Cancer Management and Research

Elevate Series

Open Access Full Text Article

ORIGINAL RESEARCH

Predictive Value of the Total Bilirubin and CA50 Screened Based on Machine Learning for Recurrence of Bladder Cancer Patients

Xiaosong Zhang[1,2], Limin Ma[1]

[1]Department of Urology, Affiliated Hospital of Nantong University, Medical School of Nantong University, Nantong, 226001, People's Republic of China; [2]Department of Urology, Nantong Tongzhou District People's Hospital, Nantong, 226300, People's Republic of China

Correspondence: Xiaosong Zhang; Limin Ma, Email 13951314220@163.com; Email ntmalimin@163.com

Purpose: Recurrence is the main factor for poor prognosis of bladder cancer. Therefore, it is necessary to develop new biomarkers to predict the prognosis of bladder cancer. In this study, we used machine learning (ML) methods based on a variety of clinical variables to screen prognostic biomarkers of bladder cancer.

Patients and Methods: A total of 345 bladder cancer patients were participated in this retrospective study and randomly divided into training and testing group. We used five supervised clustering ML algorithms: decision tree (DT), random forest (RF), adaptive boosting (AdaBoost), gradient boosting machine (GBM), and extreme gradient boosting (XGBoost) to obtained prediction information through 34 clinical parameters.

Results: By comparing five ML algorithms, we found that total bilirubin (TBIL) and CA50 had the best performance in predicting the recurrence of bladder cancer. In addition, the combined predictive performance of the two is superior to the performance of any single indicator prediction.

Conclusion: ML technology can evaluate the recurrence of bladder cancer. This study shows that the combination of TBIL and CA50 can improve the prognosis prediction of bladder cancer recurrence, which can help clinicians make decisions and develop personalized treatment strategies.

Keywords: bladder cancer, recurrence, machine learning, biomarkers, retrospective study

Introduction

Bladder cancer is the 10th most common cancer in the world, with approximately 573,000 new cases and 213,000 deaths every year. Therefore, bladder cancer is the 9th major cause of cancer deaths.[1] The incidence of bladder cancer is closely related to tobacco smoking, occupational exposure, bladder related diseases, diet and genetic factors. As a common malignant tumor in the urinary system, despite the optimal treatment for patients with bladder cancer, its high recurrence rate is still a nodus in clinical practice.[2] Although a good deal of research and progress have been made on new molecular markers used to monitor the occurrence and development of bladder cancer,[3,4] cystoscopy is still the preferred method to detect disease progress due to factors such as sensitivity and specificity. For patients undergoing total cystectomy, postoperative follow-up can only rely on imaging examinations,[5,6] which not only imposes an economic burden on the patients but also makes it difficult to detect some small lesions in the early stages. Therefore, there is an urgent need to develop a relatively objective and cost-effective high-sensitivity biomarker for detecting bladder tumor recurrence.

Clinical chemical testing and fluid analysis are the main screening methods in clinical laboratories.[7] The change of each test index can be interpreted as a relationship with diseases, for instance, white blood cell, neutrophil, and C-reactive protein, which are considered to be closely related to inflammation.[8–10] Studies have shown that CA125, AFP, CEA, and NSE are tumor markers for ovarian cancer,[11] liver cancer,[12] gastric cancer,[13] and lung cancer,[14] respectively. In addition, the physiological significance of the alteration in ions, such as potassium ions, calcium ions, sodium ions, and chloride ions is complex.[15] However, analyzing these indicators individually may lead to biases and

Received: 30 December 2023
Accepted: 27 May 2024
Published: 31 May 2024

limitations in the judgment of clinical diseases.[16] Therefore, we urgently need to adopt various effective ways to process multidimensional datasets and effectively evaluate a large number of variables.

In the era of rapid computer development, the field of artificial intelligence (AI) has shifted from primarily theoretical research to real-world applications.[17] The application of AI is not only reflected in scientific and research scenarios, but also closely related to our daily activities, such as social networks, smart devices and autopilot mode.[18,19] Machine learning (ML) belongs to AI, which can improve predictions by detecting high-dimensional and potential nonlinear effects of variables.[20,21] Tree based models, such as decision tree (DT), random forest (RF), adaptive boosting (AdaBoost), gradient boosting machine (GBM), and extreme gradient boosting (XGBoost), have been widely applied in medical research.[22–24] However, the use of ML modalities has not been explored to a large extent. The few prior reports on ML technology in bladder cancer prediction focus on diagnosis and overall survival,[15,25,26] and there is no research on combining ML algorithms with clinical laboratory data to predict the recurrence of bladder cancer.

Herein, we collected clinical laboratory data of 345 bladder cancer patients from the Affiliated Hospital of Nantong University, mainly including biochemical markers. We explored the relationship between recurrence of bladder cancer and clinical variables through five different ML methods, including DT, RF, AdaBoost, GBM and XGBoost. In addition, the best two biomarkers that can predict the recurrence of bladder cancer were obtained by combining each algorithm, and the area under the area of receiving operating characteristic curve (AUC) was calculated to evaluate the performance of the model.

