-validation as the external sampling technique. This approach ensures that samples from both the minority and majority classes are included in each of the five folds, thereby reducing bias in performance evaluation. Finally, we compare the performance of the different models to assess their respective predictive abilities.

Performance evaluation

The constructed machine learning model can be utilized to predict the data in the validation set. From these predictions, the receiver operating characteristic (ROC) curve can be drawn. This curve plots the true positive rate (sensitivity) against the false positive rate for various classification thresholds. To evaluate the prediction performance of different learners, we used indicators such as the area under the curve (AUC), sensitivity, specificity, misclassification rate, and false positive rate. The AUC reflects the overall performance of the model, with higher values indicating better discrimination ability. Sensitivity measures the model's ability to correctly identify positive cases, while specificity measures its ability to correctly identify negative cases. The misclassification rate and false positive rate provide additional insights into the model's overall accuracy and capacity to correctly classify negative cases. By comparing the performance of different learners using these indicators, the model with the highest performance can be selected as the final model.

Feature selection

To perform feature selection in the final model, a hyperparameter search algorithm was utilized. This algorithm would include a Tuning Instance Single Crit instance, which generates importance scores for all predictors. From these scores, the top 15 predictors can be selected to build the final prediction model. By using this feature selection process, only the most important predictors are included in the final model. This can help improve the model's performance and reduce overfitting.

Model interpretation

To interpret the constructed final prediction model and understand its impact on the data, we utilize the "iml" package in R. This package offers tools for interpreting machine learning models, visualizing feature effects, and assessing feature importance. Using the "iml" package, we compute feature importance scores, which indicate the relative significance of each predictor in the model's decision-making process.

Build a nomogram

After selecting the top important predictors, as mentioned before, we can build a nomogram model to further improve the clinical applicability of the model. A nomogram is a graphical representation of a prediction model that can be used to calculate the probability of a specific outcome for an individual patient.[28] By utilizing top predictors, the nomogram can provide a personalized and clinically relevant tool that can be used to predict patient outcomes. The predictive performance of the nomogram model can be reported by evaluating its discrimination and calibration capabilities. Discrimination refers to the ability of the model to distinguish between individuals who will have the outcome of interest and those who will not. It can be measured by calculating the c-statistic, or the area under

the ROC curve. Calibration, on the other hand, refers to the agreement between the predicted probabilities from the model and the actual observed outcomes in the sample data. Calibration can be assessed by visually inspecting the calibration plot or calculating the Hosmer–Lemeshow goodness-of-fit statistic. By building a nomogram model and reporting its predictive performance metrics, we can improve the clinical applicability of the model and provide clinicians with a useful tool for predicting patient outcomes. A flow diagram illustrating the model-building approach is presented in Fig. 1.

Ethical considerations

This research was approved by the ethical review agency of Affiliated Cancer Hospital and Institute of Guangzhou Medical University, Guangzhou, China (ID: GYZL-2023-ST05). During the study, we adhered to the Declaration of Helsinki and obtained written informed consent from all participants or their guardians.

Results

Participant characteristics

During the data collection stage, a total of 837 patients were initially included in the cohort. However, 82 patients had to be excluded from the analysis due to missing data exceeding 20%. As a result, the final cohort consisted of 755 patients. Table 1 provides a comparison of general information of patients in the training set and validation set. In this study, the average length of TIVAP catheter use was found to be 581.47 days. Regarding the outcome event rate, 107 patients in the cohort developed CRBSI, resulting in an overall incidence rate of 0.244/1000 catheter days. This indicates that 14.17% of the patients experienced this outcome.

Candidate predictor screening

To scrutinize the pool of potential predictors, we integrated them into a LASSO regression analysis. The cross-validation outcomes of this analysis are depicted in Fig. 2A, illustrating the correlation between the binomial deviance of the LASSO regression model and the log-transformed regularization parameter λ (Log(λ)). This figure employs cross-validation to assess model error, where each lambda's cross-validation error is marked by a red dot, and the error's standard deviation is represented by a red line. The dotted vertical line on the left

signifies the λ value that minimizes the model's binomial deviance to 0.0014 [log(λ) = −6.58]. Conversely, the dotted line on the right indicates a λ value that results in a binomial deviance one standard error above the minimum, at 0.0143 [log(λ) = −4.27]. We opted for the λ that corresponds to the lowest binomial deviance as our regularization parameter. As illustrated in Fig. 2B, at λ = 0.0143, 28 variables have non-zero regression coefficients and are thus retained in the model for the subsequent construction phase.

