A Nomogram to Predict Critical Weight Loss in Patients with Nasopharyngeal Carcinoma During (Chemo) Radiotherapy

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ABSTRACT

BACKGROUND: Weight loss is an important side effect of long-term anticancer treatment for nasopharyngeal carcinoma patients. The decline in body function will cause many adverse effects, such as local recurrence and distant metastasis, and reduce the patient's quality of life. Therefore, this study developed a predictive model for the probability of critical weight loss to provide timely appropriate nutritional interventions and prevent serious side effects.

METHODS: A 20-week prospective follow-up study of 137 nasopharyngeal carcinoma patients in West China Hospital of Sichuan University undergoing radiotherapy and chemotherapy from February 2018 to March 2020 was conducted to collect relevant clinical data. The clinical usefulness and calibration of the prediction model were assessed using the C-index, calibration plot, receiver operating curve, and decision curve analysis. Internal validation was assessed using bootstrapping validation.

RESULTS: The nomogram consisted of sex, smoking status, physical status, chemotherapy regimen, and body mass index. Good calibration was observed for the cohort, with an area under the curve of 0.924. Five independent prognostic factors were included in the nomogram, which showed a high C-index value of 0.815 in the interval validation. Decision curve analysis showed that the nomogram was clinically useful when the intervention was decided at the critical weight loss possibility threshold in the 0% to 97% range.

CONCLUSIONS: We constructed and validated a nomogram for predicting the incidence of critical weight loss in nasopharyngeal cancer patients undergoing chemotherapy and radiotherapy.

KEYWORDS: Nomogram, nasopharyngeal carcinoma, critical weight loss, radiotherapy, induction chemotherapy

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Introduction

Nasopharyngeal carcinoma (NPC), a cancer arising from the nasopharynx epithelium,[1] is characterized by its geographic distribution, such as being very common in southern and southeast China.[2,3] There were approximately 129 000 new cases of NPC diagnosed in 2018.[4] Radiotherapy is the most significant treatment for NPC, especially the implementation of intensity-modulated radiotherapy.[5] Concurrent and adjuvant chemotherapy is also used to treat NPC due to its chemotherapy sensitivity. However, it has been reported that concurrent chemotherapy significantly increases the level of III/IV haematologic toxicity and mucosal toxicity, which seriously affects the treatment process and quality of life of patients.[6] According to the National Comprehensive Cancer Network (NCCN) guidelines, concurrent radiotherapy and chemotherapy (CCRT) are recommended for treating locally advanced NPC (LANPC).[7,8]

As mentioned above, intensive and continuous anticancer treatment is administered after NPC is diagnosed, which generally causes a series of side effects. For instance, symptoms with general, gastrointestinal, nutritional, and social interaction effects have been identified as symptom clusters during radiotherapy. Patients with these symptom clusters are prone to lose weight and those with more body weight loss experience more symptom clusters.[9] Weight loss is one of the main symptoms of malnutrition, leading to a decline in physical function.[10] The decline in physical function caused by weight loss can cause many adverse effects and decreases patients' quality of life.[11]

