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Research

Risk factors and prediction models for severe radiation-induced oral mucositis in patients with nasopharyngeal carcinoma undergoing chemoradiotherapy

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Abstract

Objective This study aimed to investigate the factors associated with severe radiation-induced oral mucositis (SRIOM) in nasopharyngeal carcinoma (NPC) patients undergoing chemoradiotherapy (CRT) and to establish a prediction model for SRIOM.

Methods A total of 262 NPC patients who underwent CRT were analyzed retrospectively, including 192 in the modeling group and 70 in the validation group. The modeling group was divided into the non-SRIOM group (n = 112) and the SRIOM group (n = 80), and the validation group was divided into the non-SRIOM group (n = 40) and the SRIOM group (n = 30) according to the presence of SRIOM. Univariate and multivariate logistic logistic analyses were performed on the clinical data and general characteristics of all patients to construct a prediction model for SRIOM in NPC patients. The practical efficacy of the prediction model was evaluated using Hosmer–Lemeshow test, receiver operating characteristic curve (ROC), and decision curve analysis (DCA).

Results BMI < 23.9 kg/m^2, history of periodontal disease, history of alcohol consumption, history of smoking, non-use of oral mucosal protectants, and poor oral hygiene were independent risk factors for SRIOM in NPC patients. The prediction model showed an area under the ROC curve of 0.813 (95% CI 0.752–0.875). The prediction model demonstrated strong predictive accuracy and clinical utility, as evidenced by both calibration and DCA curves.

Conclusion The SRIOM prediction model, developed from the clinical characteristics and general information of NPC patients, is beneficial in clinical practice for identifying high-risk SRIOM and creating tailored treatment plans.

Keywords Nasopharyngeal carcinoma · Severe radiation-induced oral mucositis · Prediction model · Clinical application

1 Introduction

Nasopharyngeal carcinoma (NPC) ranks among the most common malignant tumors in humans. Patients usually present with obvious symptoms such as rhinorrhea, tinnitus, and hearing loss, which can cause irreversible damages to the nasopharynx. The diagnosis of the disease is difficult, and it is often detected in the middle or late stages, which is detrimental to the patient's survival and prognosis.

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Due to the intricate anatomy of the nasopharynx and its high radiation sensitivity, radiotherapy (RT) is the primary treatment for NPC. RT is effective in controlling and eliminating NPC cells, particularly enhancing the 5-year survival rate for early-stage NPC patients. Although RT targets tumor cells, it also affects the normal tissues around them, leading some patients to experience several complications during RT, with severe radiation-induced oral mucositis (SRIOM) being particularly common and severe [1]. RIOM is mainly caused directly by radiation and is a common dose-limiting toxic reaction during RT. It is mainly manifested as congestion, ulceration and even decay of the oral mucosa, accompanied by pain and difficulty in eating. SRIOM may disrupt RT and influence the outcome of tumor therapy. Chemotherapy (CT) is incorporated into the treatment for some NPC patients with advanced lesions, which can induce or exacerbate RIOM. RIOM can reduce RT tolerance in some patients, lowering the total dose administered, impacting treatment effectiveness, leading to tumor recurrence, and negatively affecting both quality of life and long-term survival [2, 3].

The mechanism of RIOM following chemoradiotherapy (CRT) has not been entirely identified, and preliminary studies propose that oral mucosal damages primarily consist of direct and indirect types. Direct damage is caused by radiation to the oral cell mucosa. Long-term RT can cause the vascular wall in the treated area to swell, increase its permeability, lead to inadequate blood supply to the damaged region, and trigger adverse reactions such as blistering, ulceration, hemorrhage, and necrosis [4]. Indirect damage refers to the gradual decline of the immune function, the decrease of neutrophil secretion, and the proliferation of oral bacteria and fungi, which ultimately leads to the occurrence of oral mucositis [5].

This study aimed to investigate SRIOM in NPC patients undergoing CRT, identify the primary risk factors for SRIOM, and offer insights and evidence for its prevention in NPC patients.

