# Title:

# An external validation of C-reactive protein reduction as a predictor of healing following laryngopharyngectomy

**Key Points**

* CRP reduction at day five of more than 35% from the previous highest concentration post-laryngectomy or laryngopharyngectomy has been proposed to positively predict healing without pharyngocutaneous fistula
* Retrospective cohort analysis of 163 patients has not been able to externally validate these findings.
* ROC curves and subset analyses have not identified alternative parameters to reach significance
* However, there is a non-significant association with decreasing postoperative CRP and healing without fistula.
* Multicentre prospective studies to include post-operative procalcitonin could help refine this protocol further.

**INTRODUCTION**

Pharyngocutaneous fistula (PCF) following laryngectomy or laryngopharyngectomy is a significant post-operative complication. It can result in delayed restart of oral feeding, voice rehabilitation and initiating radiotherapy as well as cause considerable morbidity and prolonged hospital stay (1). The reported incidence of PCF varies widely from 13-45% (2–4). Fistulae will usually become clinically apparent on days 7-11 (5). Contrast radiographic swallow assessments are used to predict or assess fistulae and are commonly performed around post-operative day ten (4,6). Lack of clinical or radiographic presence of PCF will trigger the beginning of oral feeding and is a significant milestone in a patient’s recovery. Alongside oncological clearance, early feeding and reduced length of hospital stay are hallmarks of a successful post-operative course.

A recently published retrospective cohort study of 55 patients identified post-operative C-reactive protein (CRP) concentrations could predict PCF as soon as day five (7). More specifically, if the post-operative day five CRP concentration dropped by more than 35% from the highest previously recorded post-operative CRP concentration, this had a positive predictive value of 97% that the patient would heal without a fistula. Employing this diagnostic tool could accelerate early feeding and form a component in an enhanced recovery programme for patients undergoing laryngectomy surgery.

**OBJECTIVES**

The primary objective of this study was to assess if a larger cohort of patients would validate the previously proposed threshold. Secondly, we wanted to see if there were any potential refinements or opportunity for direct clinical application.

**METHODS**

**Ethical considerations**

As a retrospective cohort study, ethical approval was not required. No patient identifiable information were collected.

**Reporting guideline**

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines were used in preparation of this manuscript.

**Study design, setting and size**

A retrospective cohort study was undertaken at a single tertiary Head and Neck Cancer unit between January 2014 and October 2020. This timeframe dictated the participant number and therefore study size.

**Participants**

All patients who underwent a ‘laryngectomy’ or ‘laryngopharyngectomy’ were identified using hospital admission statistics (HAS) and confirmed by reviewing electronic patient records. Patients were included if they had a laryngectomy or laryngopharyngectomy, whether primary or salvage surgery and regardless of whether primary repair, pedicled or free-flap reconstruction methods were used. Patients were excluded if there were insufficient post-operative CRP data or inadequate follow-up to determine whether they developed a fistula. Patients were assessed either clinically or radiologically for post-operative fistula development.

**Outcome measures**

Data were collected from digital hospital records and variables included patient characteristics (age and gender), operation, post-operative CRP concentrations, water soluble contrast swallow assessment, fistula formation and length of hospital stay. All CRP concentrations recorded on patients up to postoperative day eight were collected.

**Data analysis**

Data were analysed using SPSS (IBM Corp. Build 1.0.0.1508) and R (The R Foundation, version 4.0.5). Data are summarised as median and interquartile range for continuous, non-parametric data, with categorical data presented as number and percent, n (%). Continuous data are compared using the Mann-Whitney U test, and categorical data are compared using Chi-squared analysis. Receiver operating characteristic curves were generated on R and provided sensitivity analysis. Significance was set at *p* < 0.05.

Analyses were performed in accordance with the pre-established analysis plan based on the original paper. Subset analyses were performed on patients identified by operation type, reconstruction and alternative post-operative day CRP analysis.

**RESULTS**

**Participants and exclusions**

Patient and subset characteristics are summarised in Table 1. HAS coding identified 178 patients who had undergone either a ‘laryngectomy’ or ‘laryngopharyngectomy’. Of these, 15 were excluded: seven patients had ‘sub-total laryngectomies’, six with inadequate post-operative CRP recordings and two patients who died in the early post-operative period and in whom it was unknown if a fistula had developed.