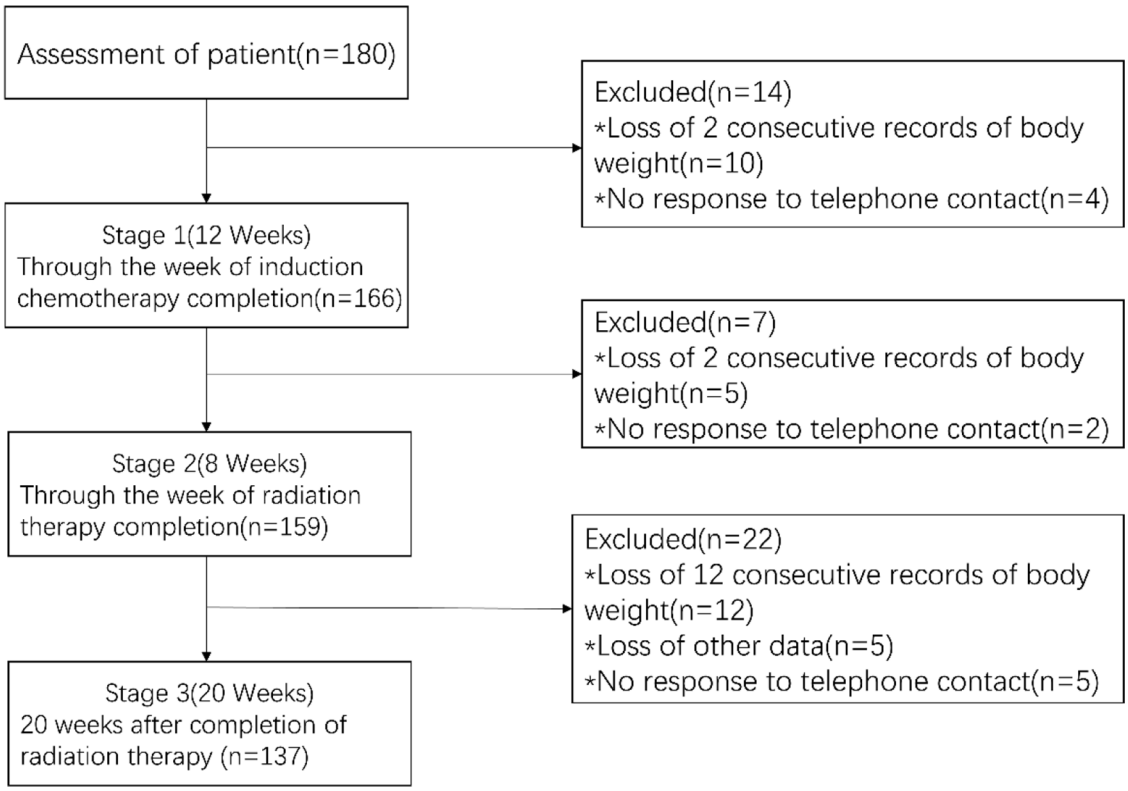

Figure 1. Flowchart. Four trained oncology nurses and an oncologist collected the data, which were categorized into 4 types: demographic and disease characteristics, treatment information, blood examination, body weight, and body mass index (BMI). Demographic and disease characteristics, including sex, age, performance status score, smoking history, and cancer stage, were collected once before induction chemotherapy. Treatment information and blood examination data were also gathered during the treatment process. Epstein–Barr virus DNA, haemoglobin, serum total protein, and albumin (ALB) levels were recorded 12 weeks before radiation therapy and at the beginning and end of radiation therapy.

Therefore, an understanding of the risk factors for weight loss in patients undergoing radiotherapy for NPC may contribute to effective treatment or the prevention of severe side effects by providing appropriate nutritional interventions.

Nomograms, an efficient and novel prognostic model, are currently widely used in predicting the probability of a certain clinical event.[12-14] In this study, we designed and validated a nomogram based on a cohort follow-up lasting 40 weeks, which consisted of 12 weeks before radiation therapy, 8 weeks during radiation therapy, and 20 weeks after radiation therapy completion. The results of this study can help to precisely predict weight loss and prevent associated side effects in patients with NPC during (chemo)radiotherapy.

Methods

Notice

This study is in the same project as our previous research, with the same team and protocol. Therefore, we cited the previous article in the same methodologic content.[15]

Patient selection and data collection

This prospective, longitudinal and observational study was conducted at West China Hospital, a 4500-bed university-affiliated medical centre (Chengdu City, Sichuan Province, China). We recruited 180 patients who were diagnosed with stage III to IVA NPC based on the seventh edition of the American Joint Committee on Cancer (AJCC) staging system. The study was approved by the ethics committee of the hospital, and written informed consent was obtained from all patients for research purposes. Our eligibility criteria were as follows: aged 18–80 years; planned to receive radical radiation therapy plus induction chemotherapy, with or without concurrent or adjuvant chemotherapy; were without physically or radiographically confirmed oedema and body cavity effusion; had an Eastern Cooperative Oncology Group Performance Status score of 2 or less; and had an estimated survival time of more than 1 year. The exclusion criteria were as follows: the existence of oedema and effusions in the body cavity confirmed by physical examination or radiographic examinations or the loss of 2 consecutive body weight records for any reason. Patients experiencing comorbidities or nutritional disorders that might have an effect on body weight, such as hyperthyroidism or hypothyroidism, or patients with chronic kidney or heart disease, were also excluded. The inclusion and exclusion criteria are described in the flowchart (Figure 1).