2 Materials and methods

2.1 Clinical samples

A retrospective analysis of 262 NPC patients who underwent CRT from January 2021 to December 2023 in Huangshi Central Hospital was performed. Among them, patients included in the modeling group were those from January 2021 to June 2022, totaling 192 cases, while the validation group consisted of patients from July 2022 to December 2023, amounting to 70 cases. These groups were used to construct the prediction model and validate its effects.

Inclusion criteria: (1) patients with a biopsy-confirmed diagnosis of NPC and first-time treatment with intensity-modulated RT (IMRT); (2) patients aged 18–75 years old; (3) patients who were conscious and able to communicate effectively; (4) patients exhibiting a healthy oral cavity, absence of oral mucosal lesions or redness, and normal oral function before RT; and (5) patients who gave informed consent and volunteered to participate in this study.

Exclusion criteria: (1) patients with other tumors or combined with distant metastases; (2) patients with difficulty in opening their mouths; (3) patients with mental disorders; (4) patients combined with other serious heart, liver, and kidney diseases; (5) patients with mid-course suspension of CRT and incomplete data; and (6) patients with the presence of oral mucositis before treatment.

The severity of RIOM was evaluated according to the RT Oncology Group (RTOG) Criteria [6]. Based on the highest grading of RIOM during radiotherapy, 192 patients in the modeling group were divided into 112 cases in the SRIOM group (grade III–IV) and 80 cases in the non-SRIOM group (grade 0–II); 70 patients in the validation group were categorized into 40 cases in the SRIOM group (grades III–IV) and 30 cases in the non-SRIOM group (grades 0–II).

2.2 Treatment programs

Target area outlining and treatment planning for all patients were unified by one or two experienced radiation oncologists to ensure consistency and accuracy. RT regimen: For all cases, IMRT was administered using a Varian linear accelerator (IX), featuring 60 pairs of MLC and 6MV X-rays at a dose rate of 400 MU/min. By referring to or combining magnetic resonance images, the target area was outlined with reference to international and national expert consensus, and complex cases were identified through multidisciplinary discussion. RT dose: The dose administered to the gross tumor volume of the nasopharynx (GTVnx) ranged from 66.0 to 70.4 Gy across 30 to 32 treatments, and the lymph nodes (GTVnd) received a dose between 66.0 and 70.0 Gy over the same number of treatments. The doses to high-risk and low-risk targets were

60.0 Gy/(30 to 32) times and 50.4 Gy/28 times, respectively. During treatment plan optimization, special attention was paid to the dose distribution to the oral mucosa. The average dose to the oral mucosa was controlled to be less than 35 Gy, with the maximum dose not exceeding 50 Gy. For high-risk patients, the high-dose area of the oral mucosa was further limited. The dose to the oral mucosa was strictly controlled using dose-limiting conditions. All treatment plans were dose-verified before implementation to ensure the consistency of the actual irradiated dose with the planned dose.

CT regimen: The treatment plan involved either induction CT combined with concurrent RT or just concurrent RT, depending on the tumor stage of the patient. For induction CT, the TP regimen was adopted, involving docetaxel at 75 mg/m^2 (or paclitaxel at 135–175 mg/m^2) per day, and cisplatin at 75 mg/m^2 administered intravenously from day 1 to day 3. This cycle was repeated once every 21 days for a total of two cycles. The concurrent CT regimen included cisplatin at 100 mg/m^2 given as an IV drip every 21 days.

2.3 SRIOM grading

Oral mucositis was assessed using the RTOG grading system. Grade 0 indicates no symptoms; grade I involves congestion and mild pain without the need for painkillers and no impact on eating; grade II includes mucositis, inflammatory secretions, moderate pain requiring painkillers and a semi-liquid diet; grade III involves fused fibrous mucositis with intense pain, necessitating anesthetic medication and a liquid-only diet; while grade IV includes ulceration, bleeding, necrosis, and severe pain that hinders eating. Physicians and nurses who received uniform training were appointed as observers to record the patient's RIOM grade at least once a week during IMRT.

