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Establishment of nomogram prediction model for distant metastasis of nasopharyngeal carcinoma after radiotherapy

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► ***Original article***

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ABSTRACT

Background: The research aims to construct a nomograph model for predicting distant metastasis of nasopharyngeal carcinoma after radiotherapy, and to evaluate the differentiation and consistency of the model. ***Materials and Methods:*** 292 nasopharyngeal carcinoma patients are selected and broken into a modeling group (204 cases) and a validation group (88 cases). The modeling group patients are further divided into a distant metastasis group (n=45) and a non-distant metastasis group (n=159). Logistic regression analysis is used to analyze the risk factors for distant metastasis of nasopharyngeal carcinoma after radiotherapy. Radiation therapy is performed on each group of patients and their lactate dehydrogenase, serum albumin, carcinoembryonic antigen are compared. ***Results:*** The proportion of age ≥ 60 years old, lymph node cystic invasion, laryngeal lymph node metastasis, T3-T4 staging, and N2-N3 staging in the distant metastasis group were higher than those in the non-distant metastasis group (P<0.05). Multiple logistic regression analysis denoted that age ≥ 60 years old, lymph node cystic invasion, laryngeal lymph node metastasis, T3-T4 stage, N2-N3 stage were risk factors for distant metastasis of nasopharyngeal carcinoma after radiotherapy (P<0.05). The Hosmer Limeshow goodness of fit test showed that the modeling group 2=5.489, P=0.601; Validation group 2=5.231, P=0.733. The areas under the receiver operating characteristic curves of the modeling group and the validation group were 0.828 and 0.822, respectively. ***Conclusion:*** The model constructed in this study for forecasting the risk of distant metastasis of nasopharyngeal carcinoma after radiotherapy has high prediction accuracy, good consistency, differentiation, and clinical applicability.

INTRODUCTION

Nasopharyngeal carcinoma (NPC) is an epithelial malignancy more sensitive to radiotherapy than other head and neck malignancies [1-3]. Clinical studies have reported that intensity-modulated radiotherapy (IMRT) is the most effective means for NPC treatment, and the combined radiochemotherapy based on IMRT can increase the 5 -year survival rate of NPC patients [4]. At present, distant metastasis still exists in NPC after combined radiochemotherapy, which is the key factor in the treatment failure of NPC. Therefore, it has significant clinical significance to search for distant metastasis indicators of NPC. At present, clinical studies have analyzed the risk factors for distant metastasis of NPC after radiotherapy [5-7]. Convenient and intuitive nomograph model can individually predict tumor prognosis and distant metastasis by integrating the risk factors shown in multiple logistic regression analysis (MLRA) [8-9]. This study used logistic regression to analyze the influencing factors of the incidence of distant metastasis in NPC after radiotherapy. At the same time, a nomogram model was constructed to intelligently predict the risk of distant metastasis of NPC after radiotherapy, which is also the novelty of this study.

MATERIALS AND METHODS

Research object

A total of 292 patients with NPC admitted to the hospital from June 2017 to June 2023 are selected and broken into modeling group (MG) (204 cases) and validation group (VG) (88 cases) in a ratio of 7:3. Inclusion criteria: ① The diagnosis of NPC is based on the criteria in the "Expert Consensus on Comprehensive Treatment of Head and Neck Tumors"; ② The diagnosis is confirmed by imaging examination before treatment at the first visit; ③ The pathological data are complete. Exclusion criteria: ① Complicated with other malignant tumors; ② Immune system diseases; ③ Patients with abnormal functions of heart, kidney and liver; ④ Patients who have not completed chemotherapy. Patients in the MG are separated into distant metastasis group (n=45) and non-distant metastasis group (n=159) based on whether distant metastasis occurred. All subjects and their families sign

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informed consent agreements, and the research is supported by the Ethics Committee of the hospital.

Observation indicators

Clinical data were collected, including gender, age, lactate dehydrogenase (LDH), aspartate aminotransferase (AST), serum albumin, (ALB), peripheral blood neutrophil/lymphocyte ratio (NLR), carbohydrate antigen 125 (CA125), squamous cell associated antigen (SCC), carcinoembryonic antigen (CEA), lymph node classification, T staging and N staging.