Machine learning model selection

The "mlr3" package was employed to build five different prediction models, including logistic regression, naive Bayes, K nearest neighbor, classification tree, and random forest. These models were then subjected to a benchmark test to compare their prediction performance. Table 2 presents the results of the benchmark test, displaying various performance metrics such as AUC (area under the ROC curve), sensitivity, specificity, misclassification rate, and false positive rate for each model. Fig. 3 showcases the ROC curves and precision-recall (PRC) curves for the five different models, providing a graphical representation of their predictive capabilities. To determine the best-performing model, the AUC values were used as the criterion, and the models were sorted accordingly. After conducting the benchmark test, it was found that the model generated by the random forest algorithm achieved the highest prediction performance (AUC = 0.94). Therefore, the random forest model was selected as the final model.

Model explanation and final model development

Furthermore, we have also analyzed and explained the importance of each variable within the model. The importance of ranking features is shown in Table 3. The top 15 features with the highest feature selection scores were identified and incorporated into the final model. This ranking allows for a clear understanding of the relative importance of each variable in predicting the outcome. These variables include procalcitonin level (PCT), catheter day, receive parenteral nutrition treatment (TPN), nutritional risk screening (NRS)-2002 score, neutrophil count levels (NEUT), and so on. These variables played a crucial role in the model's ability to predict the outcome accurately. The final random forest model consisted of 500 trees and exhibited an AUC of 0.983, an accuracy (ACC) of 0.964 and a cross entropy (CE) of 0.036.
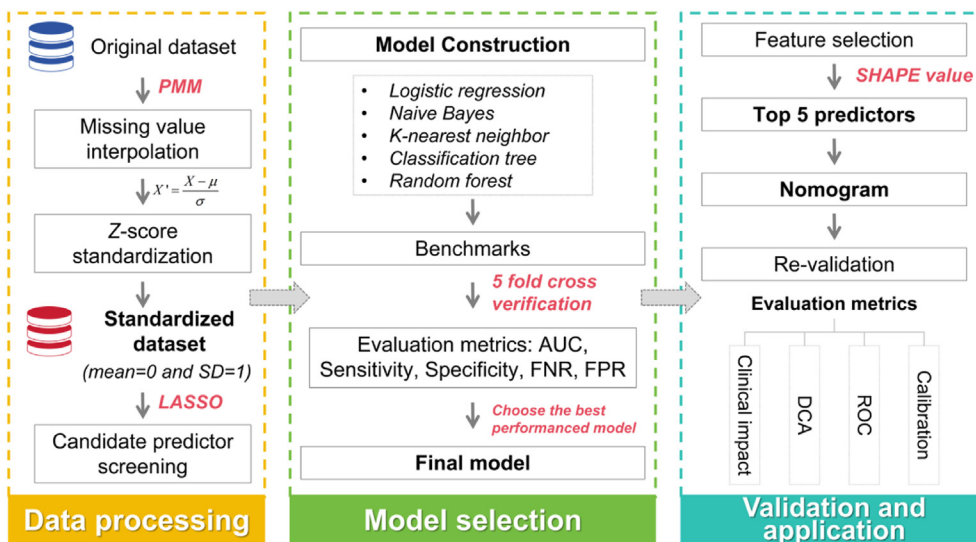

Figure 1. Flow diagram of the model-building approach. AUC, area under the curve; FNR, false negative rate; FPR, false positive rate; ROC, receiver operating characteristic; DCA, curve of nomogram.

Table 1
General information of patients in training set and validation set.

