Predictive model for totally implanted venous access ports-related long-term complications in patients with lung cancer

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Abstract. Totally implanted venous access ports (TIVAPs), which are typically used in oncological chemotherapy and parenteral nutritional support, are convenient and safe, and thus offer patients a higher quality of life. However, insertion or removal of the device requires a minor surgical operation. Long-term complications (>30 days post insertion), such as catheter migration, catheter-related thrombosis and infection, are major reasons for TIVAP removal and are associated with a number of factors such as body mass index and hemoglobin count. Since management of complications is typically time-consuming and costly, a predictive model of such events may be of great value. Therefore, in the present study, a predictive model for long-term complications following TIVAP implantation in patients with lung cancer was developed. After excluding patients with a large amount of missing data, 902 patients admitted to The First Affiliated Hospital with Nanjing Medical University (Nanjing, China) were ultimately included in the present study. Of the included patients, 28 had complications, indicating an incidence rate of 3.1%. Patients were randomly divided into training and test cohorts (7:3), and three machine learning-based anomaly detection algorithms, namely, the Isolation Forest, one-class Support Vector Machines (one-class SVM) and Local Outlier Factor, were used to construct a model. The performance of the model was initially evaluated by the Matthew's correlation coefficient (MCC), area under curve (AUC) and accuracy. The one-class SVM model demonstrated the highest performance in classifying the risk of complications associated with the use of the intracavitary electrocardiogram method for TIVAP implantation in patients with lung cancer (MCC, 0.078; AUC, 0.62; accuracy, 66.0%). In conclusion, the predictive model developed in the present study may be used to improve the early detection of TIVAP-related complications in patients with lung cancer, which could lead to the conservation of medical resources and the promotion of medical advances.

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Introduction

Lung cancer is the most prevalent malignancy worldwide, the incidence of which has increased annually among the elderly for the past 40 years according to the surveillance, epidemiology and end results (SEER) database (1). Treatment modalities for lung cancer include surgery, radiotherapy, chemotherapy, targeted therapy, antiangiogenic therapy and immunotherapy. Among these treatment modalities, chemotherapy is the cornerstone of adjuvant or palliative therapy. Routinely, the drugs for chemotherapy are administered through a central venous access, such as central venous catheters (CVCs), peripherally inserted catheters (PICCs) or totally implanted venous access ports (TIVAPs). PICCs are often used for short-term treatment (up to 3 months) in the perioperative or intensive care setting, while CVCs and TIVAPs are used for medium to long-term treatments (months to years) such as total parenteral nutrition and chemotherapy. Potential complications of central venous accesses usually include short-term (≤30 days of insertion) and long-term complications (>30 days post insertion). Short-term complications may present with symptoms of hemorrhage, hemothorax, pneumothorax, air embolism, cardiac arrhythmias or nerve palsy. Long-term complications mainly include catheter migration,

catheter-related thrombosis and infection (2-4). These three types of central venous access reduce repeated venipuncture and avoid focal venous injury and tissue necrosis caused by repeated administration of anticancer therapies. Furthermore, TIVAPs have lower reported rates of catheter-related bloodstream infections (CRBSIs) than the other two types of central access (5). TIVAPs are also more optimal for bathing and swimming, which are restricted with external vascular access, and may appeal to patients concerned about the psychological implications of the presence of visible non-implanted catheters. A meta-analysis by Yeow *et al* (6) reported that TIVAPs were superior to CVCs and PICCs in terms of complication rate and quality of life without compromising cost-effectiveness. However, insertion or removal of TIVAPs requires a minor surgical operation, and long-term complications are major reasons for removal, which include pocket infection, CRBSI, catheter-related thrombosis and catheter migration (7-9). According to the literature, the incidences of catheter-related infection, thrombosis and migration were 3-10%, 1.06-11.4% and 0.05-3.5%, respectively (10-12). Since management of complications is typically time-consuming and costly, a risk prediction model of related events may be of great value. However, such models are not well established at present. The main focus of the present study is to explore the risk factors for long-term complications after TIVAP placement and construct a predictive model.

