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Contents

Contents

Contents

ABOUT COVER

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AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Surgery* (*WJGS*, *World J Gastrointest Surg*) is to provide scholars and readers from various fields of gastrointestinal surgery with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

   WJGS mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal surgery and covering a wide range of topics including biliary tract surgical procedures, biliopancreatic diversion, colectomy, esophagectomy, esophagostomy, pancreas transplantation, and pancreatectomy, *etc*.

INDEXING/ABSTRACTING

The *WJGS* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, PubMed Central, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2022 Edition of Journal Citation Reports® cites the 2021 impact factor (IF) for *WJGS* as 2.505; IF without journal self cites: 2.473; 5-year IF: 3.099; Journal Citation Indicator: 0.49; Ranking: 104 among 211 journals in surgery; Quartile category: Q2; Ranking: 81 among 93 journals in gastroenterology and hepatology; and Quartile category: Q4.

RESPONSIBLE EDITORS FOR THIS ISSUE

ORIGINAL ARTICLE

Retrospective Cohort Study

Pain management in patients with hepatocellular carcinoma after transcatheter arterial chemoembolisation: A retrospective study

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Abstract

BACKGROUND
Pain after transcatheter arterial chemoembolisation (TACE) can seriously affect the prognosis of patients and the insertion of additional medical resources.

AIM
To develop an early warning model for predicting pain after TACE to enable the implementation of preventive analgesic measures.

METHODS
We retrospectively collected the clinical data of 857 patients (from January 2016 to January 2020) and prospectively enrolled 368 patients (from February 2020 to October 2022; as verification cohort) with hepatocellular carcinoma (HCC) who received TACE in the Hepatic Surgery Center of Tongji Hospital. Five predictive models were established using machine learning algorithms, namely, random forest model (RFM), support vector machine model, artificial neural network model, naive Bayes model and decision tree model. The efficacy of these models in predicting postoperative pain was evaluated through receiver operating characteristic curve analysis, decision curve analysis and clinical impact curve analysis.

RESULTS
A total of 24 candidate variables were included in the predictive models using the iterative algorithms. Age, preoperative pain, number of embolised tumours, distance from the liver capsule, dosage of iodised oil and preoperative prothrombin activity were closely associated with postoperative pain. The accuracy of the predictive model was compared between the training [area under the curve (AUC) = 0.798; 95% confidence interval (CI): 0.745-0.851] and verification (AUC = 0.871; 95%CI: 0.818-0.924) cohorts, with RFM having the best

predictive efficiency (training cohort: AUC = 0.869, 95%CI: 0.816-0.922; internal verification cohort: AUC = 0.871; 95%CI: 0.818-0.924).

CONCLUSION
The five predictive models based on advanced machine learning algorithms, especially RFM, can accurately predict the risk of pain after TACE in patients with HCC. RFM can be used to assess the risk of pain for facilitating preventive treatment and improving the prognosis.

Key Words: Hepatocellular carcinoma; Transcatheter arterial chemoembolization; Pain; Machine learning algorithm; Prediction

Core Tip: Machine learning-based pre-warning models can be used to predict post-transcatheter arterial chemoembolisation (TACE) pain for hierarchical management of patients at high risk of moderate and severe pain after TACE. In particular, random forest model (RFM) combined with preoperative predictors (*i.e.,* age, preoperative pain, distance from liver capsule ≤ 2 cm, prothrombin activity, iodine oil dose and increased number of emboli) has optimal discriminating power and high predictive accuracy. Therefore, RFM can be used for early prediction of the risk of pain, which can facilitate prompt pain management after TACE and improve the prognosis of patients.

INTRODUCTION

As a first-line treatment for patients with mid-stage hepatocellular carcinoma (HCC), transcatheter arterial chemoembolisation (TACE) is especially suitable for patients with multifocal HCC who are not eligible for radical treatment[1,2]. Compared with the classic supportive treatment, TACE can significantly improve the quality of life and prolong the survival time of patients[3]. However, because TACE can block the blood supply of main blood vessels and lead to local liver tissue swelling and tumour necrosis, most patients experience pain of varying intensity after receiving TACE[4]. Previous studies have shown that the incidence of pain in patients with HCC after TACE is 60%-80%, and approximately 20%-40% of patients have severe pain, prolonged bed rest time and increased likelihood of postoperative complications, resulting in increased medical costs[5-7]. Therefore, prompt and effective pain management and nursing care are of great significance for improving the prognosis and quality of life of patients receiving TACE.

Early pain management can not only significantly reduce the incidence of pain but also improve the quality of life of patients receiving TACE. Therefore, identifying predictive factors related to postoperative pain may help to assess the risk of pain after TACE to implement pain relief interventions in advance[8]. Previous studies have shown that age, portal vein tumour thrombosis and tumour diameter are associated with an increased risk of pain after TACE[9]. In addition, preoperative anxiety, depression and other psychological factors can promote postoperative pain[10,11]. However, no effective scoring strategy is available for evaluating the risk of pain in patients with HCC after TACE. Developing such strategies may facilitate hierarchical management of patients with HCC with different degrees of pain.

In recent years, scholars have constructed nomographs for quantitative scoring by integrating multi-dimensional pain-related variables. Nomographs are based on traditional logic algorithms, which can help to indicate the risk of pain in patients with HCC receiving TACE[9]. However, with the continuous innovation and improvement of machine learning algorithms, several advanced algorithms have been gradually applied to the medical field for improving the accuracy and robustness of risk stratification [12-14]. To the best of our knowledge, an early warning model integrating machine learning algorithms and clinical indicators of post-TACE pain has not yet been developed for the management of pain in patients with HCC. Therefore, in this study, we constructed a machine learning-based model to predict post-TACE pain for early identification and prompt treatment of high-risk patients in clinical settings.

