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# Mechanism of skull base osteoradionecrosis explored through laboratory assessment with propensity score-matched analysis

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**Skull base osteoradionecrosis (sbORN) is a severe complication of radiotherapy (RT) in patients with nasopharyngeal carcinoma (NPC) that can severely affect quality of life (QOL) and may even be life-threatening. The etiology and pathogenesis of sbORN remain largely unknown or uncertain. Therefore, this study aimed to identify potential risk factors for sbORN by analyzing the laboratory assessments of patients to enable early clinical interventions. This retrospective case-control study reviewed NPC patients who were pathologically diagnosed with sbORN after primary radical radiotherapy. These patients were matched 1:1 with propensity scores for patients without sbORN at our center. The impact of laboratory examination indexes on sbORN occurrence was assessed using both univariate and multivariate logistic regression analyses. We reviewed 1,200 NPC patients who were followed up in our department from 2010 to 2020; a total of 57 patients met the inclusion criteria. Each patient underwent endoscopic and pathological examinations, which confirmed the diagnosis. In addition, 98 patients without sbORN were also collected and matched 1:1 by propensity score matching, resulting in the inclusion of 38 patients. Univariate logistic regression analysis revealed statistically significant differences in hemorrhage (HB), erythrocytes (RBC), albumin (Alb), platelets (PLT), indirect bilirubin (IBil), globulin (Glo), aspartate aminotransferase (AST), and fibrinogen (Fg) between the two groups ($p < 0.05$). Multivariate logistic regression analysis revealed statistically significant differences only for Fg ($p < 0.05$). Receiver operating characteristic (ROC) curve analysis further demonstrated the diagnostic utility of Fg, yielding an area under the curve (AUC) of 0.829, with specificity and sensitivity values of 0.842 and 0.711, respectively. The occurrence of sbORN was closely associated with elevated plasma Fg levels, suggesting that high plasma Fg may be a potential risk factor for sbORN. Plasma Fg has a certain diagnostic value for sbORN and can be used as a supplementary diagnostic method.**

**Keywords** Skull base osteoradionecrosis, Risk factors, Laboratory assessment

Nasopharyngeal carcinoma (NPC) is a prevalent malignant tumor in southern China, with radiotherapy serving as the primary treatment for patients with a first diagnosis of NPC[1]. Notably, intensity-modulated radiation therapy (IMRT), as indicated by the findings of the comprehensive meta-analysis by Zhang Binglan et al., demonstrates an 80% five-year survival rate for NPC[2]. Skull base osteoradionecrosis (sbORN) is a serious complication of radiotherapy (RT), and the number of affected patients is gradually increasing. Its occurrence after initial radiotherapy for NPC ranges from 5% to 7%, escalating to 30% for patients subjected to a second course of radiotherapy due to recurrent disease[3,4]. The clinical manifestations of sbORN include headache and foul odor. In severe cases, it can lead to intracranial infection or fatal hemorrhage, significantly impacting patients' quality of life and survival[5]. Moreover, patients with sbORN have an increased risk of death, spanning from 10.3–65.8%[6]. However, there is no clear definition of sbORN, which typically refers to soft tissues or bony necrosis within the irradiated area of the skull base. In the past, scholars have graded sbORN according to the depth of necrosis, delineating degree I as mucosal necrosis, degree II as submucosal tissue necrosis, and degree III as progression to bone necrosis[7] (Fig. 1). Additionally, some investigators have classified sbORN into grades

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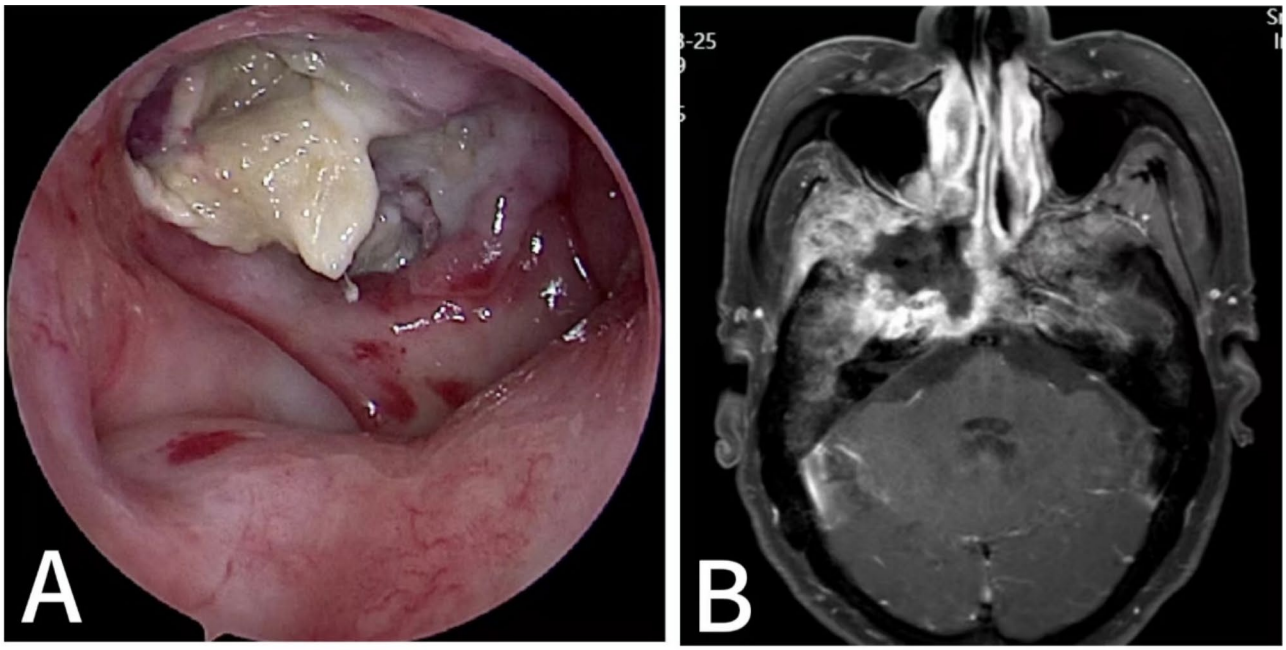