Methods

Study Population

This retrospective study enrolled the data of patients diagnosed with bladder cancer in the Affiliated Hospital of Nantong University from January 2012 to December 2017. According to some irresistible factors, the exclusion criteria for patients are as follows: 1. With incomplete data more than 20%; 2. With previous or coexisting cancers; 3. Without available follow-up data. Finally, we recruited a total of 345 eligible patients to participate in this study. In order to ensure a minimum follow-up of 5 years for patients, our final follow-up date was December 2023. This study followed the ethical principles in the Declaration of Helsinki and was approved by the Ethics Committee of the Affiliated Hospital of Nantong University. The specific workflow of this study is shown in Figure 1.

Data Collection

The data of this study are derived from 34 clinical parameters (Table 1) of bladder cancer patients at the first diagnosis: Age, White blood cell (WBC), Neutrophil count (NEU), Lymphocyte count (LYM), Mononuclear cell count (MONO),

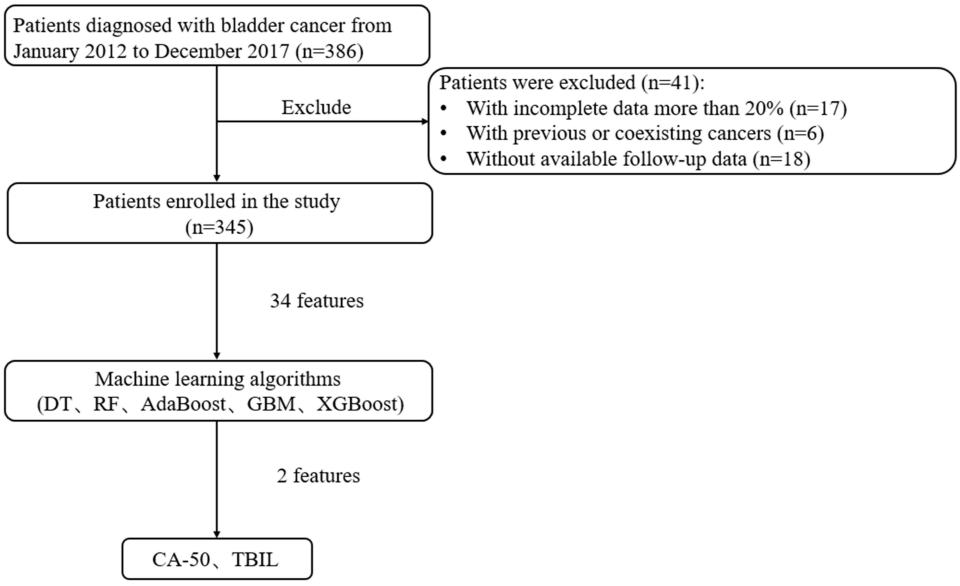

Figure 1 The schematic diagram of the overall workflow.

Table 1 Characteristics of Included Patients (345)

Characteristics	Median value
Age	70
WBC	5.8
NEU	3.7
LYM	1.4
MONO	0.37
EO	0.1
BASO	0.01
RBC	4.46
HCT	137
PCV	40.8
MCV	91.3
MCH	30.7
MCHC	333
RDW-SD	43
RDW-CV	13
PLT	191
PDW	13.4
MPV	10.7
PCT	0.21
TP	70.3
ALB	42.7
GLO	27.4
TBIL	11.7
CREA	72
PAB	26.2
K	4.03
Na	141
CL	103.1
CYFRA21-1	2.9
CA50	6.83
CEA	2.62
PT	11.5
FIB	2.79
D-dimer	0.44

Eosinophil count (EO), Basophil cell count (BASO), Red blood cell (RBC), Hematocrit (HCT), Packed cell volume (PCV), Mean corpuscular volume (MCV), Mean corpuscular hemoglobin (MCH), Mean corpuscular hemoglobin concentration (MCHC), Red blood cell distribution width-SD (RDW-SD), Red blood cell distribution width-CV (RDW-CV), Platelet count (PLT), Platelet distribution width (PDW), Mean platelet volume (MPV), Thrombocytocrit (PCT), Total protein (TP), Albumin (ALB), Globulin (GLO), Total bilirubin (TBIL), Creatinine (CREA), Prealbumin (PAB), Kalium (K), Natrium (Na), Chlorine (CL), Cytokeratin 19 fragment antigen21-1 (CYFRA21-1), Carbohydrate antigen 50 (CA50), Carcinoembryonic antigen (CEA), Prothrombin time (PT), Fibrinogen (FIB), D-dimer (DD). The missing value rate of all variables is below 20%. According to the complete queue, use the simple mean interpolation method to interpolate missing values.

Machine Learning Models

In this study, we applied five supervised ensemble based ML algorithms: DT, RF, AdaBoost, GBM, and XGBoost. The effectiveness of all ML algorithms was evaluated using the Python programming language. Using Python software for programming, using Anaconda software to install libraries and packages. Basic data processing was performed through Python libraries such as Pandas and Numpy. The four ML methods DT, RF, AdaBoost, and GBM were implemented using the Sklearn package, while XGBoost used its own dedicated software package. According to the Python function train_ Test_ Split randomly divides the samples into training and testing sets, and each ML method matches the testing group based on the results of the training group, and then compares the accuracy of each ML algorithm. Finally, determine the importance of each variable in each ML algorithm through "feature_importance_". The relevant parameters are as follows. For DT, the initial value of tree depth was set to 1–10 with a step size of 1. The kernel of this model was set to entropy or gini. For RF, the initial value of the tree number was set to 100 and increased by 100 until 500. The kernel of the model was set to entropy or gini. For AdaBoost, the step size was 0.01. For GBM, the step size was 0.005. For XGBoost, the initial value of eta was 0.01 to 0.2 with a step size of 0.05. The parameters of ML were adjusted through the training and validation groups of the dataset.

