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Early Predictors of Fistula Formation Following Head and Neck Reconstruction

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Abstract

Background: Salivary fistula formation is a common and serious complication following head and neck reconstruction. Because it can cause delayed wound healing and infection and carotid artery rupture in severe cases, early detection and treatment are crucial. This study was designed to identify early predictors of postoperative fistula formation.

Methods: We conducted a retrospective analysis of patients who underwent head and neck reconstruction between 2015 and 2022. Body temperature, serum white blood cell (WBC) count, and serum C-reactive protein (CRP) levels were assessed until postoperative day (POD) 14 and compared between patients with and without fistula.

Results: In this study, 200 patients were included. No significant differences in body temperature and WBC count were observed between the two groups during the entire study period. CRP levels after POD2 were higher in the fistula group than in the without fistula group. From the receiver operating characteristic curves comparing the two groups, the best cutoff level for CRP was 6.27 mg/dL from POD7 to POD8, with 77.1% sensitivity, 69.8% specificity, and 90.1% negative predictive value.

Conclusion: CRP is a valuable predictor of fistula formation following head and neck reconstruction. The course of CRP levels in patients with fistulas remains consistently elevated compared to patients without fistulas, and it is particularly useful for the exclusion diagnosis of fistula.

Keywords

head and neck reconstruction, salivary fistula, predictor, C-reactive protein

Introduction

Head and neck reconstruction is one of the most challenging surgeries, and its complications are difficult to treat. There are various complications after head and neck reconstruction, including necrosis of the transplanted tissue. Orocutaneous or pharyngocutaneous salivary fistula formation is also a troublesome complication during the early postoperative period and is not rare. The incidence of salivary fistulas after head and neck reconstruction has been reported to be 4.1%–56.6%[1-6] and varied depending on the patient background, such as previous chemoradiotherapy, the reconstruction site, and flap type.

Once a salivary fistula occurs, it becomes a major cause of wound infection and delayed healing, and if the infection extends to the deep plane, there is a risk of carotid artery blowout.[7] Therefore, the prevention and early prediction of fistula formation are important because early therapeutic intervention can prevent major complications.

Although many preoperative risk factors for fistula formation and surgical site infection following head and neck reconstruction have been reported, only a few studies have focused on postoperative early predictors.[8,9] Therefore, this study was designed to analyze biological markers as early predictors of fistula formation following head and neck reconstruction.

Methods

This retrospective study was approved by the Institutional Ethics Committee of the Hyogo Cancer Center (R-963). All consecutive patients who had undergone primary major head and neck reconstructive oncological surgery between October 2015 and January 2022 were identified. Oral cavity and pharyngeal reconstruction cases were included, whereas maxilla reconstruction cases in which salivary fistula formation is unlikely to occur clinically were excluded. Cases of total necrosis of transplanted tissue; those in which the reconstruction of the skin side only was performed; and those with a remote site infection, such as respiratory/urinary tract and donor site infections, were also excluded.

The patients were classified into the fistula and without fistula groups according to the presence or absence of postoperative orocutaneous or pharyngocutaneous fistula formation. The fistula group comprised patients in whom saliva had been spontaneously or surgically drained from the body surface wound leading to the formation of cutaneous fistulas.

All patients underwent neck lymph node dissection. To suture the mucosa, 3-0 Vicryl was used, with superficial and submucosal multilayer sutures wherever possible. The cervical wound was thoroughly washed with ≥1 L of saline, and several drains were placed not to create a dead space. Perioperative prophylactic antibiotics were administered from preoperative 30 min to postoperative day (POD) 2.

As an early predictor of postoperative fistula, course of body temperature, white blood cell (WBC) count, and C-reactive protein (CRP) until POD 14 were assessed. Since body temperature has diurnal variation, the highest value of the day was used for analysis. For WBC/CRP, daily data were used up to POD4, while the average of the values measured every 2 days from POD 5 to POD 14 were used.