Machine learning, with its powerful and efficient computational capabilities, can assist in the diagnosis of diseases through well-trained models (13). Thus far, machine learning has been widely used in foundation and clinical medicine, new drug development and public health (14-16). Machine learning-based abnormality detection overcomes the data imbalance problems encountered in the real healthcare world (17). To the best of the authors' knowledge, the present study is the first to develop a machine learning-based risk prediction model for long-term complications associated with TIVAP implantation in patients with lung cancer.

Materials and methods

Patients and variables. The present retrospective, low-risk study was approved by The Ethics Committee of The First Affiliated Hospital with Nanjing Medical University (Nanjing, China; approval no. 2022-SR-518) and informed patient consent was waived. Clinical data between January, 2016 and December, 2018 were obtained from the inpatient recording system. The patient inclusion criteria were as follows: i) Aged ≥60 years (according to the World Health Organization criteria for the age classification of older individuals in developing countries); ii) pathologically diagnosed with lung cancer and requiring chemotherapy; and iii) had TIVAP implanted by a physician and a nurse in the operation room and aided by ultrasound guided venipuncture and intracavitary electrocardiogram (IC-ECG) guided tip localization (18,19). Patients with large amount of missing data were excluded from the study. There were 666 males and 236 females, with a median age of 67.23±0.52 (range 60-90) years. The primary end point in the present study was long-term complications and all complications were diagnosed by the current gold standard (3,20,21).

By searching the relevant literature (2,22-32), the data collected in the present study were as follows: i) Demographic characteristics, including age, sex, body mass index (BMI), smoking history, thrombus history, history of catheter placement, comorbidities, pleural effusion, cough, pathological type based on WHO standard (33) and tumor stage based on the 8th Edition of the TNM Classification of the International Association for the Study of Lung Cancer (34); ii) laboratory indicators, including white blood cell (WBC) counts, platelet (PLT) counts, hemoglobin (HB), D-dimer, activated partial thromboplastin time (APTT), fibrinogen, albumin (ALB), total bilirubin and creatinine (Cr); iii) medication for lung cancer, including platinum, pemetrexed, bevacizumab, docetaxel, paclitaxel, radiotherapy, leukocyte stimulant and PLT stimulant; and iv) data related to the TIVAPs, including implantation site (right or left side of the body), catheter length and operation time

Model development. The occurrence and detection of abnormalities is the focus of disease prediction. Anomaly detection, also known as outlier detection, was used to build the predictive model in the present study (35). Anomaly detection has a wide range of applications in various scenarios, such as earth sciences, traffic monitoring, early diagnosis of diseases and disease outbreak detection (36-38). To improve the accuracy of the developed model and to identify relevant risk factors that have not yet been recognized, all data were incorporated into the model.

The modeling process, in which machine learning algorithms suitable for supervised learning tasks [including Isolation Forest (iForest), Local Outlier Factor (LOF) and one-class Support Vector Machines (one-class SVM)] were used, was divided into steps. First, the collected data were pre-processed, including missing value processing, feature selection and standardization. The tools used for this step were Pandas version 1.5.2 (https://github.com/pandas-dev/pandas), Numpy version 1.26.0 (https://github.com/numpy/numpy) and Seaborn version 0.12.2 (https://github.com/mwaskom/seaborn). The dataset was then divided into training and test sets, ensuring that model training was performed on a representative sample of data, while retaining an independent dataset for evaluation. Second, the model parameters were adjusted (contamination=28/902) according to the data distribution after initializing the model. Training was then performed on the training set, from which patterns and relationships between input features and implanted outcomes were learned. During the training process, the algorithm parameters were iteratively adjusted to minimize the prediction error using GridSearchCV in the hyperparameter tuning. The tool used for this step was scikit-learn (sklearn) version 1.2.2 (https://github.com/scikit-learn/scikit-learn). Finally, a model evaluation was performed and the receiver operating characteristic curves (ROC) were plotted. The tool for plotting ROC was matplotlib version 3.7.1 (https://github.com/matplotlib/matplotlib). A total of five common metrics were introduced, including accuracy, precision, recall, F1 score and area under the curve (AUC), to evaluate the performance of the model with the test set. In general, the higher the accuracy, precision, and recall of the model and the closer the F1 score is to 1, the more optimal the performance of the model. In addition, Matthew's correlation

coefficient (MCC) was introduced, which provided a more accurate assessment of performance with the unbalanced data sets to inform clinical decision-making and risk management. All the models were analyzed using Python version 3.10.5 (https://www.python.org/downloads/release/python-3105/).