Variables	Total $n = 755$	Training set $n = 529$	Validation set $n = 226$	P value
Gender				
Female	489 (64.8%)	349 (66.0%)	140 (61.9%)	0.289
Male	266 (35.2%)	180 (34.0%)	86 (38.1%)	
Age (year)	53.12 ± 11.94	53.27 ± 12.05	52.78 ± 11.83	0.607
Cancer stage				
Unstaged	17 (2.3%)	14 (2.6%)	3 (1.3%)	0.238
Stage I	141 (18.7%)	95 (18.0%)	46 (20.4%)	
Stage II	154 (20.4%)	116 (21.9%)	38 (16.8%)	
Stage III	154 (20.4%)	111 (21.0%)	43 (19.0%)	
Stage IV	289 (38.3%)	193 (36.5%)	96 (42.5%)	
Combined hypertension	79 (10.5%)	59 (11.2%)	20 (8.8%)	0.344
Combined diabetes	51 (6.8%)	32 (6.0%)	19 (8.4%)	0.237
BMI (kg/m^2)	22.45 ± 3.54	22.58 ± 3.60	22.16 ± 3.39	0.133
ADL score	95.42 ± 13.76	95.06 ± 14.20	96.26 ± 12.69	0.250
NRS-2002 score	1.70 ± 1.30	1.71 ± 1.30	1.69 ± 1.29	0.801
RBC (10^{12}/L)				
< 3.8	329 (43.6%)	222 (42.0%)	107 (47.3%)	
3.8–5.1	370 (49.0%)	265 (50.1%)	105 (46.5%)	0.345
> 5.1	56 (7.4%)	42 (7.9%)	14 (6.2%)	
WBC (10^9/L)				
< 3.5	85 (11.3%)	60 (11.3%)	25 (11.1%)	
3.5–9.5	559 (74.0%)	396 (74.9%)	163 (72.1%)	0.563
> 9.5	111 (14.7%)	73 (13.8%)	38 (16.8%)	
PLT (10^9/L)				
< 125	55 (7.3%)	39 (7.4%)	16 (7.1%)	
125–350	13 (1.7%)	11 (2.1%)	2 (0.9%)	0.590
> 350	687 (91.0%)	479 (90.5%)	208 (92.0%)	
HCT (%)				
< 35	374 (49.5%)	264 (49.9%)	110 (48.7%)	
35–45	359 (47.5%)	251 (47.4%)	108 (47.8%)	0.784
> 45	22 (2.9%)	14 (2.6%)	8 (3.5%)	
NEUT (10^9/L)				
< 1.8	45 (6.0%)	35 (6.6%)	10 (4.4%)	
1.8–6.3	449 (59.5%)	313 (59.2%)	136 (60.2%)	0.505
> 6.3	261 (34.6%)	181 (34.2%)	80 (35.4%)	
C-reactive protein (mg/L)				
0–6	391 (51.8%)	282 (53.3%)	109 (48.2%)	0.201
> 6	364 (48.2%)	247 (46.7%)	117 (51.8%)	
Serum albumin (g/L)				
< 40	434 (57.5%)	302 (57.1%)	132 (58.4%)	
40–55	321 (42.5%)	227 (42.9%)	94 (41.6%)	0.737
International normalized ratio				
< 0.85	13 (1.7%)	10 (1.9%)	3 (1.3%)	
0.85–1.2	699 (92.6%)	486 (91.9%)	213 (94.2%)	0.611
> 1.2	43 (5.7%)	33 (6.2%)	10 (4.4%)	
Activated partial thromboplastin time (s)				
< 24	100 (13.2%)	71 (13.4%)	29 (12.8%)	
24–32	557 (73.8%)	381 (72.0%)	176 (77.9%)	0.125
> 32	98 (13.0%)	77 (14.6%)	21 (9.3%)	
Procalcitonin (ng/mL)				
< 0.1	632 (83.7%)	444 (83.9%)	188 (83.2%)	0.570
0.1–0.25	39 (5.2%)	24 (4.5%)	15 (6.6%)	
0.25–0.5	18 (2.4%)	12 (2.3%)	6 (2.7%)	
> 0.5	66 (8.7%)	49 (9.3%)	17 (7.5%)	
D-dimer (ng/L)	2.50 ± 4.66	2.52 ± 4.33	2.45 ± 5.37	0.863
Catheter day (day)	581.47 ± 1706.55	605.04 ± 2007.23	526.33 ± 548.10	0.406
Incision infection	26 (3.4%)	17 (3.2%)	9 (4.0%)	0.596
Localized skin infection	20 (2.6%)	16 (3.0%)	4 (1.8%)	0.326
Receive chemotherapy	676 (89.5%)	473 (89.4%)	203 (89.8%)	0.866

BMI, body mass index; ADL, Activities of Daily Living; RBC, red cell count; WBC, white blood count; PLT, platelet; HCT, hematocrit; NEUT, neutrophil count levels; NRS, nutritional risk screening.

Construction and validation of nomogram

To build a nomogram model, we selected the top 5 predictors of features (importance score > 8) to enhance the practicality of the nomogram model, we discretized certain continuous variables based on their clinically established normal ranges. This step was taken to simplify the model's application in clinical settings, making it more user-friendly for health care professionals by aligning variable measurements with common clinical benchmarks. Fig. 4A showcases the constructed nomogram model, which depicts the relative importance of each predictor in predicting the outcome. This nomogram model exhibited an AUC value of 0.974, indicating a good predictive performance (above the acceptable threshold of 0.7). For example, as shown in Fig. 4B, the patient had procalcitonin > 0.5 ng/ml; had a catheter for 50.3 months; was
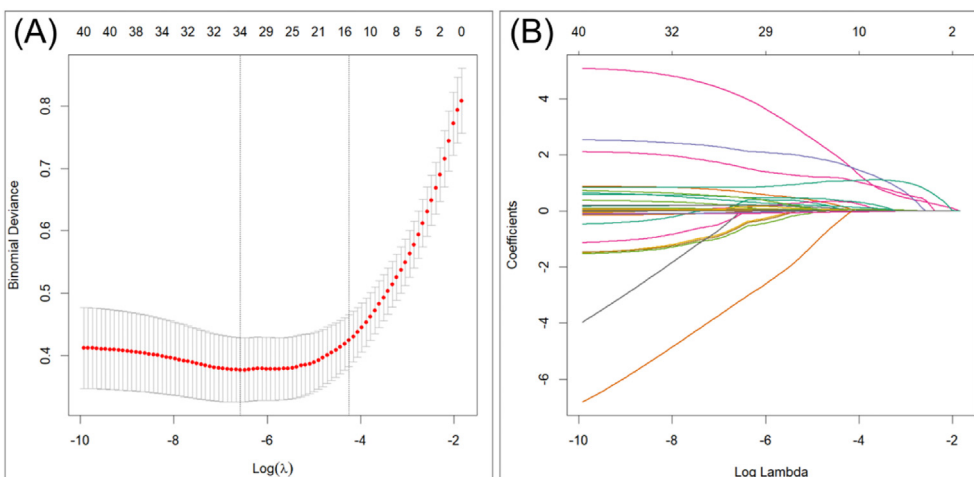
Figure 2. LASSO regression analysis result chart. A: LASSO regression cross validation plot; B: LASSO regression coefficient path diagram. LASSO, least absolute shrinkage and selection operator.

