Time-to-Event Supervised Genetic Algorithm Enables Induction Chemotherapy Decision Making for Nasopharyngeal Carcinoma

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ABSTRACT Do nasopharyngeal carcinoma (NPC) patients benefit from induction chemotherapy (IC)? This problem is of great clinical interest; however, it is difficult to obtain an accurate and interpretable model to inform IC decisions for NPC patients. In this study, a time-to-event supervised genetic algorithm was developed to obtain an IC decision-making model for NPC patients. In this algorithm, the fitness function is directly related to the time-to-event, which reflects the IC therapeutic effect for NPC. Then, the optimal models are obtained by stability and validation analysis. The comprehensive clinical model is determined by comprehensive feature analysis using the ''or'' operation. The overall survival for non-IC vs. IC patients in the potential benefit group was 63.4% vs. 81.5%, with p = 0.020, and the comprehensive clinical model exhibited good generalization ability. However, the benefits of OS according to the current NCCN guidelines are limited (p > 0.05). None of the possible processes of LASSO we tried could obtain the significant models validated in the testing cohort. The proposed method provides an interpretable model construction process, reasonable data grouping strategy, concise experimental design, and convenient clinical application. Moreover, we will develop a toolkit for the treatment decision-making model research to facilitate the use of clinicians and provide technical support for precision medicine.

INDEX TERMS Treatment decision-making, genetic algorithm, survival analysis, LASSO, retrospective study, nasopharyngeal carcinoma, induction chemotherapy.

I. INTRODUCTION

Induction chemotherapy (IC) is gaining recognition for nasopharyngeal carcinoma (NPC) and has been used consistently over the last decade [1]–[3]. However, not all patients respond well to IC, and an effective means of identifying patients who will respond well requires further study [4]. The risk of delaying standard intensity-modulated radiation therapy- based concurrent chemoradiotherapy for IC has been debated in recent years. Although many clinical trials have confirmed that IC can benefit patients with advanced NPC, various studies have also pointed out that its benefits in some patients with advanced NPC are not obvious [5]–[7]. Therefore, in addition to relying on clinical staging for patient selection as most clinical studies do, there is an urgent need for a patient selection tool or model to determine those patients who may obtain significant survival benefits from IC, and those who will receive no significant benefits can use the standard scheme earlier.

Stratification survival analysis has commonly been used to investigate whether NPC patients benefit from IC [8]–[12]. As shown in Figure 1, the NPC patients who participate in such tests are stratified into IC and non-IC groups. Univariable Cox regression analysis is performed to obtain
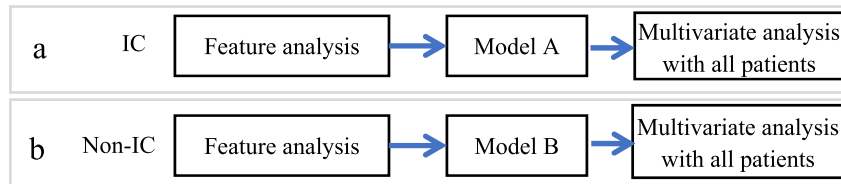
The associate editor coordinating the review of this manuscript and approving it for publication was Jagdish Chand Bansal.

FIGURE 1. Flowchart of stratification survival analysis depending on whether a treatment is performed on patients. a and b are the common stratification analysis process. IC= induction chemotherapy.

the significant feature variables, which are used to evaluate whether NPC patients benefit from IC. The prognostic score model is constructed for each group by least absolute shrinkage and selection operator (LASSO) or Cox regression analysis, and then a cut-off score to divide the high-risk and low-risk groups is identified using receiver-operating characteristic (ROC) curve analysis. Usually, Cox regression analysis with a stepwise method or more comprehensive multivariable analysis can be utilized for feature analysis when the number of candidate features is relatively small, while LASSO can be employed when the number of feature parameters is large [13]. Multivariate analysis has also been performed to confirm the benefits of IC while controlling specific parameters. The overall survival (OS) between these two groups has been evaluated using the Kaplan-Meier method and log-rank test in multivariate analysis with all patients [14]–[16]. Model A, which can be used to select NPC patients who benefit from IC, can be constructed by IC group analysis, and model B, which can be used to select NPC patients who do not benefit from IC, can be constructed by non-IC group analysis.