Statistical Analysis

We used IBM SPSS statistical software (Version 25.0) to draw the receiver operating characteristic (ROC) curves and evaluate the predictive effects of various clinical variables using the area under the receiver operating characteristic curve (AUC). The independent-sample *t*-test was employed for descriptive statistical analysis of continuous variables between the two groups. The value of $p<0.05$ was considered statistically significant.

Results

The correlation between each variable and bladder cancer recurrence can be determined by heat map (Figure 2). Among them, LYM, EO, CYFRA21-1 and CA50 were positively correlated with the recurrence of bladder cancer, while HCT, RDW-SD, PDW and TBIL were negatively correlated with the recurrence of bladder cancer.

By comparing the results of five ML algorithms: in the DT model, we found that CA50, TP, TBIL, and EO have relatively high weights (Figure 3A); in RF algorithm, CYFRA21-1, TP, ALB and MONO were in the forefront in predicting the recurrence of bladder cancer (Figure 3B); in contrast, FIB, EO, MONO, and Age were the most prominent in the AdaBoost model (Figure 3C); in addition, the results of the GBM algorithm show that the top four important variables were Age, EO, TP, and D-dimer, respectively (Figure 3D); the risk factors of recurrence of bladder cancer predicted by the final XGBoost model were CA50, FIB, LYM, TBIL and HCT (Figure 3E). Univariate and multivariate analyses were performed to identify the prominently independent prognostic factors in recurrence of bladder cancer (Table 2).

Based on the above results, we can easily found that CA50 and TBIL were significant risk factors for predicting the recurrence of bladder cancer. In order to verify this result, we evaluated the prediction performance of CA50 and TBIL by drawing ROC curves. As shown in the figure, the AUC of CA50 is 0.602, p=0.038 (Figure 4A), while the AUC of TBIL is 0.585, p=0.014 (Figure 4B). We further speculated whether combining these two vital indicators would make predictive performance more meaningful than individual indicator. It was gratifying that the AUC value of the