Table 2
Prediction performance indicators of prediction models and oversampling models built by 5 types of learners.

Learner name	AUC	Sensitivity	Specificity	FNR	FPR
Classification tree	0.82	0.50	0.95	0.50	0.05
Naive Bayes	0.85	0.55	0.91	0.45	0.09
K-nearest neighbor	0.90	0.50	0.96	0.50	0.04
Logistic regression	0.92	0.67	0.94	0.33	0.06
Random forest	0.94	0.56	0.97	0.44	0.03

AUC, area under the curve; FNR, false negative rate; FPR, false positive rate.
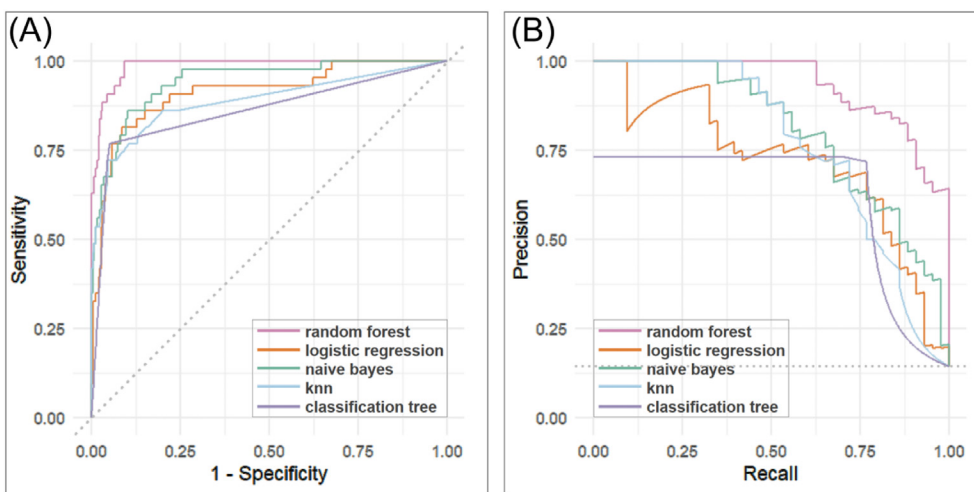

Figure 3. ROC curves and precision-recall (PRC) curves for the five different models. A: ROC curves of different machine learning models; B: PRC curves of different machine learning models. ROC, receiver operating characteristic.

receiving parenteral nutrition, had a normal neutrophil count, and had an NRS-2002 nutritional risk score of 1 point. As can be seen from the figure, the total points are 128, and the corresponding predicted probability is > 0.9, indicating that the CRBSI risk is higher, which is consistent with the actual results. To further evaluate the predictive performance of the nomogram, we conducted a performance test, and the results of which are displayed in Fig. 5.

Discussion

Superiority of totally implantable venous access port-catheter-related bloodstream infection risk prediction model

In this study, several different machine learning algorithms were employed to construct the TIVAP-CRBSI prediction model, and their

Table 3
Ranking of importance of the top 15 predictor.

Rank	Predictor	Importance score
1	Procalcitonin level	70.293
2	Catheter day	9.393
3	Receive parenteral nutrition treatment	9.257
4	NRS-2002 score	8.289
5	Neutrophil count levels	8.024
6	Hematocrit levels	6.897
7	International standardized coagulation ratio	5.497
8	White blood cell count level	5.479
9	Localized skin infection	5.221
10	Platelet count level	5.074
11	Serum albumin levels	5.016
12	Neutrophil percentage levels	4.932
13	C-reactive protein levels	4.820
14	BMI	4.735
15	D-dimer level	4.558

BMI, body mass index; NRS, nutritional risk screening.

performances were compared to select the best one for constructing the final model. This approach demonstrates the scientific and rigorous nature of the research method. Moreover, the study also addressed the low interpretability of machine learning algorithms by incorporating an importance of the explanation of predictor variables. By ranking variable importance, the more crucial variables were identified and used to construct a nomogram. This nomogram reduces the clinical use cost of the TIVAP-CRBSI prediction model and increases the convenience of risk prediction. In addition, the TIVAP-CRBSI risk prediction model built in this study has broad applicability to all tumor patients with TIVAP, without confining to specific types of tumors. This universality increases the potential practical significance of the model. Applying the TIVAP-CRBSI risk prediction model to clinical patients can assist in identifying high-risk groups and their influencing factors and provide a reference for medical staff to implement appropriate intervention measures. The

TIVAP-CRBSI prediction model developed in this study has great potential to improve patient safety and the quality of medical care.