However, these methods have several limitations. First, there are many potential features for assessing whether NPC patients benefit from IC, and the dimension of the feature space is very high. An excessive number of potential models must be validated, which is difficult to do exhaustively because this problem is a non-deterministic polynomial hard problem. It is also challenging to evaluate the therapeutic effect of NPC comprehensively using the treatment decision model constructed by Cox regression analysis. Second, although LASSO analysis can be used to construct an evaluation model when there are many feature variables, feature selection in LASSO is blind to the OS of NPC patients. In LASSO analysis, the objective function of model construction and optimization is the deviation or area under the ROC curve (AUC), which is only related to the values of the feature variables involved in the analysis and ignores the IC information in the feature selection. Hence, models obtained by LASSO analysis have difficulty making accurate IC treatment decisions for NPC patients. Third, it is difficult to determine clearly whether NPC patients will benefit from IC clinically; that is to say, it is challenging to assign the IC treatment effect label for each NPC patient. The methods of machine learning and artificial intelligence,

which can be used to construct models in high-dimensional feature space, have failed to construct a treatment decision model to evaluate whether NPC patients will benefit from IC.

To obtain an optimal treatment decision-making model, the optimal combination of feature variables must be selected from a massive number of feature variables. A high-dimensional feature space can be formed from the features obtained by feature analysis. The optimal feature set is a subset of the high-dimensional feature space. Genetic algorithms have been proven to be robust global optimization algorithms for searching the suboptimal solutions in high-dimensional space [17]–[21] and have been used for feature selection in multimodal biometric systems [22], high-dimensional cancer microarray datasets [23], etc.

In the present report, a time-to-event supervised genetic algorithm is proposed to obtain an IC decision-making model for NPC patients based on feature selection from numerous clinical characteristics. In our genetic algorithm, the fitness function is defined as the reciprocal of the p-value of the survival analysis, which is directly related to the time-to-event, directly reflects the IC therapeutic effect for NPC, and supervises the implementation process of genetic algorithm. All models with p-values less than 0.05 in the genetic algorithm were collected, and the stability and validation analysis were used to select the optimal IC decision-making model for NPC.

The main contributions of this paper are as follows. First, we take the lead to put forward the integration of the log-rank test and genetic algorithm. Time-to-event supervise the whole process of model construction which result in the result model is characterized as concise and interpretable. Second, we provides a useful new means of evaluating the therapeutic effectiveness or performing decision making for disease treatment, and the patients who benefit from a specific therapy can be effectively screened out in terms of OS. Third, we successfully constructed a comprehensive clinical IC decision-making model for NPC based on the experimental data, but the LASSO cannot. Using the new model, KM survival curves of the patients with IC is significantly higher than that of patients without IC (p<0.05). The benefits of OS according to the current NCCN guidelines are limited (p > 0.05).
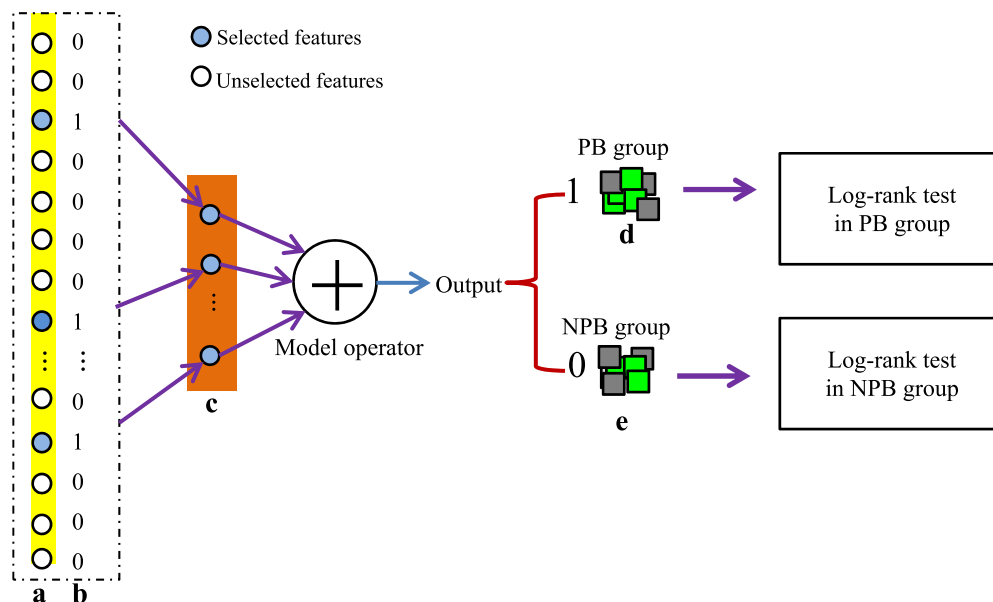
FIGURE 2. Design of IC decision-making model for NPC. a One-hot coded clinical features. b Genetic code for feature description. c Selected features as model input. d Subjects with model output of 1. e Subjects with model output of 0. The grey and green rectangles in d and e represent the subjects who received and did not receive treatment, respectively. PB group = potential benefit group; NPB group = non-potential benefit group.