Statistical analysis. Continuous variables are presented as the mean ± SD, while categorical variables are presented as numbers (n) and frequencies (%). Comparisons were conducted using χ^2 test or Fisher's exact test with scipy version 1.10.1 (https://github.com/scipy/scipy). P<0.05 was considered to indicate a statistically significant difference.

Results

Patient clinical characteristics in the training and test sets and the occurrence of complications. A total of 902 patients were included in the present study (Fig. 1). As shown in Table I, the training and test sets consisted of 631 and 271 patients, respectively. The median age of the training and test set was 67.35±0.42 and 67.10±0.62 years respectively. Males accounted for 74.8% of the training set and 71.6% of the test set. A total of 28 patients (3.1%) developed complications. There were no significant differences between the two sets except in the number of patients administered docetaxel or leukocyte stimulant (P<0.05; Table I), which suggested that the feature distribution of the two datasets was similar after data pre-processing, ensuring that the model had good generalization ability.

Feature selection; correlation analysis with heatmaps. Seaborn was used to construct correlation-based heatmaps (Fig. 2), to perform full factor analysis and to determine any correlations with the occurrence of complications. According to the heatmap, the factors that may be associated with complications include history of thrombosis, comorbidities, pleural fluid, adenocarcinoma, tumor stage, APTT, BMI, site and time of implantation, WBC, HB, D-dimer, ALB, Cr, antineoplastic agents and leukocyte stimulants. Among these factors, those with a correlation coefficient of ≥0.05 were BMI, HB, implantation time, docetaxel and leukocyte stimulants.

One-class SVM model performs the best among the three models. The performance of the one-class SVM model (MCC, 0.078; AUC, 0.62; accuracy, 66.0%) was significantly superior than the iForest (MCC, 0.015; AUC, 0.48; accuracy, 94.0%) and LOF (MCC, -0.017; AUC, 0.51; accuracy, 96.0%; Fig. 3 and Table II) models. The classification reports for patients in category 0 (without complications) and category 1 (with complications) provided more detailed performance metrics (Table II). Overall, the one-class SVM model had a positive MCC, a relatively balanced recall and performed well in the task.

Discussion

Different algorithms have different performances for specific datasets. In the present study, three common anomaly detection algorithms were applied to the same training set and their performances were compared. These three algorithms were chosen due to the following: i) iForest excels at identifying outliers by constructing random trees and isolating anomalies in shorter paths. iForest does not assume any potential data distributions and can effectively handle large datasets (39); ii) LOF is sensitive to local context, which is important in the healthcare setting as subtle changes may indicate abnormalities. Moreover, LOF is less affected by noise and different densities, which is consistent with the inherent variability of medical data (40); and iii) one-class SVM can implement boundary learning, it builds a hyperplane around most data points to isolate a few classes (anomalies). Additionally, one-class SVM is flexible to capture the complex relationships between risk factors by tweaking the kernel function and performs well when dealing with unbalanced datasets (41,42). In summary, iForest, LOF and one-class SVM were selected in the present study due to their effectiveness in detecting anomalies, robustness to noise, processing high-dimensional data and capturing complex relationships.