**Fig. 1**. Displays the performance of sbORN. (**A**) Nasal endoscopy revealed soft tissue necrosis of the nasopharyngeal roof with exposed bone. (**B**) Enhanced T1WI showed no enhancement in the center of the right necrotic foci, with edema of the surrounding tissues and disruption of mucosal continuity.

I-V based on the cumulative extent of necrotic areas within the skull base, as observed through Computed Tomography (CT) examination. Conservative treatments are often ineffective for patients with advanced disease, necessitating surgical debridement of necrotic bone. Nonetheless, surgical intervention is challenging and carries significant risk, with few hospitals equipped to perform such procedures. In addition to radiation damage, ischemia, hypoxia, and radiation-induced fibrosis, local inflammation is also considered a potential risk factor for sbORN[8–11]. Studies have shown that inflammation, fibrosis, and tissue necrosis, particularly reactive oxygen species (ROS) and TGF-β1, play important roles in the occurrence and progression of sbORN. Radiation can cause damage to local tissues and endothelial cells, leading to the release of chemokines that attract leukocytes to the injury site, triggering a series of inflammatory responses. These reactions result in endothelial damage, vascular occlusion, local ischemia, and ultimately tissue necrosis[10]. Furthermore, in clinical practice, we have observed that most bone necrosis patients exhibit significant weight loss and nutritional deficiencies, particularly in protein and calcium. These deficiencies may impair bone repair and immune function, potentially increasing the risk of radiation-induced osteonecrosis. Nevertheless, the precise mechanisms underlying the occurrence and progression of sbORN remain unclear to date. The present case-control study aims to identify the pathogenesis and risk factors of sbORN by analyzing the correlation between laboratory assessments and sbORN, in order to implement timely clinical intervention measures and reduce the risk of sbORN.

## Materials and methods

### Study overview

This study was conducted in accordance with the amended Declaration of Helsinki and was approved by The Medical Ethics Committee of Zhujiang Hospital, Southern Medical University (approval no.2024-KY-131). The study was conducted in a retrospective case–control design at Zhujiang Hospital, Southern Medical University, starting in March 2023 and ending in December 2023. We reviewed 1,200 NPC patients who were followed up in our department between 2010 and 2020, identifying a total of 89 patients with a confirmed diagnosis of sbORN. After excluding patients with recurrence, secondary radiotherapy, and other conditions, a total of 57 patients met the inclusion criteria. We identified 98 patients who met the criteria from the same hospital's electronic medical records system for comparison (Fig. 2).

### Patient selection

57 patients in the sbORN group met the following criteria: (1) All patients were initially diagnosed with nasopharyngeal carcinoma and underwent standard radical radiotherapy at a tertiary care hospital. (2) sbORN was confirmed in all patients through both endoscopic and pathological examination, with tumor recurrence excluded.

98 patients in the non-sbORN group met the following criteria: (1) All patients were first diagnosed with nasopharyngeal carcinoma and underwent standard radical radiotherapy in a tertiary care hospital; (2) Patients exhibited no clinical symptoms of sbORN, such as headache and foul odor. Nasal endoscopy revealed smooth and intact mucous membranes in the nasopharyngeal area, and CT or Magnetic Resonance Imaging (MRI)