II. MATERIALS AND METHODS

A. DATA COLLECTION

A dataset of IC on NPC was obtained as in [24]. The ethics committee of Sun Yat-sen University Cancer Center approved this study, and the need for informed consent was exempted for this study, which followed the tenets of the Helsinki Declaration. The inclusion criteria and the details regarding the image parameters can be found in the Appendix A in the supplementary material. 719 patients underwent intensity-modulated radiation therapy. Depending on the decision of the attending physician, some patients received concurrent chemotherapy, IC, or both. The first 399 patients were selected as the training cohort and the remaining 320 patients as the test cohort. The median follow-up duration for the OS of the whole cohort was 61.9 months (range, 1.4–83.4 months). The outcomes of interest were OS, progression-free survival, distant metastasis-free survival, and regional recurrence-free survival. Upon the last follow-up, 47 patients (11.8%) in the training cohort and 39 patients (12.2%) in the test cohort were confirmed dead due to tumour recurrence or metastasis. The clinical characteristics of the training and testing cohorts are summarised in Appendix B in the supplementary material. No significant differences were found between the training and test cohorts (p > 0.05), except for concurrent chemotherapy (p = 0.005); however, patients in both groups mostly (>89%) received concurrent chemotherapy. To some extent, they also received similar treatments.

A total of 289 original features were found from the clinical information, plasma parameters, and medical imaging information; most of them were from the MRI-based detailed imaging findings reported by two radiologists with the same opinion. After one-hot encoding, 532 features were extracted from the MRI according to a detailed report, including three staging-related fields, one pathological type, 43 patient basic information and laboratory- related fields such as blood testing, and 468 detail report-related fields. The descriptions of the selected features and the corresponding coefficients are listed in Appendix C in the supplementary material. Using univariable Cox regression, we selected 145 features that were the most strongly associated with OS for further analysis.

B. DESIGN OF IC DECISION-MAKING MODEL FOR NPC

Clinical features combined with survival analysis are employed to determine whether a patient may benefit from a treatment. All feature values used for the analysis are set to 0 or 1 after one-hot coding. Several features that are randomly selected from the feature set can be used as model inputs to determine a genetic code. In the genetic code, 1 represents a randomly selected feature that is given as input to the model, whereas 0 represents an unselected feature. A treatment decision-making model is determined using the genetic code based on the selected features. As shown in Figure 2, the model is defined as an 'or' operation. The model input consists of the values of the selected feature in a specific genetic code, and the model output is the result of performing the 'or' operation on the input. The subjects can be separated into two groups using a specific model. If one of the selected feature values of a patient is 1, the model considers the patient to belong in the potential benefit (PB) group. Otherwise, the patient is considered to belong in the non-potential

benefit (NPB) group. The subjects who received and did not receive treatment were included in each group.

The KM method and log-rank test can be independently conducted in each group to evaluate the model performance. When the p-value obtained from the log-rank test is less than 0.05, the model can be considered to effectively distinguish the patients who will benefit from treatment. When the survival curve of the patients who receive treatment is above that of the patients who do not receive treatment, there is reason to believe that the patients will benefit from the treatment based on the model. The p-value of the model is defined as the p-value of survival analysis in the PB group because the patients who will benefit from the treatment are of greater interest. A model with a p-value of less than 0.05 indicates that it is a potential model for treatment decision-making in the training stage or an optimized one in the test stage.

C. TIME-TO-EVENT SUPERVISED GENETIC ALGORITHM

For n formatted features, the number of possible models for treatment decision-making is 2n. This problem is a non-deterministic polynomial complete problem. Usually, the dimensions of the formatted features are significantly high. Additionally, the number of models is so large that they cannot be processed in an exhaustive manner. To determine the optimal model with significance in survival analysis, a time-to-event supervised genetic algorithm was implemented in the training stage.