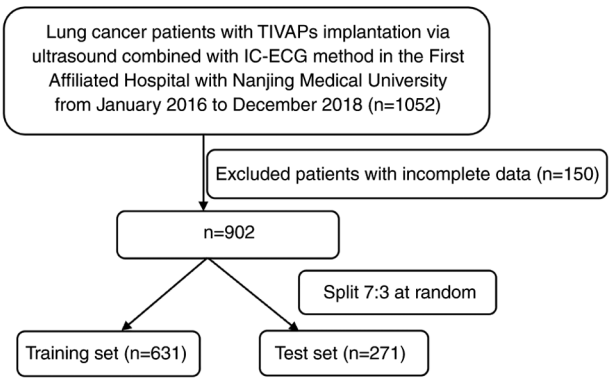

Figure 1. Study flowchart. Clinical data from January 2016 to December 2018 were collected from the inpatient and laboratory systems of The First Affiliated Hospital with Nanjing Medical University (Nanjing, China). All TIVAP implantation procedures were completed by a physician in the operating room aided by ultrasound-guided venipuncture and intracavitary electrocardiogram (IC-ECG)-guided tip localization. Patients with a large amount of missing data were excluded from the study. Ultimately, 902 patients were included in the present study. Included patients were randomly divided into the training and test sets (7:3). TIVAP, totally implanted venous access port; IC-ECG, intracavitary electrocardiogram.

The early identification of high-risk groups for long-term complications is important to improve the quality of life of patients with cancer and to reduce the waste of medical resources. To the best of our knowledge, the present study was the first to present a model that has been built on top of an anomaly detection algorithm. The results of the present study indicated that the one-class SVM model had the highest performance with an MCC, AUC and accuracy of 0.078, 0.62 and 66.0%, respectively. Reducing the occurrence of complications has always been the focus of healthcare professionals. To date, a number of factors such as catheter material, age, BMI, severe coughing, time interval from first use to placement, site of placement, hypoalbuminemia and leukopenia, have been identified in patients with cancer suffering from TIVAP-related complications (26,31,43-46).

Due to data sparseness, the present study was not able to evaluate the contribution of each variable to classification accuracy. However, the correlation-based heat map suggested that BMI, HB, implantation time, docetaxel and leukocyte stimulants may be closely related to the occurrence of

Table I. Baseline characteristics of the training (n=631) and test (n=271) sets.

Variables	Training set	Test set	P-value
Age, years	67.35±0.42	67.10±0.62	0.354
Sex, n (%)			1.000
Female	159 (25.2)	77 (28.4)	
Male	472 (74.8)	194 (71.6)	
BMI[a], n (%)			0.532
0	336 (53.2)	157 (57.9)	
1	38 (6.0)	9 (3.3)	
2	210 (33.3)	83 (30.6)	
3	47 (7.4)	22 (8.1)	
Smoking history, n (%)			0.976
No	251 (40.0)	117 (43.2)	
Yes	380 (60.0)	154 (56.8)	
Thrombosis history, n (%)			0.461
No	573 (90.8)	251 (100.0)	
Yes	58 (9.2)	20 (0.0)	
CVC history, n (%)			1.000
No	629 (99.7)	271 (100.0)	
Yes	2 (0.3)	0 (0.0)	
Comorbidities, n (%)			0.759
No	271 (42.9)	125 (46.1)	
Yes	360 (57.1)	146 (53.9)	
Pleural effusion, n (%)			0.421
No	358 (56.7)	144 (53.1)	
Yes	273 (43.3)	127 (46.9)	
Pathological type[b], n (%)			
1	376 (59.6)	153 (56.5)	0.338
2	164 (26.0)	83 (30.6)	0.833
3	71 (11.3)	30 (11.1)	0.760
4	4 (0.6)	2 (0.7)	1.000
5	14 (2.2)	8 (3.0)	1.000
Tumor stage[c], n (%)			0.482
1	72 (11.4)	47 (17.3)	
2	59 (9.4)	33 (12.2)	
3	141 (22.3)	58 (21.4)	
4	259 (41.0)	95 (35.1)	
5	58 (9.2)	23 (8.5)	
WBC, n (%)			0.758
Normal, 3.5-9.5x10^9/l	547 (86.7)	228 (84.1)	
Abnormal	84 (13.3)	43 (15.9)	
PLT, n (%)			0.686
Normal, 125-350x10^9/l	562 (89.1)	238 (87.8)	
Abnormal	69 (10.9)	33 (12.2)	
HB, n (%)			0.056
Normal, 115-150 g/l	490 (77.7)	208 (76.8)	
Abnormal	141 (22.3)	63 (23.2)	
Albumin, n (%)			1.000
Normal, 40-55 g/l	192 (30.4)	81 (30.0)	
Abnormal	439 (69.6)	190 (70.0)	
Total bilirubin, n (%)			0.287
Normal, 5.1-19 μmol/l	587 (93.0)	254 (93.7)	
Abnormal	44 (7.0)	17 (6.3)	

Table I. Continued.