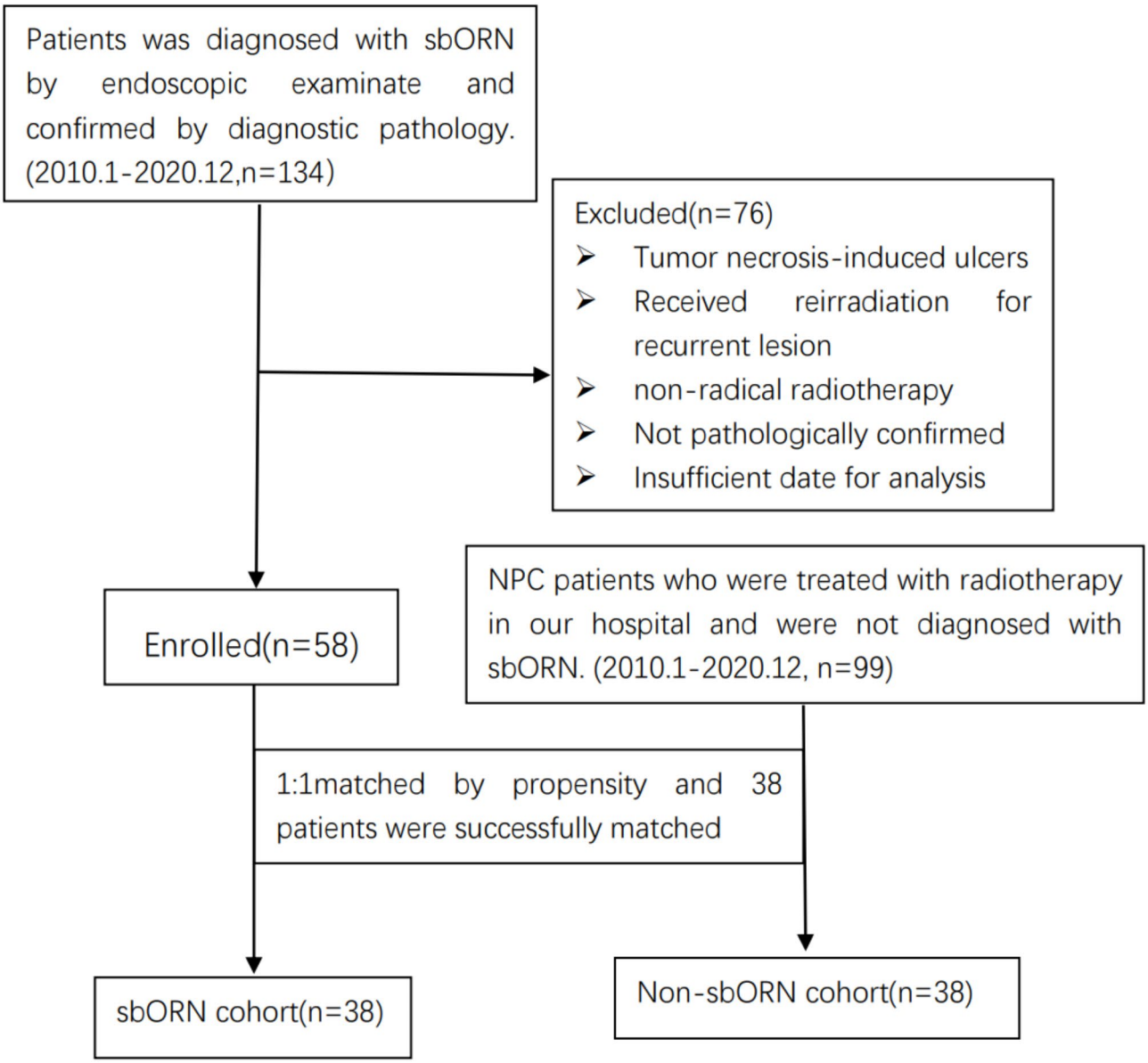


**Fig. 2**. Flowchart of patient enrollment.

examinations showed no abnormal signal shadows indicative of bony or soft tissue necrosis in the nasopharyngeal region.

### Data collection

For the sbORN cohort, we collected the admission data of these patients prior to the surgical treatment, because the patients' physical condition is worse during surgery, and infections and other conditions are more severe. Therefore, these test indicators at this point cannot represent the patients' usual physical status. In contrast, the patient returned to the hospital for routine re-examinations before surgery, and their condition were in a relatively stable state, making the test indicators more representative of the patients' general state of health. For the non-sbORN cohort, the laboratory test results collected were the most recent available in the same hospital's electronic medical records system. According to previous studies, infection, anemia, nutritional status, microthrombosis, and other factors are considered as suspected risk factors for sbORN. We focus on leukocyte (WBC), hemorrhage (HB), erythrocytes (RBC), platelets (PLT), calcium (Ca), body mass index (BMI), uric acid (UA), total protein (TP), albumin (Alb), total bilirubin (TBil), direct bilirubin (DBil), alanine aminotransferase (ALT), aspartate aminotransferase (AST), indirect bilirubin (IBil), globulin (Glo), prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen (Fg), D-dimer (DDI), and plasminogen (PLG). Additionally, baseline data were collected on patients' sex, age, smoking, drinking, renal function, liver function, history of head and neck vascular embolization, hypertension, diabetes mellitus, whether they received adjuvant chemotherapy, and incidence of cardioembolic stroke. Given that all patients underwent standard radical

radiotherapy, we assumed that there was no statistical difference in radiotherapy dose between the sbORN and non-sbORN groups. Previous studies have demonstrated that chemotherapy and targeted therapy have no effect on the occurrence of sbORN. Consequently, the data related to patients' chemotherapy and targeted therapy were not analyzed[12].

## Statistical analysis

For variables with missing data exceeding 10% of the sample size, we excluded them from the analysis. For indicators with less than 10% missing data, we used Statistical Package for the Social Sciences (SPSS) for multiple imputation for continuous data and nearest neighbor median to replace missing values for categorical data (Annex 1). After imputing the missing data, we performed univariate and multivariate logistic regression analysis on the laboratory assessments of the patients, and the results are shown in Table 1. Subsequently, we performed a 1:1 propensity-score matching with a caliper value of 0.1 on the patients' baseline data (sex, age, smoking, drinking, renal function, liver function, whether or not they had undergone head and neck vascular embolization, hypertension, diabetes and cardiovascular and cerebrovascular stroke events), which yielded 38 pairs of data (Table 2). For all cohorts, categorical data are presented as numbers and percentages, and continuous data are expressed as mean ± standard deviation. For indicators with significant statistical differences in univariate and multivariate logistic regression analysis, receiver operating characteristic (ROC) curves were drawn. A forest plot was generated using RStudio (version 4.4.0). Statistical analysis was conducted using IBM SPSS Version 27.0 (IBM Corp., Armonk, New York), and $P < 0.05$ was chosen as the cutoff for statistical significance.