2.4 General clinical data

General data of all patients were collected, including gender, age, smoking history, drinking history, hypertension, diabetes mellitus, coronary heart disease, body mass index (BMI), TNM staging, oral hygiene, and use of oral mucosal protectants. Individuals who quit smoking for over 10 years were regarded as non-smokers. According to the guidelines for prevention and control of overweight and obesity in Chinese adults, the classification for adult BMI was under 23.9 as wasting or normal, and 23.9 or above as overweight or obese. TMN staging (I–IV) was defined by the American Joint Committee on Cancer and the Union for International Cancer Control. Good oral hygiene was evaluated based on brushing teeth in the morning and evening, brushing later in the evening, rinsing after meals, and avoiding picking teeth, with three or more of these habits.

2.5 Laboratory indicators

After admission, 5 ml of early morning venous blood was collected from all patients, and serum was centrifuged (3500 r/min, 10 min). White blood cell (WBC) was measured by an automatic biochemical analyzer (Mindray, model: 7500).

2.6 Statistical analysis

For statistical analysis, SPSS 26.0 was utilized, and the Shapiro–Wilk test was applied to assess the normality of the measurement information. The measurement data in normal distribution were shown as mean±standard deviation (SD), with t-test used for comparing two groups. Non-normal distribution data were presented as M (P25, P75), with the Mann–Whitney U rank sum test being employed. The chi-square test was performed for count data. The backward stepwise multifactor logistic regression was employed to build the prediction model, analyzing statistically significant variables from the univariate analysis. In the multifactor logistic regression, continuous variables were entered with either their original values or assigned values to screen for independent influencing factors. The predictive ability of the model was evaluated by the area under the receiver operating characteristic curve (ROC). The fit of the model was verified using Hosmer–Lemeshow test. A higher p-value suggested that the actual and predicted outcomes were not significantly different and were deemed well calibrated. The clinical benefit of the prediction model was evaluated using decision curve analysis (DCA). $P < 0.05$ denoted a statistically significant difference.

3 Results

3.1 Clinical general data of patients

The 192 cases in the modeling group were divided into 112 cases in the non-SRIOM group and 80 cases in the SRIOM group, in which the incidence of SRIOM was 41.67%. The mean age of the patients in the non-SRIOM group was (53.34 ± 7.08) years, of which 42 were male and 70 were female. The mean age of the patients in the SRIOM group was (55.92 ± 7.90) years, of which 32 were male and 48 were female. A total of 127 of all patients were treated with induction CT, of which 73.75% in the SRIOM group received induction CT, which was higher than 60.71% in the non-SRIOM group, but there was no significant difference ($P > 0.05$). When comparing the two groups, a total of seven variables were statistically significant, including age, BMI, history of periodontal disease, history of alcohol consumption, history of smoking, use of oral mucosal protectants, and oral hygiene ($P < 0.05$) (Table 1).

3.2 Establishment of a prediction model for SRIOM in NPC patients

Values were assigned to the seven variables that were statistically significant ($P < 0.05$) in the univariate analysis (Table 2), and these variables were included in the univariate logistic analysis, all showing significance ($P < 0.05$) (Table 3). These seven variables were then included in the multivariate logistic regression. The results showed that BMI < 23.9 kg/m^2, history of periodontal disease, history of alcohol consumption, and history of smoking were all independent risk factors for SRIOM in NPC patients ($P < 0.05$). Non-use of oral mucosal protectants and poor oral hygiene were independent risk factors for SRIOM in NPC patients ($P < 0.05$) (Table 4). The formula used for model construction was determined to be $P = 1/(1 + e^{-z}), z = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \cdots + \beta_i X_i$. P is the probability of the ending event occurring, X_1, $X_2 \ldots X_i$ represent different independent influences, β_0 is a constant term, β_1, $\beta_2 \ldots \beta_i$ represent the partial regression coefficients of each independent influence. Logit (P) = −5.340 + 0.905 × BMI < 23.9 kg/m^2 + 0.930 × history of periodontal disease + 0.720 × history of alcohol consumption + 1.232 × smoking + 1.132 × non-use of oral mucosal protectants + 1.016 × poor oral hygiene.