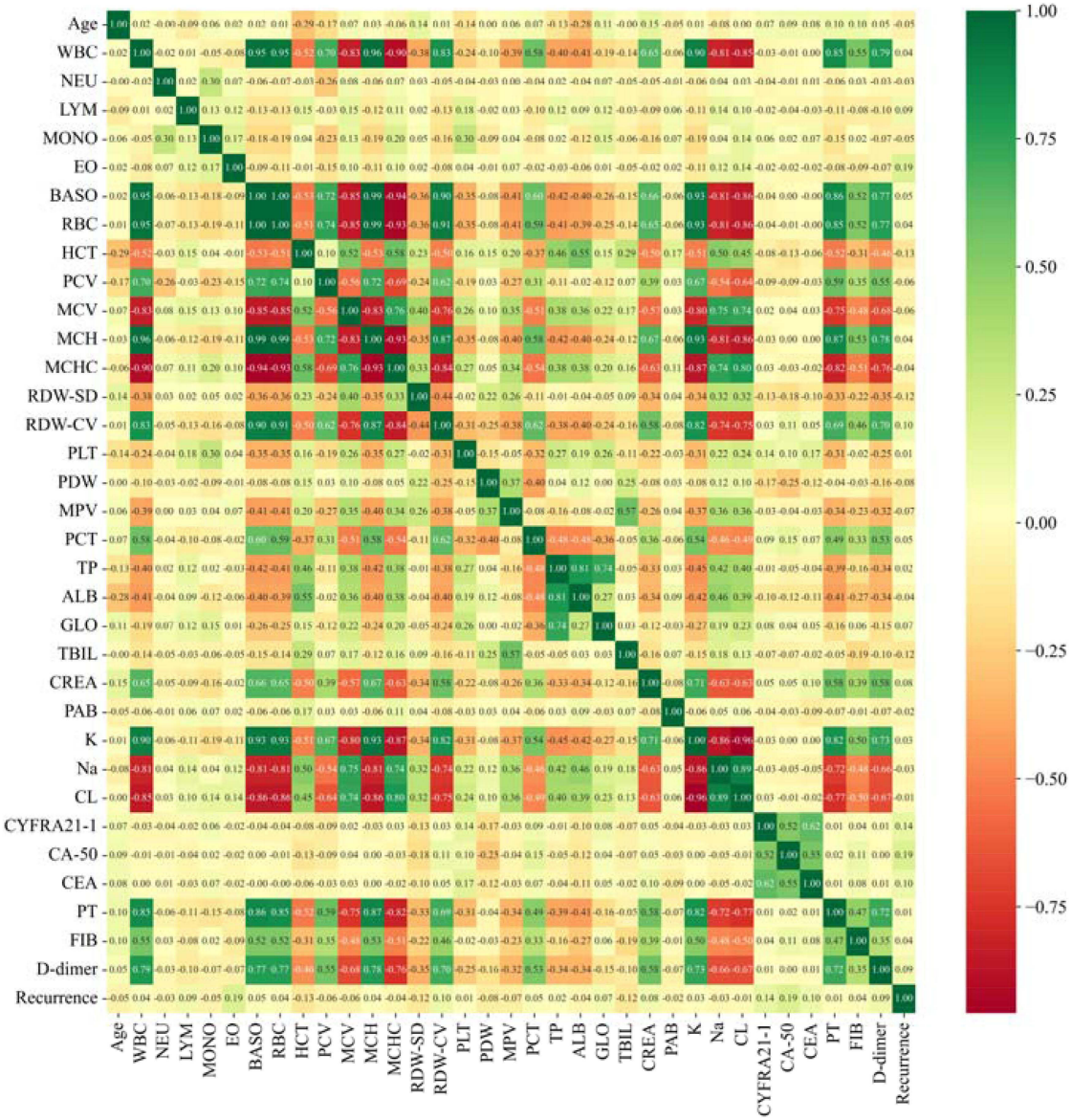

Figure 2 Correlation between variables. The gradient from green to red represents a gradient from positive to negative correlation.

combination of the two variables reached 0.623, p=0.013 (Figure 4C), which was better than the ability of any individual index to predict the recurrence of bladder cancer.

Discussion

Bladder cancer is a highly heterogeneous tumor with at least 40 histological subgroups.[27] Compared with other solid tumors, bladder cancer has a higher mutation rate, with heterogeneity of epithelial biology, interstitial fibroblasts, matrix reaction and immune infiltration.[28] Therefore, recurrence is a common phenomenon in the clinical treatment of bladder cancer, which has aroused extensive attention. At present, ML algorithms based on AI have made significant progress in the past few years, especially in the medical field, where ML models have been widely used for disease diagnosis and prognosis assessment.[29,30] The ML models can identify high-dimensional nonlinear relationships between detection variables, effectively improving the performance of traditional nomograms.[26] As far as we know, our research is the first time to employ clinical laboratory data coupled with ML algorithms to evaluate the recurrence of bladder cancer and screen out the most valuable variables.