MATERIALS AND METHODS

Study population
We retrospectively included 857 patients with HCC who received TACE in the Hepatic Surgery Center of Tongji Hospital from January 2016 to January 2020 through the electronic record system of the hospital. Additionally, we prospectively included 368 patients with HCC who underwent TACE in the hospital from February 2020 to October 2022 as the external verification cohort. The inclusion criteria were as follows: (1) Patients aged > 18 years; (2) Patients diagnosed with HCC *via* histopathological examination; (3) Patients receiving traditional TACE; and (4) The patients received corticosteroids as part of the protocol and the pain-management protocols has not changed between 2016 and 2022. The exclusion criteria were as follows: (1) Patients with incomplete medical records; and (2) Patients who underwent other surgeries and those with long-term use of painkillers before surgery. This study was approved by the Ethics Committee of Tongji Hospital, Tongji Medical College, and Huazhong University of Science and Technology and complies with the Declaration of Helsinki (2013 version). All patients with HCC who participated in this study signed an informed consent form. Figure 1 demonstrates the process of patient selection and construction of predictive models.

Selection of predictive factors
We retrospectively collected the perioperative clinical data of patients: (1) Demographic data, including age, sex and body mass index; (2) History of TACE and hepatobiliary surgery; (3) Relevant preoperative imaging data, including maximum tumour diameter, number of embolised tumours, location of embolised tumours, portal vein tumour thrombosis and distance from the liver capsule; (4) Surgery-related data, including preoperative pain (PrP) perception, Child-Pugh classification, surgical duration, use of embolic supplement (except for iodised oil, gelatin sponge, blank microspheres, polyvinyl alcohol and other granular embolic agents) and iodised oil dosage; and (5) Preoperative biochemical data, including the levels of albumin, total bilirubin, alanine aminotransferase and aspartate aminotransferase; prothrombin time; prothrombin activity and platelet count. The quality control standards for retrospective data were as follows: Variables with missing data in ≤ 5% of the total number of cases were considered for inclusion in the analysis (the missing value is filled in using median interpolation); however, those with missing data in > 5% of cases were excluded to avoid bias caused by filling the missing value.

Evaluation criteria for postoperative pain intensity
The intensity of postoperative pain was evaluated by trained professionals using the numeric rating scale. The subjective feelings of patients were considered the main observation index. Patients were evaluated every 2 h after receiving TACE and scored as follows: 0 points, no pain; 1-3 points, mild pain; 4-6, moderate pain; 7-10, severe pain. Patients with scores of ≥ 4 points are identified as having moderate and severe pain, and opioids should be considered for analgesic treatment. We considered moderate and severe pain within 24 h after surgery as the outcome variables. Patients with pain scores of ≥ 4 points within 24 h of surgery were included in the pain group, whereas those with < 4 points were included in the non-pain group.

Establishment of predictive models for post-TACE pain
Five common machine learning algorithms were used to develop predictive models: Random forest model (RFM), support vector machine model (SVMM), artificial neural network model (ANNM), decision tree model (DTM) and naive Bayes model (NBM). The efficacy of these models in predicting postoperative pain was evaluated through receiver operating characteristic analysis and decision curve analysis (DCA). In addition, continuous correction curves were plotted to evaluate the robustness of predictive models, and clinical impact curves (CICs) were plotted to evaluate the differentiation efficiency of the optimal predictive model (RFM). All predictive models were tested in the internal training, internal verification and external verification cohorts.

Statistical analysis
Statistical analysis was performed using the R software (https://www.r-project.org/). For descriptive analysis, the median (interquartile range) and frequency (%) of continuous variables and categorical variables were evaluated, respectively. Pearson correlation coefficients were evaluated to measure the degree of correlation between variables, and least absolute shrinkage and selection operator (LASSO) regression was performed for selecting significant variables for models. For variable screening and inter-group comparison (pain *vs* non-pain group), P-values of < 0.05 were considered significant.
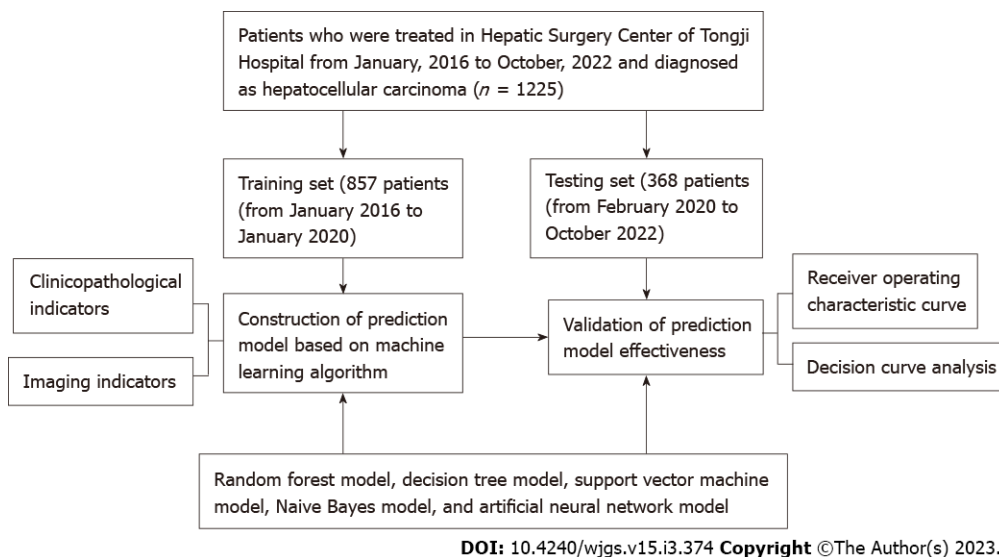
Figure 1 Flow chart of patient inclusion and prediction model construction.