3.3 Fitting of the prediction model for SRIOM and validation of predictive performance

The SRIOM prediction model was established based on independent risk factors screened by multivariate analysis. The model was validated by plotting the ROC. When Logit (P) > 0.474, the model had an AUC of 0.813 (95% CI 0.752–0.875), a sensitivity of 81.25% and a specificity of 68.75% (Fig. 1).

Based on multivariate logistic regression analysis, the value of each influence factor was scored according to its contribution to the outcome variable (SRIOM occurrence). Ultimately, the predicted value of SRIOM occurrence was derived from the total score of the six influencing factors of BMI, history of periodontal disease, history of alcohol consumption, history of smoking, use of oral mucosal protectants, and oral hygiene (Fig. 2). The calibration curves showed good agreement between the calibration and actual curves as shown in Fig. 3. When the risk falls below 20% or exceeds 60%, the solid line deviates from the reference line, causing the predicted probability to be overestimated or underestimated. When the risk ranges from 20 to 60%, the solid line aligns closely with the reference line, suggesting that the predicted probability matches the actual outcomes more accurately. The result of the Hosmer–Lemeshow goodness-of-fit test was $\chi^2 = 6.964$, $P = 0.541$. The DCA curves (Fig. 4) showed that the curves of this prediction model were far away from the two curves (None and All).

4 Discussion

NPC is commonly treated with CRT, and RIOM, an oral mucosal injury, is a typical complication caused by ionizing radiation during this process. Currently, the underlying causes and mechanisms of SRIOM are unclear, and no specific prevention or treatment is available. In this study, 262 NPC patients who had completed CRT were selected. According to the diagnostic criteria of RIOM, 227 cases (86.64%) were diagnosed with RIOM, whereas 35 cases (13.36%) were not. Among the patients with RIOM, 27 cases (11.89%) were in grade I, 90 cases (39.65%) in grade II, 104 cases (45.81%) in grade III, and 6 cases (2.64%) in grade IV, which were divided into the SRIOM and non-SRIOM groups. The risk factors for SRIOM in

Table 1 Comparison of clinical general data between patients in the Non-SRIOM group and the SRIOM group

Factors	Non-SRIOM group (n = 112)	SRIOM group (n = 80)	*P* value
Age (Years)	53.34 ± 7.08	55.92 ± 7.90	0.19
Gender			
Male	42 (37.50%)	32 (40.00%)	0.73
Female	70 (62.50%)	48 (60.00%)	
BMI (kg/m^2)			
< 23.9	52 (46.43%)	55 (68.75%)	0
≥ 23.9	60 (53.570%)	25 (31.25%)	
Diabetes	20 (17.86%)	26 (32.50%)	0.02
Hypertension	22 (19.64%)	20 (25.00%)	0.38
History of periodontal disease	22 (19.64%)	31 (38.75%)	0
Induction chemotherapy			
Yes	68 (60.71%)	59 (73.75%)	0.06
No	44 (39.29%)	21 (26.25%)	
Drinking	39 (34.82%)	42 (52.50%)	0.01
Smoking	21 (18.75%)	34 (42.50%)	0
Metastasis	42 (37.50%)	21 (26.25%)	0.1
TNM stage			
I	11 (9.82%)	7 (8.75%)	0.83
II	37 (33.04%)	23 (28.75%)	
III	38 (33.93%)	27 (33.75%)	
IV	26 (23.21%)	23 (28.75%)	
Differentiation			
No	18 (16.07%)	9 (11.25%)	0.76
Low	29 (25.89%)	24 (30.00%)	
Moderate	42 (37.50%)	29 (36.25%)	
High	23 (20.54%)	18 (22.50%)	
Oral pH			
< 7	32 (28.57%)	16 (20.00%)	0.18
≥ 7	80 (71.43%)	64 (80.00%)	
Oral mucosal protectant			
Yes	77 (68.75%)	31 (38.75%)	< 0.01
No	35 (31.25%)	49 (61.25%)	
Oral hygiene			
Excellent	72 (64.29%)	28 (35.00%)	< 0.01
Poor	40 (35.71%)	52 (65.00%)	
WBC	6.05±1.04	6.32±2.68	0.33

Data were expressed as mean ± standard deviation (SD) or number of cases (%). The t-test was used for continuous variables and the chi-square test was used for qualitative data. $P < 0.05$ was statistically different

SRIOM severe radiation-induced oral mucositis, *BMI* body mass index, *WBC* white blood cell

NPC patients were further analyzed to identify high-risk patients and improve the prognosis of patients through early diagnosis and intervention of related risk factors.