## Results

Univariate logistic regression analysis showed statistically significant differences ($p < 0.05$) between the two groups in BMI, WBC, RBC, HB, PLT, Ca, TP, Alb, TBil, IBil, Glo, PT, APTT, and Fg before propensity score matching. In contrast, multivariate logistic regression analysis identified statistically significant differences only in fibrinogen levels ($p < 0.05$) before propensity score matching (Table 1). After propensity score matching, univariate logistic regression analysis found significant differences in HB, RBC, Alb, PLT, IBil, Glo, AST, and Fg between the two groups ($p < 0.05$). However, multivariate logistic regression analysis post-matching indicated statistically significant differences only in Fg ($p < 0.05$) (Table 3; Fig. 3). In summary, plasma Fg levels are closely associated with the occurrence of sbORN and may serve as an independent risk factor for its development. ROC curves were constructed by using the occurrence of sbORN as the state variable and the fibrinogen (Fg) level as the test variable. The predictive value of serum fibrinogen (Fg) for the development of sbORN in nasopharyngeal carcinoma (NPC) patients who have undergone radical radiotherapy was assessed through ROC curve analysis. The results indicated that serum fibrinogen (Fg) could serve as a potential predictive factor for sbORN in these patients, with an AUC of 0.829, 95%CI of 0.736–0.922 ($P < 0.001$). The optimal cutoff value for fibrinogen (4.5 g/L) was determined by maximizing the Youden index (J = sensitivity + specificity − 1), which represents the point on the ROC curve that best balances diagnostic sensitivity and specificity, with specificity and sensitivity values of 0.842 and 0.711, respectively. Subsequently, we divided the plasma fibrinogen (Fg) levels of the 38 pairs of patients after propensity score matching into high Fg group (≥ 4.5 g/L) and low Fg group (< 4.5 g/L), and performed both chi-square and Fisher's tests. The results showed a significant difference

| | Univariate | | Multivariate | |
|---|---|---|---|---|
| Variables | OR (95% CI) | *P* value | OR (95% CI) | *P* value |
| BMI | 0.820(0.732–0.917) | < 0.001 | 0.858(0.728–1.011) | 0.067 |
| WBC | 1.408(1.188–1.668) | < 0.001 | 1.114(0.792–1.568) | 0.534 |
| RBC | 0.176(0.084–0.370) | < 0.001 | 0.836(0.183–3.813) | 0.817 |
| HB | 0.926(0.900-0.953) | < 0.001 | 0.974(0.922–1.030) | 0.356 |
| PLT | 1.010(1.005–1.014) | < 0.001 | 0.999(0.990–1.008) | 0.814 |
| Ca | 0.004(0.000-0.080) | < 0.001 | 0.024(0.000-5.160) | 0.173 |
| TP | 0.936(0.891–0.984) | 0.009 | 0.565(0.111–2.882) | 0.492 |
| Alb | 0.726(0.654–0.806) | < 0.001 | 1.529(0.297–7.872) | 0.611 |
| TBil | 0.874(0.788–0.970) | 0.011 | 0.868(0.583–1.293) | 0.487 |
| DBil | 0.902(0.743–1.095) | 0.299 | — | — |
| ALT | 0.980(0.952–1.008) | 0.164 | — | — |
| AST | 0.957(0.912–1.004) | 0.074 | — | — |
| IBil | 0.781(0.665–0.918) | 0.003 | 1.254(0.702–2.241) | 0.445 |
| Glo | 1.156(1.079–1.239) | < 0.001 | 1.917(0.379–9.696) | 0.432 |
| PT | 1.789(1.313–2.436) | < 0.001 | 1.180(0.609–2.288) | 0.624 |
| APTT | 1.051(1.000-1.103) | 0.048 | 0.979(0.866–1.106) | 0.729 |
| Fg | 3.438(2.331–5.071) | < 0.001 | 2.679(1.528–4.697) | < 0.001 |

**Table 1**. Univariate and multivariate regression analyses were performed directly on the laboratory indicators of 57 patients in the SbORN group and 98 patients in the non-sbORN group without propensity score matching. The results are shown in the table.

| Baseline information | Original date set($n=38$) | Matched data set ($n=38$) | $P$ |
|---|---|---|---|
| Gender | | | |
| Male | 28 | 28 | 1 |
| Female | 10 | 10 | 1 |
| Age (y) | | | |
| Median; Range | 53.39(24–70) | 53.21(38–74) | 0.937 |
| Hypertension | 7 | 8 | 0.584 |
| Diabetes | 6 | 6 | 1 |
| Smoking | 2 | 5 | 0.435 |
| Drinking | 3 | 1 | 0.251 |
| Liver function | 4 | 3 | 0.407 |
| Renal function | 5 | 7 | 0.696 |
| Cardiovascular and cerebrovascular stroke events | 3 | 5 | 0.455 |
| Head and neck vascular intervention | 1 | 1 | 1 |