A genetic algorithm starts from a population that represents the potential solution set of the problem; a population is composed of a certain number of individuals encoded by gene. Each individual is actually a chromosomal entity with features. Coding in the genetic algorithm is utilized to build a mapping from the genotype to phenotype. The binary coding technology was used for genetic encoding because it is concise and easy to decode. For gene coding, the clinical feature used for the model input is the feature with a coding value of 1; subsequently, a binary coding sequence can produce a treatment decision-making model. The model p-value, which can describe the difference in survival between the patients with and without treatment based on the dataset, can be obtained by survival analysis. The lower the p-value, the stronger the adaptability of the population. Therefore, the fitness function of an individual is set as the reciprocal of the model p-value to supervise the iterative process of the genetic algorithm. A given iteration I_n generated the population P_n from the population P_{n-1} through the genetic operators. In each iteration, the individual with the largest fitness function value was directly inherited by the next population. The individual pairs were randomly selected from population P_n, and each pair was submitted to a crossing over process, thereby generating a couple of children for population P_{n+1}. Each child had a 0.15% chance of mutation, where one position was randomly selected for substitution. When a new population was generated, it was checked whether the individual in the new population adhered to the coding rules. If not, the individual was discarded and
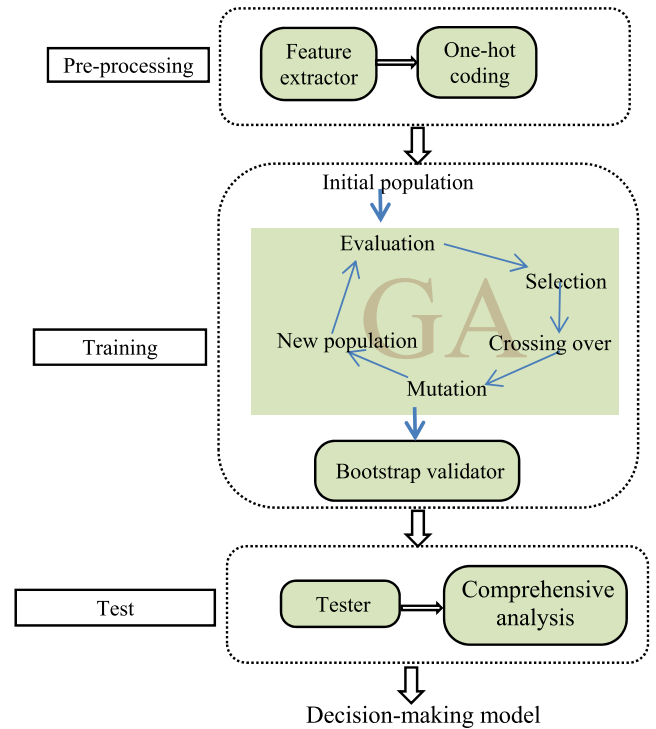

FIGURE 3. The process of IC decision-making model construction.

a new random individual who satisfied the coding rules was generated to maintain a stable number of individuals in the population.

D. TREATMENT DECISION-MAKING MODEL CONSTRUCTION

The process of treatment decision-making model construction is shown in Figure 3. In the pre-processing stage, the dataset was independently divided into training and test cohorts. Each cohort included the treated and non-treated patients. The clinical and survival features were extracted and collected; the formatted features can be obtained after one-hot encoding.

In the training stage, the time-to-event supervised genetic algorithm is used to obtain the potential models, which p-values of less than 0.05 during population evolution. And then, bootstrap is used to evaluate the stability of all potential models. Partial data from the training cohort were resampled 1,000 times. For each potential model, survival analysis was performed on each resampled dataset. The stability coefficient was defined as SC = F/1000, where F represents the number of resampled datasets for which the p-value of the model was less than 0.05 in survival analysis. Larger values of SC indicate a more stable model. The first 2% of the most stable potential models were selected as candidate models.

In the validation stage, The KM method and log-rank test were performed using the test cohort and candidate models to identify models with p-values of less than 0.05 in the test stage as the optimal model. The optimal models were stable in

TABLE 1. Model patient distribution and selected features.

Model	Training (N = 399)	Test (N = 320)	Chi-square	Selected features
Optimal model 1			0.074	CNI, B.ASS, BU.CLN, L.CLN, SLN, N2/3 classification
IC not recommended	278 (69.7%)	203 (63.4%)		
IC recommended	121 (30.3%)	117 (36.6%)		
Optimal model 2			0.376	CNI, B.ASS, CSI, BU.CLN, BNGU.CLN, N2/3 classification
IC not recommended	269 (67.4%)	205 (64.1%)		
IC recommended	130 (32.6%)	115 (35.9%)		
Optimal model 3			0.295	CNI, CSI, ONI, N2 classification
IC not recommended	292 (73.2%)	245 (76.6%)		
IC recommended	107 (26.8%)	75 (23.4%)		
Comprehensive model			0.341	CNI, B.ASS, CSI, SLN, and N2/3 classification
IC not recommended	265 (66.4%)	201 (62.8%)		
IC recommended	134 (33.6%)	119 (37.2%)		