Clinical staging was performed according to the criteria by the Union for International Cancer Control/American Joint Committee on Cancer (UICC/AJCC). CT image features were evaluated by two radiologists (respectively with more than 5 years and more than 10 years of experiences), and consultation was needed for determination in case of disagreement. For data that can be collected without the use of equipment, manual recording is used to collect it, and the remaining data is obtained through the instrument interaction system. The detailed information of the instruments utilized is expressed in table 1.

Table 1. Detailed description of instruments and equipment involved in the experiment.

Brand	Type	Trade name	Country of origin	Parameter
Siemens	SOMATOM Force 76637	X-ray computed tomography equipment	Germany	150KV/1300*2mA
Toshiba	Aquilion ONE TSX301A	CT machine	Japan	135KV、500mA
STORZ	26003BA	Endoscopy	Germany	10mm diameter, ultra wide angle, effective depth of field range 3-200mm

Treatment methods

All patients received IMRT treatment at a dose of 68-72 Gy in the nasopharyngeal and positive lymph node target areas, with a word dose of approximately 2.2 Gy. The high-risk lymphatic drainage area was 60-66 Gy, with a word dose of approximately 2.0 Gy. The low-risk clinical target area and neck drainage area were 50-56 Gy, with a word dose of approximately 1.7 Gy. The treatment frequency is as follows: once a day, 5 times a week, a total of 30-33 times of separation. Chemotherapy regimen: 90 cases of induction chemotherapy alone, 135 cases of induction + adjuvant chemotherapy, 31 cases of induction + concurrent + adjuvant chemotherapy, 36 cases of induction + concurrent chemotherapy.

Diagnostic criteria

All patients with NPC were examined by nasopharyngoscopy, abdominal color ultrasound, chest imaging, nasopharyngeal + neck MRI and CT. Distant metastasis's diagnose standards were as bellows: (1) The diagnosis was based on tumor markers; (2) The metastases in liver, lung, chest wall and armpit were mainly diagnosed by imaging, while the cases where tissue samples can be collected were confirmed by pathological tissue as far as possible; (3) When imaging indicates distant metastasis in organs such as lung, liver, distant metastasis can only be diagnosed after excluding other primary cancers; (4) For single bone metastases, bone metastases can be diagnosed when both imaging (such as MRI, PET, etc.) indicate bone metastases and other primary cancer metastases were excluded.

Follow-up visit

It needs to conduct follow-up visit to patients by outpatient records, medical records or phone calls after treatment. The patients were followed up once every 3 months in the first 1~3 years after treatment, and once every 6 months in the 4~5 years after treatment for 60 months until death or June 2023.

Statistical methods

SPSS 21.0 wss used for data processing, the count data is described as rate (%), and comparison between the two groups was tested by χ^2 test. Measurement data were expressed as mean ± standard deviation ($\bar{x}\pm s$), and independent sample t test was conducted for comparison. Risk factors were analyzed by logistic regression. The recognized risk factors are brought into R 3.6.3 software to construct a nomograph model for forecasting distant metastasis of NPC after radiotherapy. Receiver operating characteristic (ROC) curve is plotted to assess its differentiation. $P< 0.05$ indicates statistically significant difference.

RESULTS

Comparison of clinical data between the MG and the VG

The data in parentheses in table 2 represent the percentage of people involved in this item, while LDH, ALB, NLR, and CA125 represent LDH, ALB, NLR, and CA125, respectively. According to table 2, it has $P>0.05$ between the MG and the VG in all clinical data items.

Univariate analysis on distant metastasis of NPC after radiotherapy

The partial CT and MRI image display results of the patient during IMRT treatment are shown in figure 1. Subimages (a) and (b) in figure 1 represent CT and MRI images, respectively. As shown in figure 1, the CT and MRI image acquisition scheme set up in this study was reasonable, and the collected images had sufficient clarity.