RESULTS

Baseline characteristics of patients with or without postoperative pain

Patients were divided into pain and non-pain groups based on whether they had moderate or severe pain within 24 h of TACE. Among 1225 patients, 205 (16.73%) had pain after TACE. The cumulative incidence of moderate and severe post-TACE pain at < 6 h, 6-12 h and 12-24 h after TACE was 15.12%, 17.26% and 13.15%, respectively, in the training cohort, and 14.86%, 18.26% and 15.11%, respectively, in the external verification cohort.

On comparing the baseline data of patients with HCC between the pain and non-pain groups, significant differences ($P < 0.05$) were observed in age, PrP, maximum tumour diameter, number of embolised tumours (NOETs), distance from the liver capsule (DFLS), use of embolic supplements and dosage of iodised oil. On comparison of biochemical indicators, post-TACE pain was found to be significantly associated with prothrombin activity and platelet count ($P < 0.05$). The detailed baseline data of the two groups are summarised in Table 1.

Selection of predictors of postoperative pain

According to the distribution of Pearson correlation coefficients, postoperative pain was considered an 'outcome variable', and its correlation with 24 candidate variables was examined (Figure 2A). Postoperative pain was significantly correlated with age, PrP, NOET, DFLS, dosage of iodised oil (LOD) and preoperative prothrombin activity (PTA). Similarly, LASSO regression was used to determine the optimal penalty coefficient (Figures 2B and 2C) to screen for candidate variables for the predictive models. For four models, age, PrP, NOET, DFLS, LOD and PTA were identified as significant predictive factors, which was consistent with the results obtained by generalized linear modelthrough univariate and multivariate logistic regression analyses (Figure 2D). Altogether, these results indicate that age, PrP, NOET, DFLS, LOD and PTA can efficiently predict postoperative pain in patients with HCC.

Construction of predictive models for postoperative pain

RFM and DTM were constructed based on the principle of 'branching' to discriminate and classify each included variable (Figure 3 and Supplementary Table 1). Age, PrP, NOET, DFLS, LOD and PTA were the major variables included in RFM, whereas the 'branch' variable in the decision tree included only PTA and DFLS. In addition, ANNM was constructed based on the algorithms of the 'input layer', 'hidden layer' and 'output layer' (Figure 4). After iteration of the input and hidden layers, age, tumour size and pathological type could accurately stratify the pain risk. Consistent with the candidate variables included in ANNM, SVMM was based on a class of generalised linear classifiers that categorise data in a binary way according to supervised learning, which can convert the problem into a convex quadratic programming problem. Furthermore, age, NOET, DLFS, LOD and PTA were the major variables included in NBM. These results suggest that predictive models of postoperative pain can be developed using the abovementioned variables, and the contribution of the intersecting variables among these models cannot be ignored.

Effectiveness of the five predictive models

DCA was performed to evaluate the differentiation efficiency and robustness of the five predictive

Table 1 Baseline demographic and clinicopathological characteristics of patients with hepatocellular carcinoma

Variables	Training set			*P* value	Testing set
	Overall (*n* = 857)	Pain (*n* = 139)	No-pain (*n* = 718)		Overall (*n* = 368)
Age (%), yr					
≤ 50	199 (23.2)	119 (85.6)	80 (11.1)	< 0.001	86 (23.4)
> 50	658 (76.8)	20 (14.4)	638 (88.9)		282 (76.6)
Gender (%)					
Male	445 (51.9)	74 (53.2)	371 (51.7)	0.806	151 (41.0)
Female	412 (48.1)	65 (46.8)	347 (48.3)		217 (59.0)
BMI [median (IQR)], kg/m^2	24.00 (21.10, 27.10)	23.70 (21.10, 27.45)	24.00 (21.02, 27.08)	0.658	24.00 (21.20, 26.70)
Pathogeny (%)					
Hepatitis B	218 (25.4)	31 (22.3)	187 (26.0)	0.089	104 (28.3)
HCV	226 (26.4)	28 (20.1)	198 (27.6)		88 (23.9)
Alcoholic liver	214 (25.0)	39 (28.1)	175 (24.4)		95 (25.8)
Others	199 (23.2)	41 (29.5)	158 (22.0)		81 (22.0)
ECOG (%)					
0	417 (48.7)	63 (45.3)	354 (49.3)	0.443	187 (50.8)
1	440 (51.3)	76 (54.7)	364 (50.7)		181 (49.2)
TACE (%)					
Yes	445 (51.9)	70 (50.4)	375 (52.2)	0.756	169 (45.9)
No	412 (48.1)	69 (49.6)	343 (47.8)		199 (54.1)
HHS (%)					
Yes	414 (48.3)	73 (52.5)	341 (47.5)	0.321	195 (53.0)
No	443 (51.7)	66 (47.5)	377 (52.5)		173 (47.0)
PrP (%)					
Yes	204 (23.8)	130 (93.5)	74 (10.3)	< 0.001	91 (24.7)
No	653 (76.2)	9 (6.5)	644 (89.7)		277 (75.3)
MDT (%), cm					
≤ 10	416 (48.5)	76 (54.7)	340 (47.4)	0.137	193 (52.4)
> 10	441 (51.5)	63 (45.3)	378 (52.6)		175 (47.6)
LOET (%)					
Left	437 (51.0)	80 (57.6)	357 (49.7)	0.11	189 (51.4)
Right	420 (49.0)	59 (42.4)	361 (50.3)		179 (48.6)
NOET (%)					
Single	683 (79.7)	21 (15.1)	662 (92.2)	< 0.001	280 (76.1)
Multiple	174 (20.3)	118 (84.9)	56 (7.8)		88 (23.9)
PVTT (%)					
Yes	438 (51.1)	72 (51.8)	366 (51.0)	0.932	185 (50.3)
No	419 (48.9)	67 (48.2)	352 (49.0)		183 (49.7)
DFLS (%), cm					
> 2	646 (75.4)	16 (11.5)	630 (87.7)	< 0.001	268 (72.8)
≤ 2	211 (24.6)	123 (88.5)	88 (12.3)		100 (27.2)
CTPG (%)					