In the present study, the incidence of SRIOM in NPC patients was 41.67%. BMI, history of periodontal disease, history of alcohol consumption, non-use of oral mucosal protectants, and poor oral hygiene were all independent risk factors for SRIOM in NPC patients. This study included factors that showed significance in both univariate and multivariate logistic regression analyses to establish a prediction model for SRIOM in NPC patients. As suggested, low BMI, history of periodontal disease, history of smoking and alcohol consumption, non-use of oral mucosal protectants, and poor oral hygiene predisposed to SRIOM.

Table 2 Independent variable assignment

Factors	Assignment
Age (year)	Original value
BMI (kg/m^2)	≥ 23.9 kg/m^2 = 0, < 23.9 kg/m^2 = 1
Diabetes	No = 0, Yes = 1
History of periodontal disease	No = 0, Yes = 1
Drinking	No = 0, Yes = 1
Smoking	No = 0, Yes = 1
Oral mucosal protectant	Yes = 0, No = 1
Oral hygiene	Good = 0, Poor = 1

Table 3 Univariate logistic analysis of risk factors for SRIOM in patients

Indicators	Univariate logistic analysis			
	β	SE	OR (95%CI)	P value
Age (year)	0.047	0.02	1.048 (1.007–1.091)	0.021
BMI (kg/m^2)	0.932	0.307	2.538 (1.392–4.631)	0.002
Diabetes	0.795	0.343	2.215 (1.130–4.341)	0.021
History of periodontal disease	0.951	0.331	2.588 (1.354–4.947)	0.004
Drinking	0.727	0.299	2.069 (1.151–3.718)	0.015
Smoking	1.164	0.331	3.203 (1.673–6.131)	< 0.001
Oral mucosal protectant	1.246	0.307	3.477 (1.905–6.347)	< 0.001
Oral hygiene	1.207	0.306	3.343 (1.834–6.093)	< 0.001

SRIOM seriously radiation-induced oral mucositis, *BMI* body mass index, *OR* odds radio, *CI* confident interval

Table 4 Multivariate logistic analysis of independent risk factors for SRIOM in patients

Indicators	Multivariate logistic analysis			
	β	SE	OR (95%CI)	P
BMI (kg/m^2)	0.905	0.36	2.473 (1.221–5.008)	0.012
History of periodontal disease	0.93	0.394	2.536 (1.172–5.487)	0.018
Drinking	0.72	0.355	2.054 (1.024–4.120)	0.043
Smoking	1.232	0.387	3.428 (1.604–7.327)	0.001
Oral mucosal protectant	1.132	0.356	3.103 (1.543–6.237)	0.001
Oral hygiene	1.016	0.353	2.763 (1.383–5.522)	0.004
Constant	−5.34	1.434	–	< 0.001

SRIOM seriously radiation-induced oral mucositis, *BMI* body mass index, *OR* odds radio, *CI* confident interval

Alcohol consumption and smoking are risk factors for SRIOM [7]. In this study, the prevalence of SRIOM in smokers was 42.50%, which was higher than that in non-smokers. Multivariate analysis revealed that the risk of SRIOM in smokers was 3.428 times higher than that in non-smokers (95% CI 1.604–7.327, $P = 0.001$). The increase in RIOM due to smoking may be attributed to the presence of phenols and other toxic substances in tobacco, which stimulate oral mucosal cells and exacerbate inflammation; on the other hand, smoking increases the temperature of the oral cavity, which not only burns the mucosa but also leads to poor blood circulation, affecting humoral immunity. Extended periods of smoking decrease the proliferation of oral mucosal epithelial cells, lower their self-repair ability, and impact normal blood circulation and immune system, leading to a higher chance of RT failure [8].