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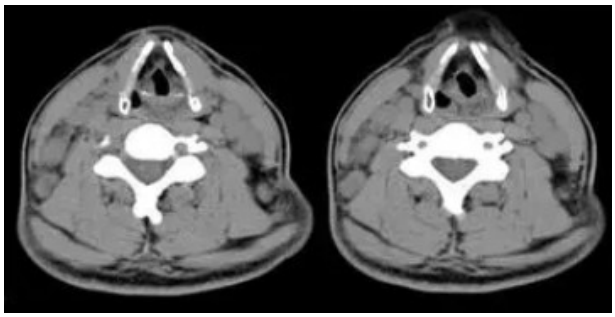
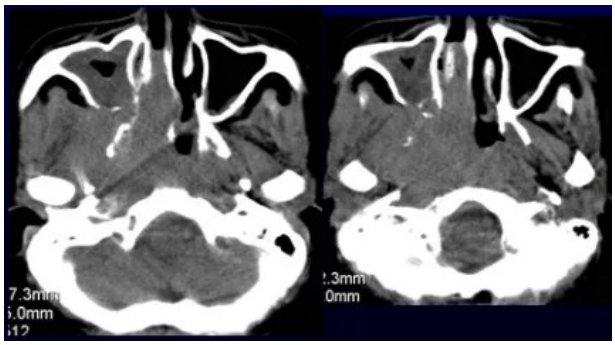
Table 2. Comparison of clinical data between MG and VG [n (%), ($\bar{x} \pm s$)].

Factor	MG (n=204)	VG (n=88)	t/χ^2	*P*
Age (years)			0.233	0.629
≥60	105 (51.47)	48 (54.55)		
＜60	99 (48.53)	40 (45.45)		
Gender			0.315	0.574
male	139 (68.14)	57 (64.77)		
female	65 (31.86)	31 (35.23)		
LDH (U/L)	409.91±59.08	407.43±59.27	0.330	0.742
AST (U/L)	72.31±10.89	71.57±10.92	0.534	0.594
ALB (g/L)	36.97±6.06	37.18±6.14	0.271	0.786
NLR	2.72±0.55	2.70±0.58	0.281	0.779
SCC (ng/mL)	0.68±0.16	0.67±0.18	0.473	0.636
CEA (ng/mL)	1.90±0.29	1.88±0.30	0.537	0.592
CA125 (U/mL)	53.64±9.22	53.18±9.36	0.391	0.696
Clinical stages			1.689	0.639
Ⅰ	9 (4.41)	3 (3.41)		
Ⅱ	83 (40.69)	31 (35.23)		
Ⅲ	87 (42.65)	39 (44.32)		
Ⅳ	25 (12.25)	15 (17.05)		
Lymph gland			1.558	0.459
Liquefying necrosis	84 (41.18)	31 (35.23)		
Capsular invasion	64 (31.37)	34 (38.64)		
Lymph node metastasis of pharynx and larynx	56 (27.45)	23 (26.14)		
T stages			0.595	0.441
T1-T2	76 (37.25)	37 (42.05)		
T3-T4	128 (62.75)	51 (57.95)		
N stages			0.409	0.522
N0-N1	108 (52.94)	43 (48.86)		
N2-N3	96 (47.06)	45 (51.14)		



(a) CT Images of Nasopharynx in Patients with NPC



(b) MRI images of the nasopharynx in patients with NPC

Figure 1. Partial CT and MRI images of patients during IMRT treatment.

In table 3, LDH, ALB, NLR, and CA125 represent lactate dehydrogenase, serum albumin, peripheral blood neutrophil/lymphocyte ratio, and carbohydrate antigen 125, respectively. According to Table 3, 45 out of 204 NPC patients developed distant metastasis after radiotherapy, with an incidence rate of 22.06% (45/204). The proportion of patients aged ≥ 60 years, lymph node cystic invasion, laryngeal lymph node metastasis, T3-T4 staging, and N2-N3 staging in the distant metastasis group were obviously higher than those in the non-distant metastasis group (P<0.05).