Grade A	442 (51.6)	75 (54.0)	367 (51.1)	0.602	176 (47.8)
Grade B	415 (48.4)	64 (46.0)	351 (48.9)		192 (52.2)
OpD (%), h					
≤ 1	452 (52.7)	83 (59.7)	369 (51.4)	0.088	184 (50.0)
> 1	405 (47.3)	56 (40.3)	349 (48.6)		184 (50.0)
ES (%)					
Yes	437 (51.0)	72 (51.8)	365 (50.8)	0.908	187 (50.8)
No	420 (49.0)	67 (48.2)	353 (49.2)		181 (49.2)
LOD (%), mL					
≤ 10	630 (73.5)	21 (15.1)	609 (84.8)	< 0.001	260 (70.7)
> 10	227 (26.5)	118 (84.9)	109 (15.2)		108 (29.3)
Albumin [median (IQR)], g/L	36.12 (33.45, 38.63)	36.11 (33.50, 38.81)	36.12 (33.43, 38.57)	0.688	36.03 (33.42, 38.73)
PT [median (IQR)], s	12.70 (12.30, 13.20)	12.60 (12.30, 13.10)	12.70 (12.30, 13.20)	0.559	12.70 (12.30, 13.10)
PTA [median (IQR)], %	82.25 (77.12, 86.60)	90.20 (87.26, 93.18)	80.33 (76.45, 84.36)	< 0.001	82.29 (77.81, 86.83)
TBIL [median (IQR)], g/L	16.17 (12.95, 19.37)	16.20 (13.34, 19.27)	16.16 (12.88, 19.39)	0.972	16.12 (13.25, 19.23)
ALT [median (IQR)], U/L	33.00 (27.00, 40.00)	34.00 (24.50, 40.00)	33.00 (27.00, 40.75)	0.446	34.00 (26.00, 41.00)
AST [median (IQR)], U/L	42.00 (35.00, 48.00)	44.00 (35.00, 49.00)	41.00 (35.00, 48.00)	0.091	42.00 (34.00, 48.25)
PLT [median (IQR)], 10^9	136.00 (104.00, 163.00)	138.00 (104.00, 160.00)	135.50 (104.00, 164.00)	0.749	130.50 (100.00, 160.25)

IQR: Interquartile range; BMI: Body mass index; ECOG: Eastern cooperative oncology group; HHS: History of hepatobiliary surgery; PrP: Preoperative_pain; MTD: Maximum tumor diameter; LOET: Location of embolized tumor; NOET: Number of embolized tumors; PVTT: Portal vein tumor thrombus; DFLS: Distance from liver capsule; CTBG: Child-pugh grade; OpD: Operation_duration; ES: Embolization supplement; LOD: Iodine oil dosage; PT: Prothrombin time; PTA: Prothrombin activity; TBIL: Total bilirubin; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; PLT: Platelet count.

models. The predictive efficiency of RFM was most optimal, followed by DTM. The predictive efficiency of ANNM and SVMM was better than that of NBM (Figure 5). The area under the curve (AUC) values of RFM were 0.869 [95% confidence interval (CI): 0.816-0.922) and 0.871 (95%CI: 0.818-0.924) in the training and internal verification sets, respectively. Additionally, the prediction accuracy of DTM, ANNM, SVMM, and NBM in the training cohort was between (AUC = 0.798; 95%CI: 0.745-0.851) and (AUC = 0.871; 95%CI: 0.818-0.924) (Table 2). These results indicate that although the candidate variables used in the five predictive models were similar, the predictive efficiency of the models was significantly different, with RFM having the best predictive efficiency.

Clinical evaluation of the optimal predictive model

CIC curves were plotted to verify the predictive efficiency of RFM. As shown in Supplementary Figure 1, RFM significantly distinguished between high- and low-risk patients in the training, internal verification and external verification sets, and its stratification effect was very stable. These results suggest that RFM as a predictive tool for evaluating post-TACE pain has clinical significance and can be used to guide early management of pain hierarchically.