Treatment regimen

Radiation therapy. For patients with NPC, intensity-modulated radiation therapy (IMRT) is the primary treatment. The primary gross tumour volume of the nasopharynx (GTVnx)

and involved lymph nodes (GTVnd) included all known lesions as determined by clinical, imaging, and nasopharyngoscopy examination. Clinical target volume–1 (CTV-1) was defined as the high-risk area that included the GTV plus a 5 to 10 mm margin. Clinical target volume–2 (CTV-2) was defined as the potentially involved area that included CTV-1 plus a 5 to 10 mm margin. In principle, the planned doses of radiation therapy for GTVnx, GTVnd, CTV-1, and CTV-2 were 66–70, 60–70, 60–66, and 54–58 Gy, respectively, in 30 to 35 fractions. Radiation therapy was delivered at 1 fraction per day, 5 days per week.

Chemotherapy. Docetaxel, cisplatin, and 5-fluorouracil (TPF) and gemcitabine and cisplatin (GP) delivered every 21 days per cycle were the mainstay regimens for induction chemotherapy. During chemotherapy, dexamethasone was routinely prescribed at 8 mg per day and taken orally the day before, on the day of, and the day after docetaxel administration. Generally, patients received 3 cycles of induction chemotherapy, and cisplatin-based chemotherapy (every 21 days per cycle) was prescribed concurrently during radiation therapy.

Nursing protocol. During periods of intensive anticancer treatment, patients were encouraged to eat nutritious foods; obtain as much protein and calories as they could; consume enough fresh fruits, vegetables, and water; and have multiple small meals. For patients with severe oropharyngeal pain during radiation therapy, lidocaine diluent was given orally before eating to reduce the pain. For patients whose nutritional status was affecting their anticancer treatment, oncologists consulted nutritionists for nutritional prescriptions. However, the nutritional intervention was a selective treatment rather than a regular measure. There was no unanimously recognized standard for nutritional consultation, and consultation was dependent upon the subjective judgement and clinical experiences of oncologists. Only the patients who had received nutritional consultation were likely to be prescribed an additional nutritional intervention.

Critical weight loss

Definition. According to the international consensus statement,[16] critical weight loss (CWL) was defined as the loss of body weight >5% from the start of radiotherapy until week 8 or >7.5% until week 12.

Assessment procedure. Body weight assessments started from the NPC diagnosis and lasted for 20 weeks after radiation therapy completion. Body weight was recorded weekly during the intensive anticancer treatment period (ie, during the induction chemotherapy and radiation therapy period). Considering that weight loss can be severe during radiation therapy, body weight was measured 1 day before radiation therapy as the baseline for radiation therapy. According to the current authors' preliminary study (n = 10), the trend of weight loss lasted for 2 weeks after radiation therapy. Therefore, weekly measurements of body weight needed to be continued until the second week after radiation therapy completion. After that, body weight was recorded every 2 weeks. For patients who received induction chemotherapy for more than 12 weeks, even if their body weight was measured for more than 12 weeks, only the weight measurements for the 12 weeks before radiation therapy were analysed.

All patients were given a predesigned booklet to record their body weight and any special events that patients considered to be related to their treatment. Body weight was collected by oncology nurses biweekly either by telephone calls or in person if the patients were hospitalized. For any week where no body weight data were recorded, the average weight value from the week before and the week after was estimated as the weight for that week. Body mass index (BMI) was defined as weight (kg) divided by the square of height (m^2). Body weight was assessed on a calibrated digital scale with an accuracy of 0.01 kg. Patients were required to measure their body weight on an empty stomach after urination in the morning, after taking off their shoes and any thick coats, while wearing light indoor clothes. Their body weight was measured twice, and the average value was recorded to ensure accuracy.

Feature selection

The least absolute shrinkage and selection operator (LASSO) regression model is a penalizing regression method that estimates the regression coefficients by maximizing the log-likelihood function while restraining the sum of the absolute values of the regression coefficients, which could avoid overfitting and was shown to be near-minimax optimal[17] to obtain the first-rank predictive features in risk factors from patients who underwent (chemo)radiotherapy.[18] Thus, LASSO is a better choice to handle the selected variables, especially high-dimensional data, by using the 'glmnet' package of R software.[19] A minimum lambda (λ) can be used for the selection of characteristics. Finally, multivariable logistic regression was performed using the characteristics selected by LASSO to construct the prediction model.