Table 3. Univariate analysis on distant metastasis of NPC after radiotherapy [n (%), ($\bar{x} \pm s$)]

Factor	Distant metastasis group (*n*=45)	No distant metastasis group (n=159)	t/χ^2	*P*
Age (years)			8.916	0.003
≥60	32 (71.11)	73 (45.91)		
>60	13 (28.89)	86 (54.09)		
Gender			0.363	0.547
male	29 (64.44)	110 (69.18)		
female	16 (35.56)	49 (30.82)		
LDH (U/L)	422.26±60.18	406.42±58.74	1.588	0.114
AST (U/L)	74.31±10.18	71.74±11.09	1.397	0.164
ALB (g/L)	35.89±5.64	37.27±6.18	1.347	0.179
NLR	2.86±0.58	2.68±0.54	1.295	0.197
SCC (ng/mL)	0.71±0.18	0.67±0.16	1.440	0.152
CEA (ng/mL)	1.96±0.32	1.88±0.28	1.638	0.103
CA125 (U/mL)	55.06±9.43	53.24±9.17	1.168	0.244
Clinical stages			5.956	0.114
Ⅰ	1 (2.22)	8 (5.03)		
Ⅱ	13 (28.89)	70 (44.03)		
Ⅲ	22 (48.89)	65 (40.88)		
Ⅳ	9 (20.00)	16 (10.06)		
Lymph gland			16.648	0.000
Liquefying necrosis	7 (15.56)	77 (48.43)		
Capsular invasion	18 (40.00)	46 (28.93)		
Lymph node metastasis of pharynx and larynx	20 (44.44)	36 (22.61)		
T stages			9.370	0.002
T1-T2	8 (17.78)	68 (42.77)		
T3-T4	37 (82.22)	91 (57.23)		
N stages			11.044	0.001
N0-N1	14 (31.11)	94 (59.12)		
N2-N3	31 (68.89)	65 (40.88)		

Logistic analysis of distant metastasis

Distant metastasis after radiotherapy of NPC was utilized as the dependent variable (no distant metastasis=0, distant metastasis=1) and statistically significant criteria (age, lymph nodes, T stage, N stage) in univariate analysis were utilized as independent variables. MLRA was conducted. The assignment mode of the model is denoted in Table 4, and the MLRA results are indicated in Table 5. The purpose of Table 4 was to convert character type variables into numerical type variables for conducting MLRA. The amplitudes of lymph nodes, T stage, and N stage were divided according to the severity of symptoms. MLRA expressed that age ≥60

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years old, lymph node capsule invasion, laryngeal lymph node metastasis, T3-T4 staging and N2-N3 staging were risk factors for distant metastasis of NPC after radiotherapy (P<0.05) (table 5).

Table 4. Variable assignment mode.

Variable	Assignment mode
Age	<60 years=0, ≥60 years=1
Lymph gland	Liquefying necrosis=0, Capsular invasion=1, Lymph node metastasis of pharynx and larynx=2
T stages	T1-T2=0，T3-T4=1
N stages	N0-N1=0，N2-N3=1

Table 5. Multivariate analysis on distant metastasis of NPC after radiotherapy.

Variable	*β*	*SE*	*wald*	*P*	*OR*	95%CI
Age	1.069	0.448	5.695	0.017	2.911	1.210~7.002
Lymph gland				0.002		
Capsular invasion	1.070	0.489	4.788	0.029	2.917	1.118~7.609
Lymph node metastasis of pharynx and larynx	1.827	0.518	12.417	0.000	6.213	2.249~17.160
T stages	1.232	0.451	7.453	0.006	3.428	1.416~8.301
N stages	1.590	0.408	15.214	0.000	4.905	2.209~10.907
Constant	-4.514	0.674	44.840	0.000	0.011	

Construction of nomination graph model

A nomination map model for predicting distant metastasis of NPC after radiotherapy was constructed using R software. The numerical mapping relationship of each indicator in the model is denoted in Figure 2. The leftmost text in Figure 2 is the feature to be studied, and the corresponding peer's right side displays the value range of the feature. Moreover, the impact of all factors on distant metastasis in Figure 2 is presented in the form of scores. The corresponding rules for their impact scores were as follows: age ≥ 60 years old, 58.5 points; Lymph node sac invasion, 58.5 points; Laryngeal lymph node metastasis, 100 points; T3-T4 staging, 67.5 points; N2-N3 staging, 87 points. If the patient was ≥ 60 years old (58.5 points), lymph node cystic invasion (58.5 points), T3-T4 staging (67.5 points), N2-N3 staging (87 points), the total score of the patient was 271.5 points, and the prediction probability corresponding to the vertical line at the total score coordinate 271.5 points was about 62%. Based on the above data, the predicted value of distant metastasis in NPC patients after radiotherapy was 62%.