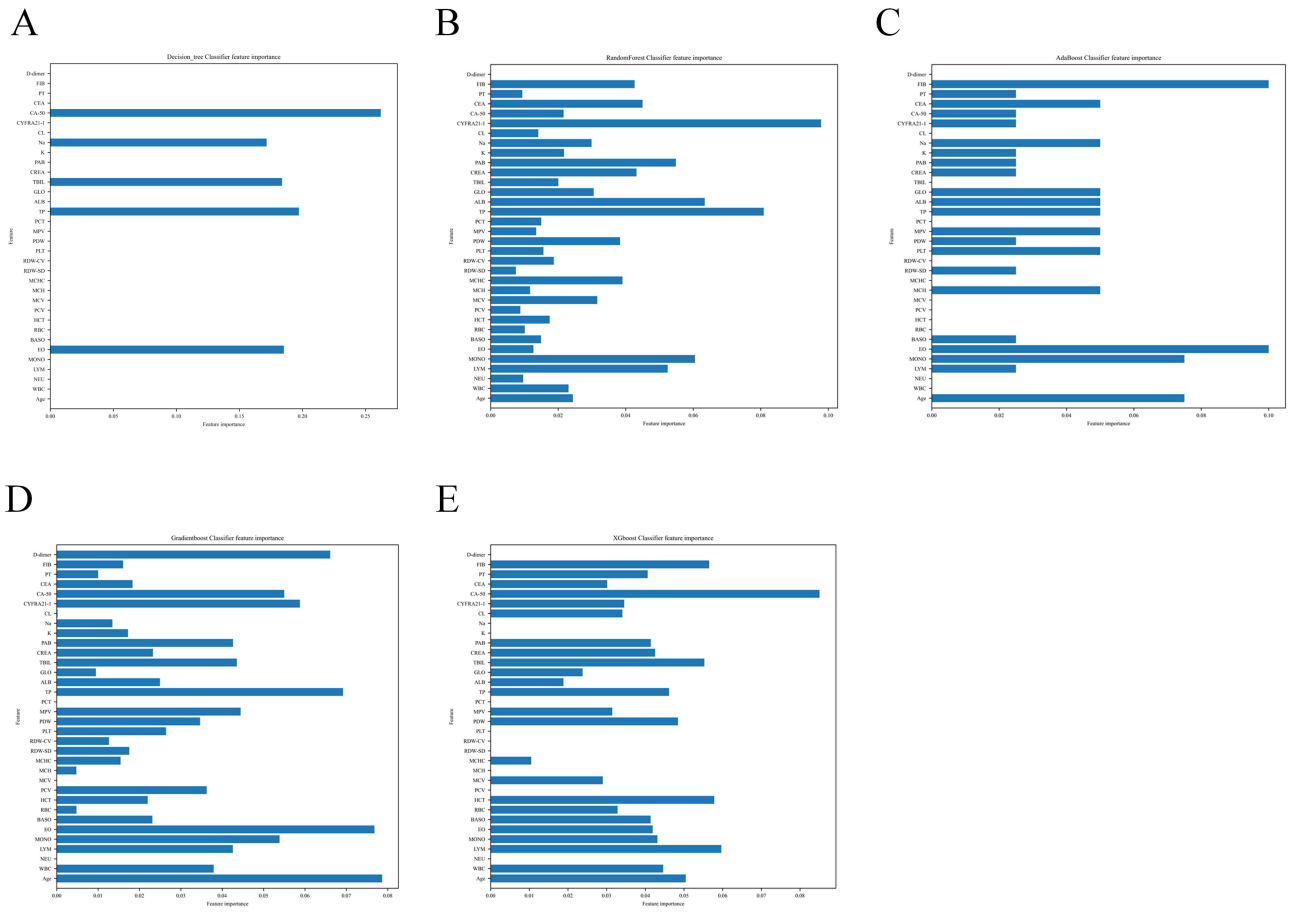

Figure 3 Variable importance of features included in five ML algorithms for predicting the recurrence of bladder cancer. (**A**) DT. (**B**) RF. (**C**)AdaBoost. (**D**) GBM. (**E**) XGBoost.

Bladder cancer is a fairly common and costly malignant tumor, as it requires lifelong routine monitoring and treatment after diagnosis.[31] Tumor recurrence is the most common clinical phenomenon after treatment, and once cancer recurrence occurs, it may develop into high grade and bring huge economic burden to patients.[32] In this study, we applied ML models to process multidimensional datasets and evaluate a large number of variables to predict bladder cancer

Table 2 Univariate and Multivariate Analyses for Factors Predicting Recurrence in Bladder Cancer

	Univariate		**Multivariate**	
	HR (95% CI)	**P values**	**HR (95% CI)**	**P values**
CA50				
<6.83	Ref		Ref	
≥6.83	1.224 (0.778–1.638)	0.008**	0.638 (0.275–1.247)	0.024*
TP				
<70.3	Ref			
≥70.3	2.816 (1.085–3.285)	0.148		
TBIL				
<11.7	Ref		Ref	
≥11.7	2.478 (1.739–3.802)	<0.001***	1.205 (0.872–1.927)	0.009**

(*Continued*)

Table 2 (Continued).

	Univariate		Multivariate	
	HR (95% CI)	**P values**	**HR (95% CI)**	**P values**
EO				
<0.1	Ref		Ref	
≥0.1	0.361 (0.129–1.247)	0.022*	0.197 (0.075–0.313)	0.042*
CYFRA21-1				
<2.9	Ref			
≥2.9	1.247 (0.897–2.295)	0.031*		
ALB				
<42.7	Ref			
≥42.7	3.469 (2.948–4.965)	0.304		
MONO				
<0.37	Ref			
≥0.37	0.103 (0.069–0.954)	0.625		
FIB				
<2.79	Ref			
≥2.79	0.592 (0.256–1.096)	0.059		
Age				
<70	Ref			
≥70	3.574 (2.317–4.973)	0.420		
D-dimer				
<0.44	Ref		Ref	
≥0.44	0.201 (0.098–0.834)	0.009**	0.191 (0.074–0.482)	0.036*
LYM				
<1.4	Ref			
≥1.4	0.235 (0.106–0.859)	0.047*		
HCT				
<137	Ref		Ref	
≥137	5.642 (4.485–6.875)	0.028*	2.156 (1.241–3.082)	0.048*

Notes: *P<0.05, **P<0.01, ***P<0.001.

recurrence. We explored five ML algorithms based on 34 clinical variables to predict recurrence in patients of bladder cancer. The collected 34 biological indicators cover various clinical parameters in the patient's age and peripheral blood to achieve more accurate disease prediction. By integrating the results of five ML algorithms, we identified the key factors of the recurrence of bladder cancer, CA50 and TBIL. Our research not only improves prognosis diagnosis, but also greatly reduces medical costs for patients and provides valuable patient information for clinicians.

Bile acids are the final products of cholesterol catabolite, appearing in three forms: TBIL, DBIL, and IDBIL in hepatocytes and peripheral blood.[33] For a long time, serum bilirubin has been used as a marker for liver, gallbladder, and hematological disorders.[34] Interestingly, several studies in recent years have shown that high levels of serum bilirubin are beneficial for cancer patients.[35] A slightly higher TBIL level indicates a better prognosis for pancreatic cancer,[36] breast cancer[37] and lung cancer.[38] Therefore, the prognostic significance of TBIL is inconsistent in different types of tumors, and further research is needed to determine whether pretreatment level of TBIL is a protective or harmful prognostic factor for bladder cancer. In our study, a higher level of TBIL indicates that patients with bladder cancer are less prone to