Nomogram establishment and validation

After variable selection, the nomogram was generated by the 'rms' package of R software.[17] The receiver operating characteristic (ROC) curve is a graph showing the false positive rate as the horizontal axis and the true positive rate as the vertical axis.[20] The area under the curve (AUC) was used to evaluate the discrimination ability of the nomogram. A calibration plot was used to evaluate the goodness of fit between the observed values and the predicted values. The Harrell C-index is a measure for assessing the accuracy of a nomogram at distinguishing patients who will have CWL from patients who will not.[21] To assess the clinical usefulness of the nomogram by quantifying the net benefit under different threshold probabilities in the cohort, we performed decision curve analysis (DCA).[22,23]

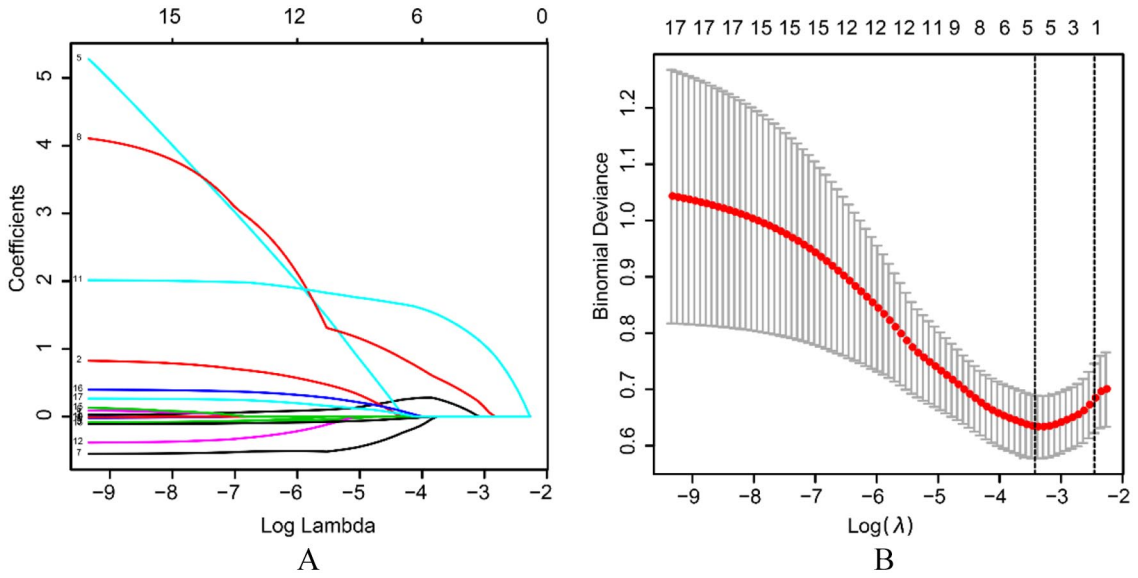

Figure 2. The least absolute shrinkage and selection operator (LASSO) binary logistic regression model was used for feature selection. Optimal parameter (λ) selection in the LASSO model used 10-fold cross-validation via minimum criteria. The partial likelihood deviance (binomial deviance) curve was plotted versus log (λ). Dotted vertical lines were drawn at the optimal values by using the minimum criteria and the 1 standard error (*SE*) of the minimum criteria (the 1-*SE* criteria). Ten-time cross-validation was used for tuning the parameter (*k*) selection in the LASSO model and optimal lambda resulted in five features with a vertical line drawn at the value selected.

Statistical analysis

All statistical analyses were performed using R software (version 3.4.0; www.r-project.org). All tests were 2-sided, and values of $P < .05$ were considered statistically significant.

Results

Feature selection

Through univariate analysis, we selected 20 characteristics for the LASSO regression model. We selected an optimal λ of 0.032 with the smallest binomial deviance, and the initial variables were reduced to 5 potential predictors under penalizing conditions (Figure 2A, B). These features included sex, smoke, physical status score (PS), chemotherapy regimen (CT), and BMI.

Nomogram establishment and validation

According to the results of the LASSO regression, some statistically significant features were retained, including sex, smoking status, physical condition, CT, and BMI. Then, we constructed a nomogram based on the above independent features to accurately estimate the incidence of weight loss and prevent the occurrence probability of CWL during (chemo) radiotherapy (Figure 3). As shown in Figure 4, according to the calibration curves made to verify the consistency of the prediction model, we found good consistency between the probability of CWL predicted by the nomogram and the observed probability during (chemo)radiotherapy, and the consistency index was 0.815, indicating a high level of predictive discrimination. In addition, the AUC-ROC was 0.924, as shown in Figure 5. This indicates that there was good discrimination, suitable for clinical patients after radiotherapy and chemotherapy, for the incidence of CWL prediction and prevention.