Fisher's exact test was used in analyzing qualitative variables between groups, and Student's t-test or the Mann–Whitney U-test was used in analyzing quantitative variables. *P*-values of less than 0.05 were used to denote statistical significance. Furthermore, a receiver operating characteristic (ROC) analysis was performed between the two groups to determine the cutoff values. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, a modified version of R Commander designed to add statistical functions frequently used in biostatistics was used.[10]

Results

In the analysis, 200 patients were included. The demographic profiles and preoperative

clinical characteristics of the patients are shown in Table 1. Fifty patients were classified into the fistula group. As preoperative risk factors, the fistula group had a statistically high rate of alcohol consumption and peripheral artery disease and long operation time. No significant differences in smoking, previous chemoradiotherapy, preoperative serum total protein, serum albumin, neck dissection range, reconstruction site, and flap type were observed between the two groups. An external fistula was formed after on average 12 days (range, 4–30 days), and 40 patients received conservative treatment and 10 patients received surgical treatment after fistula formation. Two cases in the fistula group died of carotid artery rupture, and the other two cases died of the primary disease without fistula healing. Other cases in the fistula group eventually healed.

Figures 1–3 show the postoperative course of the mean values of body temperature, WBC, and CRP in each group. Body temperature and WBC values increased at POD 1 and then gradually decreased but sometimes remained unchanged or re-increased in all groups. No significant differences in body temperature and WBC count were observed between the two groups during the entire period up to POD 14. In contrast, the peak mean values of CRP were reached at POD 2 in both groups, CRP values in the without fistula group decreased rapidly, whereas those in the fistula group showed a prolonged decrease or re-increased after the decrease. Although no statistically significant difference in CRP values at POD 1 was observed between the two groups, CRP values after POD 2 in the fistula group were statistically higher than those in the without fistula group ($p < 0.05$).

Table 2 shows the cutoff value, area under the ROC curve (AUC), sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) of CRP obtained from the ROC curve analysis from the preoperative period to POD 14 between the fistula and without fistula groups. The NPV after POD 4 was approximately 90%, and the AUC on POD 7 to POD 12 was >0.700, and the values became more credible over time after surgery. The

best combination was CRP on POD 7 to POD 8, with a cutoff value of 6.27 mg/dL, an AUC value of 0.78, a sensitivity of 77.1%, a specificity of 69.8%, and an NPV of 90.1%.

Discussion

This study revealed that CRP levels were significantly increased up to 2 weeks after head and neck reconstruction in cases with salivary fistula formation compared with those in cases without fistula formation. Postoperative CRP levels were considered an early predictor of fistula formation. The CRP values on POD 7 to POD 8 were the most important in terms of the ability to predict fistula formation, with a cutoff of 6.27 mg/dL.

Salivary fistula formation is one of the serious postoperative complications of head and neck reconstruction. Once it occurs, it results in wound dehiscence, infection, and healing inhibition; moreover, prolonged infections can also lead to carotid artery blowout if not properly treated. Thus, predicting salivary fistula formation at an early stage is essential to take appropriate treatment. Although fistulas may cause several clinical symptoms, such as redness and swelling of the neck, these symptoms take some time to appear and may be unclear in patients with previous radiation therapy. Because clinical symptoms include uncertainties and delays in the detection of salivary fistulas, determining early predictors, such as clinical parameters and biological markers, is important. Few studies have focused on the postoperative early predictors of salivary fistula formation, including surgical site infection, following head and neck reconstruction. Yu et al. reported the usefulness of serum albumin and WBC count after free jejunal flap reconstruction; albumin levels after POD 3 and WBC counts after POD 7 were statistically significantly different between patients with salivary leakage and those without.[8] According to a report examining the changes in serum CRP levels after head and neck reconstruction, abnormal changes in the CRP levels, such as a delayed decrease and a second rise, were predictors of surgical site infection, and the risk

126 increases when the CRP levels after POD 7 were >4.0 mg/dL.[9]