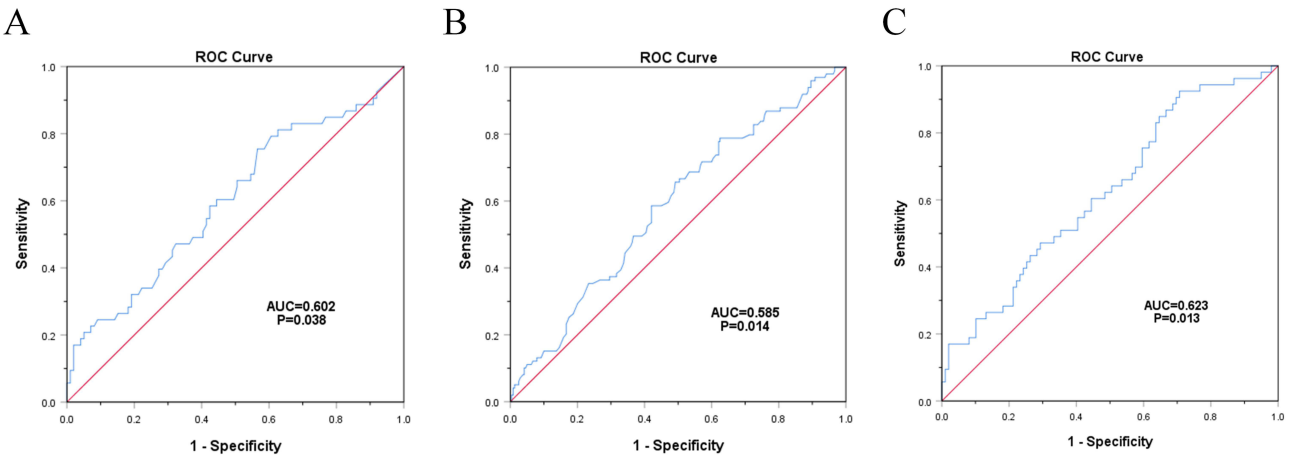

Figure 4 ROC curve analysis. (**A**) CA50 predicts the AUC value of recurrence. (**B**) TBIL predicts the AUC value of recurrence. (**C**) CA50 and TBIL predicts the AUC value of recurrence.

recurrence and have a better prognosis. To our best knowledge, this is the first study to show the beneficial prognostic value of TBIL in bladder cancer patients.

Although individual serum biomarkers are beneficial prognostic factors in cancer patient studies, single biomarkers may not be sufficient to predict disease progression in clinical settings. Combining other biomarkers together can improve their predictive ability.[39] In this study, we included CA50 to improve the predictive ability of recurrence of bladder cancer patients. CA50 is a glycolipid antigen that was first discovered in human colorectal cancer.[40] With continuous in-depth research, CA50 plays a vital role in cell growth and differentiation, indicating that tumor cells expressing glycolipid antigens may have increased proliferative activity.[41] Previous studies have shown that CA50 is highly expressed in many types of cancers, such as pancreatic cancer, liver cancer, gastric cancer, colorectal cancer, and cervical cancer.[42] The elevated levels of CA50 in patients with intrahepatic cholangiocarcinoma suggest that the expression of CA50 may help distinguish between benign and malignant bile duct diseases.[43] It has been reported that the level of serum tumor marker CA50 can serve as an auxiliary indicator for diagnosing early pancreatic ductal adenocarcinoma, which is of great significance for improving the diagnostic sensitivity and accuracy of early pancreatic ductal adenocarcinoma.[44] The high levels of serum CA50 detected in patients with colorectal cancer can be used to assist in monitoring disease recurrence and metastasis.[45] Consistently, our results showed that a high level of CA50 indicates a worse prognosis in patients with bladder cancer. In addition, if TBIL combined with CA50 to predict the recurrence of bladder cancer patients, the results revealed that the combined prediction effect is better than any individual prediction effect.

This study has important clinical application value. Preoperative laboratory examination is a low-cost and minimally invasive blood routine examination. If applied in clinical practice, it can effectively minimize medical costs. Due to objective limitations, there are some shortcomings in this study. Firstly, this is a single center study that includes a small number of cases, so it is necessary to further expand the sample size or conduct multicenter studies in subsequent studies. Moreover, due to the retrospective design was used in this study, there may be confounding factors that may affect the results. Therefore, more detailed prospective studies are needed to further elucidate these relationships. Finally, the data processing in this study only focuses on ML algorithms, which may lead to overfitting of the data. Therefore, traditional statistical analysis such as LASSO regression can be considered in combination to screen variables.

Conclusions

Accurate prognostic prediction tools are helpful for clinical decision-making of bladder cancer. In this retrospective study of 345 bladder cancer patients, ML methods revealed the correlation between clinical parameters and bladder cancer recurrence. Our research showed that the combination of TBIL and CA50 may improve the prognosis prediction of bladder cancer recurrence.

Ethics Statement

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Affiliated Hospital of Nantong University. Individual consent was waived because of the retrospective nature of our study. Patients' data were anonymized and maintained with confidentiality.

Funding

This study was supported by grants from Jiangsu Provincial Research Hospital (YJXYY202204-XKB08).