Clinical usefulness assessment

To assess the clinical usefulness of our nomogram for predicting CWL, we performed a graphical DCA (Figure 6). The curve showed that the nomogram was clinically valid within probability thresholds in the 0% to 97% range for predicting CWL in NPC patients undergoing radiotherapy and chemotherapy.

Discussion

In this study, we prospectively collected the weight data of NPC patients before and after radiotherapy and chemotherapy for 40 weeks and evaluated the predictive value of several known clinical factors that affect weight changes in predicting the incidence of CWL. Based on these results, we established a nomogram that combines 5 important clinical factors to predict the incidence of CWL in NPC patients. When developed, validated, and used correctly, the nomogram can provide important information about patient care.[24] Compared with previous studies, this study takes into account the important role of radiotherapy in the treatment of NPC and incorporates weight information before, during, and after radiotherapy. At the same time, the absolute value and relative value of weight changes during radiotherapy were evaluated to eliminate incomparability due to differences in individual baselines. In addition, we collected many potential predictors and used the LASSO regression model to screen them, and applied a variety of methods to evaluate the performance and effectiveness of the nomogram. For the study on weight changes in patients

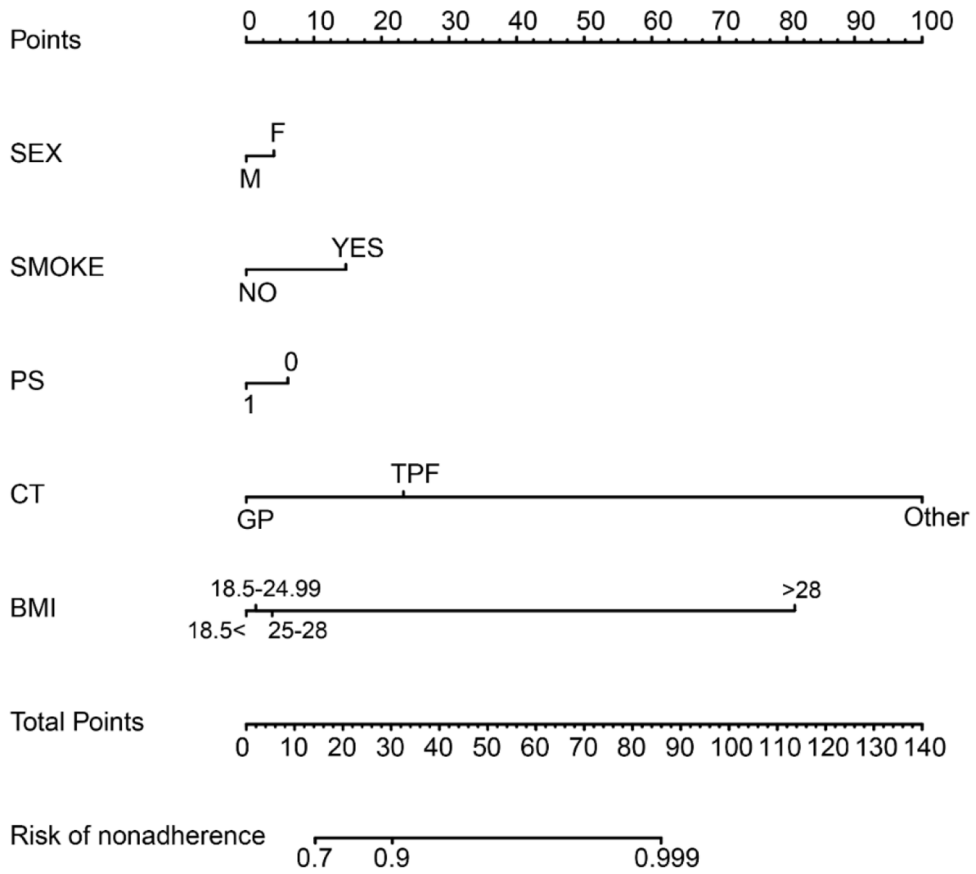

Figure 3. A nomogram for predicting the incidence of weight loss and preventing associated side effects during (chemo)radiotherapy. In the figure, the axes are marked with different features and the information corresponding to the patient can be found on each axis. Then, a vertical line can be drawn up along the 'point' axis to calculate the point sum of each variable for each patient. At the bottom of the graph, the corresponding total score for each patient can be found on the 'Total Score' axis and a vertical line can be drawn down to determine the corresponding value on the 'Predicted Probability (%)' axis. This is an accurate (chemical) predicted probability of the incidence of weight loss during radiotherapy. CT indicates chemotherapy regimen; PS, physical status score.

during the peri-radiation period, the sample size and follow-up time of this study are much larger than any similar studies conducted thus far, which guarantees the reliability of the results to a certain extent.