DISCUSSION

At present, TACE is considered the first-line non-surgical treatment for HCC. TACE can effectively control the growth of HCC cells, significantly prolong the survival of patients and benefit patients with HCC; therefore, it is the first therapeutic option and the most effective treatment for patients with advanced HCC who are not eligible for surgical resection[15,16]. Although the trauma of TACE is minor, several adverse reactions may occur postoperatively[17]. Pain is one of the common postoperative complications; however, its pathophysiological mechanism remains unclear[18]. It may be caused by acute liver parenchyma ischaemia, liver capsule tension caused by transient liver swelling and chemical damage of hepatic arteries[19]. Previous studies have shown that pain can prolong the length of hospital stay, reduce the quality of life of patients and harm the physiology and psychology of patients[19,20]. Therefore, early treatment of postoperative pain is necessary for improving the

Table 2 The receiver operating characteristic curve analyses for pain risk in each machine learning-based model

| Model	Training set		Testing set	
	AUC mean	AUC 95%CI	AUC mean	AUC 95%CI
RFM	0.869	0.816-0.922	0.871	0.818-0.924
DTM	0.861	0.808-0.914	0.864	0.811-0.917
ANNM	0.826	0.773-0.879	0.827	0.774-0.880
SVMM	0.803	0.750-0.856	0.808	0.755-0.861
NBM	0.798	0.745-0.851	0.803	0.750-0.856

RFM: Random forest model; SVMM: Support vector machine model; DTM: Decision tree model; ANNM: Artificial neural network model; NBM: Naive Bayesian model; AUC: Area under curve; 95%CI: 95% confidence interval.
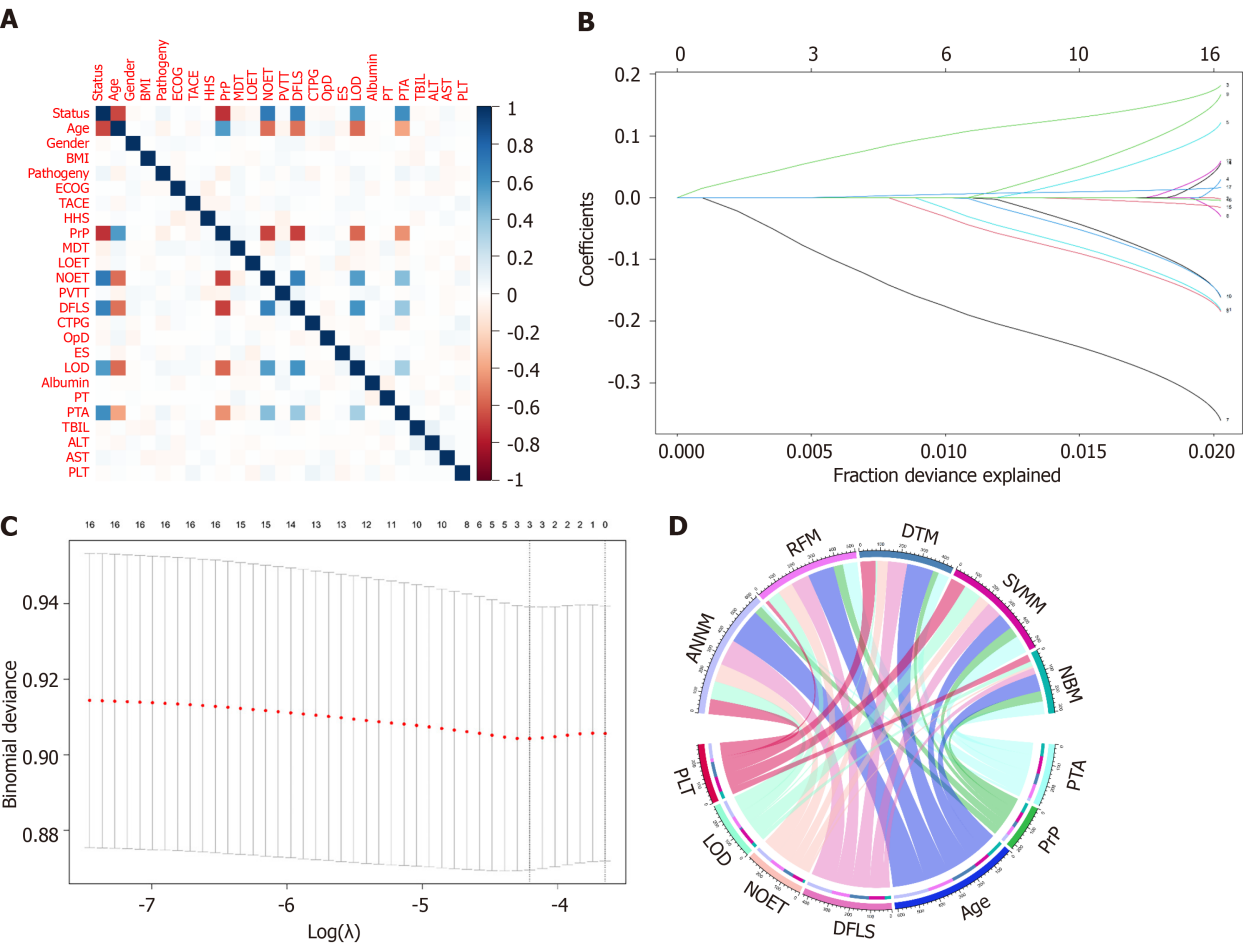
Figure 2 Variable screening and weight allocation. A: Correlation matrix analysis of candidate features; B and C: Feature selection by least absolute shrinkage and selection operator regression; D: The weight distribution of the candidate variables of each ML-based model. BMI: Body mass index; ECOG: Eastern Cooperative Oncology Group; TACE: Transcatheter arterial chemoembolisation; HHS: History of hepatobiliary surgery; PrP: Preoperative pain; MDT: Maximum tumor diameter; LOET: Location of embolized tumor; NOET: Number of embolised tumours; PVTT: Portal vein tumor thrombus; DFLS: Distance from the liver capsule; CTPG: Child-pugh grade; OpD: Operation_duration; ES: Embolization supplement; LOD: Iodine oil dosage; PT: Prothrombin time; PTA: Prothrombin activity; TBIL: Total bilirubin; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; PLT: Platelet count; RFM: Random forest model; DTM: Decision tree model; SVMM: Support vector machine model; NBM: Naive Bayes model; ANNM: Artificial neural network model.

prognosis of patients with HCC. To the best of our knowledge, this study is the first to use machine learning algorithms to build a multi-course model for predicting post-TACE pain. The model can help to assess the risk of post-TACE pain objectively in order to improve clinical diagnosis and treatment.