Disclosure

All of the authors declare that they have no conflicts of interest for this work.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 Countries. *CA Cancer J Clin*. 2021;71(3):209–249. doi:10.3322/caac.21660
2. Lin Y, Wang Y, Wu Q, et al. Association between obesity and bladder cancer recurrence: A meta-analysis. *Clin Chim Acta*. 2018;480:41–46. doi:10.1016/j.cca.2018.01.039
3. Liu C, Xu P, Shao S, et al. The value of urinary exosomal lncRNA SNHG16 as a diagnostic biomarker for bladder cancer. *Mol Biol Rep*. 2023;50 (10):8297–8304. doi:10.1007/s11033-023-08667-z
4. Miyake M, Nishimura N, Ohnishi S, et al. Diagnostic and prognostic roles of Urine Nectin-2 and Nectin-4 in human bladder cancer. *Cancers*. 2023;15(9):2565. doi:10.3390/cancers15092565
5. Flaig TW, Spiess PE, Abern M, et al. NCCN Guidelines® insights: Bladder cancer, version 2.2022. *J Natl Compr Canc Netw*. 2022;20(8):866–878. doi:10.6004/jnccn.2022.0041
6. Serafetinidis E, Campos-Juanatey F, Hallscheidt P, et al. Summary paper of the updated 2023 European Association of Urology guidelines on urological trauma. *Eur Urol Focus*. 2023;13(23):00196.
7. Hindmarsh JT, Lyon AW. Strategies to promote rational clinical chemistry test utilization. *Clin Biochem*. 1996;29(4):291–299. doi:10.1016/0009-9120(96)00042-2
8. Zheng HL, Lu J, Xie JW, et al. Exploring the value of new preoperative inflammation prognostic score: white blood cell to hemoglobin for gastric adenocarcinoma patients. *BMC Cancer*. 2019;19(1):1127. doi:10.1186/s12885-019-6213-0
9. Bongers SH, Chen N, van Grinsven E, et al. Kinetics of neutrophil subsets in acute, subacute, and chronic inflammation. *Front Imm*. 2021;12:674079. doi:10.3389/fimmu.2021.674079
10. Sproston NR, Ashworth JJ. Role of C-Reactive Protein at Sites of Inflammation and Infection. *Front Imm*. 2018;9:754. doi:10.3389/fimmu.2018.00754
11. Zhang L, Guan Z, Yin Y, et al. Predictive value of indicator of CA125 combined with D-dimer (ICD) for lymph node metastasis in patients with ovarian cancer: a two center cohort study. *J Cancer*. 2022;13(8):2447–2456. doi:10.7150/jca.70737
12. Xu R, Wang J, Huang X, et al. Clinical value of spectral CT imaging combined with AFP in identifying liver cancer and hepatic focal nodular hyperplasia. *J BUON*. 2019;24(4):1429–1434.
13. Moriyama J, Oshima Y, Nanami T, et al. Prognostic impact of CEA/CA19-9 at the time of recurrence in patients with gastric cancer. *Surg Today*. 2021;51(10):1638–1648. doi:10.1007/s00595-021-02248-y
14. Xia X, Li K, Wu R, et al. Predictive value of neuron-specific enolase, neutrophil-to-lymphocyte-ratio and lymph node metastasis for distant metastasis in small cell lung cancer. *Clin Respir J*. 2020;14(11):1060–1066. doi:10.1111/crj.13242
15. Tsai IJ, Shen WC, Lee CL, Wang HD, Lin CY. Machine Learning in prediction of bladder cancer on clinical laboratory data. *Diagnostics*. 2022;12 (1):203. doi:10.3390/diagnostics12010203
16. Ismail AA. When laboratory tests can mislead even when they appear plausible. *Clin Med Lond*. 2017;17(4):329–332. doi:10.7861/clinmedicine.17-4-329
17. Saboury B, Morris M, Siegel E. Future directions in artificial intelligence. *Radiol Clin North Am*. 2021;59(6):1085–1095. doi:10.1016/j.rcl.2021.07.008
18. Stilgoe J. Machine learning, social learning and the governance of self-driving cars. *Soc Stud Sci*. 2018;48(1):25–56. doi:10.1177/0306312717741687
19. O'Connor S. Open artificial intelligence platforms in nursing education: tools for academic progress or abuse? *Nurse Educ Pract*. 2023;66:103537. doi:10.1016/j.nepr.2022.103537
20. Kourou K, Exarchos TP, Exarchos KP, Karamouzis MV, Fotiadis DI. Machine learning applications in cancer prognosis and prediction. *Comput Struct Biotechl J*. 2014;13:8–17. doi:10.1016/j.csbj.2014.11.005
21. Cruz JA, Wishart DS. Applications of machine learning in cancer prediction and prognosis. *Cancer Inform*. 2007;2:59–77.
22. Banerjee M, Reynolds E, Andersson HB, Nallamothu BK. Tree-Based Analysis. *Circ Cardiovasc Qual Out*. 2019;12(5):e004879. doi:10.1161/CIRCOUTCOMES.118.004879
23. Nadeem MW, Goh HG, Ponnusamy V, Andonovic I, Khan MA, Hussain M. A fusion-based machine learning approach for the prediction of the onset of diabetes. *Healthcare*. 2021;9(10):1393. doi:10.3390/healthcare9101393
24. Zhong X, Yu J, Jiang F, et al. A risk prediction model based on machine learning for early cognitive impairment in hypertension: development and validation study. *Front Public Health*. 2023;11:1143019. doi:10.3389/fpubh.2023.1143019
25. Lee J, Choo MS, Yoo S, Cho MC, Son H, Jeong H. Intravesical prostatic protrusion and prognosis of non-muscle invasive bladder cancer: analysis of long-term data over 5 years with machine-learning algorithms. *J Clin Med*. 2021;10(18):4263. doi:10.3390/jcm10184263