Because the location of NPC overlaps with the upper gastrointestinal tract, cancer usually affects the anatomical structure of the masticatory system, thereby causing obstacles to food intake and reducing patient weight.[25] According to previous studies, during IMRT treatment, patients with head and neck cancer are more likely to experience dysphagia, xerostomia, and mucositis, all of which affect food intake.[26] These are the causes of CWL after radiotherapy. CWL is an independent prognostic factor for decreased overall survival and locoregional recurrence-free survival.[27] Therefore, timely prediction of the occurrence of CWL and interventions can effectively improve the prognosis of patients with NPC.

Moreover, this study found that as BMI increases, the probability of CWL also increases. It is worth noting that although studies have shown that among patients receiving radiotherapy, underweight patients are more likely to suffer serious side effects than normal-weight patients,[28-30] patients with a high BMI are more likely to develop CWL. We speculate that this may be due to radiotherapy and prenutrition status. Although the incidence of CWL is higher in patients with a high BMI, its severity is less than that in patients with a low BMI.[21] According to the research of Shen et al,[31] we should pay more attention to the occurrence of CWL in patients with a low BMI before radiotherapy to avoid serious adverse consequences. The GP and TPF regimens can reduce the incidence of CWL, which may be because these 2 regimens are administered every 21 days per cycle, and the relatively long interval is helpful for body weight recovery.[15]

Because smoking is related to a poor prognosis and a poor treatment effect of NPC, [32] we first focused on the relationship between smoking status and weight loss in our research, but our study suggests that the association between smoking and NPC is limited, which is consistent with the results of Tang et al.[32] Peng et al[33] found that Epstein–Barr virus (EBV) DNA has good prognostic value in a long-term survival study of NPC patients after IMRT, but our study found that this index has no significance for predicting the incidence of CWL in patients.

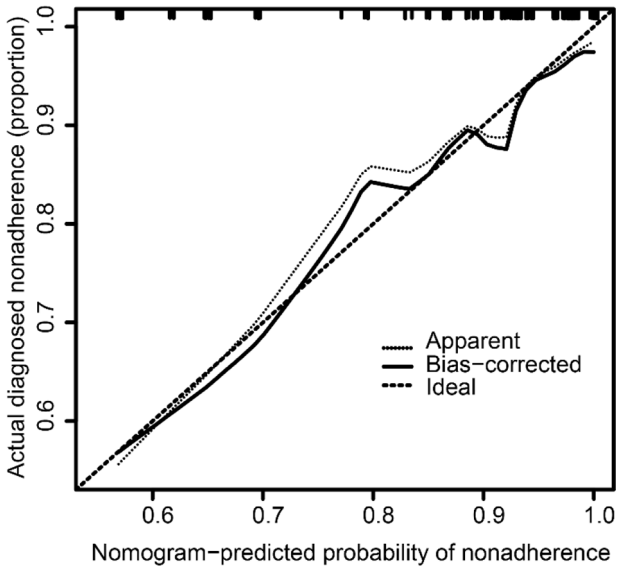

Figure 4. Cohort calibration curve and internally validated critical weight loss (CWL) prediction nomogram for 137 replicates using the bootstrap technique. In this graph, the x-axis represents the predicted risk of drug nonadherence. The y-axis represents the actual diagnosis of nonadherence. The diagonal dashed line represents the perfect prediction of the ideal model, so a solid line representing prediction performance closer to this dashed line represents a better prediction. The estimated concordance index was 0.811 and was determined to be 0.716 by bootstrapping validation (137 bootstrapped samples).