Note: Optimal models 1–3 are the models obtained using the proposed method, and the comprehensive model was obtained by the comprehensive clinical analysis of models 1–3. Abbreviations: CNI, cranial nerve invasion; B.ASS, bilateral invasion of anterior styloid space; BU.CLN, bilateral upper cervical lymph nodes; L.CLN, lower cervical lymph node; SLN, skip lymph node; CSI, carotid sheath invasion; BNGU.CLN, bilateral nodal grouping of upper cervical lymph node; ONI, orbital or optic nerve invasion.

the training cohort and had statistical significance in the test cohort; they were selected for further comprehensive clinical analysis. There may be many optimal models that pass the test, and the variables in these models may have correlation. Therefore, the comprehensive clinical model was determined by the comprehensive analysis of features based on the 'or' operation in the model design.

E. PERFORMANCE EVALUATION

To illustrate the superiority of the algorithm, the LASSO analyses have been carried out on the same dataset. We will discuss the performance of the proposed method and LASSO from the process of model construction, data grouping strategy, experimental design and clinical application.

III. EXPERIMENTAL RESULTS AND DISCUSSION

A. IMPLEMENTATION OF TIME-TO-EVENT SUPERVISED GENETIC ALGORITHM

The algorithm was implemented in MATLAB 2016a on Microsoft Windows 10 home. The source code of the algorithm can be found at https://github.com/GUET-LDM/TesGA_IC_NPC.

The parameters of the genetic algorithm were set as follows: 145 variables after one-hot coding, 200 sequences in the population, one million iterations, and 0.15% probability of mutation. The maximum number of features selected in one model was limited to 15. In the iteration process, the genes for the model with more than 15 selected features were discarded to prevent the population from precocity. The fitness function was set to the reciprocal of the p-value from the survival analysis to supervise the evolutionary process of the genetic algorithm.

72,904 potential models were collected within one million iterations, and 1458 candidate models were obtained after stability analysis. Only three of the candidate models in the test cohort had p-values of less than 0.05 in the test stage by tester, which were called the optimal models and selected for further clinical analysis.

B. COMPREHENSIVE CLINICAL IC DECISION-MAKING MODEL FOR NPC

The information regarding the three optimal models is summarized in Table 1. Nine feature variables were listed as a sample of the aforementioned 145 features ($p < 0.05$), including cranial nerve invasion (CNI), bilateral invasion of anterior styloid space (B.ASS), bilateral upper cervical lymph nodes (BU.CLN), lower cervical lymph node (L.CLN), skip lymph node (SLN), carotid sheath invasion (CSI), bilateral nodal grouping of upper cervical lymph node (BNGU.CLN), orbital or optic nerve invasion (ONI), and N2/3 classification. The clinical analysis results for the PB and NPB groups are shown in Appendixes E and F in the supplementary material, respectively, in the training and test cohorts. The patients who received IC exhibited significantly better survival rate than the non-IC patients in models 1–3 in the PB group, but not in the NPB group. The chi-square test results demonstrated no significant difference in the number of patients in the training and test sets who were recommended to receive IC. These results imply that the selected three optimal models have strong generalization ability.