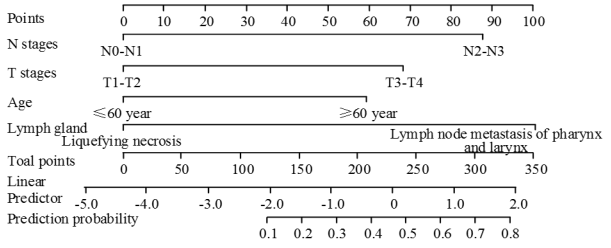

Figure 2. A nomograph model for predicting distant metastasis of NPC after radiotherapy.

Performance validation of nomination graph model

Now, the ROC curve and calibration curve of the nomination graph model to were drawn evaluate the differences in predicting distant metastasis, as shown in Figure 3. Figures (a) and (b) in Figure 3 show ROC curves, with the horizontal axis representing the specificity and sensitivity coefficients, respectively. Figures 3 (c) and (d) show the calibration curves, with the horizontal and vertical axes representing the predicted and the true likelihood coefficients, respectively. Analyzing figure 3, the area under ROC curve was 0.828 (95%CI: 0.765-0.892) for the MG (figure 3A) and 0.822 (95%CI: 0.758~0.886) for the VG (figure 3B). Hosmer-Lemeshow goodness-of-fit test showed that MG had c^2= 5.489, P = 0.601, the VG had c^2 = 5.231, P = 0.733. The predicted calibration curve value of the nomograph model was basically consistent with the actual value (figures 3C, 3D).

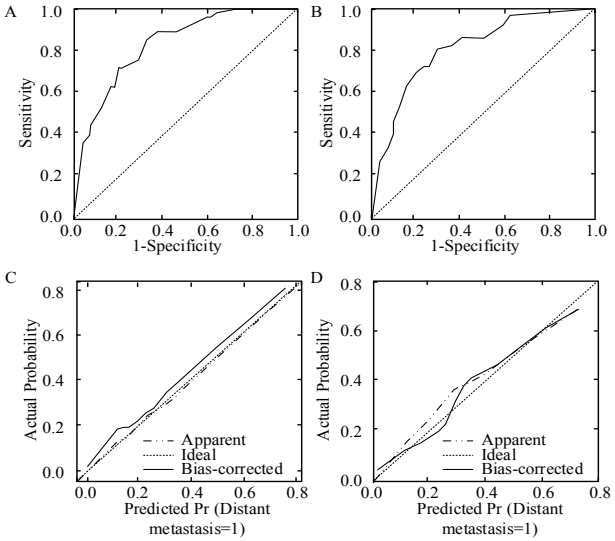

Figure 3. ROC and calibration curve A of the MG: ROC curve of the MG; **B:** The ROC curve of the VG; **C:** Calibration curve of the MG; **D:** Calibration curve of VG.

DISCUSSION

NPC, a tumor originating from the mucosal epithelial cells of nasopharynx, is prevalent in the south of China. NPC is sensitive to radiation, and with the advancement of IMRT technology, the local control rate is significantly higher. Clinical studies have shown that the wide application of IMRT and the optimization of chemotherapy strategies (induction, synchronization and adjuvant) in the treatment of NPC can help improve survival rate and reduce toxicity [9]. Concurrent chemoradiotherapy (CRT) is the standard treatment for locally advanced NPC. Clinical studies have reported that concurrent CRT can greatly improve the local control rate and survival rate of patients with advanced NPC, while induction chemotherapy before concurrent CRT can further improve the tumor control of patients with

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advanced NPC, but distant metastasis is the major cause of failure after combined CRT [10]. According to epidemiological reports, the cumulative distant metastasis rate of NPC after IMRT is about 10-20% in 5 years [11]. Analysis in this study revealed 22.06% possibility in distant metastasis of NPC after radiotherapy, showing a relatively high incidence, which may vary depending on different subjects. Therefore, it has crucial clinical significance to establish a nomograph model for predicting the risk in distant metastasis of NPC after radiotherapy.