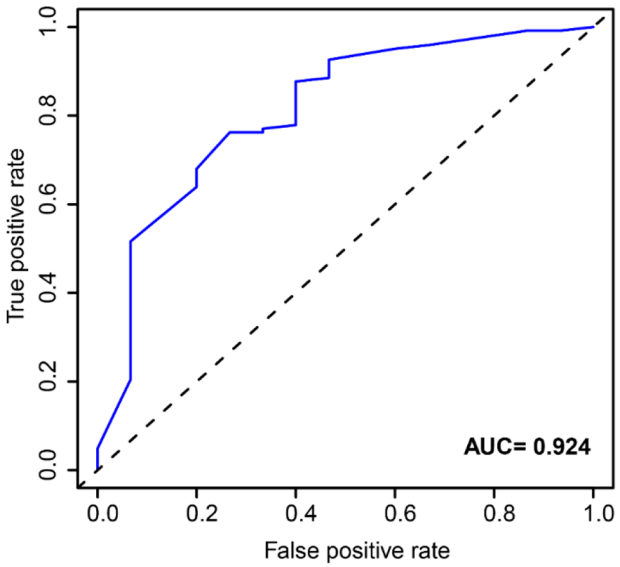

Figure 5. Receiver operating characteristic (ROC) curve for predicting weight loss and the prevention of associated side effects during (chemo) radiotherapy. ROC curves are often used to assess the clinical utility of diagnostic and prognostic models, and their area under the curve (AUC) is a global measure that tests the ability to distinguish the presence or absence of a particular condition. The AUC value is between 0.5 and 1, where an AUC of 0.5 represents a test without discrimination, and an AUC closer to 1.0 represents a more perfect test of discrimination.[20]

This study still has certain limitations, including survivor bias, the exclusion of patients with more serious complications, and a failure to evaluate factors related to weight changes (such as caloric intake and daily activities). These reasons are related to the long follow-up time (40 weeks) and the complete intensive antitumor therapy period of complete follow-up. However, weight loss is the main symptom of NPC patients undergoing radiotherapy and is a comprehensive indicator reflecting radiotherapy-related adverse effects. It is also the most critical item for evaluating and diagnosing nutritional risks.[9,34,35] Therefore, we believe that the above restrictions do not affect the authenticity and reliability of our research results.

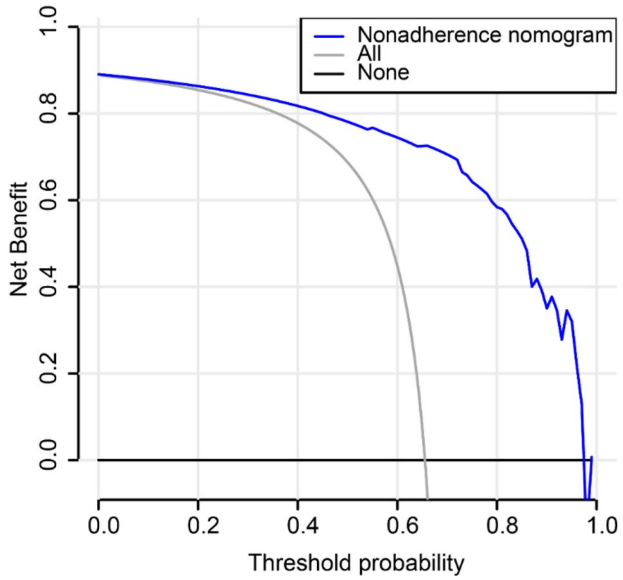

Figure 6. Decision curve analysis showed that using this nomogram to predict the risk of borderline weight loss in the current study added more benefit than extreme curves if the threshold probability was in the range of 0% to 97%. In this graph, the y-axis measures net income. Dotted lines represent key weight loss nomograms with radiation and chemotherapy. The thin solid line represents the assumption that critical weight loss (CWL) occurred in all patients. The thin and thick solid lines represent the hypothesis that none of the patients developed CWL.

Conclusion

We constructed and validated a nomogram for predicting the incidence of severe weight loss in NPC patients undergoing chemotherapy and radiotherapy. The nomogram is helpful for identification and calibration. There are few studies with such a long follow-up time, so our results can provide a more reliable reference for clinical decision-making.

Author Contributions

CH performed the data analyses and wrote the manuscript; HC, JL, and HY contributed significantly to the data analyses and manuscript preparation; YH and ZL helped perform the data analyses with constructive discussions; XZ and QZ contributed to the conception of the study.

Availability of Data and Material

The data sets supporting the results of this article are included within the article and its additional files.

Code Availability

I agree to allow the researcher(s) to take code of me and grant permission for these to be used by the researcher(s) for non-profit-making purposes.

Ethics Approval

The study was approved by the ethics committee of West China Hospital (2017[470]), and written informed consent was obtained from all patients for research purposes.

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