We can further determine that there is a correlation between the features in models 1 and 2. As is known clinically, the N2/3 classification feature includes BU.CLN, L.CLN, and BNGU.CLN. Among these, N2/3 classification has been more widely used clinically. Therefore, the comprehensive
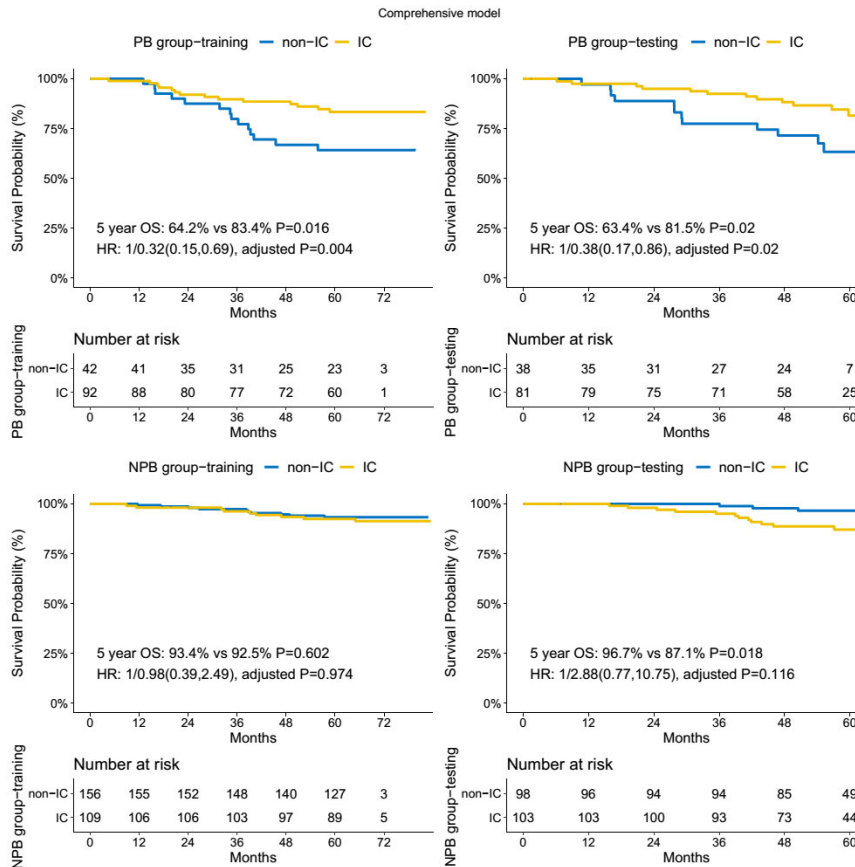
FIGURE 4. OS for the comprehensive clinical model. Patients who belonged to the non-IC (blue) and IC (yellow) groups show significant differences both in training and testing. KM survival curves were used to calculate the five-year OS, and the p-values were calculated using the log-rank test. HR(CI) and the adjusted p-values were calculated by multivariable Cox regression analysis, as described in detail in appendix D in the supplementary material. Abbreviations: OS, overall survival; KM, Kaplan-Meier; HR, hazard ratio; CI, confident interval; IC, induction chemotherapy.

clinical model was determined by the comprehensive analysis of features based on the 'or' operation in the model design. The features in the comprehensive clinical model are CNI, B.ASS, CSI, SLN, and N2/3 classification. The information for the comprehensive clinical model is summarized in Table 1. In addition, the comprehensive clinical model has good generalization ability. The clinical analysis results for the comprehensive clinical model are presented in Figure 4. For the PB group, the overall survival for the non-IC vs. IC group was (64.2% vs. 83.4% p = 0.016; HR: 1/0.32(0.15, 0.69) adjusted p = 0.004) in the training cohort and (63.4% vs. 81.5% p = 0.020; HR: 1/0.38(0.17, 0.86) adjusted p = 0.020) in the test cohort. For the NPB group, patients who received IC exhibited a slightly, but not significantly. Based on the current NCCN guidelines, stage III/IV patients (right two images) with or without stage II should receive IC. The benefits of OS according to the current guidelines are limited, and the KM curves between the IC and non-IC groups overlap with each other (p > 0.05) as shown in Figure 5. Thus, the above results suggest that the comprehensive clinical

model was successful in identifying patients who would benefit from IC in terms of OS.