In the present study, it was found by multivariate analysis that poor oral hygiene led to a higher risk of RIOM. This is consistent with previous findings that oral hygiene is thought to increase the risk of RIOM and exacerbate the symptoms of RIOM [9]. It is evident that oral care is a crucial component in effectively preventing the growth of pathogenic bacteria, reducing mucosal damage, and promoting mucosal repair. Good oral hygiene can effectively

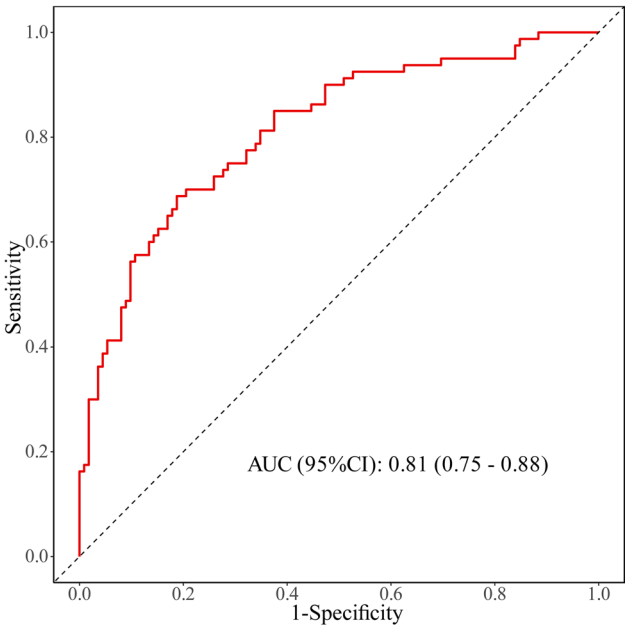

Fig. 1 ROC curve of the prediction model for SRIOM in NPC patients

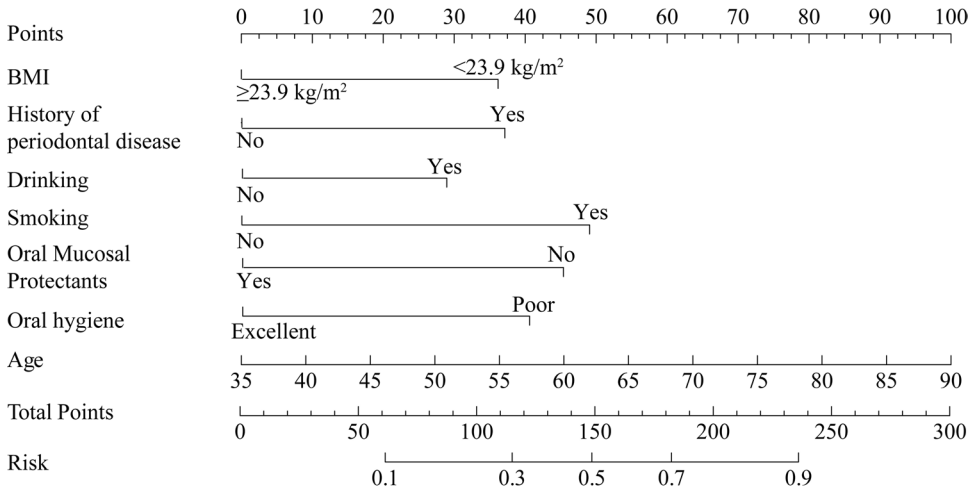

Fig. 2 Column line graph of the prediction model of SRIOM in NPC patients

inhibit the proliferation of aerobic gram-negative bacteria and prevent the release of toxins, thus reducing the occurrence of RIOM [10]. The role of aerobic Gram-negative bacteria is significant in the progression of the mucosal response from erythematous to mucositis phases. During the phase where bacteria and ulcers are present along with pseudomembrane formation, the disrupted mucosa begins to accumulate aerobic Gram-positive bacteria, releasing endotoxins that stimulate cytokine release and worsen the situation [11]. In addition, non-use of oral mucosal protectants was also a risk factor for SRIOM. The main ingredients of oral mucosal protectants are peppermint, lidocaine, dexamethasone, gentamicin, and vitamin B12, of which lidocaine is effective for local pain relief, gentamicin has the ability to kill oral bacteria, vitamin B12 repairs damaged oral cells, and dexamethasone is anti-inflammatory and antiseptic, reducing inflammatory response. This study also found that history of periodontal disease was a risk factor for SRIOM in NPC patients, which is similar to the findings of Eilers et al. [12]. Periodontal disease is a common oral disease, and long-term recurrent inflammation of periodontal tissues not only affects oral function, but also deteriorates oral mucosal defense. NPC patients with poor periodontal health undergoing RT have a more severe response to RIOM [13]. During RT, the composition of oral bacterial colonies changes over time, with a significant rise in the relative presence of specific Gram-negative bacteria, and the prediction model based on these alterations demonstrates high predictive accuracy [14]. Khaw et al. pointed out that periodontitis and other oral diseases are correlated with the occurrence of RIOM [15]. These studies further validate that ensuring oral hygiene and mucosal defenses, along with addressing oral diseases, has a major effect on the risk of SRIOM.