Previous studies have shown that the incidence of pain is high among patients with HCC after 6-12 h of TACE[19,21,22]. However, this study showed that the incidence of moderate and severe pain in
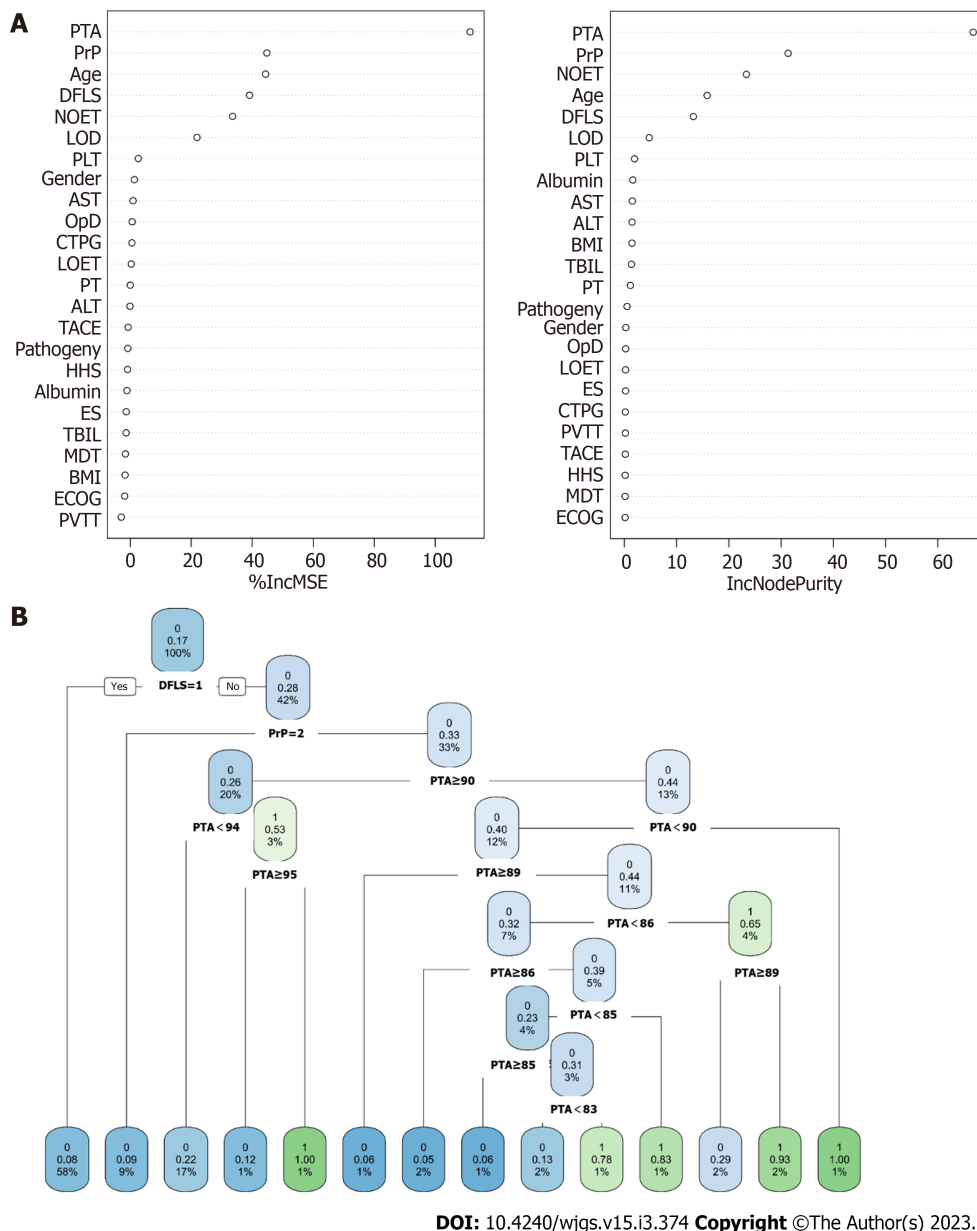
Figure 3 Predictive model visualization based on machine learning-based algorithm. A: Random forest model; B: Decision tree model. The candidate factors associated with fracture risk were ordered *via* random forest algorithm (A) and (B) prediction node and weight were allocated *via* decision tree algorithm. BMI: Body mass index; ECOG: Eastern Cooperative Oncology Group; TACE: Transcatheter arterial chemoembolisation; HHS: History of hepatobiliary surgery; PrP: Preoperative pain; MDT: Maximum tumor diameter; LOET: Location of embolized tumor; NOET: Number of embolised tumours; PVTT: Portal vein tumor thrombus; DFLS: Distance from the liver capsule; CTPG: Child-pugh grade; OpD: Operation_duration; ES: Embolization supplement; LOD: Iodine oil dosage; PT: Prothrombin time; PTA: Preoperative prothrombin activity; TBIL: Total bilirubin; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; PLT: Platelet count; RFM: Random forest model; DTM: Decision tree model; SVMM: Support vector machine model; NBM: Naive Bayes model; ANNM: Artificial neural network model.

patients with HCC was 16.73% within 24 h of TACE. Based on the analysis of pain occurrence at various time points, the incidence of pain was highest at 6 h after TACE. A possible reason is that postoperative pain is mostly caused by tumour tissue embolism and necrosis, the liver volume increases, and the right upper quadrant pain is caused by pulling the capsule. In this study, patients with HCC were uniformly administered preventive analgesic drugs before surgery, thus delaying the occurrence of pain. However, medical staff should strengthen the early inspection of patients with HCC, pay close attention to the symptoms and signs of patients and implement preventive measures, whenever necessary, to alleviate postoperative pain symptoms.