**Table 2**. After performing propensity score matching for clinical characteristics such as gender, age, and underlying diseases between 57 SbORN patients and 98 non-sbORN patients, a total of 38 matched pairs were successfully identified. The clinical characteristics and differences between the two groups after matching are shown in the table.

| Variables | Univariate | | Multivariate | |
|---|---|---|---|---|
| | OR (95% IC) | $p$ value | OR (95% IC) | $p$ value |
| BMI | 0.874(0.764–1.001) | 0.052 | — | — |
| WBC | 1.158(0.959–1.398) | 0.127 | — | — |
| RBC | 0.407(0.172–0.962) | 0.041 | 1.881(0.245–14.432) | 0.544 |
| HB | 0.941(0.907–0.976) | 0.001 | 0.950(0.881–1.024) | 0.179 |
| PLT | 1.006(1.000-1.012) | 0.041 | 1.000(0.993–1.007) | 0.988 |
| Ca | 0.237(0.008–6.936) | 0.403 | — | — |
| TP | 1.006(0.942–1.074) | 0.861 | — | — |
| Alb | 0.831(0.743–0.928) | 0.001 | 0.950(0.804–1.124) | 0.550 |
| TBil | 0.867(0.744–1.011) | 0.069 | — | — |
| DBil | 0.918(0.702–1.201) | 0.534 | — | — |
| ALT | 0.959(0.919–1.002) | 0.061 | — | — |
| AST | 0.926(0.861–0.996) | 0.039 | 0.943(0.863–1.031) | 0.198 |
| IBil | 0.744(0.615–0.972) | 0.028 | 1.025(0.763–1.378) | 0.868 |
| Glo | 1.150(1.050–1.260) | 0.003 | 1.084(0.967–1.216) | 0.166 |
| PT | 1.345(0.917–1.971) | 0.129 | — | — |
| APTT | 1.010(0.942–1.084) | 0.773 | — | — |
| Fg | 2.636(1.654–4.201) | < 0.001 | 1.805(1.056–3.085) | 0.031 |

**Table 3**. Univariate and multivariate regression analyses were performed on the laboratory indicators of the 38 matched pairs of SbORN group and non-sbORN group patients. The results are shown in the table.

in plasma fibrinogen levels between the sbORN group and the non-sbORN group ($P<0.001$). We applied this cutoff value of Fg = 4.5 g/L to the original data (155 patients before propensity score matching) and calculated the positive predictive value (PPV) and negative predictive value (NPV), which were 0.822 and 0.818, respectively. (Table 4; Fig. 4). These findings suggest that plasma Fg has potential diagnostic value for sbORN and could be used as a supplementary indicator.

## Discussion

sbORN frequently presents with severe headache and foul odor, significantly affecting patients' quality of life. The 2-year survival rate for patients is less than 60%, and if accompanied by internal carotid artery exposure, the mortality rate can reach 72.7%[6]. The pathogenesis and risk factors of this disease are not yet fully understood. Early studies suggested that post-radiation trauma and infection are major factors, and in 1983, Marx proposed that radiation leads to tissue hypoxia-hypocellularity-hypovascular, which in turn causes chronic non-healing wounds. Delanian further proposed a model of radiation-induced fibrotic atrophy, emphasizing early inflammation, fibrosis, and tissue necrosis, in which reactive oxygen species (ROS) and TGF-β1 play key roles[13,14]. Lyons, Bras, and others also support the role of fibrosis-induced vascular changes in osteoradionecrosis

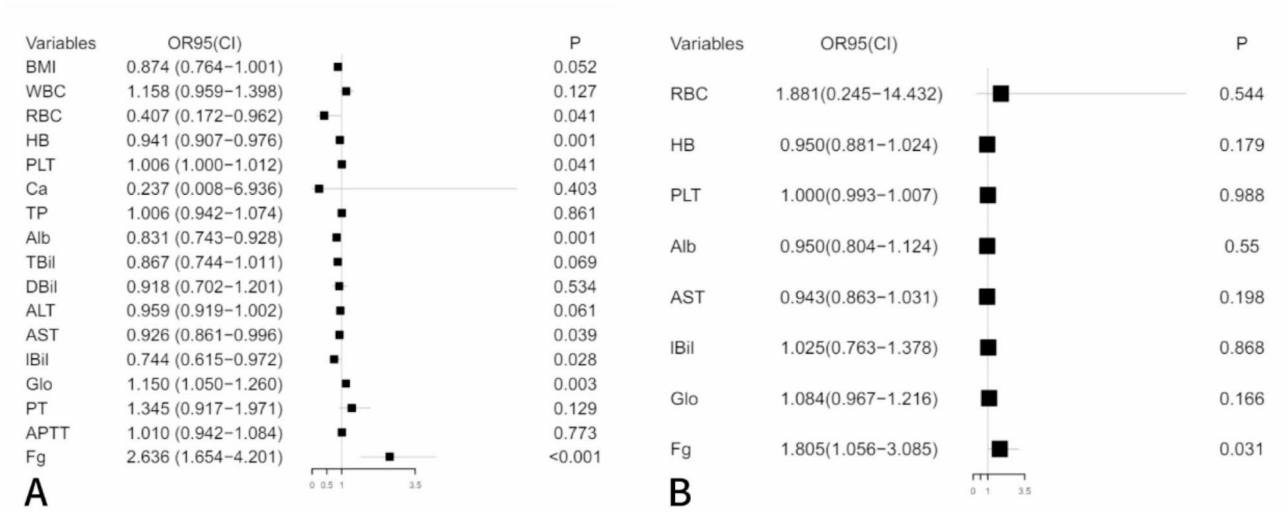


**Fig. 3**. We used RStudio (version 4.4.0) to draw the forest plot. (**A**) Univariate regression analysis was performed on all laboratory assessments. (**B**) Multivariate regression analysis was conducted on laboratory indicators with statistically significant differences ($P < 0.05$) from the univariate analysis.