The incidence of CRBSI in TIVAP varies across different studies due to varying indications for TIVAP implantation and individual patient conditions. Currently, the global incidence ranges from approximately 0.38%–12.5%.[13] Late CRBSI in TIVAP occurs at a rate of 5.6%–9.26%, and 30% of TIVAP patients discontinue anti-tumor chemotherapy due to bloodstream infections.[14] Despite the low incidence, the prevention and treatment of TIVAP-CRBSI cannot be overlooked in clinical practice. Although previous studies have explored the risk factors of TIVAP-CRBSI, there is a wide variation in research findings, and no consensus has been reached. This discrepancy may be attributed to differences in clinical workflows, inpatient settings, and the strengths and weaknesses of study designs. Risk factors reported in previous studies for TIVAP-CRBSI typically include elevated C-reactive protein levels, TIVAP combined with other surgeries, hospitalization environment, patient source, and a history of hematological malignancies.[29,30] The key to preventing TIVAP-CRBSI lies in the early identification of its risk factors and prompt intervention. By constructing a TIVAP-CRBSI risk prediction model, clinical medical staff can have a concise and convenient tool for quickly identifying high-risk groups and factors associated with infection. This model provides support for early intervention to prevent TIVAP-CRBSI, reduce infection incidence, extend catheter lifespan, and ensure effective patient treatment.

Researchers have extensively studied the risk factors, prevention, and control strategies for CRBSI. However, there is a lack of studies focusing on early warning models for CRBSI risk scores and even fewer specific risk assessment tools for TIVAP patients. Currently, one of the more established models is the Michigan Peripherally Inserted Central Venous Catheters (PICC) related bloodstream infection scoring model (MPC).[31] Erica Herc et al. used the Cox proportional hazard model to construct the MPC model. They followed a total of 23,088 patients with PICC implants and analyzed the risk factors associated with PICC-CRABSI to develop the MPC score. The research findings indicate a significant correlation between the MPC score
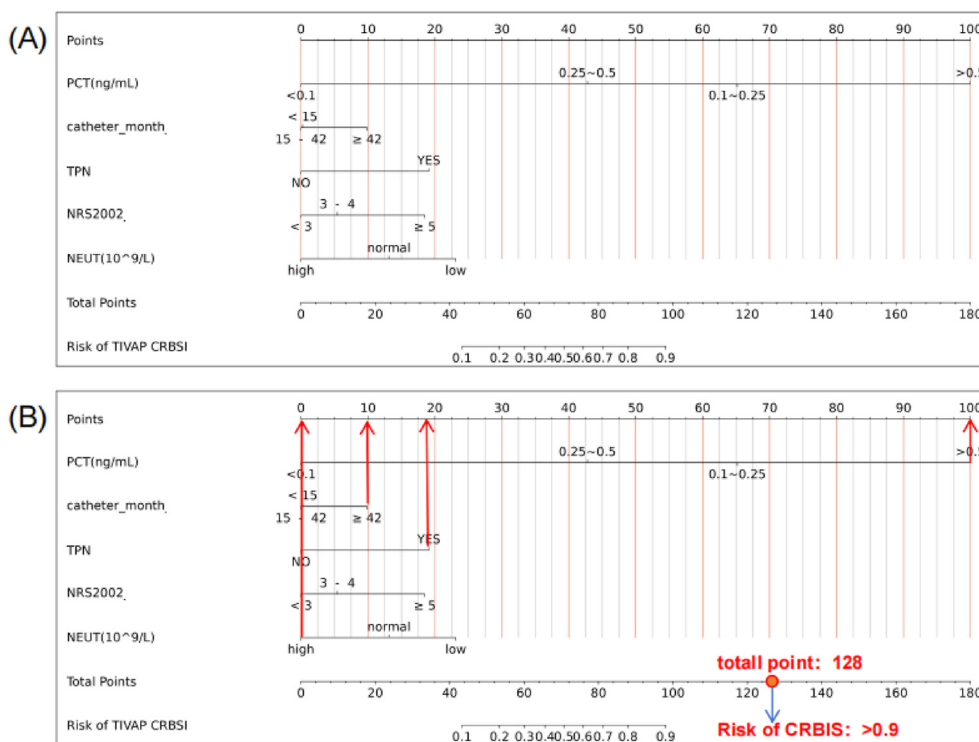