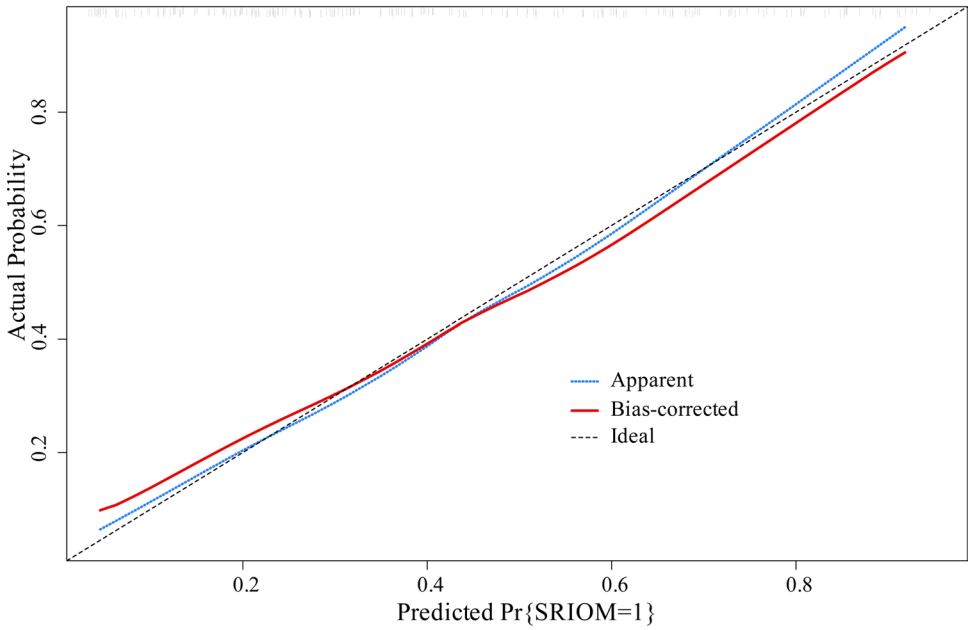

Fig. 3 Calibration plot for model validation

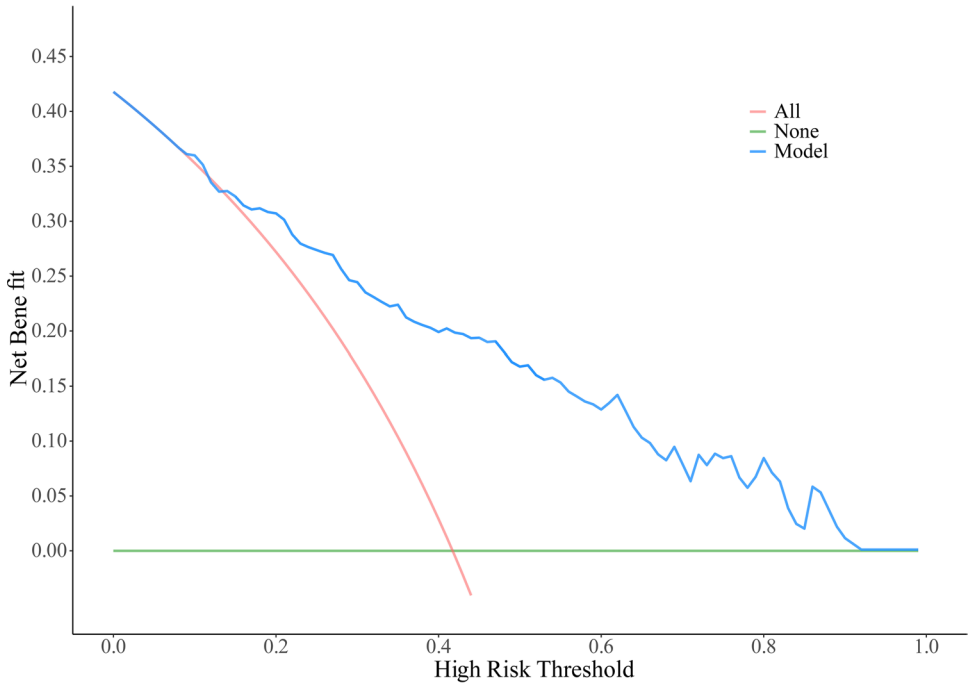

Fig. 4 DCA curve analyzing the clinical benefit of the prediction model

Previous studies have focused on nutritional status of NPC patients and nutritional interventions for SRIOM patients [16, 17]. Compared to nutritional status and weight fluctuations, BMI is more accessible and consistent data. Nutritional interventions fail to reduce weight and BMI in patients with advanced NPC [18], but the study's findings are unreliable due to significant selection bias and a small sample size. In contrast, lower BMI is found to be significantly associated with SRIOM [19, 20]. Studies have clearly indicated that patients with BMI below 22 kg/m^2 have a higher risk of moderate to severe oral mucositis during RT compared to patients with normal BMI [21, 22]. This is almost consistent with the findings of the present study. The potential mechanism may be that malnutrition leads to decreased cell migration and renewal and interferes with mucosal regeneration. Nonetheless, because RIOM can cause anorexia, swallowing difficulties, and a drop in BMI during CRT, it is hard to determine if a low BMI leads to oral mucositis or if RIOM causes a decrease in BMI.

Several studies have shown that women are more likely to develop grade 3–4 mucositis than men [23, 24]. Similar results were observed in this study, but they were not statistically significant. There is also no consensus on whether

age is an independent risk factor for RIOM. It has been reported that the risk of mucositis during RT tends to be higher in older patients with head and neck tumors than in younger patients [25]. The mean age of patients in the non-SRIOM group in our findings was younger than that of patients in the SRIOM group, but it was not statistically significant. Further investigation is still needed regarding whether gender and age are risk factors for SRIOM in patients with NPC.

There are some limitations to this study. First, the column line graph has limited application value because this study was based on data from NPC patients who received CRT. It was not possible to determine the predictive ability of the model for patients with head and neck tumors other than NPC. Second, because the retrospective data used in this study were incomplete, some potential influencing factors could not be obtained during predictor selection, and there are more clinical factors influencing SRIOM. Prospective large-sample studies are still needed in the future to further improve and correct them in clinical practice. Furthermore, identifying effective strategies to prevent and slow the onset and progression of RIOM remains a topic for future research.

In summary, the risk of SRIOM in NPC patients with CRT is high, in which BMI < 23.9 kg/m^2, history of periodontal disease, history of alcohol consumption, non-use of oral mucosal protectants and poor oral hygiene are independent risk factors for SRIOM. Based on this, we developed a prediction model and confirmed its strong predictive performance.

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Data availability Data is available from the corresponding author on request.

Declarations

Ethics approval and consent to participate All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All subjects were approved by Huangshi Central Hospital (No.201803HS71).

Consent for publication Written informed consent was obtained from each subject.

Competing interests The authors have no conflicts of interest to declare.

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