26. Bhambhvani HP, Zamora A, Shkolyar E, et al. Development of robust artificial neural networks for prediction of 5-year survival in bladder cancer. *Urol Oncol*. 2021;39(3):193.e7–193.e12. doi:10.1016/j.urolonc.2020.05.009
27. Goetze OT, Al-Batran SE, Chevallay M, Mönig SP. Multimodal treatment in locally advanced gastric cancer. *Updates Surg*. 2018;70(2):173–179. doi:10.1007/s13304-018-0539-z
28. Choi W, Ochoa A, McConkey DJ, et al. Genetic alterations in the molecular subtypes of bladder cancer: illustration in the cancer genome atlas dataset. *Eur Urol*. 2017;72(3):354–365. doi:10.1016/j.eururo.2017.03.010
29. Painuli D, Bhardwaj S, Köse U. Recent advancement in cancer diagnosis using machine learning and deep learning techniques: a comprehensive review. *Comput Biol Med*. 2022;146:105580. doi:10.1016/j.compbiomed.2022.105580
30. Gaur K, Jagtap MM. Role of artificial intelligence and machine learning in prediction, diagnosis, and prognosis of cancer. *Cureus*. 2022;14(11):e31008. doi:10.7759/cureus.31008
31. Botteman MF, Pashos CL, Redaelli A, Laskin B, Hauser R. The health economics of bladder cancer: a comprehensive review of the published literature. *Pharmacoecono*. 2003;21(18):1315–1330. doi:10.1007/BF03262330
32. de Kok JB, van Balken MR, Roelofs RW, van Aarssen YA, Swinkels DW, Klein Gunnewiek JM. Quantification of hTERT mRNA and telomerase activity in bladder washings of patients with recurrent urothelial cell carcinomas. *Clin Chem*. 2000;46(12):2003–2007. doi:10.1093/clinchem/46.12.2003
33. Cao Y, Deng S, Yan L, et al. A nomogram based on pretreatment levels of serum bilirubin and total bile acid levels predicts survival in colorectal cancer patients. *BMC Cancer*. 2021;21(1):85. doi:10.1186/s12885-021-07805-9
34. Feng L, Gu S, Wang P, et al. Pretreatment values of bilirubin and albumin are not prognostic predictors in patients with advanced pancreatic cancer. *Cancer Med*. 2018;7(12):5943–5951. doi:10.1002/cam4.1848
35. Geng Y, Mei Y, Xi Y, et al. Bilirubin can be used as a prognostic factor for lung adenocarcinoma patients with EGFR mutations. *Onco Targets Ther*. 2020;13:11089–11095. doi:10.2147/OTT.S266477
36. Haas M, Heinemann V, Kullmann F, et al. Prognostic value of CA 19-9, CEA, CRP, LDH and bilirubin levels in locally advanced and metastatic pancreatic cancer: results from a multicenter, pooled analysis of patients receiving palliative chemotherapy. *J Cancer Res Clin Oncol*. 2013;139(4):681–689. doi:10.1007/s00432-012-1371-3
37. Liu X, Meng QH, Ye Y, Hildebrandt MA, Gu J, Wu X. Prognostic significance of pretreatment serum levels of albumin, LDH and total bilirubin in patients with non-metastatic breast cancer. *Carcinogenesis*. 2015;36(2):243–248. doi:10.1093/carcin/bgu247
38. Li N, Xu M, Cai MY, et al. Elevated serum bilirubin levels are associated with improved survival in patients with curatively resected non-small-cell lung cancer. *Cancer Epidemiol*. 2015;39(5):763–768. doi:10.1016/j.canep.2015.06.007
39. Ogłuszka M, Orzechowska M, Jędroszka D, Witas P, Bednarek AK. Evaluate Cutpoints: Adaptable continuous data distribution system for determining survival in Kaplan-Meier estimator. *Comput Meth Prog Biomed*. 2019;177:133–139. doi:10.1016/j.cmpb.2019.05.023
40. Lindholm L, Holmgren J, Svennerholm L, et al. Monoclonal antibodies against gastrointestinal tumour-associated antigens isolated as monosialogangliosides. *Int Arch Allergy Appl Imm*. 1983;71(2):178–181. doi:10.1159/000233384
41. Kokocińska D, Jarzab B, Król R, Ziaja K, Szejbak K, Kuśmierski S. A comparison of the clinical usefulness of CA 19-9 and CA 50 in the diagnosis and monitoring of gastrointestinal cancers. *J Environ Pathol Toxicol Oncol*. 1996;15(2–4).
42. Shan M, Tian Q, Zhang L. Serum CA50 levels in patients with cancers and other diseases. *Prog Mol Biol Transl Sci*. 2019;162:187–198.
43. Luang S, Teeravirote K, Saentaweesuk W, Ma-In P, Silsirivanit A. Carbohydrate Antigen 50: values for diagnosis and prognostic prediction of intrahepatic cholangiocarcinoma. *Medicina*. 2020;56(11):616. doi:10.3390/medicina56110616
44. Lei XF, Jia SZ, Ye J, et al. Application values of detection of serum CA199, CA242 and CA50 in the diagnosis of pancreatic cancer. *J Biol Regul Homeost Agents*. 2017;31(2):383–388.
45. Li Q, Dai W, Li Y, Xu Y, Li X, Cai S. Nomograms for predicting the prognostic value of serological tumor biomarkers in colorectal cancer patients after radical resection. *Sci Rep*. 2017;7:46345. doi:10.1038/srep46345