Figure 4. Risk prediction nomogram for *TIVAP-CRBSI*. PCT: procalcitonin; catheter month: catheter usage time, in months; TPN: receiving parenteral nutrition; NRS-2002: nutritional risk screening assessment score; NEUT: neutrophil count, normal value is 1.8–6.3×10^9/L. NEUT, neutrophil count levels; NRS, nutritional risk screening; PCT, procalcitonin level; TIVAP-CRBSI, totally implantable venous access port-catheter-related bloodstream infection; TPN, total parenteral nutrition.
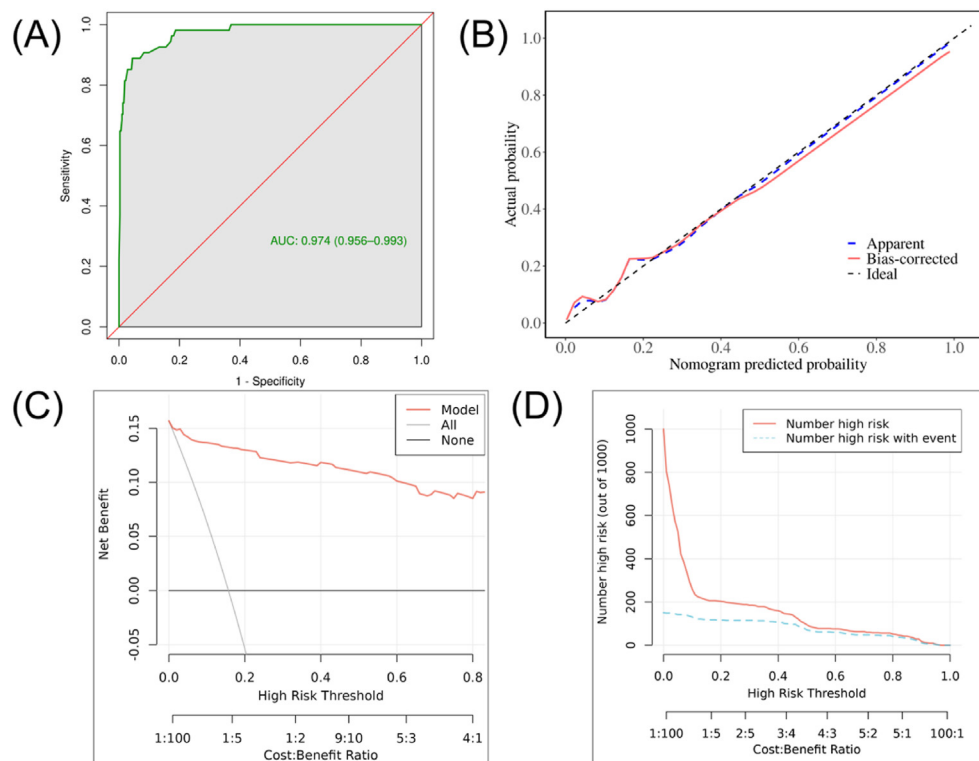
Figure 5. Predictive performance of the nomogram. A: ROC curve of nomogram; B: calibration curve of nomogram; C: DCA curve of nomogram; D: nomogram clinical impact curve. ROC, receiver operating characteristic.

and the risk of CRBSI ($P < 0.001$), and the model demonstrates an average prediction performance with an area under the ROC curve of 0.67–0.77. However, it is important to note that this model is specifically designed for PICC patients and cannot be applied to TIVAP patients. Therefore, there is a need for the development of specific risk assessment tools and models specifically tailored to TIVAP patients. This study would provide a more accurate and targeted approach for assessing the risk of CRBSI in this specific patient population. In 2023, Gao et al.[32] reported a systematic review of CRBSI prediction models, highlighting considerable variability in target populations, predictors, catheter types, and outcome definitions. But it also highlights the generally high risk of bias and concerns about the suitability of the assessment model. In Gao's study, the models included in the review mainly used traditional regression techniques, which, although valuable, may not fully capture the complex and dynamic relationships in clinical data. Our model leverages advanced machine learning algorithms specifically designed to address these limitations by leveraging models of complex, nonlinear interactions, potentially providing a more nuanced understanding of risk factors. This systematic review also identifies significant shortcomings of existing models, such as insufficient sample size and inappropriate handling of missing data, which are areas to which we paid careful attention in model development. Therefore, our machine learning-based model not only meets the outstanding needs for methodological rigor and transparency, but also sets a new benchmark for predictive modeling of TIVAP-related bloodstream infections, paving the way for improved clinical decision-making and patient outcomes.