| | AUC | AUC95%CI | *P* | cut-off | Specificity | Sensitivity | Youden index |
|---|---|---|---|---|---|---|---|
| Fg | 0.829 | 0.736–0.922 | < 0.001 | 4.57 | 0.842 | 0.711 | 0.553 |

**Table 4**. The predictive value of serum fibrinogen (Fg) for the development of skull base osteoradionecrosis (sbORN) in nasopharyngeal carcinoma (NPC) patients who have undergone radical radiotherapy was assessed through ROC curve analysis. The results indicated that serum fibrinogen (Fg) could serve as a potential predictive factor for SbORN in these patients, with an AUC of 0.829, 95% CI of 0.736–0.922, a cut-off value of 4.57, sensitivity of 71.1%, and specificity of 84.2% ($P < 0.001$). ROC, receiver operating characteristic; AUC, area under the curve; CI, confidence interval

(ORN)[10,15]. A 2012 study using a small pig animal model observed histological changes after radiation therapy, finding osteocyte damage as early as 4 h post-radiation, with edema in endothelial cells and subsequent small vessel occlusion observed 1 day after radiation. Two weeks post-radiation, blood flow briefly increases and then gradually decreases. However, it is noteworthy that microvascular damage occurs histologically before bone destruction is observed[16]. A 2018 study in the Netherlands confirmed that patients in the radiation group showed reduced vascular density in the mandible, especially at doses ≥ 50 Gy, with microvessels preferentially occluded. Additionally, clinical data showed that the incidence of mandibular osteoradionecrosis (ORN) was six times higher than that of the more vascularized maxilla, further supporting the vascular etiology of ORN[17].

Studies have shown that the risk of osteoradionecrosis (ORN) is closely related to radiation dose. The MD Anderson study found that the average radiation dose to the mandible in ORN patients was significantly higher than in the control group (48.1 Gy vs. 43.6 Gy). Recursive partitioning analysis revealed that the risk of ORN increased when the volume of tissue receiving 44 Gy (V44) was ≥ 42% and the volume receiving 58 Gy (V58) was ≥ 25%, suggesting that the volume of lower-dose radiation may contribute more significantly to ORN than the maximum dose. This is consistent with the proposed pathogenesis of osteoradionecrosis (ORN), as a larger volume of microvascular damage is more likely to lead to hypoxic, hypocellular, and hypovascular tissue[18]. MSKCC data show that 96% of ORN cases occur in regions receiving doses ≥ 60 Gy, with an estimated 7% increase in ORN risk for every 1 Gy increase in dose[19]. Radiation-induced microvascular damage plays an important role in the occurrence and development of radiation-induced basilar skull necrosis. However, we have observed that there is often a gap of several years between the end of radiation therapy and the development of radiation-induced bone necrosis. During this time, various complex mechanisms may contribute to microvascular occlusion and subsequent vascular remodeling, promoting the occurrence and progression of radiation-induced bone necrosis. This study broadly analyzed common clinical laboratory markers and found that fibrinogen levels were significantly elevated in patients with radiation-induced bone necrosis compared to the control group. We hypothesize that fibrinogen (Fg) plays a crucial role in the occurrence and development of sbORN.

Fg is one of the most abundant plasma proteins. Its molecule consists of 6 polypeptide chains linked by 29 disulfide bonds to form a symmetrical dimer[20]. Fg plays a pivotal role in the processes of coagulation, hemostasis and thrombosis within the body. It is also subject to degradation by fibrinolytic enzymes and is in the process of dynamic destruction to maintain the normal coagulation function of the body. At present, many studies have shown that abnormal elevations of fibrinogen are associated with non-traumatic osteonecrosis of the femoral