C. PERFORMANCE COMPARISON WITH LASSO

To illustrate the superiority of the algorithm, the LASSO analyses have been carried out on the dataset. Flow chart of LASSO analysis for IC decision on NPC has been shown in Appendix G in the supplementary material. There were three steps for retrospective study based on LASSO analysis. The first step was that a model could be built using the LASSO with or without stepwise on the treatment group or non-treatment group based on a specific hypothesis. The second step was the subjects could be divided into high risk group and low risk one according to a cut-off score. And then, the performance of the model was validated using Log-rank test and KM survival analysis on the validation cohort. The results were shown in the Appendix G in the supplementary material. The overall survival for the non-IC vs. IC group was (82.9% vs. 80.3% p = 0.972) for all patients in LASSO analysis, (74.7% vs. 80.7% p = 0.387) for only
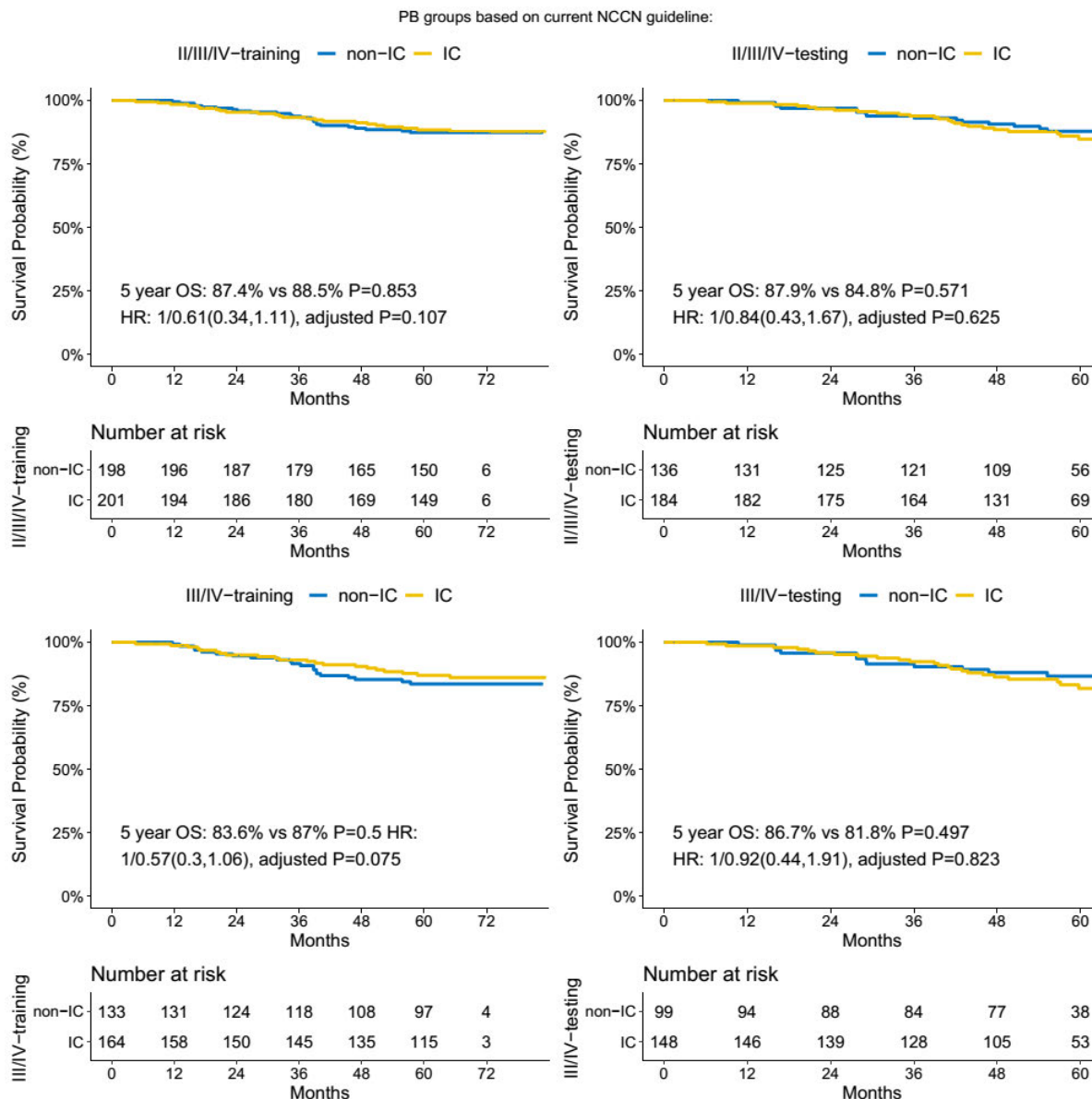
FIGURE 5. Background based on current NCCN guideline. Kaplan-Meier survival curves were used to calculate the 5 year OS, and the P-values were calculated using the log-rank test. The HR(CI) and adjusted P-values were calculated by multivariable Cox regression analysis. OS: overall survival; HR: hazard ratio; CI: confident interval; IC: induction chemotherapy.

patients with IC, and (54.0% vs. 72.9% p = 0.249) for only patients without IC. None of the possible processes we tried could obtain the significant models validated in the testing cohort.

IV. DISCUSSIONS AND CONCLUSION
Can we determine the patients who may benefit from a treatment? For example, non-small cell lung cancer patients from epidermal growth factor receptor -tyrosine kinase inhibitors therapy [25], [26], hepatocellular carcinoma patients from interventional therapy [27]–[29], etc. These clinical problems are of great interest to doctors; however, they cannot be answered directly. Researchers usually collect information

about clinical features related to a treatment and follow up with patients for a long time. Then, a retrospective study is performed to estimate whether the treatment has been effective, and inform clinical decisions for follow-up patients [30], [31]. At present, LASSO is the most popular analysis method, and KM survival analysis is the most effective means of model evaluation [32].