Risk factors for totally implantable venous access port-catheter-related bloodstream infection

In our risk prediction model for TIVAP-CRBSI, we have identified the key variables that significantly contribute to the risk assessment. These variables include procalcitonin level (PCT), catheter day, administration of parenteral nutrition (TPN), NRS-2002 score, and neutrophil count (NEUT). PCT is an important biomarker that can indicate whether the

body is infected, making it a valuable variable in our model. Previous research has established a correlation between PCT levels and CRBSIs, particularly those associated with TIVAP.[33] In this investigation, a PCT level exceeding 0.1 ng/ml significantly elevates the risk of CRBSI in patients. PCT is the biomarker, it experiences elevated plasma concentrations in response to severe infections caused by bacteria, fungi, and parasites, as well as conditions like sepsis and organ failure. Unlike autoimmune, allergic, or viral infections, PCT levels do not rise. Additionally, localized bacterial infections, minor infections, and chronic inflammation do not trigger an increase in PCT levels, with bacterial endotoxins playing a pivotal role in its induction. PCT levels mirror the systemic inflammatory response, influenced by factors such as the size and type of the infected organ, bacterial species, inflammation severity, and the immune response state. Vasiliki's study found that in patients with CRBSI, PCT levels increased by more than 0.2 ng/mL within four days prior to diagnosis, and levels exceeding 0.7 ng/mL were indicative of CRBSI.[33] A meta-analysis, including 7 studies and 347 participants concluded that elevated PCT levels are significantly associated with CRBSI, demonstrating the effectiveness of this biomarker in predicting CRBSI. Pooled analysis showed that the pooled odds ratio (OR) of high PCT levels was 23.36, with a sensitivity of 85% and a specificity of 89%, indicating that PCT is an effective predictor of CRBSI.[34] This suggests that monitoring blood cell counts can provide insights into the risk of TIVAP-CRBSI.[35] As a biomarker, PCT not only indicates signs of infection in patients but also guides clinicians in formulating antibiotic strategies.[36] Increasing evidence shows that using PCT to guide antibiotic treatment can reduce overall antibiotic use,[37] shorten treatment duration, and effectively lower the risk of death.[38] In the diagnosis of CRBSI, blood culture results are often regarded as the gold standard. However, the long testing time and high requirements for specimen collection make it challenging to confirm infections promptly, leading to delayed treatment or premature removal of TIVAPs in undiagnosed cases. Inflammatory biomarkers play an irreplaceable role in identifying, monitoring, and evaluating the clinical severity and antibiotic treatment effects in

infected patients. Therefore, in clinical practice, inflammatory biomarkers such as PCT should be closely monitored, and early intervention should be applied upon detecting abnormalities to avoid sepsis or septic shock induced by TIVAPs-related CRBSI.[39] Regarding the duration of TIVAP use, our study reveals that longer TIVAP use is associated with a higher likelihood of TIVAP-CRBSI. This may be due to the fact that the risk of infection gradually increases with the prolongation of use. TIVAP is most commonly used in chemotherapy and supportive treatments for patients with various malignant tumors who face severe immune system suppression during these treatments. As the duration of anti-tumor treatment extends, the patient's ability to combat infections is significantly reduced. This immunosuppressive state makes patients more susceptible to external pathogens, thereby increasing the risk of CRBSI. Therefore, continuous monitoring and timely feedback on patient infections are essential, especially for those who have been using TIVAP for extended periods. Medical institutions should leverage information systems to facilitate collaboration among multiple departments, jointly manage and supervise, regularly collect and analyze CRBSI data at infusion ports, identify problems and deficiencies in infection control, and adjust and improve relevant measures accordingly to ensure the safety of patient diagnosis and treatment. The NRS-2002 nutritional risk screening score, along with the administration of parenteral nutrition, serves as a significant predictor for CRBSI associated with TIVAP. These elements collectively gauge the nutritional health of patients, indicating that individuals with elevated NRS-2002 scores face an increased malnutrition risk.[36,40] The NRS-2002 Nutritional Risk Screening tool, developed by the European Society for Clinical Nutrition and Metabolism (ESPEN), is an objective method for assessing nutritional risk. The NRS-2002 score predicts the risk of malnutrition, with higher scores indicating poorer nutritional status. Typically, Total Parenteral Nutrition (TPN) is reserved for those identified at nutritional risk or confirmed to be malnourished, and receiving parenteral nutrition through TIVAP has been identified as a risk factor for developing TIVAP-CRBSI, which is consistent with previous research findings.[11,41] Our study reveals that patients with compromised nutritional status exhibit a heightened susceptibility to CRBSI. In addition, a study involving patients with advanced solid tumors on home parenteral nutrition managed using a standardized catheter care protocol evaluated the incidence of and factors associated with CRBSI.[42] The study found that the majority of the patient population was moderately to severely malnourished at baseline and had received chemotherapy or radiotherapy during home parenteral nutrition. Therefore, for tumor patients, standardized nutritional support therapy is a crucial component of CRBSI prevention measures at infusion ports. For patients with poor nutritional status, priority should be given to nutritional support and improvement through reasonable dietary adjustments, oral nutritional supplements, or parenteral nutrition treatment to enhance nutritional levels and immunity, thereby reducing the risk of CRBSI. Additionally, for patients receiving TPN, special attention should be paid to preventing CRBSI. Strict aseptic techniques must be followed during parenteral nutrition therapy to ensure the safety of nutrient solution preparation, storage, and infusion. This emphasizes the importance of closely monitoring and implementing appropriate infection prevention measures during the administration of parenteral nutrition through TIVAP to reduce the risk of CRBSI.[43] Neutrophil counts confirm and reflect the patient's immune function. Immunosuppression is an almost unavoidable complication in antitumor therapy. Previous studies have shown that many patients with malignant tumors inevitably experience a decrease in white blood cells, lymphocytes, or neutrophils after long-term chemotherapy,[44] which further weakens their ability to fight infections, particularly CRBSI. In this study, decreased neutrophil levels were an important predictor of TIVAP-CRBSI in patients. Lower neutrophil levels imply poorer immune function, making these patients more susceptible to systemic bloodstream infections.[45] In clinical practice, special attention should be given to patients whose immune function is continuously suppressed due to chemotherapy or other anti-tumor