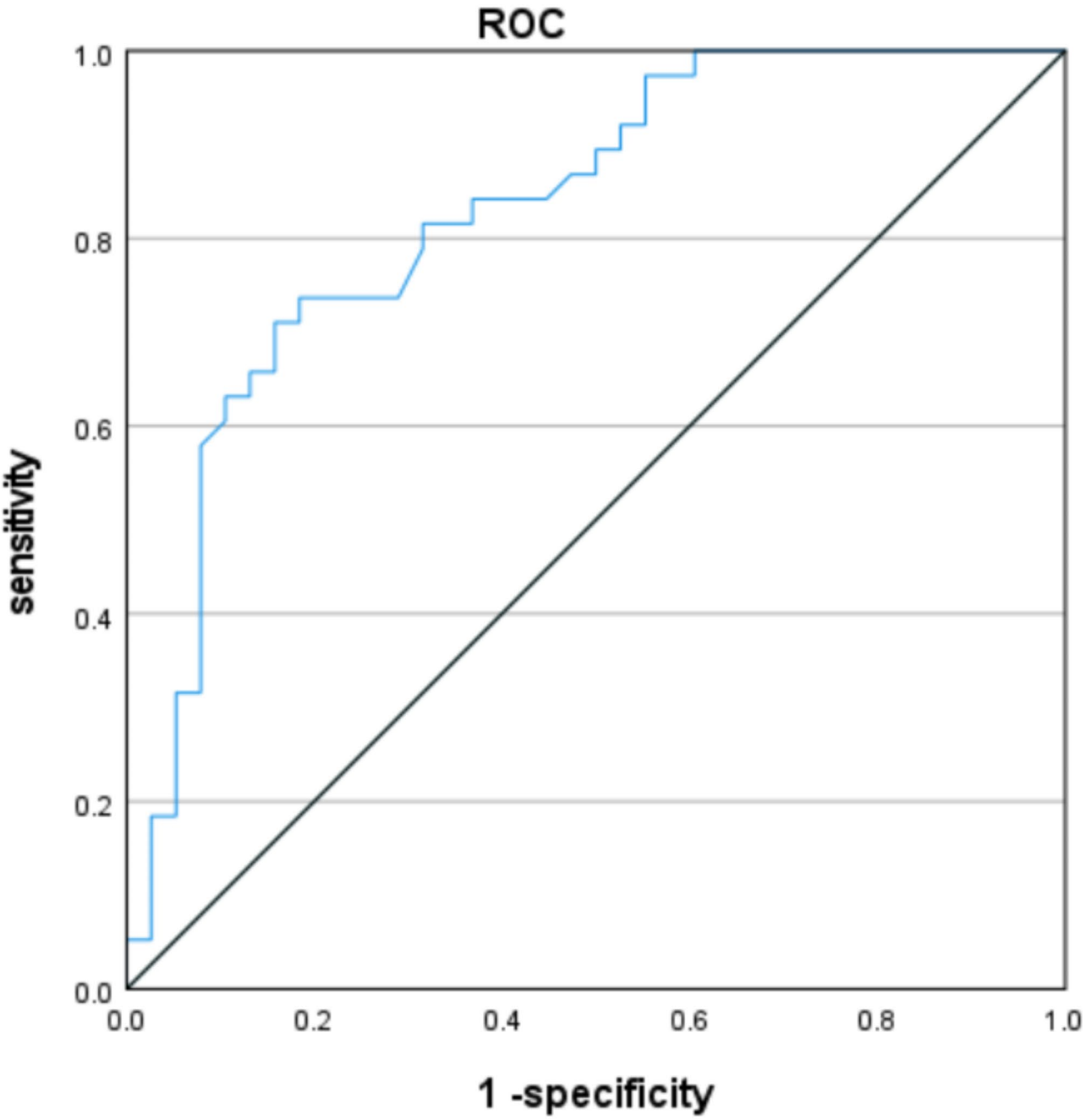


**Fig. 4**. ROC curve analysis of serum fibrinogen (Fg) as a predictive factor for skull base osteoradionecrosis (sbORN) in nasopharyngeal carcinoma (NPC) patients post-radiotherapy.

head. For instance, a study by Liu Li-Ying et al. found that isoform 1 of the fibrinogen alpha chain precursor was significantly higher in patients with steroid-induced osteonecrosis of the femoral head than in healthy controls[21]. In a large case-control study by Xiaolong Yu, plasma fibrinogen levels were found to be significantly higher in patients with non-traumatic femoral head necrosis than in controls[22]. In the study of Cheng-Ta Wu et al., it was found that the levels of fibrinogen, FDP, protein S and antithrombin III in patients with osteonecrosis of the femoral head (ONFH) were significantly higher than those in patients without osteonecrosis of the femoral head, and the risk of bilateral hip involvement was significantly higher in patients with risk factors such as hyperfibrinogenemia and elevated FDP levels[23]. In the study by Kou-Ti Peng et al., it was found that up to 87.6% of patients with osteonecrosis of the femoral head had abnormal coagulation function, including excessive fibrinogen, elevated fibrinogen degradation products, and elevated D-dimer[24]. In our study, we performed univariate and multivariate logistic regression analysis. The results showed higher fibrinogen levels in the sbORN cohort than in the non-sbORN cohort ($p < 0.05$), suggesting a correlation between fibrinogen levels and sbORN.

Although the specific mechanism of fibrinogen (Fg) in the occurrence and development of radiation-induced bone necrosis is not yet clear, many studies have shown that Fg plays an important role in inflammation, microthrombus formation, and tissue repair. On one hand, radiation therapy-induced endothelial damage activates the coagulation system, converting fibrinogen into fibrin and promoting microthrombus formation. These microthrombi occlude local microvessels, leading to tissue ischemia and hypoxia, which in turn results in the occurrence of radiation-induced bone necrosis[25,26]. On the other hand, fibrinogen (Fg) regulates the expression of various cell types, including leukocytes, endothelial cells, and fibroblasts, by binding to multiple cell surface receptors (such as VE-cadherin, ICAM-1, αIIbβ3, α5β1, αVβ3, etc.). This promotes the recruitment and activation of inflammatory cells and the release of pro-inflammatory factors (such as IL-6, TNF-α), thereby exacerbating the local inflammatory response. This inflammatory response may lead to local ischemia and bone necrosis by damaging the endothelial cells and promoting microthrombus formation[25–28]. Additionally, studies have shown that fibrinogen deposition in bone tissue may promote inflammation and inhibit bone remodeling, leading to osteoporosis and bone necrosis. This mechanism may also apply to sbORN, especially in the context of persistently elevated fibrinogen levels following radiation therapy. Animal experiments have also shown that specific domains of fibrinogen (such as the γ390–396 motif) play a key role in inflammation and fibrosis. Targeting the γ390–396 motif could provide protection against inflammation and downstream organ/tissue damage without negatively affecting hemostasis, potentially becoming a new strategy for treating sbORN, though further studies are needed for confirmation[29,30].