In this study, machine learning-based models were developed to predict post-TACE pain, and candidate predictors were identified based on the clinical baseline data of patients before surgery. The results were consistent with those of previous studies[20,23,24]. For example, this study showed that age of > 50 years was an independent risk factor for moderate-to-severe pain after TACE. The reason for the high incidence of postoperative pain in young patients is that the pain threshold of the human body
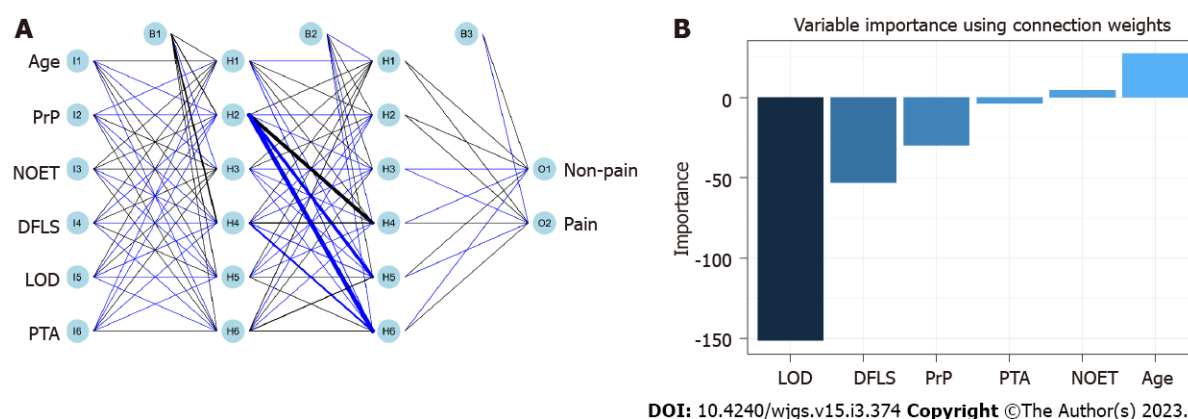
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Figure 4 Predictive model visualization based on artificial neural network model algorithm. A: Artificial neural network model; B: Variable importance using connection weight. PrP: Preoperative pain; NOET: Number of embolised tumours; DFLS: Distance from the liver capsule; LOD: Iodine oil dosage; PTA: Preoperative prothrombin activity.
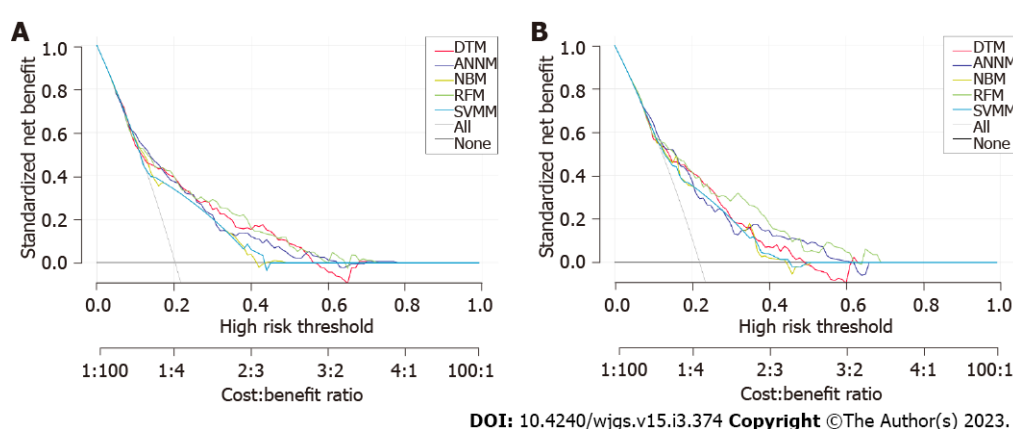

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Figure 5 Prediction pain risk performance of candidate models based on machine learning-based algorithm. A: Decision curve analysis (DCA) for five machine learning (ML)-based models in the training set; B: DCA for five ML-based models in the testing set. DTM: Decision tree model; ANNM: Artificial neural network model; NBM: Naive Bayes model; RFM: Random forest model; SVMM: Support vector machine model.

increases with age, and the sensitivity of elderly patients to pain is lower than that of young patients, resulting in changes in pain tolerance[25]. Therefore, medical staff should closely observe the symptoms and signs of young patients after surgery, and if necessary, pre-emptive analgesia should be implemented to reduce the incidence of postoperative pain. Furthermore, PrP was also identified as an important predictor of moderate-to-severe pain after TACE, which is consistent with the results of previous studies[26,27]. A meta-analysis reported that PrP is an important predictor of postoperative pain[26]. A possible reason is that the influx of PrP signals can enhance the excitability of spinal dorsal horn neurons and their responsiveness to pain transmission, which can be further maintained through transcriptional changes[28]. For example, cyclooxygenase-2 is induced to produce prostaglandin E2, which leads to postoperative pain[21]. Therefore, selective cyclooxygenase-2 inhibitors should be administered to high-risk patients preoperatively to reduce the incidence of moderate and severe pain postoperatively.