The main objective of this work was to develop a concise and interpretable method for the construction of treatment decision-making models. In this method, a time-to-event genetic algorithm was utilized to supervise the optimal model selection process. The optimal model was verified via stability analysis and validation with the test dataset, thereby

resulting in a reliable clinical decision model. The new method has four characteristics.

First, the process of model construction using the proposed method is more easily interpretable than the traditional process. Feature selection and model evaluation are indispensable steps in retrospective analysis via the LASSO method [33], [34]. In this case, feature selection for the model was performed using the deviation, mean squared error, or area under the curve [35]. These feature selection methods are related to the dataset itself, but not directly to the OS. Then, the KM and log-rank test were implemented after determining the model cut-off score. In the proposed method, the log-rank test, which is related to clinical processing, supervises the entire feature selection process. The features that contribute to the evaluation of the therapeutic effectiveness of the treatment have a higher priority in the selection process for constructing models for treatment decision-making.

Second, the data grouping strategy in the new method is more reasonable than the conventional approach. To obtain a reliable model, the dataset should be divided into training and test cohorts in retrospective analysis. In LASSO, each cohort only includes the patients who receive or do not receive treatment, but not both [26], [36]. This cohort partition scheme is effective for retrospective analysis by LASSO only with big data from participants and a balance between the amounts of data corresponding to the treated and untreated subjects. However, it is difficult to obtain sufficient data for a clinical dataset in medical research owing to the potential risk factors, which could reduce the credibility of the decision model. In the proposed method, the subjects for the analysis were divided into training and test cohorts as well. Each cohort included patients who received and did not receive treatment. The model construction and KM survival analysis were implemented using the training cohort to identify the candidate treatment decision models. The test cohort was used to test the candidate models to obtain the optimal models. The new method is more suitable for constructing a treatment decision-making model because the expected model can be obtained with an appropriate amount of data.

Third, the experimental design is more concise than the currently utilized design. Information about whether patients can benefit from clinical treatment is unknown. Patients have generally been categorized into high and low risk groups in the traditional experimental design of retrospective analysis according to a specific hypothesis [37]–[39]. Is there a medium risk group? For example, the NPC patients diagnosed as stage III/IV had a higher risk of distant metastasis than those of stage I/II [40]. However, some NPC patients with early stage II benefit from IC [41], 42]. Therefore, it was difficult to align the hypotheses with clinical practice because it could have resulted in some NPC patients losing the opportunity for IC treatment. In the new method, the significant feature variables in the dataset can be selected without any hypothesis, and the optimal treatment decision model can be obtained after stability analysis and verification. The patients participating in the analysis did not need to be grouped according to the risk level. According to the feature distribution in the dataset, all patients at all risk levels participated in the model construction and analysis, and all patients who would benefit from the treatment could be identified.

Fourth, clinical application in terms of the proposed method is more convenient than that of in the standard approach. After applying the LASSO, the model becomes a multivariate equation or a nomogram scoring table system, and subsequent comparisons with the cut-off value are necessary to predict the result. This process minimally requires the clinician to record the results on a small note with a calculator, which is inconvenient. At present, our method yields a series of only five variables for IC decision-making for NPC. CNI and N2/3 classification of NPC patients were associated with poor prognosis in the late stages (stage III/IV); thus, both features are familiar to clinicians and prove that our model can select the variables effectively [43]. SLN [44], [45] and CSI 46] can be easily identified via MRI and they are related to poor outcomes. However, they are not mentioned in the current American Joint Committee on Cancer (AJCC) staging system manual for NPC [47]. It is well known that the bilateral invasion of the anterior styloid space produces a larger tumor volume than unilateral invasion. Importantly, all these features are basic structures that can be further extended to the reports of the radiology department with a wide range of clinical applications.

In summary, we developed a time-to-event supervised genetic algorithm to identify a concise and interpretable treatment decision-making model that can help doctors in effectively determining the patients who will benefit from a specific therapy. The proposed method provides a useful new means of evaluating the therapeutic effectiveness or performing decision making for disease treatment.

There are two interesting directions for future research. First, we will further verify the performance of the algorithm under different conditions, such as small samples, which are common in medical research data. Second, we will develop a toolkit for the treatment decision-making model research to facilitate clinical usage and provide technical support for precision medicine.

V. DATA AVAILABILITY
All data and the developed software in this manuscript are available from the authors upon reasonable request.

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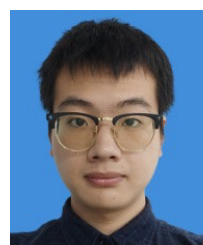

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