therapies.[46] Additional protective measures should be implemented to prevent the development of CRBSI in these patients.

Implications for nursing practice and research

One of the main strengths of this study is the utilization of machine learning algorithms to construct the model, which enhances the effectiveness and accuracy of the predictive model. Additionally, the quality of the data are ensured by conducting manual reviews of the data entry process. Furthermore, adherence to the reporting recommendations outlined in the TRIPOD guidelines[47] adds strength to the study by promoting transparency and reducing the risk of bias. By considering the variables in our risk prediction model, clinicians can have a more comprehensive assessment tool to identify high-risk patients and implement timely interventions to prevent TIVAP-CRBSI. Ensuring the interpretability of our models within clinical environments is paramount, as it equips health care professionals with practical insights. Despite the inherent complexity of machine learning models, considerable effort has been directed towards making their outputs accessible and pertinent for clinical decision-making. This work involves reformulating the model's conclusions into a format that aligns with the established workflows and decision-making processes of clinicians. Such an approach aids in seamlessly integrating these models into everyday clinical practice, enhancing their utility and adoption. Our purpose in building this model is to enable clinical staff to identify the risk of CRBSI as much as possible when the patient is hospitalized, so the time point for assessment using the model should be when the patient is admitted. This should be a routine medical evaluation item during the patient's hospitalization and continues as the patient's condition changes. In addition, the visualization of the model by the nomogram also has significant benefits for treating, identifying, or predicting the occurrence of CRBSI, that is, we can identify high-risk factors through implementation assessment and make early changes.

Limitations

However, there are certain limitations that should be acknowledged. Firstly, the lack of external validation is a limitation of this study. Although internal validation was performed, it is important to validate the model using data from different sources or settings to assess its generalizability and robustness. Another limitation is that all the data used in this study were obtained from a single cancer center, which could introduce some limitations in terms of the diversity and representativeness of the study population. This may hinder the widespread application of the model in other health care settings. While this study benefits from the use of machine learning algorithms, manual data review, and adherence to reporting guidelines, the lack of external validation, and the reliance on data from a single cancer center should be considered as limitations. Future research should focus on validating the model externally and exploring the applicability of the model in diverse health care settings to further establish its utility.

Conclusions

In conclusion, the application of machine learning techniques has enabled the development of a reliable and accurate predictive model for CRBSI in cancer patients with TIVAP implants. By utilizing the predictive model, clinicians can identify high-risk patients and tailor preventive strategies accordingly, leading to a reduction in CRBSI rates and improving patient outcomes. Moreover, patients can benefit from being informed about their individual risk profiles, allowing them to actively participate in their health care and take necessary precautions to minimize the risk of CRBSI. Overall, the integration of this predictive model into clinical practice enhances the management and care of cancer patients with TIVAP implants, leading to more effective prevention and reduced rates of CRBSI.

CRediT authorship contribution statement

Fan Wang: Formal analysis, Data curation, Writing – original draft, Writing – review & editing. **Yanyi Zhu & Lijuan Wang:** Conceptualization, Writing – original draft. **Caiying Huang:** Data curation, Writing – original draft. **Ranran Mei**: Writing – original draft. **Li-e Deng, Xiulan Yang, & Yan Xu**: Data curation; **Lingling Zhang & Min Xu**: Conceptualization, Writing – original draft, Supervision. All authors had full access to all the data in the study, and the corresponding author had final responsibility for the decision to submit for publication. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author, M.X. The data are not publicly available due to their containing information that could compromise the privacy of research participants.

Code availability statement

The code used to build the model is available on https://github.com/WadeWang0527/tivap_crbsi_model.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used chatGPT 3.5 in order to check, confirm the grammar of the sentence and suggest changes. After using this tool, the authors reviewed and edited the content as needed and takes full responsibility for the content of the publication.

Declaration of competing interest

The authors declare no conflict of interest.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.apjon.2024.100546.

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