Variables	Training set	Test set	P-value
Cr, n (%)			0.515
Normal, 41-81 μmol/l	524 (83.0)	211 (77.9)	
Abnormal	107 (17.0)	60 (22.1)	
D-Dimer, n (%)			0.438
Normal, ≤0.55 mg/l	287 (45.4)	116 (42.8)	
Abnormal	344 (54.5)	155 (57.2)	
Fibrinogen, n (%)			1.000
Normal, 2-4 g/l	412 (65.3)	178 (65.7)	
Abnormal	219 (34.7)	93 (34.3)	
APTT, n (%)			0.929
Normal, 25-31.3 sec	473 (75.0)	194 (71.6)	
Abnormal	158 (25.0)	77 (28.4)	
Implant site[d], n (%)			0.590
1	274 (43.4%)	112 (41.3%)	
2	307 (48.7%)	137 (50.6%)	
3	16 (2.5%)	4 (1.5%)	
4	34 (5.4%)	18 (6.6%)	
Depth, cm	23.58±0.27	23.36±0.43	0.231
Time, min	11.34±0.32	11.28±0.46	0.448
Treatments n (%)			
Platinum			1.000
No	54 (8.6)	19 (7.0)	
Yes	577 (91.4)	252 (93.0)	
Pemetrexed			0.870
No	261 (41.4)	123 (45.4)	
Yes	370 (58.6)	148 (54.6)	
Bevacizumab			0.858
No	598 (94.8)	262 (96.7)	
Yes	33 (5.2)	9 (3.3)	
Docetaxel			0.049[e]
no	559 (88.6)	239 (88.2)	
yes	72 (11.4)	32 (11.8)	
Paclitaxel			0.661
No	467 (74.0)	193 (71.2)	
Yes	164 (26.0)	78 (28.8)	
Radiotherapy			1.000
No	526 (83.4)	224 (82.7)	
Yes	105 (16.6)	47 (17.3)	
Leukocyte-stimulant			0.012[e]
No	173 (27.4)	61 (22.5)	
Yes	458 (72.6)	210 (77.5)	
PLT-stimulant			0.874
No	525 (83.2)	222 (81.9)	
Yes	106 (16.8)	49 (18.1)	
Complications n (%)			
No	610 (96.7)	264 (97.4)	
Yes	21 (3.3)	7 (2.6)	

[a]0 represents the normal range (18.5-23.9), 1 represents underweight (≤18.4), 2 represents overweight (24-27.9) and 3 represents obese (≥28). [b]1 represents adenocarcinoma, 2 represents squamous cell carcinoma, 3 represents small cell lung cancer, 4 represents metastatic lung cancer and 5 represents other cancer types. [c]1 represents stage I, 2 represents stage II, 3 represents stage III, 4 represents stage IV and 5 represents the other stages. [d]1 represents left axillary vein, 2 represents left internal jugular vein, 3 represents right axillary vein and 4 represents right internal jugular vein. [e]Indicates that the difference is statistically significant. BMI, body mass index; CVC, central venous catheters; WBC, white blood cell; PLT, platelet; HB, hemoglobin; Cr, creatinine; APTT, activated partial thromboplastin time.