127

128 Recently, CRP has been widely reported as an early predictor of postoperative
129 complications, such as anastomotic leakage, after colorectal surgery.[11-17] Sala et al. conducted
130 a multicenter prospective study involving 2,501 cases undergoing colorectal surgery and
131 concluded that CRP is a reliable marker for detecting leakage, with a cutoff level of 11.9
132 mg/dL on POD 4, a sensitivity of 70%, a specificity of 81%, and an NPV of 97%.[11] Yeung et
133 al. conducted a systematic review involving 6,647 cases undergoing colorectal surgery and
134 found a significant difference in the CRP values on POD 1 to POD 7 between the leaked and
135 non-leak groups, particularly on POD 4 to POD 7, with a specificity of 100%.[12] Although
136 these reports were in the field of colorectal surgery, oropharyngeal surgery is classified as
137 class II/clean-contaminated operative wound according to the Centers for Disease Control
138 and Prevention criteria similar to colorectal surgery; therefore, CRP can be applied as a
139 predictor of postoperative leakage.[18]
140 CRP levels increase within 6–12 h after surgery and peak after approximately 48 h
141 postoperatively and return to the normal ranges by POD 7 in a typical postoperative
142 course.[19,20] An elevated CRP level is not a specific infectious reaction in the early
143 postoperative period, and CRP has a delayed response that peaks 3 days after infective
144 symptoms; some researchers have reported that CRP cannot be used as an isolated diagnostic
145 marker in the early postoperative period.[21,22] Detecting fistulas on POD 2 to POD 3 may be
146 difficult; however, if the postoperative course is complicated, CRP levels remain increased
147 and may even increase to higher concentrations.[19] In this study, fistulas became clinically
148 apparent, on average, by POD12, but the postoperative CRP levels in the “fistula” group were
149 statistically higher than the “no-fistula,” starting from POD 2. Fistula did not occur on POD2,
150 but a minor salivary leakage probably induced internal inflammation, leading to an elevation

of CRP. If CRP levels are elevated and remain high in the early postoperative period, a subclinical minor salivary fistula may manifest before the development of a cutaneous fistula. Therefore, a CT scan may be necessary to investigate the presence of fluid collections or observe minor leaks through a barium swallowing test. CRP monitoring after POD 2 is considered essential for detecting postoperative fistula formation.

In this study, postoperative body temperature and WBC counts were not significantly different between the two groups, and, therefore, they were not considered predictors of fistula formation. CRP suggested fistula formation since the early postoperative period and therefore was considered a predictor of fistula formation following head and neck reconstruction. Although the specificity was not high, the NPV was high and reached approximately 90% after POD 4, indicating that serum CRP levels play an important role in the exclusion diagnosis. Clinically, CRP can be assessed as a negative test because prolonged inflammatory response with high CRP levels can be seen even in patients without complications due to the severity of surgical trauma and the duration of surgery[13,14,23]; a low postoperative CRP level can help predict patients who are unlikely to develop fistula.

Risk factors for postoperative fistula formation, such as the pedicled flaps[24] usage and the presence of sarcopenia[25], have been reported as risk factors for postoperative fistula formation. In our study, no significant difference in fistula occurrence was observed between the pedicled and free flaps. On the contrary, there was a significantly high incidence of alcohol abuse in the fistula group. Although we did not conduct preoperative sarcopenia assessments, sarcopenia is often linked to alcohol abuse. This raises the possibility that there were more patients with sarcopenia in the fistula group.

The limitations of this study include the following: the CRP cutoff value for clinical application remains uncertain because remote site infections, such as respiratory and urinary tract infections, were excluded in this study. CRP values may increase even in patients

without fistulas when accompanied by remote site infections. This was a retrospective single-center study with a limited number of patients; therefore, prospective multicenter studies with a larger number of patients are necessary to confirm our findings and clarify the CRP cutoff values presented in this study.

Conclusions

Postoperative CRP levels are a reliable predictor of salivary fistula formation following head and neck reconstruction. The course of CRP levels in patients with fistulas remains elevated and gradually declines compared with that in patients without fistulas. This cost-effective marker is particularly useful for the exclusion diagnosis of fistula.

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Figure legends

Figure 1. Body temperature (℃) of patients with and without fistula from the period preoperative to POD 14.

POD, postoperative day.

Figure 2. White blood cell count ($\times 10^2/\mu L$) of patients with and without fistula from the preoperative period to POD 14.

POD, postoperative day.

Figure 3. C-reactive protein levels (mg/dL) of patients with and without fistula from the preoperative period to POD 14.

* Significant difference ($p < 0.05$) between the two groups.

** Highly significant difference ($p < 0.001$) between the two groups.

POD, postoperative day.

275 **Table 1.** Demographic profiles and clinical characteristics among the two groups.