In addition, more studies are showing that elevated fibrinogen levels are important for the diagnosis of many diseases, such as cerebral infarction and heart attack. To investigate whether the fibrinogen level also has diagnostic value for sbORN, the ROC curve was plotted, which demonstrated that fibrinogen levels had some diagnostic value for the occurrence of sbORN. Although the diagnosis of sbORN primarily relies on nasal endoscopy and imaging examination, in cases where sbORN is difficult to distinguish from tumor recurrence, the diagnostic value of these methods is significantly reduced. While pathological examination is the most accurate, there remains a possibility of false negatives. The potential diagnostic value of Fg for sbORN may serve as a supplementary diagnostic tool, but further research and exploration are needed to fully assess its diagnostic value.

Research has shown that elevated fibrinogen plays an important role in the pathogenesis of sudden deafness. Elevated fibrinogen levels increase blood viscosity and reduce the integrity of the vascular endothelium, while infections can cause swelling of the vascular endothelium of the inner ear, leading to a reduction in blood flow and circulation. Early use of bacitracin improves the efficacy of treatment for sudden deafness by reducing fibrinogen and increasing local blood flow[31–34]. Investigating whether reducing fibrinogen levels could aid in the prevention and treatment of sbORN represents a clinically significant question deserving further exploration.

Previous studies have demonstrated that anaemia is a risk factor for the development of sbORN[8]. However, the results of the multivariate logistic regression analysis in our study did not support this conclusion. We believe that there are two possible explanations for this discrepancy. The first is the difference in research methods. This study is a case-control study design, and HB and RBC of patients were only collected once, which may not accurately reflect their usual physical conditions. Additionally, the criteria for evaluating anemia in the study by Ping Han et al. may differ from those used in our study. In the future, the quality of this study can be improved by increasing the sample size and evaluation indicators.

Currently, clinical studies on the risk factors of sbORN mainly focus on radiation dose, infection, and tumor staging. However, there is limited research exploring the underlying mechanisms of the occurrence and development of sbORN. In our clinical practice, we have found that certain laboratory indicators in sbORN patients are significantly abnormal. Therefore, we aim to explore the mechanisms of occurrence and development of sbORN by analyzing these abnormal laboratory indicators, in order to better intervene in the disease's progression in clinical settings. To our knowledge, this is the first study to explore the relationship between laboratory indicators and sbORN. Our review of previous studies found that many of them did not have a strict criterion for the diagnosis of sbORN, either. All patients with sbORN in our study had necrosis observed endoscopically or intraoperatively and were pathologically confirmed and excluded from tumor recurrence. It must be acknowledged that there are certain limitations to our study. Firstly, it should be noted that a significant proportion of the sbORN patients do not receive their initial treatment at our hospital, and that the TNM stage, the clinical stage, the dose of radiotherapy and the type of tumor could not be found for the majority of the patients in the sbORN cohort, despite our best efforts. We conducted independent sample t-tests on the currently collected TNM stage, clinical stage and tumor type separately, and the results demonstrated no statistical difference between the two groups of data (Annex 2). Consequently, we proceeded with the analysis of the two groups of data without matching them in terms of propensity score. Secondly, the Fg level is influenced by a multitude of factors, and the current experiment was unable to eliminate all of them. The results of this study demonstrate a correlation between Fg elevation and sbORN, but the specific mechanism by which fibrinogen (Fg) contributes to sbORN has not been explored. Future experiments could be designed to clarify its role. Additionally, the laboratory tests documented in our medical record system were limited, and thus, we were unable to investigate the potential correlation between other suspicious tests, such as coagulation system, fibrinolytic system, immune cells and inflammatory factors, and sbORN. Future research will continue to incorporate additional parameters.

## Conclusions

The occurrence of sbORN was shown to be closely associated with plasma Fg, which may be a potential risk factor for sbORN. Plasma Fg has a certain diagnostic value for sbORN and can be used as a supplementary diagnostic method.

## Data availability

All data that support the findings of this study are available on request from the corresponding author, ChaoSheng Yu upon reasonable request.

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## Author contributions

Study concepts: Jing Li; Study design: Jing Li, ChaoSheng Yu; Data acquisition: Jing Li, Xueyong Hu, Tingfeng Liang, Quality control of data and algorithms: Hongzheng Zhang, ChaoSheng Yu; Data analysis and interpretation: Jing Li; Statistical analysis: Jing Li; Manuscript preparation: Jing Li; Manuscript editing: Jing Li; Manuscript review: Hongzheng Zhang, ChaoSheng Yu. All authors read and approved the final manuscript.

## Declarations

## Competing interests

The authors declare no competing interests.

## Consent statement

The informed consent has been waived by the Medical Ethics Committee of Zhujiang Hospital, Southern Medical University, as this is a retrospective study.

## Additional information

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