**Outcome data**

One-hundred and sixty-three patients met the inclusion criteria with 131 (80.4%) having primary surgery. Thirty-seven (22.7%) patients developed a post-operative fistula confirmed clinically or by water soluble contrast study. Post-operative day 5 or 6 CRP concentrations were recorded in 123 patients.

**Validation of post-operative CRP reduction**

Analysis of our cohort of patients with the diagnostic criteria for successful healing as post-operative day 5 CRP dropping by 35% from the previous maximum is contained in Table 2 and highlights a non-significant positive predictive value of 84.1% (c2 *p*=0.157).

**Secondary analysis of post-operative CRP concentrations**

Area under the receiver operating characteristic (ROC) curves were calculated to assess the relationship between percentage CRP drop and healing without fistula. Comparing day five post-operative CRP with the previous maximum CRP concentration in all patients generated a ROC curve with an area of 0.647 and optimal cutpoint of 36.8% - namely the optimum percentage CRP reduction from previous maximum that provides the greatest sensitivity and specificity of 58.1% and 75.0% respectively (Chart 1).

To attempt to refine the ROC curves we excluded all patients who had a rising CRP trend rather than a decreasing trend as these patients would ordinarily be identified as unsuitable for progression on an enhanced recovery programme and would be treated with greater caution. Alternative subset analysis looked at primary laryngectomy and salvage laryngectomy patients independently. None of these analyses identified a significant trend in CRP concentrations that could be used as a discriminator to predict pharyngocutaneous fistula. These subset analyses are summarised in Table 3.

**DISCUSSION**

This retrospective analysis of 163 patients has not been able to validate a reduction in C-reactive protein (CRP) on day five as being predictive of healing without pharyngocutaneous fistula (PCF) after laryngectomy or laryngopharyngectomy.

A systematic review has suggested the potential value of a decreasing serum CRP concentration in predicting bowel anastomotic healing(8). Although more recently it has been shown that using trend, rather than specific cut-offs may allow wider applicability (9). Halliday and George have subsequently examined sequential measurement of serum CRP in patients undergoing total laryngectomy with pharyngeal anastomosis. CRP is an acute phase protein of hepatic origin that increases with inflammation, tissue injury and infection, and decreases in concentration over 20 hours once the initial stimulus ends. Given this, they have postulated that assessing CRP trend can be both sensitive and specific in predicting PCF formation as soon as day five post-operatively (7). More specifically, they concluded that after daily post-operative CRP measurements, if the day five CRP had dropped by 35% from the previous highest recorded concentration, then there was a 97% likelihood of favourable anastomosis healing without fistula. This should subsequently allow earlier restart of oral intake, accelerating recovery and reducing hospital length of stay. Of note, their conclusion was produced on a relatively small cohort of patients and after analysis and pooling of CRP data from all patients undergoing any laryngectomy or laryngopharyngectomy, regardless of reconstruction method or whether it was primary or salvage surgery.

The failure to validate the findings of Halliday and George suggests their findings were unique to their specific dataset. Therefore, we examined whether other CRP thresholds could predict clinical outcome. Further subset analyses did not identify any with an area under the receiver operating characteristic curve of >0.7. These were therefore deemed unable to demonstrate a significant relationship between alternative post-operative CRP concentration assessments and healthy anastomosis in this patient group, though the data does support a non-significant association with some models. We therefore suggest post-operative CRP to continue to be used to assess for post-operative complication of any sort, especially if rising. However, currently the evidence does not support the routine use of post-operative CRP to predict healing without fistula and therefore should not be used when making decisions regarding early post-operative feeding.

The lack of significant correlation may highlight a need to combine CRP with other measurable parameters to predict pharyngocutaneous fistula rather than be used in isolation. This is supported by growing evidence from large, prospective multicentre studies that have shown CRP levels have an excellent negative predictive value of anastomotic leak in colon and rectal surgery when used in conjunction with other biomarkers such as serum procalcitonin or calprotectin(10).