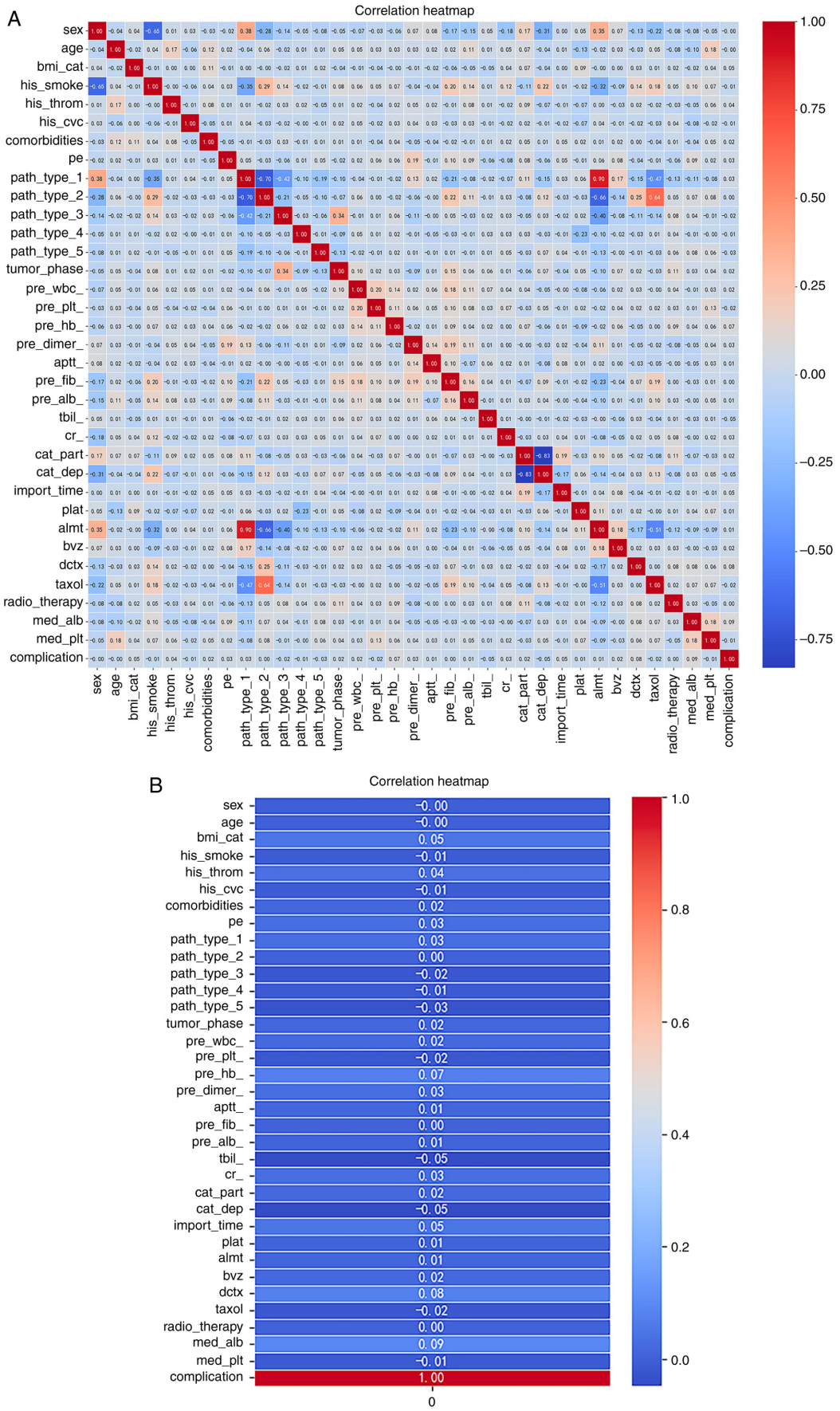

Figure 2. Correlation-based heatmap. (A) Seaborn was used to construct correlation-based heatmaps to perform full factor analysis and to determine any correlations with the occurrence of complications. (B) The detailed heatmap shows that the history of thrombosis, comorbidities, pleural fluid, adenocarcinoma, tumor phase, APTT, BMI, site and time of implantation, WBC, HB, D-dimer, ALB, Cr, antineoplastic agents and leukocyte stimulants may be associated with the development of complications. APTT, activated partial thromboplastin time; BMI, body mass index; WBC, white blood cell; HB, hemoglobin; ALB, albumin; Cr, creatinine.