Patients with NPC face a variety of treatment options, and it has been reported in previous literature that concurrent chemoraotherapy + adjuvant chemotherapy can bring survival benefits for patients with NPC [12-13]. A 10-year long-term follow-up study confirmed that adjuvant chemotherapy with cisplatin and cisplatin fluorouracil could significantly improve survival rate of patients with advanced NPC without significantly increasing the toxicity in late stage. Liu *et al.* [14] confirmed that adjuvant chemotherapy could reduce distant metastasis and improve overall survival of high-risk NPC patients. It has been reported in the literature that the residual lymph node rate was 33% ~38% after traditional radiotherapy, a term referring to the residual lymph node in the original lymph node region and neck. The 3-year progression-free survival rate was obviously lower in NPC patients with residual positive cervical lymph nodes than in NPC patients with residual negative cervical lymph nodes [15]. Multivariate analysis in this study showed that age, lymph nodes, T staging and N staging were risk factors for distant metastasis of NPC after radiotherapy. At present, it is a difficult clinical problem to quantify the risk of distant metastasis in NPC patients after radiotherapy.

The nomination chart can visualize the results of MLRA and accurately predict the risk of adverse events [16]. This study established a nomination map model for predicting the risk of distant metastasis of NPC after radiotherapy based on four factors: age, lymph nodes, T stage, and N stage. According to the results of table 5, the effects of age ≥ 60 years old, lymph node cystic invasion, laryngeal lymph node metastasis, T3-T4 staging, and N2-N3 staging on the incidence of distant metastasis in NPC patients were 58.5 points, 58.5 points, 100 points, 67.5 points, and 87 points, respectively. This indicated that laryngeal lymph node metastasis and N2-N3 staging had the greatest impact on distant metastasis in NPC patients. The reason for this may be due to organ dysfunction, decreased immunity, and a higher risk of lymph node metastasis after radiotherapy and chemotherapy in elderly patients. The research results of Yeung DCM et al. also confirm this conclusion [17].

The TNM staging system has always been considered an important indicator for predicting the survival of NPC patients, and the clinical treatment plans for NPC patients at different stages are also different. Jiang *et al.* [13] used nomograph to predict the prognosis of locally advanced NPC patients. According to the results shown in figure 3, the nomination chart outperformed the TNM staging system in predicting the survival rate of locally advanced NPC patients receiving IMRT and chemotherapy. Zhong L *et al.* also found that the TNM staging system had insufficient accuracy in predicting patient survival rate, but this study did not propose a better prediction model [18].

Evidence showed that 75% of patients with distant metastasis of NPC were distributed in stage N2~N3, with poor prognosis and a median survival time of 7~16 months [18]. Currently, the TNM staging of NPC in the 8th edition of the AJCC staging system has been modified based on the 7th edition to reduce the involvement of the medial and lateral alary muscles from stage T4 to stage T2, so that there is better distinction between progression-free survival and overall survival. N staging is a key factor for predicting distant metastasis, and about 70%~85% of NPC patients have regional lymph node metastasis. Laryngeal lymph nodes are risk factors for distant metastasis, which may cause radiotherapy resistance and then distant metastasis due to heavy tumor load and cell hypoxia [19].

As a statistical model for accurate prediction of clinical events, nomograph model has been used to guide treatment protocols for cancer patients [20-21]. To establish nomograph model to predict distant metastasis, it not only need to evaluate patient survival, but more importantly, treatment guidance is needed. Patients with locally advanced NPC face various CRT regimens in clinical practice, but optimal chemotherapy regimen and treatment regimen are not standardized. In this study, it externally verified the nomograph model for predicting the risk in distant metastasis of NPC after radiotherapy, proving its good differentiation and consistency.

In conclusion, based on age, lymph nodes, T staging and N staging, this study established a nomograph model for predicting distant metastasis of NPC after radiotherapy. Showing good consistency, differentiation and clinical applicability, the model is worthy of clinical promotion.

***Conflicts of interest*:** All author(s) declares that they have no conflect of interest.

***Consent for publication*:** All authors give consent for publication.

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***Research involving human participants and/or animal*:** This retrospective study involving human participants was in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The research was supported by our institution's ethics review board.

***Data availability statement*:** The [DATA TYPE] data used to support the findings of this study are included within the article.

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