Furthermore, the distance between the tumour and liver capsule (≤ 2 cm), presence of multiple embolic tumours and dosage of lipiodol greater than 10 mL were also identified as risk factors for moderate-to-severe pain after TACE, which is consistent with the results of previous studies[10,29]. If the tumour tissue is close to the liver capsule, it may become necrotic and oedematous after hepatic arterial chemoembolisation, leading to increased tension in the liver capsule. Consequently, the patient is more likely to feel pain and discomfort. Moreover, if more tumours are embolised, more iodised oil is required, and a larger embolised area may increase the pain caused by tumour necrosis. we speculated that embolization of nodules close to the gallbladder might also be an alternative cuase of pain, especially if cystic artery vessels provided bllod to the nodules and had to be embolized. Prothrombin activity is an important indicator of liver coagulation because high prothrombin activity often indicates that the body is in a hypercoagulable state[30,31]. High prothrombin activity may be a primary cause of postoperative pain. Alternatively, injured tissue cells release a large amount of thromboplastin during surgery, which can also lead to a temporary hypercoagulable state in the early postoperative period[32,

33]. Consequently, the blood flow is slow, and the risk of postoperative micro-thrombosis and pain is increased. Therefore, medical staff should promptly evaluate the liver function of patients, detect changes in prothrombin time and control the abnormal indicators of coagulation function for effective pain management.

Although the candidate variables included in this study can be used to develop different machine learning-based predictive models, the predictive accuracy of the models may differ. In this study, RFM was found to have the best prediction efficiency, which is consistent with the results reported in previous studies[34,35]. RFM can realise multiple iterations of subsequent variables based on the 'bagging' algorithm, which signifies that the predictive efficiency of the included variables can be optimised after adding numerous 'branches' and 'pruning'[35,36]. Although ANNM can be used for risk stratification of patients with post-TACE pain, its predictive efficiency is slightly inferior to that of RFM, which reflects the practicability of the input- and hidden-layer algorithms in this study. However, the algorithm requires to be constantly updated to reflect the robustness of its 'output layer'[37]. The predictive performance of machine learning algorithms is undoubtedly better than that of logical regression algorithms because machine learning has incomparable advantages in terms of the number of iterations. Altogether, in this study, we developed an efficient predictive model based on candidate variables that can be adopted clinically. The model can be used for stratifying the risk of post-TACE pain to facilitate early management and improve the prognosis of patients.

However, this study has some limitations. First, this study had a retrospective design and only focused on patients undergoing traditional lipiodol-based embolisation, while the latter focused on patients using drug-eluting microspheres for embolisation. Therefore, the results may have been affected by selection bias. Second, although some clinical variables were included in this study, the psychological status and psychosocial factors of patients were not included, and no suggestion was made to further improve the predictive model by adding these factors. Third, this study relied on only single-centre internal verification; therefore, external spatial verification is required to accurately evaluate the predictive efficiency of the predictive models. Fourth, this study included only patients receiving traditional TACE; therefore, patients undergoing different types of TACE should be included in future studies to improve the universality of the predictive model.

CONCLUSION

Machine learning-based pre-warning models can be developed to predict post-TACE pain for hierarchical management of patients at high risk of moderate and severe pain after TACE. In particular, RFM combined with preoperative predictors (*i.e.,* age, PrP, DFLS ≤ 2cm, prothrombin activity, iodine oil dose and presence of multiple emboli) has optimal discriminating power and high predictive accuracy. Therefore, RFM can be used for early prediction of the risk of postoperative pain, which can facilitate prompt pain management after TACE and improve the prognosis of patients.

ARTICLE HIGHLIGHTS

Research background
Pain after transcatheter arterial chemoembolisation (TACE) can seriously affect the prognosis of patients and the insertion of additional medical resources.

Research motivation
To develop a practical model for predicting pain after TACE.

Research objectives
This study aimed to predict pain after TACE to enable the implementation of preventive analgesic measures.

Research methods
Of 857 patients (from January 2016 to January 2020) and prospectively enrolled 368 patients (from February 2020 to October 2022; as verification cohort) with hepatocellular carcinoma (HCC) who received TACE were collected from the Hepatic Surgery Center of Tongji Hospital. Five predictive models were established using machine learning algorithms were used to predicting postoperative pain and receiver operating characteristic curve analysis, decision curve analysis and clinical impact curve analysis were used to evaluate the effectiveness of the model.

Research results
Of 24 candidate variables were to build prediction model, among them, the age, preoperative pain,

number of embolised tumours, distance from the liver capsule, dosage of iodised oil and preoperative prothrombin activity were closely associated with postoperative pain. The random forest model (RFM) had the best predictive efficiency [training cohort: Area under the curve (AUC) = 0.869, 95% confidence interval (CI): 0.816-0.922; internal verification cohort: AUC = 0.871; 95%CI: 0.818-0.924].

Research conclusions

The five prediction models based on advanced machine learning algorithms are extremely suitable for the pain management of liver cancer patients after TACE, especially the RFM can accurately classify the pain risk of patients.

Research perspectives

Machine learning-based pre-warning models can be developed to predict post-TACE pain for hierarchical management of patients at high risk of moderate and severe pain after TACE. Alarmingly, the RFM can be used for early prediction of the risk of postoperative pain, which can facilitate prompt pain management after TACE and improve the prognosis of patients.

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FOOTNOTES

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