Table II. Comparison of the performance metrics of the three models.

Algorithm	Precision	F1 score	Recall	MCC	AUC	Accuracy, %
iForest				0.015	0.48	94.0
0	0.97	0.97	0.97			
1	0.00	0.00	0.00			
One-class SVM				0.078	0.62	66.0
0	0.98	0.79	0.66			
1	0.04	0.08	0.57			
LOF				-0.017	0.51	96.0
0	0.97	0.98	0.99			
1	0.00	0.00	0.00			

0 represents no complications and 1 represents complications. MCC, Matthew's correlation coefficient; AUC, area under the curve; iForest, Isolation Forest; LOF, Local Outlier Factor; one-class SVM, one-class Support Vector Machines.

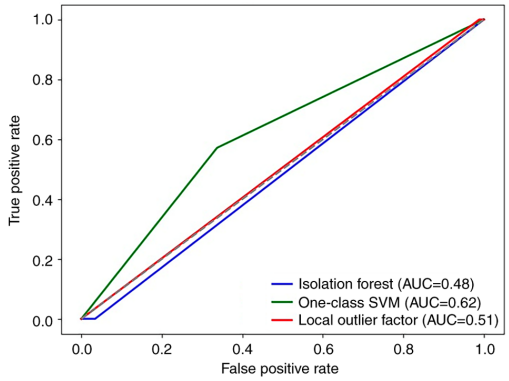

Figure 3. ROC curves for the three models. The AUC of the one-class SVM model was 0.62, which was a significant improvement compared with the Isolation Forest model (AUC, 0.48) and the Local Outlier Factor model (AUC, 0.51). ROC, receiver operating characteristic; AUC, area under the curve; one-class SVM, one-class Support Vector Machines.

long-term complications following port implantation. These findings were consistent with the real-world observations such that the occurrence and progression of an outcome event are often influenced by a combination of several factors. A previous study assessing the risk of venous thromboembolism in patients with cancer included BMI, HB and WBC count in the risk score (47), suggesting that the relationship between BMI, HB, leukocyte stimulants and catheter related thrombosis should be further studied using prediction models. Adverse reactions to antitumor drugs should also be noted. For instance, docetaxel may cause bone marrow suppression, manifesting as neutropenia, thrombocytopenia or anemia (48). This will undoubtedly increase the incidence of TIVAP-related infections. Hypoalbuminemia was found to be an independent risk factor for infections (26). However, the relationship between albumin correction and improved prognosis was not definitively identified; it can be further explored in larger datasets in the future. In the present study, the duration of implantation was shown to be associated with the development of long-term complications. However, a multicenter prospective French cohort study (ONCOCIP) showed that an average surgery duration of 25 min was not a risk factor (49). Therefore, this factor needs to be verified by further research.

In conclusion, a machine learning-based prediction model for the long-term complications associated with TIVAPs in patients with lung cancer was developed in the present study. The model will help to identify individuals at high risk of complications, which can improve their quality of life and prevent unnecessary waste of medical resources. However, the present study did have several limitations. First, since it was a single-center retrospective study, the generalizability of the conclusions was limited. Second, all of the participants were older (aged ≥60 years) and had a small number of complications. Third, no predictive model was developed for specific complications, which was mainly due to the low complication rate in the dataset. Therefore, predictive models for specific complications among individuals of different ages with other diseases should be developed in the future by building larger sample sets or conducting multicenter collaborative studies.

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Availability of data and materials

The data generated in the present study are included in the figures and/or tables of this article.

Authors' contributions

JJ, XTF, WHZ, YYZ and BQF contributed to the study design. XTF, ZYX and MW contributed to the data acquisition and table organization;. XTF contributed to data analysis. XTF contributed to writing the original draft. JJ contributed to review and editing. YYZ contributed to funding acquisition. JJ, XTF, YYZ and BQF confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The research protocol was approved by The Ethics Committee of the First Affiliated Hospital with Nanjing Medical University (Nanjing, China; approval no. 2022-SR-518) and patient informed consent was waived.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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