	Total (n = 200)	Without fistula group (n = 150)	Fistula group (n = 50)	*P*-value
Age, years	67 (57–74)	67 (57–73)	68 (56–75)	0.75
Gender				0.48
Male	139 (69.5)	102 (68.0)	37 (74.0)	
Female	61 (30.5)	48 (32.0)	13 (26.0)	
Body mass index, kg/m^2	21.4 ± 3.6	21.6 ± 3.6	20.8 ± 3.6	0.21
Smoking	131 (65.5)	94 (62.7)	37 (74.0)	0.17
Alcohol	136 (68.0)	90 (60.0)	46 (92.0)	<0.001
Previous chemotherapy	28 (14.0)	18 (12.0)	10 (20.0)	0.16
Previous radiotherapy	25 (12.5)	17 (11.3)	8 (16.0)	0.46
Comorbidities				
Hypertension	56 (28.0)	39 (26.0)	17 (34.0)	0.28
Diabetes mellitus	22 (11.0)	15 (10.0)	7 (14.0)	0.44
Peripheral artery disease	6 (3.0)	1 (0.7)	5 (10.0)	0.004
Ischemic heart disease	5 (2.5)	3 (2.0)	2 (4.0)	0.6
Cerebrovascular disease	12 (6.0)	7 (4.7)	5 (10.0)	0.18
Serum total protein, g/dL				1.0
≥6.5	177 (88.5)	133 (88.7)	44 (88.0)	
<6.5	23 (11.5)	17 (11.3)	6 (12.0)	
Serum albumin, g/dL				0.44
≥3.5	178 (89.0)	135 (90.0)	43 (86.0)	
<3.5	22 (11.0)	15 (10.0)	7 (14.0)	
Neck dissection				0.13
Unilateral	126 (63.0)	99 (66.0)	27 (54.0)	
Bilateral	74 (37.0)	51 (34.0)	23 (46.0)	
Operation time, min	513 ± 96	504 ± 91	541 ± 107	0.02
Reconstruction site				0.08
Buccal mucosa	17 (8.5)	14 (9.3)	3 (6.0)	
Tongue	82 (41.0)	67 (44.7)	15 (30.0)	
Oral floor	15 (7.5)	9 (6.0)	6 (12.0)	
Mandible	23 (11.5)	14 (9.3)	9 (18.0)	
Oropharynx	3 (1.5)	1 (0.7)	2 (4.0)	

Hypopharynx	60 (30.0)	45 (30.0)	15 (30.0)	
Flap type				0.3
Free flaps	178 (89.0)	137 (91.3)	41 (82.0)	
RFFF	79 (39.5)	62 (41.3)	17 (34.0)	
RAM	40 (20.0)	28 (18.7)	12 (24.0)	
jejunum	40 (20.0)	33 (22.0)	7 (14.0)	
FF	12 (6.0)	8 (5.3)	4 (8.0)	
ALT	5 (2.5)	4 (2.7)	1 (2.0)	
LD	2 (1.0)	2 (1.5)	0 (0.0)	
Pedicled flaps	22 (11.0)	13 (8.7)	9 (18.0)	
PMMC	21 (10.5)	13 (8.7)	8 (16.0)	
LD	1 (0.5)	0 (0.0)	1 (2.0)	

Continuous data are presented as means ± standard deviations or medians (interquartile ranges) depending on the Gaussian distribution; categorical data are presented as absolute and relative frequencies, N(%).

RFFF, radial forearm free flap; RAM, rectus abdominis myocutaneous flap; FF, fibula osteocutaneous free flap; ALT, anterolateral thigh flap; LD, latissimus dorsi myocutaneous flap; PMMC, pectoralis major myocutaneous flap.

Table 2. Diagnostic value of C-reactive protein levels for predicting fistula formation.

	CRP cutoff, mg/dL	AUC	Sensitivity, %	Specificity, %	PPV, %	NPV, %
Preop	0.58	0.593	48.0	70.7	35.3	80.3
POD 1	11.72	0.586	48.0	68.7	33.8	79.9
POD 2	21.4	0.594	55.1	62.4	32.8	80.7
POD 3	13.62	0.621	71.7	51.4	33.0	84.5
POD 4	9.88	0.62	87.2	44.4	34.3	91.2
POD 5–6	5.77	0.695	84.4	45.4	34.0	89.7
POD 7–8	6.27	0.78	77.1	69.8	46.0	90.1
POD 9–10	2.92	0.74	80.0	63.0	41.9	90.4
POD 11–12	5.39	0.746	57.1	87.3	60.0	85.9
POD 13–14	0.52	0.685	97.5	35.5	33.5	97.7

C-reactive protein (CRP) cutoff value optimized on Youden's index.

AUC, area under the receiver operating characteristic (ROC) curve; PPV, positive predictive value; NPV, negative predictive value; POD, postoperative day.