Therefore, multi-centre prospective research in post-operative serological CRP and alternative biomarkers to predict anastomotic leak is indeed precedented, is easily translatable to assess for post-laryngectomy pharyngocutaneous fistula and would undoubtably provide improved insights to refine this model further as we look to improve the postoperative course of this complex patient cohort.

**Limitations and generalisability**

As demonstrated by Stephensen *et al.* when looking at CRP trends predicting colon anastomotic leak rates, smaller single-unit studies often saw exaggerated claims of sensitivity and specificity when compared with their prospective, multi-centre collaboration(9). Although this is a retrospective study with the limitations associated with such a design, including an inconsistency of when CRP measurements were taken in each patient, the larger cohort compared with previous studies has perhaps helped provide a more moderated and generalisable conclusion at this time.

**Conclusion**

We have been unable to demonstrate a significant association between decreasing post-operative C-reactive protein and healing without pharyngocutaneous fistula following laryngectomy or laryngopharyngectomy. This supports current practices in post-operative contrast swallow or clinical assessment prior to resuming oral intake in this patient group.

**Conflicts of Interest**

None.

Tables and Figures:

In order or appearance:

Table 1

Table 2

Chart 1

Table 3

**REFERENCES**

1. Saki N, Nikakhlagh S, Kazemi M. Pharyngocutaneous fistula after laryngectomy: incidence, predisposing factors, and outcome. Arch Iran Med. 2008 May;11(3):314–7.

2. Markou KD, Vlachtsis KC, Nikolaou AC, Petridis DG, Kouloulas AI, Daniilidis IC. Incidence and predisposing factors of pharyngocutaneous fistula formation after total laryngectomy. Is there a relationship with tumor recurrence? Eur Arch Oto-Rhino-Laryngol Head Neck. 2004 Feb 1;261(2):61–7.

3. Šifrer R, Aničin A, Pohar MP, Žargi M, Pukl P, Soklič T, et al. Pharyngocutaneous fistula: the incidence and the risk factors. Eur Arch Otorhinolaryngol. 2016 Oct 1;273(10):3393–9.

4. Morton RP, Mehanna H, Hall FT, McIvor NP. Prediction of pharyngocutaneous fistulas after laryngectomy. Otolaryngol Neck Surg. 2007 Apr 1;136(4\_suppl):s46–9.

5. Mäkitie A, Irish J, Gullane P. Pharyngocutaneous fistula. Curr Opin Otolaryngol Head Neck Surg. 2003 Apr;11(2):78–84.

6. van la Parra RFD, Kon M, Schellekens PPA, Braunius WW, Pameijer FA. The prognostic value of abnormal findings on radiographic swallowing studies after total laryngectomy. Cancer Imaging Off Publ Int Cancer Imaging Soc. 2007 Jun 11;7(1):119–25.

7. Halliday E, George A. Using post-operative trend in C-reactive protein to predict fistula in neopharyngeal repairs following laryngectomy and pharyngectomy surgery in fifty-five patients. Clin Otolaryngol [Internet]. 2020 Sep 2 [cited 2020 Oct 28];n/a(n/a). Available from: https://doi.org/10.1111/coa.13645

8. Singh PP, Zeng ISL, Srinivasa S, Lemanu DP, Connolly AB, Hill AG. Systematic review and meta-analysis of use of serum C-reactive protein levels to predict anastomotic leak after colorectal surgery. Br J Surg. 2014 Feb 17;101(4):339–46.

9. Stephensen BD, Reid F, Shaikh S, Carroll R, Smith SR, Pockney P, et al. C-reactive protein trajectory to predict colorectal anastomotic leak: PREDICT Study: C-reactive protein trajectory to predict colorectal anastomotic leak. Br J Surg [Internet]. 2020 Jul 16 [cited 2020 Dec 31]; Available from: http://doi.wiley.com/10.1002/bjs.11812

10. Su’a BU, Mikaere HL, Rahiri JL, Bissett IB, Hill AG. Systematic review of the role of biomarkers in diagnosing anastomotic leakage following colorectal surgery. Br J Surg. 2017 Mar 14;104(5):503–12.